What is the role of endotherapy in chronic pancreatitis?

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Abstract: Chronic pancreatitis (CP) can have debilitating clinical course due to chronic abdominal pain, malnutrition and related complications. Medical, endoscopic and surgical treatment of CP should aim at control of symptoms, prevention of progression of the disease and correction of complications. Endoscopic management plays a specific role in carefully selected patients as primary interventional therapy when medical measures fail or in high-risk surgical candidates. Endotherapy for CP is utilized also as a bridge to surgery or to assess potential response to pancreatic surgery. In this review we address the role of endotherapy for the relief of obstruction of the pancreatic duct (PD) and bile duct, closure of PD leaks and drainage of pseudocysts in the setting of CP. In addition, endotherapy for relief of pancreatic pain by endoscopic ultrasound-guided celiac plexus block for CP is discussed.

Keywords: chronic pancreatitis, endotherapy, ERCP, pancreatic duct stricture, pancreatic duct stone, pseudocyst

Introduction

Chronic pancreatitis (CP) is a progressive and often irreversible inflammatory and fibrotic disease of the pancreas. In moderate-to-severe forms, CP can have a debilitating clinical course due to chronic abdominal pain, attacks of acute pancreatitis, malnutrition and related complications including increased risk for pancreatic cancer. Pain in CP is multifactorial in origin and can result from increased pressure in the main pancreatic duct (PD) leading to intrapancreatic/interstitial hypertension, and from peripancreatic/celiac neural inflammation [Ceyhan *et al.* 2009; Bockman *et al.* 1988]. Intraductal hypertension occurs primarily due to obstruction of pancreatic juice outflow from PD strictures, intraductal stones, decreased compliance of the main PD and major/minor papillary sphincter stenosis [Jalleh *et al.* 1991]. Complications of CP such as pseudocysts, PD leaks/ascites, biliary and duodenal obstruction can contribute to abdominal pain.

Medical, endoscopic and surgical treatment of CP should aim at control of symptoms, prevention of progression of the disease and correction of complications. There had been much debate whether endoscopic therapy or surgery should be the optimal initial therapy for CP. Dite and

colleagues presented the results of a randomized study comparing surgery with endoscopic treatment in 72 patients with a dilated PD with stones, strictures or both [Dite *et al.* 2003]. An additional 68 patients who refused randomization and opted for endoscopic therapy or surgery were included in the final analysis, which indicated that surgical outcomes were more durable. A second prospective nonblinded randomized study by Cahen and colleagues showed better outcome (pain-free or partial improvement) with surgery (75%) than in the endoscopic group (32%) [Cahen *et al.* 2007]. However, the subjectivity of the pain assessment, lack of blinding and small sample size could lead to bias. In addition, the specific disease characteristics such as the presence of multiple pancreatic stones and the location of the strictures were not clearly mentioned in the surgical group, which suggests there was a possibility of chance randomization of more refractory patients to the endoscopy treatment. Hence, authorities believe endoscopic management plays a specific role in carefully selected patients [Elta, 2007] as primary interventional therapy when medical measures fail or in high-risk surgical candidates. Endotherapy for CP is utilized also as a bridge to surgery or to assess potential response to pancreatic surgery [Delhaye *et al.* 2005]. Last but not least,

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endotherapy is selectively employed by the authors for treatment of recurrent abdominal pain or complications after pancreatic surgery for CP.

In this review we address the role of endotherapy for the relief of obstruction of the PD and bile duct, closure of PD leaks and drainage of pseudocysts in the setting of CP. In addition, endotherapy for the relief of pancreatic pain by endoscopic ultrasound (EUS)-guided celiac plexus block for CP is discussed. All of the techniques described require a high level of expertise and should be performed only by experienced pancreaticobiliary endoscopists.

Pancreatic endotherapy: general principles

The aim of most endoscopic therapies for patients with CP is to alleviate the outflow obstruction to exocrine juice flow. This presumes that PD hypertension is the cause of the patient's symptoms. Failure to respond to endoscopic therapy suggests that PD hypertension is not the primary cause of the patient's symptoms or the intraductal pressure was not adequately reduced to achieve clinical benefit. There are certain pathologic alterations of the PD, biliary tree or sphincter that lend themselves to endoscopic treatment. The techniques (e.g. sphincterotomy, dilation, stenting) and instruments (e.g. sphincterotome, dilating balloon, pancreatic stent) used to treat biliary tract disease have been adapted for use in the pancreas.

Main PD deep cannulation is the vital step to successful pancreatic endotherapy. General principles to attain this crucial step are briefly described here and have been explained in detail in our review of endoscopic retrograde pancreatography (ERP) [Barkay *et al.* 2009]. With the endoscope in the short position and the papilla viewed *en face*, the main PD can be accessed with a regular cannula at the 1–4 o'clock position of the native major papilla orifice and at 5 o'clock position of papilla with prior biliary sphincterotomy. Minor papilla cannulation, when indicated, is typically achieved with the endoscope in the long position using a highly tapered catheter with a 0.018–0.021" guide wire. When the orifice of the desired papilla is not identified, secretin administration to promote pancreatic juice flow and/or methylene blue flushes over the papilla may help [Park *et al.* 2003]. In addition, EUS-guided pancreatography has been described for both identification of the desired papillary orifice

and successful PD drainage [Will *et al.* 2007; Dewitt *et al.* 2004; Kahaleh *et al.* 2003]. In failed main PD deep cannulation due to obstruction or extreme tortuosity of the ventral duct, access to the main PD may be obtained via the minor papilla when the minor papilla and accessory duct are patent. Pancreatic endotherapy specific to each of the conditions that can occur in CP are discussed in the following sections.

Pancreatic duct strictures

The majority of PD strictures are benign secondary to previous stone disease, inflammation [Cremer *et al.* 1991] or fibrosis. The risk of malignancy in isolated PD strictures was 12% in a retrospective series of 355 patients reported by Kalady and colleagues, although the actual incidence of malignancy is unknown in PD strictures associated with CP [Kalady *et al.* 2004]. It is crucial to have a high index of suspicion for malignancy and obtain pancreatic imaging with dual-phase CT scan and/or EUS. The goal of this review is not specifically to discuss the role of screening for pancreatic cancer. A pancreatic protocol CT scan is routinely performed on patients with PD stricture and suspected or proven CP prior to endoscopic retrograde cholangiopancreatography (ERCP). If no mass is found, ERCP will be performed. However, any patient found to have PD stricture without a risk factor for CP, presence of concerning symptoms such as weight loss and anorexia, or no other evidence of CP on pancreatography should undergo tissue sampling of the stricture at ERCP and additional imaging if needed. Most EUS with fine needle aspiration (FNA) can further assist in evaluation of the nature of stricture. It is important to appreciate that the sensitivity of EUS–FNA in diagnosing pancreatic cancer in the presence of CP is less than in the absence of CP [Eloubeidi *et al.* 2008; Varadarajulu *et al.* 2005b]. While planning and assessing the utility of endotherapy, it is important to note the location, number and length of the strictures, and the presence of upstream dilation. PD strictures in the tail of the pancreas and multiple strictures along the length of the main PD are more difficult to manage by endotherapy. The best outcomes of endotherapy are achieved when strictures of the main PD in the head with upstream dilation (Figure 1(a)) are stented.

Technique of endotherapy. After PD cannulation, a guidewire is maneuvered across the stricture. A pancreatic sphincterotomy (major and/or minor papilla) is frequently performed initially.

Figure 1. (a) Main pancreatic duct (PD) stricture in the head with upstream dilation. (b) Balloon dilation of the PD stricture. (c) Complete obliteration of narrow segment of the balloon indicating successful dilation. (d) PD stent.

Stricture dilation with a graduated dilating catheter or balloon dilators (Figure 1(b) and (c)) should be considered. Finally the PD stent (Figure 1(d)) is advanced over the guidewire across the stricture using a pusher tube. Choice of the PD stent depends on the size of the PD downstream from the stricture (toward the duodenum). In smaller ducts, 4–7 French stents are used, whereas 10–11.5 French stents are used in markedly dilated PDs. We prefer to use a pancreatic stent with an external pigtail and an internal flange in order to prevent proximal and distal migration, respectively. The timing of pancreatic stent exchange is variable in practice: routine every 6–12 weeks prior to stent occlusion *versus* on-demand exchange based on recurrence of symptoms. Although authors routinely

exchange the stents every 6–12 weeks (depending on stent diameter), on-demand exchange is effective as well, as shown by Delhaye and colleagues [Delhaye *et al.* 2004]. This is based on the theory that pancreatic juices can drain around the stent, even when it is occluded.

Results of endotherapy. Wilcox summarized the results of PD stent placement, usually with ancillary procedures [Weber *et al.* 2007; Costamagna *et al.* 2006; Eleftheriadis *et al.* 2005; Wilcox, 2005; Eisendrath and Deviere, 1999; Layer *et al.* 1994; Cremer *et al.* 1990]. Among the 1500 patients treated in 15 series, benefit was seen in 31–100% during a follow-up interval of 8–72 months. The greatest benefit is seen in patients with dominant strictures and dilated

ducts [Gabbrielli *et al.* 2005, 2002]. As with surgical decompressive procedures, it appears that the response attenuates over time.

In the largest published study, 1018 patients with CP were followed prospectively for a mean of 4.9 years after endoscopic intervention [Rosch *et al.* 2002]. At follow up, 60% of patients had completed endotherapy, 16% were still undergoing endoscopic treatments and 24% had undergone surgery. Complete (69%) or partial (19%) technical success of endoscopic therapy was achieved in 88%. All patients had pain initially, but only 34% had pain at follow up; a significant reduction in pain (no or weak pain) was achieved in 85%. Rates of pain relief were similar in patients with dominant strictures in the head and/or body, pancreatic stones in the head and/or body, a combination of stones and strictures and complex pathology. It appears that complete stricture resolution is not mandatory for symptom improvement, which implies that luminal patency was sufficient or that other therapies performed along with the stenting contributed to the benefit. In all of these studies plastic stents are usually sequentially changed at multiple ERCP sessions. In an attempt to reduce the number of procedures and improve outcome from stenting, the group from Brussels evaluated the self-expandable metal stent for PD stricture management [Eisendrath and Deviere, 1999]. Unfortunately, after 6 months of treating 29 patients with 18 French diameter and 23-mm long metal stents, most patients developed stent occlusion due to mucosal hyperplasia.

Costamagna and colleagues, who popularized the approach of placing 'as many biliary stents as could fit' for the treatment of postoperative strictures, evaluated a similar approach in the pancreas [Costamagna *et al.* 2006]. Nineteen patients with dominant PD strictures in the pancreatic head and who had pain relief by a single previously placed PD stent underwent balloon dilation of the stricture and placement of 8.5–10 French, 4–7-cm long pancreatic stents (median of 3 stents; range 2–4 based on the tightness of the stricture) for 6–12 months. Stricture resolution was seen in 95% of patients at stent removal. After a median follow-up period of 38 months after the stent removal, 84% remained pain free and there was recurrence of PD stricture in 10.5% (two patients) which was subsequently treated with single stent placement. In studies using a single pancreatic stent, initial

stricture resolution was nearly as good as seen in studies using multiple stents, but long-term stricture recurrence was higher. In a long-term outcome study, 100 patients with severe CP and PD strictures were treated with plastic pancreatic stents (median duration 23 months) and were followed for 69 months from study entry, including a median period of 27 months after stent removal [Eleftheriadis *et al.* 2005]. The stents were exchanged when the patient developed recurrent pain and removed based on defined clinical and endoscopic parameters. After stent removal, 30 patients (30%) required re-stenting within the first year of follow up, while in 70 patients (70%) pain control was adequate during that period. The stricture recurrence rate was 38% requiring repeat endoscopic intervention and/or pancreatico-duodenectomy. To date no trials comparing single *versus* multiple stenting for PD strictures secondary to CP have been reported.

Some natural history studies of CP have shown spontaneous pain relief in late stages due to pancreatic 'burn out' [Mullhaupt *et al.* 2005; Layer *et al.* 1994], where as one study by Lankisch and colleagues showed that even after 10 years of follow up of severe pancreatitis more than 50% of patients continued to have pain [Lankisch *et al.* 1993]. This variation in natural history can bias the results of outcome studies of endotherapy for pancreatic strictures due to lack of sham procedure control. Wilcox and colleagues recently proposed a much-awaited trial studying pain and psychosocial outcomes in patients with symptomatic PD strictures, randomized to pancreatic endotherapy or sham procedure [Wilcox and Lopes, 2009]. If there is less than 50% improvement in pain in patients randomized to sham procedure, there will be crossover to the endoscopic intervention group, otherwise they will be followed clinically for the proposed duration of 3 years.

Pancreatic duct stones

The prevalence of stones in CP ranges from 20% to 60% [Rosch *et al.* 2002; Brand *et al.* 2000]. The majority of pancreatic stones are radio opaque (Figure 2(a)) due to calcium content, although a small percentage can be radiolucent. Increased intraductal pressure upstream of an obstructed focus within the PD, as with PD stones, is one of the potential mechanisms responsible for attacks of acute pancreatitis or exacerbations of chronic abdominal pain in

Figure 2. (a) Radio-opaque stones (arrows) in the pancreatic head and body. (b) Fragmented stones by extracorporeal shockwave lithotripsy (ESWL). (c) Numerous pancreatic stone fragments seen as filling defects on a pancreatogram. (d) Balloon extraction of stone fragments. (e) White pancreatic stone fragments. (f) Pancreatogram without filling defects after complete extraction of the stone fragments.

patients with CP. Reports indicating that endoscopic or surgical removal of pancreatic calculi with or without extracorporeal shockwave lithotripsy (ESWL) results in improvement in symptoms support this notion.

Technique of endotherapy. Small pancreatic stones can be removed after pancreatic (major/minor) sphincterotomy using balloon or basket extraction (Figure 2(d), (e) and (f)). If there is a stricture downstream (toward the duodenum) from the stone, it is usually necessary to dilate the stricture prior to attempting stone extraction. Sherman and colleagues found the following factors favored complete stone removal by endoscopic techniques alone [Sherman *et al.* 1991]: stones < 1 cm in size, presence of three or fewer stones, stones confined to the head and body and absence of impacted stones or stones upstream (towards the tail) to a stricture. Stones that are larger, impacted or upstream to a stricture frequently require fragmentation (mechanical, electrohydraulic or ESWL) prior to attempted extraction. Among the three options for fragmentation, ESWL (Figure 2(b)) is the most utilized method, although there are no comparative trials among different forms of lithotripsy.

ESWL can often be performed under moderate sedation using fluoroscopic localization of the radio-opaque PD stones. Ultrasound localization of the pancreatic stones, used in some centers, resulted in lower fragmentation rates [Brand *et al.* 2000; Adamek *et al.* 1999]. Following ESWL, endoscopic removal of the stone fragments is performed in the same manner as for small stones, during the same or in a different session (based on the availability of a local lithotripter and personnel). However, there are reports of spontaneous passage of stone fragments after ESWL without the need for endoscopic removal [Dumonceau *et al.* 2007; Adamek *et al.* 1999].

Larger radiolucent pancreatic stones, which cannot be targeted by fluoroscopy for ESWL, have been reported to be removed by various methods, such as pancreatoscopy directed electrohydraulic and laser lithotripsy [Howell *et al.* 1999] or by mechanical lithotripsy. Mechanical lithotripsy requires stone capture in a basket which may be difficult for impacted stones. Mechanical lithotripsy has been reported to have a three times greater complication rate when performed in the PD compared with the

bile duct [Thomas *et al.* 2007]. In some centers, endoscopic placement of a nasopancreatic drain for contrast localization of the radiolucent stone at the time of ESWL is utilized. In addition, large radiolucent stones have been successfully removed following endoscopic pancreatic sphincterotomy and balloon pancreatic orifice dilation [Maydeo *et al.* 2009]. It is important to confirm stone clearance by repeating the pancreatogram at the end of the procedure. In addition, associated pancreatic ductal disease such as a stricture should be simultaneously treated to get the best outcome of therapy [Sasahira *et al.* 2007].

Results. The technical success of endoscopic removal of pancreatic stones depends on the size, number and location of the stones [Rosch *et al.* 2002], the presence of a ductal stricture and whether the stone is impacted [Sherman *et al.* 1991]. In the series by Sherman and colleagues, using endoscopic techniques alone, 72% had complete or partial stone removal and 68% had symptomatic improvement [Sherman *et al.* 1991]. Symptomatic improvement was most evident in the group of patients with chronic relapsing pancreatitis (*versus* those presenting with chronic continuous pain alone; 83% *versus* 46%). When ESWL is combined with endoscopic therapy the success of stone clearance and longer-term symptomatic relief were improved [Kozarek *et al.* 2002; Brand *et al.* 2000; Adamek *et al.* 1999; Deviere *et al.* 1998; Dumonceau *et al.* 1996; Delhay *et al.* 1992]. Delhay and colleagues studied 123 patients with main PD stones and upstream dilation, treated with an electromagnetic lithotripter [Delhay *et al.* 1992]. Stones were fragmented in 99% of patients resulting in decrease in duct dilation in 90%. The main duct was completely cleared of stones in 59% with pain improvement in 85% of patients at a mean follow up of 14 months. However, 41% had clinical relapse due to stone migration into the main PD, progressive stricture or stent occlusion. Kozarek and colleagues reported clinical outcomes in 40 patients who underwent ESWL for chronic calcific pancreatitis [Kozarek *et al.* 2002]. Surgery was avoided in 80% of patients after a mean follow up 2.4 years with significant decrease in pain scores, narcotic use and hospitalizations. Brand and colleagues reported an improved global quality of life in 68% undergoing ESWL [Brand *et al.* 2000]. A meta-analysis of 16 studies that included 588 patients showed that ESWL when combined with pancreatic endotherapy had a

significant impact on reducing pancreatic stone burden and improving pain [Guda *et al.* 2005]. Good long-term results after ESWL for pancreatic stones were confirmed in a study of 70 patients [Tadenuma *et al.* 2005]. Forty nine patients (70%) experienced pain relief after a follow up of 77 months. In a prospective randomized study by Dumonceau and colleagues, ESWL alone and ESWL with pancreatic endotherapy for painful chronic calcific pancreatitis were compared [Dumonceau *et al.* 2007]. Pain relapse at the end of the 2-year period was not statistically different between ESWL alone (38%) and ESWL with endotherapy (45%). The cost of ESWL alone was three times lower. Patient selection with refractory disease may partly explain the much higher rates of pain relapse compared with previous studies. On an intention-to-treat analysis, this study also demonstrated that the median delay between the onset of CP and persistent pain relief was 1.1 years in the treated (ESWL alone or combined therapy) group ($N=55$) compared with 4 years in the untreated reference cohort ($N=42$) ($p < 0.001$). Overall, the endoscopist is encouraged to remove PD stones in symptomatic patients when the stones are located in the main duct (in the head and/or body) and are thus readily accessible. Ancillary ESWL will be required for more difficult stones.

Pancreatic duct leaks/fistulae

PD leaks in patients with CP manifest as pancreatic ascites, internal fistulae (e.g. pseudocyst, pleural effusion, to other organs) or external cutaneous fistulae. Leaks may arise from the main duct or side branches. If the leak arises from the main duct, the duct may be partially disrupted in which case the duct retains continuity or completely disrupted where there is a disconnection between the upstream and downstream main duct. On pancreatogram the PD leak/disruption is seen as extravasation of the contrast outside the ductal structure or quick disappearance of contrast from the duct at the site of leak without clearance of contrast in the downstream duct (toward the head of the pancreas). When an abrupt cut off of the PD is seen in a patient with a clinical suspicion of a pancreatic leak, a disconnected duct (also known as disconnected duct syndrome or disconnected pancreatic tail) is likely, in which case viable pancreatic tissue is seen upstream on cross sectional imaging. Diverting the pancreatic juice flow away from the fistulae and if possible

bridging the pancreatic leak with transpapillary stents can successfully treat the fistulae.

Telford and colleagues showed that 58% (25 of 43 patients) of pancreatic leaks resolved with pancreatic stenting with no recurrence during a 2-year follow-up period [Telford *et al.* 2002]. A multivariate analysis has shown that bridging the pancreatic disruption when identified resulted in improved outcome [Varadarajulu *et al.* 2005a; Telford *et al.* 2002]. Endoscopic injection of fibrin glue into the fistulous tract as an adjunct to the standard endoscopic treatment resulted in resolution of 66% of fistulae (8/12) at a median follow up of 20.7 months [Seewald *et al.* 2004]. However, this is not routinely utilized. In addition, a complete disruption of the PD is less amenable to endoscopic therapy. In a report of 22 patients with disconnected pancreatic tail syndrome, when treated endoscopically, 13 (59%) had either had no initial response or recurrence of pancreatic leak [Lawrence *et al.* 2008]. Although all patients in this series had acute necrotizing pancreatitis, about half had underlying CP. Endoscopic treatment of the disconnected PD syndrome is complex because the upstream disconnected segment of the pancreas still secretes and has no communication with the duodenum. As long as this part of the pancreas remains viable, any 'temporary' therapy will lead to a high recurrence rate. Thus, one endoscopic option is to drain the collection associated with the leak with 'permanent' transmural stents or until the upstream pancreas becomes atrophic and therefore no longer secretes.

Pancreatic pseudocysts

Pseudocysts are encapsulated collections of pancreatic juice, either pure and/or containing inflammatory/necrotic debris which are situated either outside or within the limits of the pancreas from which they arise. They complicate the course of pancreatitis in 20–40% of patients [Beckingham *et al.* 1997]. In CP, pseudocysts can occur as a result of rupture of a side branch or the main PD (Figure 3(a)) itself due to PD hypertension or occur as a consequence of the ongoing inflammatory process. Although many pseudocysts fail to resolve spontaneously, not all of them need drainage. Indications for pseudocyst drainage are: (a) patient symptoms such as abdominal pain; (b) complications such as an infected pseudocyst or duodenal or biliary obstruction secondary to pseudocyst compression; and (c) an enlarging pseudocyst.

Figure 3. (a) Computed tomography (CT) scan showing pancreatic head pseudocyst (left arrow) causing dilation of the upstream main pancreatic duct (right arrow). A smaller cyst is seen in the region of the pancreatic tail. (b) Transduodenal guidewire placement into the pseudocyst cavity. (c) Balloon dilation of the transduodenal tract. (d) Endoscopic view of the dilated transduodenal tract. (e) Transduodenal placement of two double pigtail stents on (i) fluoroscopic view and (ii) endoscopic view. (f) Transpapillary deep cannulation of the pancreatic duct and placement of the guidewire upstream from the site of a pancreatic duct stricture (arrow; presumably related to the cyst) into the upstream dilated duct. (g) Transpapillary pancreatic stent (arrows) bridging the pancreatic duct stricture. (h) Follow-up CT scan of the abdomen at 3 months showing complete resolution of the pseudocyst in the pancreatic head. Transduodenal and transpapillary stents are still in place (arrows).

Optimal management of a pseudocyst requires a multidisciplinary approach with input from surgery, gastroenterology and interventional radiology. Technical and long-term success of endoscopic pseudocyst drainage increases for a single-compartment cyst with mature wall and absence of necrosis.

The selection of the route (transpapillary *versus* transmural) of endoscopic drainage depends on the presence of communication between the pseudocyst and pancreatic ductal system and the size of the cyst. This information can be ascertained from any combination of imaging with EUS, magnetic resonance cholangiopancreatography (MRCP) with secretin stimulation or ERP. Endoscopic transmural drainage is chosen if the cyst is not communicating with the duct and transpapillary route is preferred if there is communication with PD and the cyst size is relatively small (usually <5–6 cm). If the communicating pseudocyst is particularly large, a combined transpapillary and transmural drainage can be performed. Transpapillary drainage usually requires a pancreatic sphincterotomy prior to placement of the pancreatic stent. Conventional transmural drainage can be performed without EUS guidance when (a) gastric bulge/luminal impression by the cyst is present, (b) collateral blood vessels from portal hypertension are absent and (c) the distance from the pseudocyst to the gastric/duodenal lumen on imaging studies is <1 cm. For pseudocysts that are not amenable to such conventional endoscopic drainage, EUS-guided drainage has been shown to be equally successful with no increased risk of complications [Kahaleh *et al.* 2006]. Broad-spectrum antibiotic coverage by intravenous route is given immediately prior to the endoscopic drainage procedure.

Technique of transmural drainage. The aim of direct cystoenterostomy is to create a communication between the cyst lumen and the gastric or duodenal lumen. The first step is to puncture the gut wall at the apex of the visible bulge using a needle knife via a duodenoscope or, if EUS is indicated, a 19-gauge FNA needle via a linear echoendoscope [Seewald *et al.* 2009a, 2009b]. Once the puncture is achieved, a guidewire is advanced through the needle knife or FNA needle into the cyst cavity and looped 360° to secure positioning, under fluoroscopic guidance (Figure 3(b)). The newly created tract is then balloon dilated to 8–10 mm in size or larger (Figure 3(c) and (d)) if necrotic material is present. This is usually followed by vigorous flow of

pseudocyst fluid into the gut lumen, prior to which care should be taken to have aspiration precautions in place with elevated head of the fluoroscopy table and oropharyngeal suction. Two or more double pigtail stents are placed transmurally into the cyst cavity (Figure 3(e), parts (i) and (ii)). Pre-assembled EUS-guided puncture kits are now commercially available to circumvent numerous steps of cyst entry, exchange of guide wires and stent placement. A nasocystic drain is placed in the presence of significant debris/necrosis or infection, to allow for lavage of the cyst cavity. Following the drainage, the size of the cyst cavity is followed via ultrasound or CT scan at 4–6-week intervals to assess for resolution (Figure 3(h)). Once the cyst resolves, the transmural stents can be removed. If a pancreatogram had not been obtained and ductal disease treated at the initial endoscopic procedure, this should be done at the time of stent removal (Figure 3(f) and (g)).

Results. Procedural technical success ranged from 85% to 100% and successful resolution of the cyst was approximately 90% in pooled patients from multiple series [Baron *et al.* 2002; Howell *et al.* 1998, 1996; Binmoeller *et al.* 1995; Catalano *et al.* 1995; Smits *et al.* 1995; Kozarek *et al.* 1991; Sahel, 1991; Cremer *et al.* 1989; Grimm *et al.* 1989] (Table 1). In these series, the long-term recurrence rate was 10–15% and complications rates were 10–34%. Complications were primarily bleeding and perforation. More recent studies had similar results with technical success greater than 90%, long-term cyst and symptom resolution rates ranged from 71% to 91% and recurrence rates ranged from 16% to 18% [Arvanitakis *et al.* 2007; Kahaleh *et al.* 2006; Cahen *et al.* 2005a]. Baron and colleagues showed that the pseudocyst resolution is higher (92%) in patients with CP than in those with acute pancreatitis (74%), with comparable complication rate between the groups (17% and 19%, *p*-value nonsignificant) [Baron *et al.* 2002]. These excellent results support the use of endoscopic drainage in appropriate patients and the overall complication rates compare favorably to surgical interventions.

Coexisting sphincter of Oddi dysfunction

Pancreatic sphincter of Oddi dysfunction (SOD) can occur primarily or secondarily to deposition of protein plugs on the sphincter and extension of scarring of the pancreas [Tarnasky *et al.* 1997; Laugier, 1994]. This results in pancreatic

Table 1 Results of endoscopic management of the pseudocysts.

Author	Technical success	Chronic pancreatitis	Transpapillary	Cystogastrostomy	Cystoduodenostomy	Complications	Death
Grimm	14/16	16	5	1	8	5	1
Cremer	32/33	33	0	11	21	3	0
Kozarek	12/14	8	12	0	0	5	0
Sahel	58/67	67	26	1	31	9	1
Catalano	17/21	12	17	0	0	1	0
Smits	31/37*	37	16	8	7	6	0
Binmoeller	47/53*	49	31	6	10	6	0
Howell	100/108	NM	37	38	25	25	0
Baron	82/95	64	NM	NM	NM	17	0
Total	93/444 (89%)	286**	144**	65**	102**	83 (19%)	2 (0.45%)

NM, not mentioned.
 *Combination therapy in several patients
 **Does not include numbers from Baron *et al.* or Howell *et al.*

ductal obstruction and hypertension. Pancreatic SOD is suspected with worsening symptoms and/or dilated main PD without any other structural abnormalities. This condition can be evaluated and documented by pancreatic sphincter manometry. It is primarily treated by pancreatic sphincterotomy at the major papilla and placement of temporary pancreatic stent for prophylaxis against post-ERCP pancreatitis. Sixty per cent of patients with pancreatic SOD (40 had CP) who underwent endoscopic pancreatic sphincterotomy alone had improved pain scored at a median follow up of 16 months [Okolo *et al.* 2000]. In another study by Gabbrielli and colleagues, 64% of CP patients with a dilated PD had absence of pain at a mean follow up of 6.5 years, with pancreatic sphincterotomy alone [Gabbrielli *et al.* 2002]. These data and our experience show that pancreatic sphincterotomy can be used as a solo therapy in documented pancreatic sphincter hypertension, coexisting with CP. In our experience, we have found that at least 40% of patients with CP have associated sphincter of Oddi hypertension. However, it is unclear if it contributed to CP or is the result of CP. There is no published literature regarding the outcomes of pancreatic sphincterotomy in patients with elevated sphincter of Oddi pressures in the setting of nondilated PD. We are currently conducting a prospective trial studying outcomes of sphincterotomy in patients with pancreatic SOD with and without CP.

Coexisting pancreas divisum

Pancreas divisum is the most common congenital variant of pancreatic ductal anatomy and occurs

when the dorsal and ventral PDs fail to fuse during the second month of gestation. With duct nonunion, the major portion of the pancreatic exocrine juice drains into the duodenum via the dorsal duct and minor papilla. It has been proposed that a relative obstruction to pancreatic exocrine juice flow through the minor papilla could result in pancreatic-type abdominal pain, acute pancreatitis or CP in a sub-population of pancreas divisum patients [Gregg, 1977]. Endoscopic attempts to decompress the dorsal duct in symptomatic pancreas divisum patients have been performed primarily by dilation, stent insertion and/or minor papilla sphincterotomy. The reported symptom improvement following endoscopic therapy for pancreas divisum in the setting of CP is much lower than for the recurrent acute pancreatitis. Lehman and colleagues studied pancreas divisum patients ($n=52$) presenting with CP ($n=11$), idiopathic recurrent acute pancreatitis ($n=17$) and disabling pancreatic type pain ($n=24$) [Lehman *et al.* 1993]. Minor sphincterotomy over a short 4–7 French pancreatic stent was performed. At a mean follow up of 1.5 years and minimum follow up of 6 months, 27% of the CP group benefited compared with 76.5% of the acute recurrent pancreatitis group. Longer-term study was recently reported by Borak and colleagues, who studied 113 patients with pancreas divisum and (a) CP ($n=22$), (b) acute idiopathic recurrent pancreatitis ($n=62$), or (c) chronic pancreatic type pain ($n=29$) [Borak *et al.* 2009]. At a median follow up of 43 months the outcomes were reported as primary success (symptom improvement with one ERCP only) and secondary success

Table 2 Summary of selected studies evaluating the efficacy of endoscopic biliary polyethylene stent insertion for the treatment of chronic-pancreatitis-induced common bile duct (CBD) strictures.

Investigator	N	Technical success (%)	Stricture resolution (%)	Stent occlusion (%)	Stent migration (%)	Follow up (months)
Deviere	25	100	3 (12)	32	40	14
Barthet	19	100	2 (11)	0	5	18
Smits	58	100	16 (28)	62	7	49
Kiehe	14	100	2 (16)	36	NM	NM
Vitale	25	100	20 (80)	12	8	32
Farnbacher	31	100	10 (32)	29	23	24
Eickhoff	39	100	12 (31)	33	10	58

NM, not mentioned.

(symptom improvement with at most two additional ERCPs). If three or more ERCPs were required for symptom improvement they were not included in successful (neither primary nor secondary) outcome. Primary and secondary success rates for the three groups were 18.2%/45.4%, 53.2%/71% and 41.4%/55.2%, respectively. The data show that minor papilla therapy of pancreas divisum patients with CP is less effective than in patients with acute recurrent pancreatitis. However, endoscopic therapy can still be offered to the patient with disabling symptoms. It should be appreciated that the endoscopic approach to ductal disease in patients with pancreas divisum is the same as in nondivisum patients.

Endotherapy on adjacent structures

Distal common bile duct strictures

Common bile duct strictures in CP can be malignant or from benign disease. It is important to rule out malignancy with a CT scan of the abdomen with pancreatic protocol and EUS with or without FNA prior to endoscopic treatment if clinical suspicion exists. Once the biliary stricture is determined to be benign, it is important to identify correctable causes such as pseudocyst causing extrinsic compression on the bile duct or pancreatic inflammation/edema in the setting of acute exacerbation of CP. The exact incidence of benign biliary strictures (BBSs) secondary to fibrosis and calcification within the pancreatic head is unknown, although in most series it is reported to be approximately 10% and can be as high as 46% [Abdallah *et al.* 2007]. This type of BBS is irreversible without intervention and can result in jaundice, cholangitis and progressive secondary biliary cirrhosis. In fact, in

CP-related BBSs, when the CBD is surgically drained there was a regression of hepatic fibrosis [Hammel *et al.* 2001]. Although, traditionally, BBSs in CP are treated by surgery with good long-term success, there is significant surgical morbidity in frequently debilitated patients with alcoholic CP and associated liver disease. Deviere and colleagues were first to report the use of endoscopic treatment of the BBS in CP with endoscopic sphincterotomy, followed by insertion of one or two 10 French biliary stents with as needed stent change [Deviere *et al.* 1990]. Although technical success and short-term resolution of cholestasis and cholangitis was 100%, long-term (mean: 14 months; range 4–72 months) stricture resolution was much less satisfactory occurring in 12%. Other series also reported low stricture resolution rates of only 10–33% over a mean follow up of 12 months and maximum follow up to 52 months [Cahen *et al.* 2005b; Eickhoff *et al.* 2001; Farnbacher *et al.* 2000; Kiehne *et al.* 2000; Vitale *et al.* 2000; Smits *et al.* 1996; Barthet *et al.* 1994] (Table 2).

Owing to the low success rate with one or two plastic biliary stents, various studies evaluating outcomes of multiple plastic stents and metal stents were conducted across the world. Serial placement of multiple simultaneous biliary stents in order to achieve gradual dilation of the BBS has improved outcomes as shown in a prospective trial by Catalano and colleagues [Catalano *et al.* 2004]. The long-term resolution rate of BBSs with multiple plastic stents ranged from 44% to 90% over a 13–48-month follow-up period in three studies [Catalano *et al.* 2004; Pozsar *et al.* 2004; Draganov *et al.* 2002]. Self-expandable metal (uncovered and partially

covered) stents (SEMSs) designed for permanent placement was evaluated for BBSs in the setting of CP [Cantu *et al.* 2005; van Berkel *et al.* 2004; Deviere *et al.* 1994]. Again, technical success and initial reversal of cholestasis and cholangitis were 100%, although at long-term follow up ranging from 22 to 50 months, the stents were occluded in 10–62% of cases. Stent patency rate dropped from 100% at 12 months to 40% at 24 months and 37.5 at 30 months. In such patients, subsequent options are to refer for surgery or repeat endoscopic procedures for stent-in-stent placement. In an attempt to decrease the number of serial endoscopic procedures and avoid the disadvantage of clogged permanent stents, more recently mid-term results of utilizing partially and fully covered removable metal stents were reported for BBSs in CP. Kahaleh and colleagues reported stricture resolution after a median stenting interval of 4 months with a partially covered metal stent and no recurrent symptoms during a 12-month follow-up period after stent removal in 17 of 22 (77%) patients [Kahaleh *et al.* 2008]. In the study by Mahajan and colleagues, 11 of 17 patients stented for a median of 3.3 months with a fully covered metal stent had resolution of their stricture and no recurrent symptoms after stent removal during a 3.8-month follow-up period [Mahajan *et al.* 2009]. In short, in select patients who are high-risk surgical candidates and those who wish to pursue endoscopic treatment for BBSs, endoscopic stenting with multiple plastic stents and/or self-expandable removable metal stents appears to be a potential second-line therapy. However, more data on long-term outcomes preferably in randomized trials with large numbers of patients treated will be necessary before this therapy can be advocated as routine.

EUS-guided celiac plexus block

One of the mechanisms for pain related to CP is peripancreatic and celiac neuronal inflammation. There has been a long-standing interest in decreasing neuronal inflammation with steroids and decreasing the perception of pain with anesthetic nerve block or neurolysis with alcohol. Traditionally percutaneous (via lumbosacral muscles) or surgical approaches have been used. Transgastric EUS-guided celiac plexus block (EUS-CPB) has gained favor in the last decade due to accompanying high technical success, lower complication rates and simplicity of performing the procedure.

Technique. Using a curvilinear array echoendoscope, the origin of the celiac trunk from the abdominal aorta is identified. With careful rotational examination, celiac ganglia can be visualized directly as 1–5-mm, elongated and hypoechoic structures [Levy *et al.* 2008]. A 22- or 19-gauge EUS FNA needle is used for injection into the celiac region or, if feasible, directly in to the celiac ganglion. Once the FNA needle is advanced to the appropriate location, aspiration is first performed to make certain a vascular puncture has not occurred. Bupivacaine is first injected followed by triamcinolone. Injection can be performed on one or both sides of the celiac trunk. In a prospective randomized trial, LeBlanc and colleagues showed no difference in technical success, symptom response or complication rates between one or two sites of injection during the same EUS-CPB session [LeBlanc *et al.* 2009]. Owing to the risk of hypotension, patients should be closely monitored for 2–4 hours after the procedure.

Results. In a retrospective series [Faigel *et al.* 1996] and two prospective series [Gress *et al.* 2001, 1999], overall technical success rate for EUS-CPB was 95%. The short-term pain improvement rate was 50–55% and long-term pain relief at 12 weeks was 26%, at 24 weeks was 10%. Younger patients (<45 years of age) and those with previous pancreatic surgery for CP were unlikely to have pain relief with EUS-CPB [Gress *et al.* 2001]. In a recent meta-analysis of 221 pooled patients from six studies, Kaufman and colleagues found that the short-term relief of abdominal pain from CP was 51.46% [Kaufman *et al.* 2009]. Owing to the relatively low response rates and requirement for repeat procedures given the short duration of pain relief, EUS-CPB should be considered a temporizing measure reserved for those where oral analgesia is ineffective or who are intolerant to medication side-effects pending a more definitive intervention.

Conclusion

CP is a debilitating disease with several complications such as ductal strictures, ductal stones, pseudocysts and pancreatic cancer contributing to significant morbidity and mortality. A multidisciplinary approach on a case-by-case basis involving the medical, endoscopic and surgical management is the ideal approach to CP. Although two randomized studies have shown that surgical management is more durable for

the treatment of a select group of patients with PD strictures/stones in the head and upstream dilation, it may not always be a feasible option due to patient comorbidities or preferences. Endotherapy can be performed with various combinations of pancreatic sphincterotomy, stent placement, stricture dilation, ESWL, pseudocyst drainage and EUS-guided access and therapy. Endoscopic management has shown reasonable success in select patient populations, although the true rate of success is difficult to delineate due to the retrospective nature of majority of studies and due to variability in the natural history of the CP. Further randomized comparative controlled trials are warranted to define the role of endoscopic treatment of CP. Further refinements in endoscopic accessories dedicated to the pancreas and advancements in technology may help to improve the outcomes of endoscopic treatment.

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Conflict of interest statement

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