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Endoscopic management of local complications of chronic pancreatitis

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ABSTRACT

Endoscopic treatment of local complications in patients with chronic pancreatitis has gained ground over the surgical alternative in the last few years. The lower aggressiveness of endoscopic treatment, as well as the possibility to use it repeatedly in high-risk patients, has favored this development. In addition, the incorporation of new, highly accurate endoscopic therapeutic options such as pancreatoscopy-guided lithotripsy and endoscopic ultrasound-guided treatments make endoscopic treatment the first choice in many cases, despite discordant data in the literature. This article reviews the endoscopic treatment of the most common local complications of chronic pancreatitis, such as pancreatolithiasis, pseudocysts, and pancreatic, biliary, and duodenal ductal stenosis.

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Keywords: Chronic pancreatitis. Endoscopic retrograde cholangiopancreatography. Endoscopic ultrasound. Pancreatoscopy. Lithotripsy. Pancreatic stent.

INTRODUCTION

Chronic pancreatitis is characterized by recurrent episodes of inflammation causing the replacement of the pancreatic parenchyma by fibrous tissue, which sometimes leads to pancreatic endocrine and exocrine insufficiency (1).

The main clinical manifestation of chronic pancreatitis is abdominal pain. This is partly related to hyperpressure in the pancreatic duct, which can be secondary to different local complications. Although decompressive surgical treatment provides longer lasting pain relief, from a practical point of view, surgery is usually indicated only when endoscopic treatment has already been tried and failed, and not as first-line treatment (2,3).

Endoscopic treatment is considered when the patient with chronic pancreatitis has pain or other symptoms associated with the following local complications: pancreatic ductal stones, pancreatic ductal stenosis, pancreatic pseudocyst, biliary stricture, and duodenal stenosis. It is not indicated in patients with asymptomatic or uncomplicated chronic pancreatitis (1). The goals of endoscopic treatment are to ensure pancreatic drainage, to relieve and reduce the frequency of pain episodes, and to resolve local complications.

Two procedures are available for the endoscopic treatment of local complications of chronic pancreatitis: endoscopic retrograde cholangiopancreatography (ERCP) and therapeutic endoscopic ultrasound (EUS).

In this article we will provide an update on the endoscopic management of said local complications using these two endoscopic procedures, reviewing the current literature, and making recommendations in this regard.

PANCREATIC DUCTAL LITHIASIS

The prevalence of pancreatic ductal lithiasis in chronic pancreatitis varies between 50 % and 90 %. It is higher in men with high alcohol and tobacco consumption. Most of these stones are calcified, located in the head of the pancreas, and have a mean

diameter of 10 mm. They are associated with pancreatic ductal stenosis in approximately 50 % of cases, which hinders endoscopic treatment (4).

The first-line treatment for pancreatic ductal lithiasis > 5 mm is extracorporeal shock-wave lithotripsy (ESWL) (4,5), although its use with this indication in our country is not very widespread for various reasons. From an endoscopic point of view, we have three treatment options: classical or standard treatment, pancreatoscopy-guided lithotripsy, and minor papilla drainage.

Standard endoscopic treatment consists of performing a pancreatic sphincterotomy, associated or not with balloon sphincteroplasty, followed by cleaning of the pancreatic duct with a Fogarty balloon or Dormia basket. It is the most widely used treatment, although the results are modest. Complete cleaning of the pancreatic duct is achieved in < 50 % of cases. Despite this, it is considered as the treatment of choice for stones ≤ 5 mm located in the head of the pancreas (4). These stones are frequently associated with pancreatic duct strictures. In such cases prior stricture dilation is often required, which improves endoscopic treatment outcomes.

The results of endoscopic treatment are worse with stones > 10 mm, multiple ductal stones along the pancreatic duct, impacted stones, and stones lodged above a stricture.

The second therapeutic option is pancreatoscopy with laser (LL) or electrohydraulic lithotripsy (EHL). Both techniques have experienced important progress thanks to the popularization of single-operator cholangioscopy and pancreatoscopy systems. Overall, the technical success rate exceeds 80 % with a variable rate of adverse events ranging from 0 % to 28 % (Table 1). The largest study is a retrospective research that compares ERCP treatment with standard technique *versus* pancreatoscopy and intraductal lithotripsy (6). It includes 94 patients in the lithotripsy group and 129 in the standard therapy group. Technical success was significantly higher in the former group (98.9 % *vs* 87.6 %). The overall stone recurrence rate was 36 % after a median follow-up of 180 days (range: 27-1,865), without significant differences between both groups. Lithotripsy was used more frequently to treat lithiases that were larger, more numerous, impacted, and located in the body and tail of the pancreas. In other words, it was used to treat more difficult cases. Clinical success was similar in both groups

(82.9 % *vs* 84.5 %) and there were no differences in need for subsequent surgery, mean Emergency Room visits, mean hospitalizations, or incidence of adverse effects, which was 6.3 % and 8.1 %, respectively.

Therefore, ERCP and lithotripsy treatment allows the resolution of symptomatic lithiasis in a high percentage of patients, especially when the standard technique has fewer options for success. In addition, it does not carry a greater risk of complications.

A non-dilated pancreatic duct may limit the use of pancreatoscopy and lithotripsy, since at least 3-4 mm are required for the introduction of the pancreatoscope. This may occur in patients with a normal duct diameter in the head and a proximal stricture with retrograde chronic pancreatitis, although this situation is rare (Fig. 1).

The third option for endoscopic treatment is the placement of a stent through the minor papilla. The goal of this therapy is to decompress the dorsal pancreatic duct, but it can be effective when the stone is located in the ventral duct. In a series of 16 cases, a clinical success rate of 75 % was obtained with an incidence of adverse events of 6.3 % (7). It is a rescue technique that can be used as a bridge to surgical or ESWL treatment, or as a definitive treatment in poor candidates for any of the alternatives. In our center we have had the opportunity to perform this treatment on several patients with good results.

Following the recommendations of other authors (6), in our center the first-choice treatment for pancreatic ductal lithiasis is endoscopic. Initially, stone resolution is attempted with the standard technique, and in case of failure LL or EHL are used at the discretion of the endoscopist (Fig. 2), although a tendency to obtain better results with LL has been described (8). If endoscopic therapy is not feasible or fails, we propose using ESWL or surgery.

DUCTAL PANCREATIC STENOSIS

A dominant pancreatic ductal stenosis is defined as a stricture that conditions an upstream ductal dilation > 6 mm in diameter or that prevents the outflow of the contrast injected with a 6 F catheter inserted through the narrowed segment (1,4). The recommended treatment is the placement of a 10 F plastic stent as short as possible by conventional ERCP. It should be maintained for at least one year. Some authors

recommend stent replacement on demand, but the preferred strategy is to make at least one exchange at six months (1,4). In our hospital we follow this policy, making an exchange at six months or earlier in patients with pain recurrence. The stent should be straight or single-pigtail, although less proximal migration has been described with the latter (5).

Performing this treatment, a resolution of stenosis is achieved in 9-50 % of cases, although long-term clinical success reaches 32-94 % (Table 2).

Persistent symptomatic strictures after one year of treatment with a 10 F plastic stent are considered as refractory strictures (1,4). In such case, endoscopic treatment with multiple simultaneous plastic stents (MPS), or with a fully covered self-expandable metal stent (cSEMS), or surgical treatment should be considered. Treatment with MPS improves the results of endoscopic treatment. In a study that included 48 patients with refractory stenosis treated with MPS for a mean of 6.8 months, resolution of the stenosis was achieved in 89.6 % of cases (9). After a mean follow-up of 9.5 years, 74.4 % of these patients remained asymptomatic, with a stenosis recurrence rate of 7 %.

Alternatively, a cSEMS can be placed (Table 3). The results are encouraging in terms of stricture resolution and clinical success, but they carry a high rate of adverse events, especially *de novo* stenosis, secondary to the pressure exerted by the stent at its proximal end, and stent migration, which can reach 50 %.

Most of these studies were analyzed in a meta-analysis showing a 93 % stenosis resolution rate, regardless of whether the treatment was longer or shorter than three months; a stenosis recurrence of 5 %, and an overall adverse events rate of 34.9 % (10). These adverse events included a 14.1 % of stent migrations and 7.4 % of *de novo* stenoses. The authors concluded that the treatment of pancreatic ductal stenosis with cSEMS was effective and had an acceptable rate of adverse effects.

In addition, the first experiences of treating pancreatic ductal stenosis with biodegradable stents have recently been published. These stents degrade over time and produce less ductal hyperplastic reaction thanks to their biocompatibility. Among their proposed advantages we would underline that the duration of their effect can be predicted, and that the ERCP to remove the stent can be avoided. Furthermore, stent

removal would not be necessary in the event of proximal migration. One study included 19 patients with no improvement in pancreatic stenosis after at least six months with a plastic stent (11). A self-expanding biodegradable stent was correctly placed in all patients. Adverse events related to the procedure and stent were reported in 21 % of cases, and events related to the chronic pancreatitis disease in 42 %. There was one case of abdominal pain and another case of jejunal perforation related to the procedure. Among the adverse events related to the stent and underlying disease we highlight the development of *de novo* stenosis in one case, and another case of stent migration. Stenosis resolution and clinical success were reached in 58 % and 53 % of cases, respectively, after a 12-month follow-up. Therefore, although these stents appear to avoid the main adverse effects of cSEMS, new data are needed to define their role.

In any case, in 10-30 % of patients it will not be possible to permanently remove the stents due to stenosis and pain recurrence, making it necessary for regular ERCP procedures to replace these stents when there is no surgical alternative. The endoscopic alternative in such cases is EUS-guided ductal drainage.

PANCREATIC PSEUDOCYST

Spontaneous resolution of a pseudocyst in patients with chronic pancreatitis occurs in less than 10 % of cases. Drainage is recommended of symptomatic pseudocysts with abdominal pain, fever, upper digestive tract obstruction symptoms, etc. Pseudocysts that cause vascular or biliary compression, those that result in pancreato-pleural fistula, pseudocysts > 5 cm that will not reduce their size after six weeks, pseudocysts with wall thickness > 5 mm, and pseudocysts associated with significant distortion of the main pancreatic duct or pancreatolithiasis are deemed a relative indication for drainage (1,5).

Endoscopic treatment has shown its superiority over percutaneous and surgical treatment, and is first-choice (1). In a meta-analysis including 490 patients, endoscopic treatment obtained greater clinical success, lower reoperation rates, and shorter hospital stay than percutaneous treatment (12). However, most of the collections included in this meta-analysis were produced after an acute pancreatitis bout in

patients without chronic pancreatitis.

On the other hand, compared with surgical treatment, endoscopic treatment offers similar results in terms of technical success, recurrence, and adverse events. In a randomized trial with 20 patients per arm, technical success (95 % *vs* 100 %), recurrence (0 *vs* 5 %), need for reoperation (5 % *vs* 5 %), and complication rates (0 % *vs* 10 %) were similar for endoscopic and surgical treatment (13). Hospital stay and costs were significantly lower with endoscopic treatment. Most of these pseudocysts did correspond to patients with chronic pancreatitis. Similar results have been described in a recent meta-analysis on this topic (14).

Endoscopic drainage of pancreatic pseudocysts can be performed transpapillary, when they are < 5 cm and communicated with the pancreatic duct, or transmurally, which should be EUS-guided (1). This allows a higher technical success rate, probably associated with a lower rate of adverse events (15).

The type of stent to be used is not well defined. In case of pancreatic pseudocysts, with exclusively liquid content, it is commonly accepted that double-pigtail plastic stents are preferable over lumen-apposing metal stents, due to their lower cost, although several studies show better results with the latter. A retrospective study comparing the drainage of pseudocysts with lumen-apposing metal stents *versus* double-pigtail plastic stents did not show any significant differences in terms of technical success (97.5 % *vs* 99.2 %), need for surgery (1.3 % *vs* 4.9 %), post-procedure hospital stay (6.3 days *vs* 3.7 days), or pseudocyst recurrence at six months (6.7 % *vs* 18.8 %). However, lumen-apposing metal stents offered better results in terms of clinical success (96.3 % *vs* 87.2 %), need for percutaneous drainage (1.3 % *vs* 8.8 %), and adverse events (7.5 % *vs* 17.6 %) (16).

Ductal pathology apt to condition pseudocyst recurrence, such as ductal stenosis, ductal disconnection syndrome, or pancreatic ductal lithiasis, should be ruled out before stent removal. Magnetic resonance cholangiopancreatography generally allows to diagnose these conditions. If any of them is present, an ERCP should be performed before stent removal to avoid pseudocyst recurrence. If the ductal pathology cannot be resolved by endoscopic treatment, surgical treatment should be considered (5).

BILIARY STENOSIS

The reported incidence of biliary strictures in chronic pancreatitis varies between 3 % and 46 %, since not all these strictures are associated with jaundice or may be transient. Biliary drainage is indicated in symptomatic cases, and in asymptomatic cases with an increase in alkaline phosphatase level > 2-3 times the upper limit of normal, regardless of bilirubin levels, for more than one month (4,5).

Endoscopy, using MPS o cSEMSs, is the first-choice treatment. In a randomized study comparing these two options, success rates (88 % *vs* 90.9 %, respectively) and adverse events rates (23 % *vs* 29 %) were similar (17). In another randomized comparative study in which all types of benign biliary strictures were included, the stricture resolution rate was also similar, but with a cSEMS it was achieved earlier (225 *vs* 181 days) and with fewer ERCPs (3.24 *vs* 2.14) (18). There were no differences in terms of adverse events, but in this study patients with an intact gallbladder, in whom a cSEMS might have occluded the cystic duct outlet, were excluded.

A systematic review described a higher stricture resolution rate with fewer ERCP procedures and adverse events in patients treated with a cSEMS *versus* MPS (19). Finally, in a study in which cSEMSs were placed for 10-12 months without scheduled replacements, more than 60 % of patients remained free of symptoms and/or cholestasis for up to five years without additional interventions (20).

The recommended stenting duration is at least one year, with replacements every six months if a cSEMS is chosen. The replacements should be done every 3-4 months if we opt for MPS, increasing the number of plastic stents to a maximum of six when possible, and removing the occluded ones.

Therefore, it seems that cSEMSs offer some advantages over MPS, although both treatments are currently accepted as equally valid. In our center we use both strategies, considering gallbladder status when deciding between them.

If the stricture does not respond to endoscopic treatment or recurs in the subsequent first year, the surgical option should be considered (5).

DUODENAL STENOSIS

Another local complication of chronic pancreatitis is duodenal stenosis secondary to groove pancreatitis or duodenal cystic dystrophy. This is a form of focal chronic pancreatitis characterized by inflammation of the paraduodenal area around the pancreatic head. In these cases, it is important to make a good differential diagnosis with duodenal stenosis secondary to pancreatic cancer (5).

Conservative treatment with analgesia and both alcohol and tobacco abstinence is usually the first-line approach. Some patients require surgery, mostly a cephalic duodenopancreatectomy. However, a few cases or small series of patients managed with endoscopic treatment have also been published.

In a systematic review including 335 patients with groove pancreatitis, endoscopic treatment was performed for 62 of them (19 %) (21). This treatment consisted of adjacent pseudocyst drainage (63 %), placement of a pancreatic (24 %) or biliary (16 %) stent, duodenal dilatation (8 %), or placement of a duodenal stent (2 %). In all, 13 % of these patients developed adverse events, all of them controlled with conservative management.

The placement of a pancreatic stent through the minor papilla is considered as the most effective endoscopic treatment since a possible cause of this entity may be insufficient drainage of pancreatic secretion through the Santorini duct. This treatment is, however, technically challenging due to duodenal inflammatory changes. Of the last seven cases with this condition who were treated by ERCP in our center, we were only able to place a stent through the minor papilla in one of them, leaving the stent through the major papilla in the other six.

EUS-GUIDED DUCTAL DRAINAGE

Most of the studies that evaluate the therapeutic role of endoscopy include patients treated by ERCP. However, in patients with pain due to ductal hyperpressure secondary to ductal stenosis and/or pancreatolithiasis, in whom ERCP fails and who are not good surgical candidates, EUS-guided pancreatic ductal drainage may be considered. In our experience, we have also been able to verify the benefit of this technique in patients with pancreatic collections associated with complete ductal disruption.

By means of this technique, a transmural drainage is achieved by communicating the pancreatic duct with the gastric or duodenal lumen, thus completing a pancreaticogastrostomy or pancreaticoduodenostomy, respectively.

It is a complex technique that offers a technical success rate of 76 %, and development of adverse effects in 18.9 % of cases (22). A Spanish multicenter series that included 27 patients reported an 85 % technical success rate (23). Adverse events were detected in 15 % of cases.

In our experience, this technique also offers an important advantage over ERCP since periodic stent replacements are not necessary. We maintain an on-demand replacement strategy. Following this policy, we have had to make stent exchanges in 15 % of cases after a follow-up period ranging from one to nine years.

The latest published guidelines consider this technique as a therapeutic option applicable only in centers with adequate experience and support (4,5), but it is likely that it will play a relevant role in the future treatment algorithm for chronic pancreatitis.

In conclusion, thanks to the incorporation of new therapeutic options and the improvement of existing ones, endoscopy is accepted as first-line in the treatment of chronic pancreatitis complications. Its efficacy is, in many patients, comparable to that of surgery with a low rate of adverse events. In addition, it can be performed repeatedly even in patients considered to be poor surgical candidates. When endoscopic treatment is not successful, it can serve as a bridge to other surgical or non-surgical options.

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Table 1. Outcomes of patients with pancreatic stones managed by means of ERCP and lithotripsy

Author/Year	*Type of study*	*Device*	*Method*	*n*	*Technical success*	*Adverse events*
Howell et al. 1999 (24)	Case series	Olympus MB®	EHL	6	83 %	0 %
Fishman et al. 2009 (25)	Retrospective	SpyGlass®	EHL	6	50 %	0 %
Maydeo et al. 2011 (26)	Prospective	SpyGlass®	LL	4	100 %	13.5 %
Alatawi et al. 2013 (27)	Prospective	SpyGlass®	LL	5	80 %	0 %
Ito et al. 2014 (28)	Retrospective	SpyGlass®	EHL	7	43 %	28 %
Attwell et al. 2014 (29)	Retrospective	Olympus MB® *vs* SpyGlass®	EHL/LL	46	68 % *vs* 73 %	10 %
Navaneethan et al. 2016 (30)	Retrospective	SpyGlass®	LL	5	80 %	0 %
Bekkali et al. 2017 (31)	Retrospective	SpyGlass®	EHL	6	83 %	0 %
Ogura et al. 2019 (32)	Retrospective	SpyGlass®	EHL	21	85.7 %	4.7 %
Han et al. 2019 (6)	Retrospective	Olympus MB®, SpyGlass®	EHL/LL	94	98.9 %	9.8 %

ERCP: endoscopic retrograde cholangiopancreatography; EHL: electrohydraulic lithotripsy; LL: laser lithotripsy.

Table 2. Outcomes of the treatment of dominant pancreatic ductal stenosis with a single 10 F plastic stent

Author and year	*n*	*Technical success*	*Clinical success*	*Adverse events*	*Follow-up (months)*
Ito et al. 2018 (33)	59	69.5 %	90.2 %	13 %	27
Cremer et al. 1991 (34)	75	100 %	---	5.3 %	37
Ponchon et al. 1995 (35)	23	100 %	52 %	43 %	12
Smits et al. 1995 (36)	51	96 %	55 %	18 %	34
Cahen et al. 2007 (37)	16	100 %	32 %	58 %	24
Boursier et al. 2008 (38)	13	100 %	85 %	10 %	11

Clinical success is evaluated at the end of follow-up.

Table 3. Outcomes of the management of refractory pancreatic ductal stenosis with a cSEMS

Author/ Year	*n*	*Mean duration of therapy (months)*	*Stenosis resolution*	*Clinical success*	*Follow-up (months)*	*Adverse events*
Park et al. 2008 (39)	13	2	100 %	100 %	5	4 migration 2 cholestasis 3 acute pancreatitis
Sauer et al. 2008 (40)	6	3	67 %	33 %	4.25	No complication
Moon et al. 2010 (41)	32	3	100 %	90.6 %	5	5 *de novo* stenosis 3 acute pancreatitis
Giacino et al. 2012 (42)	10	5.7	100 %	90 %	19.8	2 cholestasis
Matsubara et al. 2016 (43)	10	2.7	80 %	30 %	35	2 migration 2 *de novo* stenosis 1 pain 1 acute pancreatitis
Ogura et al. 2016 (44)	13	5.8	84.6 %	84.6 %	8.6	2 migration 1 pain
Yamada et al. 2018 (45)	22	4.7	86.3 %	86.3 %	13.9	1 *de novo* stenosis
Tringali et al. 2018 (46)	15	7.1	93.3 %	53.3 %	38.9	7 migration 4 *de novo* stenosis 3 acute pancreatitis
Oh et al. 2018 (47)	18	7.5	83.3 %	72.2 %	47.3	3 pain

Korpela et al. 2019 (48)	17	5.6	70.6 %	70.6 %	29	7 migration 1 cholestasis 4 acute pancreatitis
Sharaiha et al. 2019 (49)	33	3.5	100 %	87.1 %	14	2 pain 2 cholestasis
Lee et al. 2020 (50)	25	3.6	100 %	88 %	34	1 migration

Clinical success is evaluated at the end of follow-up.

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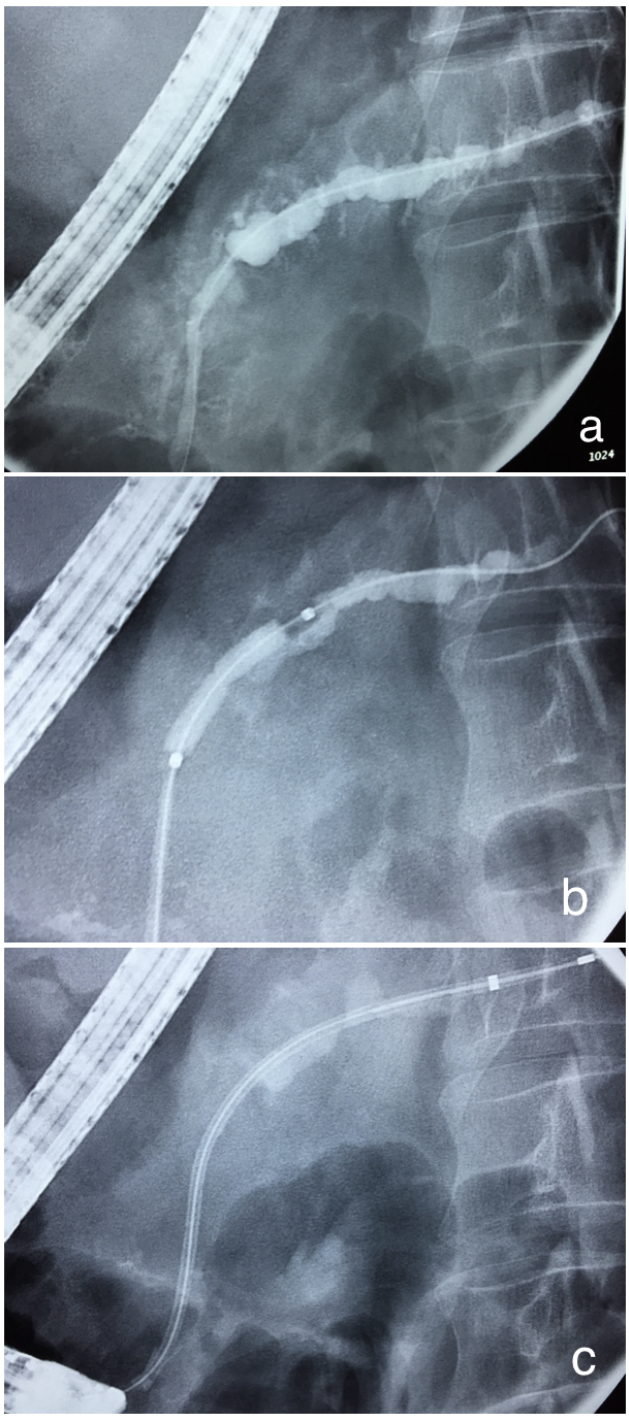

Fig. 1. A. A focal stenosis in the pancreatic isthmus with retrograde dilation of the pancreatic duct, signs of chronic pancreatitis, and normal distal duct may be seen in this pancreatogram. B. The stenosis is dilated to 4 mm. C. Since the cephalic duct has a normal caliber, a 7 F-gauge, 11 cm-long stent is placed for stenosis dilation.

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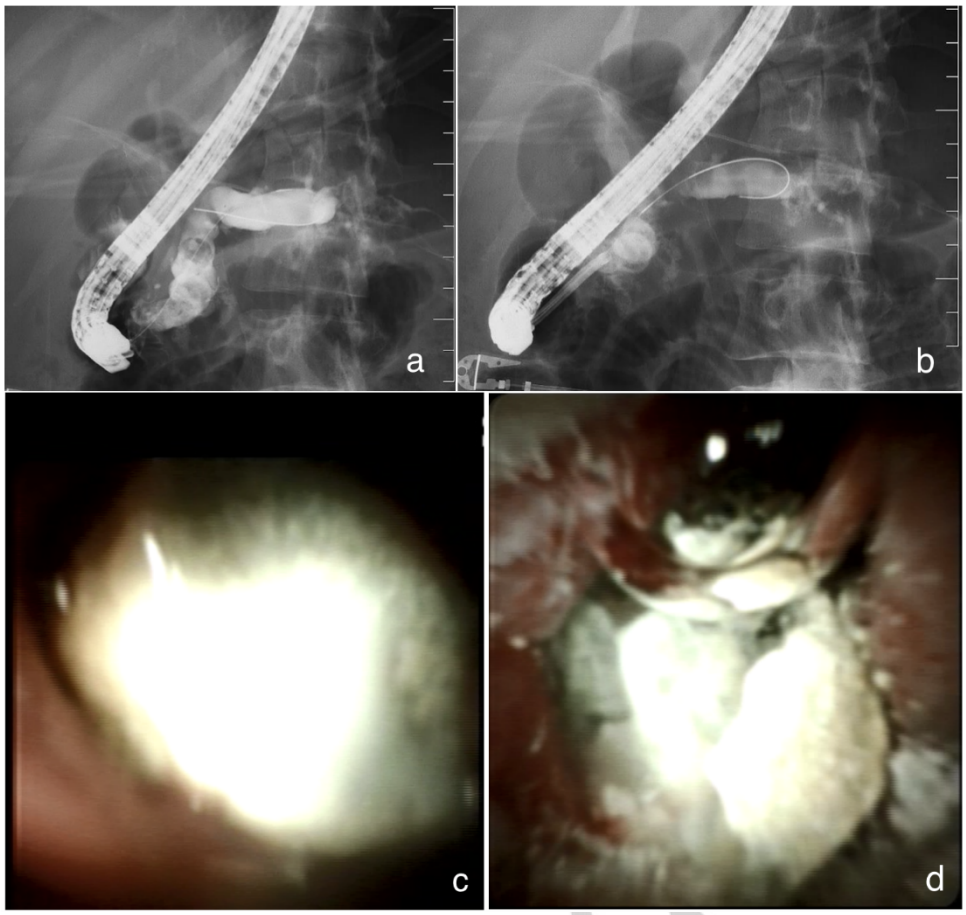

Fig. 2. A. Patient with chronic pancreatitis, prepapillary stenosis, and several large pancreatic stones. B. A pancreatoscope is advanced facing the distal stones. C. Endoscopic image of the pancreatic stones. D. Stone fragmentation after several shocks using EHL.