Endoscopic pancreatic duct stent placement for inflammatory pancreatic diseases

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Abstract

The role of endoscopic therapy in the management of pancreatic diseases is continuously evolving; at present most pathological conditions of the pancreas are successfully treated by endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS), or both. Endoscopic placement of stents has played and still plays a major role in the treatment of chronic pancreatitis, pseudocysts, pancreas divisum, main pancreatic duct injuries, pancreatic fistulae, complications of acute pancreatitis, recurrent idiopathic pancreatitis, and in the prevention of post-ERCP pancreatitis. These stents are currently routinely placed to reduce intraductal hypertension, bypass obstructing stones, restore lumen patency in cases with dominant, symptomatic strictures, seal main pancreatic duct disruption, drain pseudocysts or fluid collections, treat symptomatic major or minor papilla sphincter stenosis, and prevent procedure-induced acute pancreatitis. The present review aims at updating and discussing techniques, indications, and results of endoscopic pancreatic duct stent placement in acute and chronic inflammatory diseases of the pancreas.

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Key words: Chronic pancreatitis; Pancreas divisum; Pancreatic pseudocyst; Pancreatic fistulas; Idiopathic recurrent pancreatitis; Main pancreatic duct stenting; Pancreatic dorsal duct stenting

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INTRODUCTION

The role of endoscopic therapy in the management of

pancreatic diseases is continuously evolving; at present most pathological conditions of the pancreas are successfully treated by endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS), or both. After the initial courageous experimental therapy tested in a few centers, pancreatic endotherapy has become an evidence-based method for carefully selected patients; because of the high level of technical skill required and the small numbers of patients who need this approach, pancreatic endotherapy should ideally only be carried out in selected centers where a multidisciplinary team is available.

Endoscopic placement of stents has played and still plays a major role in the treatment of chronic pancreatitis, pseudocysts, pancreas divisum, main pancreatic duct injuries, pancreatic fistulae, complications of acute pancreatitis, recurrent idiopathic pancreatitis, and in the prevention of post-ERCP pancreatitis. These stents are currently routinely placed to reduce intraductal hypertension, bypass obstructing stones, restore lumen patency in cases with dominant, symptomatic strictures, seal main pancreatic duct disruption, drain pseudocysts or fluid collections, treat symptomatic major or minor papilla sphincter stenosis, and prevent procedure-induced acute pancreatitis.

On the assumption that intraductal hypertension caused by obstructive lesions of the main pancreatic duct (MPD) is one cause of the pain often present in either chronic or acute pancreatic diseases, stent insertion beyond the obstruction to decompress the hypertension has a pivotal role in their therapeutic management.

The present review aims at updating and discussing the role of endoscopic pancreatic duct stent placement in acute and chronic inflammatory diseases of the pancreas.

TECHNIQUE OF PANCREATIC STENT PLACEMENT

The technique employed for placing pancreatic stents is similar to that used to place stents in the biliary tract. Once the main or accessory pancreatic duct has been deeply cannulated, a hydrophilic 0.035" (for 5F, 7F, 10F stents) or 0.018" (for 3F stents or when the minor papilla is cannulated) guidewire is introduced into the duct and maneuvered if possible beyond the stricture or leakage. The stent is then introduced over the guidewire (Figure 1). Stents can be placed with or without pancreatic sphincterotomy; pancreatic sphincter can be ablated by using the standard sphincterome in a single step procedure or after biliary sphincterotomy. The multiple step procedure is more time consuming but permits to better control the section of the

Figure 1 Chronic obstructive pancreatitis involving the head of the gland. **A:** Pancreatography showing a distal stricture of the main pancreatic duct; **B:** Insertion of the guidewire into the main pancreatic duct; **C:** Placement of a 10F plastic stent over the guidewire.

Figure 2 Placement of a pancreatic stent after pancreatic sphincterotomy. **A:** Once biliary sphincterotomy has been performed leaving a guidewire into the common bile duct, pancreatic sphincter ablation is done with the standard sphincterotome; **B:** A plastic stent is then pushed over the guidewire into the main pancreatic duct; **C:** Pancreatic stent in place.

Figure 3 Chronic obstructive pancreatitis involving the head of the gland: insertion of an S-shaped stent into the main pancreatic duct.

sphincter so it is generally my preferred approach (Figure 2).

Pancreatic stents are generally made of polyethylene and are similar to biliary stents except for side holes along their length to allow flow from side branches. To prevent migration into the pancreatic duct, small-diameter stents have a J or "pig-tail" shape. For transpapillary stenting of a pseudocyst, a double pig-tail stent should be used to prevent displacement outside the cyst cavity. Recently, an S-shaped stent with many side holes has been proposed for MPD stenting in chronic pancreatitis^[1]; this stent is made of ethylene vinyl acetate, which is more flexible than polyethylene. The S-shape enables the stent to adapt better to the course of the MPD and reportedly achieves a better outcome in patients with chronic pancreatitis and upstream duct dilatation than in patients treated with the standard straight polyethylene stents (Figure 3).

The diameter of the stent should not exceed the size of a normal downstream duct, so 5F and 7F stents should be used in cases with non-dilated ducts, while 10F and sometimes 11.5F can be used when the ducts are dilated, as in advanced chronic pancreatitis. Sometimes in advanced chronic disease the stricture is too tight to place a stent across it; in these cases the stricture must be dilated with a balloon or bouginage to permit insertion. In some cases the Soehendra stent retriever (5F or 8F) can be used

to dilate the stricture and allow insertion.

How long stents are best left in place is not yet known. Pancreatic stents have been left in place for six months and long-term therapy requires multiple stent exchange. However, the duration of a single stent placement depends on the stent diameter: the larger the diameter, the longer the stent can be left in place.

CHRONIC PANCREATITIS

In chronic pancreatitis the MPD may be partially occluded by strictures or stones; the rise of intraductal pressure in the ductal segment above the obstruction causes dilation and obstructive pain. Pancreatic intraductal hypertension occurs regardless of the etiology and whether or not the MPD is dilated; ductal and interstitial hypertension, together with reduced acinar blood flow, may further contribute to the formation of fibrosis and progression toward more severe damage^[2]. Removing the barriers to outflow of pancreatic juice may relieve chronic pain or exacerbation of chronic pancreatitis. Obstruction-related reduced outflow of pancreatic juice into the duodenum may also cause mal-digestion of nutrients even in cases with still conserved pancreatic enzyme secretion, or worsening of mal-digestion already present in advanced cases.

Although pancreatic ductal strictures can be treated by catheter or balloon dilation alone, a stent usually has to be inserted because stricture relapse is commonplace. Insertion of a stent beyond the ductal blockage achieves lasting relief of the intraductal hypertension and subsequent pain and possible mal-digestion, also restoring the lumen patency, by dilating the stricture. If a 10F stent or larger is used, the patient generally requires sphincterotomy of both the pancreatic and biliary segments of the sphincter, followed by stricture dilation (Figure 4).

The presence of both obstruction and ductal dilation is vital for predicting which patients are most likely to benefit

Figure 4 Symptomatic, chronic obstructive pancreatitis at early stage with moderate dilation of the main pancreatic duct. **A:** Mechanical dilation of the pre-papillary stricture by a 10F dilator; **B:** Insertion of the guidewire; **C:** Insertion of a plastic 10F stent throughout the dilated stricture over the guidewire.

from stricture therapy: the best candidates for stenting are those with a distal stricture and upstream dilation (Figure 5).

Most investigators and recent guidelines from the American Society for Gastrointestinal Endoscopy consider endoscopic management to be the preferred interventional approach for chronic pancreatitis in patients selected on the basis of anatomical changes caused by the disease; endoscopic treatment is generally safe, minimally invasive, can be repeated, and does not interfere with eventual surgery^[3,4]. Other investigators, however, found surgery superior to endotherapy for long-term pain reduction. Dite *et al*^[5], in a prospective randomized trial comparing endoscopic and surgical therapy for chronic, painful, obstructive pancreatitis, reported complete resolution of pain at the five-year follow-up in 37% of patients after surgery and in 14% of those after endotherapy; short-term results were similar in the two groups. Similar data have been recently published by Cahen *et al*^[6].

The technical success of endoscopic stricture manipulation can range from 80% to 100% of patients with or without prior pancreatic sphincterotomy. In chronic pancreatitis patients with dominant stricture, pain relief was obtained in 52%-95% of cases over a follow-up ranging from 8 to 72 mo^[1,7-19]. Stenting was also associated with weight gain and fewer hospital visits. Good clinical outcomes were related to cessation of alcohol consumption and/or smoking^[15]. Early complications were reported in about 17% of cases and were related mainly to pancreatic and/or biliary sphincterotomy, stent clogging (juice infection) and inward migration.

It is not clear how long stents should best be left in place. Although the plastic 10F stents are thought to remain clinically patent for a year on average, generally they are removed and replaced every 6-9 mo. In fact, stent dysfunction leading to pancreatitis, recurrent pain or

Figure 5 Chronic obstructive pancreatitis. **A:** Severe stricture of the main pancreatic duct with marked upstream dilation; **B:** Placement of a 10F plastic stent after mechanical dilation of the stricture.

Figure 6 Refractory dominant stricture of the main pancreatic duct in chronic pancreatitis patient already treated by dilation and temporary stenting. Placement of two plastic stents. Endoscopic (**A**) and radiological (**B**) features.

infection can occur before the scheduled exchange time in about half the cases, so repeated stent exchange is required in the long term. This may make it difficult to ensure compliance with long-term stenting treatment.

Despite encouraging medium- and long-term results, duct stricture may persist or recur after removal of a stent so definitive removal seems impracticable in a subset of patients, because of the recurrence of pain. In an intention-to-treat analysis, a German multicenter study on long-term outcomes in 1000 patients with chronic pancreatitis after pancreatic stenting reported unsatisfactory results in 35%; 16% of these patients continued with endotherapy and 24% opted for surgery^[11].

A multiple stenting approach was proposed by Costamagna *et al*^[20] in a subset of patients with refractory dominant MPD strictures: they reported lasting stricture dilation in 84% of their patients at 38-mo follow-up. Although placing a mean of three stents within pancreatic strictures may be difficult, this approach appears feasible and safe and could in fact dramatically reduce the need for surgery in the majority of patients with chronic obstructive pancreatitis (Figure 6).

Self-expandable metal stents have been proposed for patients with relapsing dominant strictures to achieve long-term stent patency and avoid the need for stent exchange^[21]. The success rate of stent placement was 100% and patients enjoyed immediate relief of symptoms and reduction of duct diameter; however, during follow-up these patients have had high occlusion rates of the stent from mucosal hyperplasia, and it becomes impossible to remove the stent, so this approach has in fact been abandoned.

Figure 7 Pancreas divisum with chronic obstructive pancreatitis at early stage. **A:** Extensive dorsal duct stricture with moderate upstream dilation of the pancreatic duct; **B:** Guidewire insertion into the dorsal duct throughout the minor papilla, without sphincterotomy; **C:** 7F plastic stent in place. Long-term stenting rather than minor papilla sphincterotomy appears an appropriate approach in this case with extensive dorsal duct stricture.

Figure 8 Chronic obstructive pancreatitis in incomplete pancreas divisum. **A:** Minor papilla stenosis associated with diffuse upstream dilation of the pancreatic duct and normal parietal morphology; **B:** Minor papilla sphincterotomy over-the-stent performed with a needle-knife sphincterotome. Minor papilla sphincterotomy rather than long-term stenting appears an appropriate approach in this case with stricture located at the level of the minor papilla.

PANCREAS DIVISUM

Pancreas divisum is present in about 7% of the population; it occurs when the ventral and dorsal ducts of the gland fail to fuse during embryological development. This anatomical variant is asymptomatic in the majority of cases but in some cases it may cause pancreatic pain due to functional obstruction at the level of the minor papilla or recurrent episodes of acute pancreatitis; persistence of the obstruction over time may lead to chronic obstructive pancreatitis. Kamisawa *et al* reported acute recurrent pancreatitis and chronic pancreatitis associated with pancreas divisum in respectively 17.1% and 28.6% of their patients^[22].

Endoscopic therapy with minor papilla sphincterotomy and/or stent placement appears to be the treatment of choice at present. Critical issues concerning endotherapy in pancreas divisum are patient selection, difficulty of papillary cannulation, technique for endotherapy (minor papilla sphincterotomy or dorsal duct stenting, or both), stent-induced duct injury, and risks of post-ERCP pancreatitis. Patients with acute recurrent pancreatitis are the best candidates for endotherapy as in this group the predicted sustained response rate is around 75%; the response rate in patients with chronic pancreatitis is 40%-60%, whereas patients with recurrent or chronic abdominal pain respond poorly (20%-40%)^[23].

The minor papilla is often difficult to visualize, but its orifice can be easily identified by spraying methylene blue over the duodenal mucosa in the papillary area or injecting it directly into the ventral duct, in cases with incomplete

pancreas divisum^[24], or by EUS^[25], or by enhancing pancreatic secretion with i.v. secretin^[26].

Endotherapy of pancreas divisum includes minor papilla sphincterotomy and dorsal duct stenting with 5F, 7F and 10F stents, depending on the level of obstruction and degree of dilation (Figure 7 and Figure 8). Dorsal duct stenting without sphincterotomy was adopted by McCarthy *et al*^[27], Lans *et al*^[28] and Ertan^[29], who reported satisfactory long-term results in respectively 89%, 90% and 76% of cases. However, Heyries *et al* reported more favorable long-term results with minor papilla sphincterotomy than with stenting^[30]; they also observed fewer complications after sphincterotomy (25%) than after stenting (44%). More recently however, 45% of patients with chronic pancreatitis associated with pancreas divisum, undergone successful dorsal duct stenting and followed for a median period of 59.6 mo, required surgery after stent removal because of recurrence of symptoms^[31]. Of course, stenting is the only option in cases with dorsal duct strictures proximal to the papillary orifice. A strategy of empiric 3-6 mo dorsal duct stenting may be adopted in patients with recurrent pain or pancreatitis with non-dilated dorsal duct or normal minor papilla motor function, investigated by manometry or MRCP and secretin test, in order to decide whether sphincterotomy would be appropriate. This approach in patients with non-pathological duct morphology, however, could lead to ductal changes consistent with chronic pancreatitis in about one third of cases.

PANCREATIC PSEUDOCYST WITH DUCTAL COMMUNICATION

Pseudocysts complicate acute and chronic pancreatitis in up to 20% of cases; approximately 50% of pseudocysts regress spontaneously within 6 to 12 wk. Pseudocysts that are symptomatic, or become larger on follow-up imaging, or are associated with complications, require a drainage procedure. The pseudocyst communicates directly with the MPD in up to 40%-66% of cases^[32]. Pseudocysts with ductal communication can only be resolved by duct drainage^[33]. This can be achieved during ERCP by a trans-papillary approach, thus avoiding the usual risks (bleeding and perforation) of endoscopic cysto-gastrostomy or cysto-duodenostomy, especially when endoscopic ultrasound (EUS) guidance is not available. Trans-papillary 5F, 7F or 10F stents can be placed beyond the strictured segment of the MPD but not into the pseudocyst in cases with duct strictures downstream of the pseudocyst, or

Figure 9 Large pancreatic pseudocyst communicating with the main pancreatic duct: combined endoscopic trans-papillary and trans-gastric drainage. **A:** Contrast injection into the MPD shows a stricture of the main pancreatic duct at the level of the cyst; **B:** After pancreatic sphincterotomy, the stricture is dilated, a guidewire is inserted into the cyst cavity, and a plastic stent is placed; **C and D:** Under EUS guidance, a double pig-tail plastic stent is also placed by a single step procedure; **D:** X-ray imaging shows trans-papillary and trans-gastric stents at the end of the procedure.

Table 1 Endoscopic transmural drainage of pancreatic pseudocyst¹

Endoscopic centers	198
EUS-guided drainage	65%
Successful drainage	91%
Clinical success	71%
Mean number of stents inserted	2
Mean duration of stenting	6 wk
Complications rate	
Infection	12.70%
Bleeding	11.40%
Perforation	2.20%

¹: International survey of ASGE members.

directly into the pseudocyst cavity if no MPD strictures are found^[34], or into the MPD bridging the communication between the duct and the cyst cavity. When the stent is placed directly in the pseudocyst cavity, a double pig-tail stent should be preferred to avoid the risk of displacement. In the presence of a large and symptomatic pseudocyst, MPD drainage is generally associated with a trans-parietal drainage in order to achieve a more rapid decompression of the cyst cavity and resolution of symptoms (Figure 9). EUS-guided pseudocyst drainage has become popular in recent years because it has many advantages compared to the endoscopic approach^[35]. Bulging is not required; ultrasound guidance permits assessment of the optimal area to access vascular structures, cyst content and communication with the main pancreatic duct (Table 1). Pseudocyst drainage is feasible even if the distance between the cyst and G.I. lumen exceeds one cm, and the procedure may be performed in a single step.

Stents should be changed routinely every 6-8 wk, to avoid clogging and the risk of infection or pancreatitis.

Features predictive of a successful trans-papillary approach are MPD dilation upstream of the ductal stricture when the stent is placed across the stricture and

a non-dilated pancreatic duct when the stent is placed to bridge the communication of the cyst with the pancreatic duct. Placing a stent in the pseudocyst in a case with non-dilated MPD is associated with a higher risk of pancreatitis.

PANCREATIC FISTULAS

Fistulas can occur as a consequence of partial or complete rupture of the pancreatic duct caused by trauma, pancreatic surgery, or complicating severe acute pancreatitis. During an attack of acute severe pancreatitis, ERCP found a pancreatic duct leak in 37% of cases and this was significantly associated with a higher incidence of necrosis and longer hospital stay^[36]; the early recognition and treatment of such leaks and eventually associated fluid collections is likely to improve outcomes^[37].

At present, the diagnostic approach to pancreatic fistulas and suspected pancreatic duct leaks should be MRCP with secretin stimulation, leaving ERCP and EUS only for therapeutic purposes, once the lesion has been identified and staged. Before planning endoscopic treatment of fistulas or duct leaks several points must be clarified: the location of the lesion within the pancreatic ductal system, the presence and type of pancreatic duct strictures downstream of the lesion, whether pancreatic duct disruption is complete or incomplete, whether there is any communication with a fluid collection, and its anatomical characteristics.

Fifteen years ago Kozarek *et al* reported that bridging a pancreatic duct leakage by trans-papillary stent placement was effective for either internal or external pancreatic fistulas^[38]. Transpapillary stenting of the MPD has now become the “gold standard” for the treatment of fistulas and duct leaks, with success rates ranging from 55%^[39] to 100%^[40], although higher than 80% in most series (Figure 10 and Figure 11). Telford *et al* reported that the position of the bridging stent was the only variable related with a good outcome (92%), while stents placed at the level of

Figure 10 Main pancreatic duct disruption with pancreatic juice leakage (A) successfully treated by plastic stent insertion bridging the leak (B).

Figure 11 Pancreatic duct leakage at the level of the tail of the gland, following surgical resection of neuroendocrine tumor. A: The leakage site is identified by contrast injection into the main pancreatic duct; B and C: Over a guidewire, a long plastic stent is inserted at the level of the tail of the gland.

the leakage or distally were more often associated with approximately 50% of failures^[41]. A partially disrupted MPD, the location of the disruption at the level of the body of the pancreas, the stent positioned to bridge the disruption, and a longer duration of stent therapy were identified as predictors of a favorable outcome in the endoscopic management of duct disruption on a large series of patients^[39]. The stent should be left in place for four to six weeks. A shorter period of stenting may involve a higher rate of failure^[41], while a longer period may increase the risk of stent occlusion and stent-induced alterations in ductal morphology.

SMOLDERING PANCREATITIS AND IDIOPATHIC RECURRENT PANCREATITIS

“Smoldering” pancreatitis refers to a syndrome in which patients recovering from acute pancreatitis suffer from unremitting abdominal pain, intolerance of food, persistently elevated serum levels of pancreatic enzymes, and persisting inflammatory changes in and around the pancreas at imaging studies. Functional obstruction of the papillary orifice, induced by edema or sphincter spasm, and inflammation-related fibrotic strictures of the MPD may account for the unremitting course in a subset of patients with smoldering pancreatitis. In these cases, insertion of a stent into the MPD provided permanent relief of pain in 91% of patients within a mean of nine days (range 3-20 d) and discontinuation of parenteral nutrition within a mean of 15 d (range 7-39 d); the stents were left in place for a mean of seven weeks (range 2-19 wk)^[42].

Today the etiology of acute pancreatitis remains undefined in 2%-30% of cases, despite a careful diagnostic work-up including imaging techniques for pancreatic morphology (CT scan, MRCP, EUS), functional investigation

of the sphincter of Oddi (manometry, secretin test), and tests for gene mutations and autoimmune disorders. In these cases the term “idiopathic pancreatitis” is generally adopted and the failure to identify the cause predisposes to further recurrences. Despite the absence of morphofunctional alterations, however, it is generally believed that biliary sludge or microlithiasis or unrecognized transient sphincter of Oddi dysfunction (Type 2) plays a causal role. In a therapeutic protocol study adopted in our institution we found that the placement of a 5F or 7F stent into the MPD in cases with pancreatitis still recurring after biliary sphincterotomy served to identify those patients with residual hypertension of the pancreatic segment of the sphincter of Oddi who benefit from pancreatic sphincterotomy, as documented during a 27-mo follow-up. In these patients with a non-dilated MPD stents were routinely changed every three months. This empiric approach can be suggested for patients with recurrent pancreatitis but no evidence of morphofunctional abnormalities, presenting at least two or three acute attacks over one year, in whom three to six months’ stenting can provide a reliable basis for deciding on pancreatic sphincterotomy^[43].

Jacob *et al*^[44] reported the results of a prospective randomized nonblinded trial evaluating the effectiveness of pancreatic stent placement in preventing attacks of pancreatitis in patients with idiopathic recurrent pancreatitis over a five-year period. The stent group received three stents in one year while the control group underwent selective pancreatic duct opacification without stenting. Pancreatitis recurred in 53% of the control group and in 11% in the stent group. The authors concluded that unrecognized intermittent pancreatic duct sphincter dysfunction or relative outlet obstruction might be a cause of recurrent pancreatitis that can be prevented by stent

Figure 12 Experimental winged 5 and 7F stents. The new stent design with a wing shape permits an adequate flow of pancreatic juice even alongside the stent and does not compress the duct over its entire circumference, thus avoiding the risk of impaired drainage of pancreatic juice and mechanical trauma to the duct.

placement. However, long-term stenting of the pancreatic duct may in itself cause ductal damage, so only short-term stenting in patients with frequent episodes of pancreatitis is justifiable.

COMPLICATIONS OF STENT PLACEMENT

Several complications have been reported after pancreatic duct stent placement in benign diseases, ranging from 5%-39%. These include inward or outward migration of the stent, occlusion, and anatomic changes of the pancreatic duct^[45,46]. The latter limits the long-term use of stents in the treatment of benign disorders especially when pancreatic ducts are non-dilated. Changes of MPD morphology consistent with chronic pancreatitis have been reported after stent placement in 36%-83% of patients; ductal changes of the pancreatogram appear as early as three months and seem not to revert to normal in some cases after removal of the stent. Pancreatic stents placed in dogs were found to induce both radiological and histological changes of chronic pancreatitis in the ductal segment treated with the stent, within eight weeks^[47].

Although the mechanism by which changes are induced is not known, there is evidence that stenting the pancreatic duct leads to the formation of intraductal plugs in as little as three weeks even though pancreatograms may remain normal. These protein precipitates have the same composition as plugs removed from patients with chronic pancreatitis. Moreover, the conventional plastic stent does not provide enough side openings for unencumbered drainage at all sites where secondary ducts join the MPD; this obstruction and the pancreatic duct compression along the whole length of the stent induce a fibrotic reaction. A new pancreatic stent design with a wing shape has now been tested in dogs, with encouraging results, since this model permits an adequate flow of pancreatic juice even alongside the stent and does not compress the duct over its entire circumference, thus avoiding the risk of impaired drainage of pancreatic juice and mechanical trauma to the duct^[48] (Figure 12).

In conclusion, in about the last 20 years endotherapy of pancreatic disorders has evolved from an experimental approach for some pathological conditions in selected

cases where there is a fear of severe complications, to the “gold standard” for most acute and chronic inflammatory disorders involving the gland.

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