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Endoscopic management of complications of chronic pancreatitis

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Abstract

Pseudocysts and biliary obstructions will affect approximately one third of patients with chronic pancreatitis (CP). For CP-related, uncomplicated, pancreatic pseudocysts (PPC), endoscopy is the first-choice therapeutic option. Recent advances have focused on endosonography-guided PPC transmural drainage, which tends to replace the conventional, duodenoscope-based coma immediately approach. Ancillary material is being tested to facilitate the endosonography-guided procedure. In this review, the most adequate techniques depending on PPC characteristics are presented along with supporting evidence. For CP-related biliary obstructions, endoscopy and surgery are valid therapeutic options. Patient co-morbidities (*e.g.*, portal cavernoma) and expected patient compliance to repeat endoscopic procedures are important factors when selecting the most adapted option. Malignancy should be reasonably ruled out before embarking on the endoscopic treatment of presumed CP-related biliary strictures. In endoscopy,

the gold standard technique consists of placing simultaneous, multiple, side-by-side, plastic stents for a one-year period. Fully covered self-expandable metal stents are challenging this method and have provided 50% mid-term success.

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Key words: Biliary stricture; Chronic pancreatitis; Pseudocyst; Endoscopic retrograde cholangio-pancreatography; Endoscopic ultrasonography; Stent

Core tip: Endoscopy is the first-choice treatment of pancreatic pseudocysts. The transduodenal route may be preferable over the transgastric route. Two transmural double pigtail stents should be left for at least 2 mo. In the case of a disconnected pancreatic tail, secretin-enhanced magnetic resonance pancreatography should be obtained to decide about stent removal. Biliary strictures should be thoroughly investigated to rule out malignancy. To this aim, improved methods of biliary sampling have become available. Even with multiple biliary stents, potentially fatal cholangitis is frequent in the absence of regular stent revision. Fully covered self-expandable metal stents have provided 50% mid-term success.

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INTRODUCTION

Common local complications of chronic pancreatitis (CP) include pancreatic pseudocysts (PPCs) and bili-

ary obstructions. These two complications develop in patients during the course of CP at a rate of 20%-40% for PPCs and 3%-23% for biliary obstructions^[1,2]. PPCs consist of a collection of pancreatic juice enclosed by a wall of fibrous granulation tissue, which may arise as a consequence of acute pancreatitis, pancreatic trauma or CP^[3]. Biliary obstruction may be caused by fibrosis, compression by a PPC or cancer. The present review covers the full spectrum of endoscopic management of local complications of CP; it is not an analysis of specific studies and it does not encompass the management of uncomplicated CP, which has recently been reviewed elsewhere^[4].

SEARCHES

Searches for relevant articles were conducted in Medline through PubMed on May 2013, without time limits, using the following search terms: “pancreatitis, chronic”[MeSH Terms] OR (“pancreatitis”[All Fields] AND “chronic”[All Fields]) OR “chronic pancreatitis”[All Fields] OR (“chronic”[All Fields] AND “pancreatitis”[All Fields]) AND pseudocyst[All Fields] AND (“endoscopy”[MeSH Terms] OR “endoscopy”[All Fields]) OR “pancreatitis, chronic”[MeSH Terms] OR (“pancreatitis”[All Fields] AND “chronic”[All Fields]) OR “chronic pancreatitis”[All Fields] OR (“chronic”[All Fields] AND “pancreatitis”[All Fields]) AND pseudocysts[All Fields] AND (“surgery”[Subheading] OR “surgery”[All Fields] OR “surgical procedures, operative”[MeSH Terms] OR (“surgical”[All Fields] AND “procedures”[All Fields] AND “operative”[All Fields]) OR “operative surgical procedures”[All Fields] OR “surgery”[All Fields] OR “general surgery”[MeSH Terms] OR (“general”[All Fields] AND “surgery”[All Fields]) OR “general surgery”[All Fields]); “pancreatitis, chronic”[MeSH Terms] OR (“pancreatitis”[All Fields] AND “chronic”[All Fields]) OR “chronic pancreatitis”[All Fields] OR (“chronic”[All Fields] AND “pancreatitis”[All Fields]) AND biliary[All Fields] AND (“endoscopy”[MeSH Terms] OR “endoscopy”[All Fields]). Articles written in English were selected for complete review on the basis of the abstract. Additional papers were identified by manually checking the reference lists of the articles selected for review.

PANCREATIC PSEUDOCYSTS

Differential diagnosis of pseudocyst-cystic neoplasm

Pseudocysts are the most frequent pancreatic fluid collections. The differential diagnosis between PPCs and cystic neoplasms or, less frequently, necrotized tumors, may be difficult in patients who present for the first time with a pancreatic fluid collection. Amongst the various cystic neoplasms that may affect the pancreas, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms harbor a malignant potential-many of which require surgical resection^[5]. As only a few of the available tests provide a high degree of certainty, a diagnosis is usually

made by analyzing a set of data, including demographic data and clinical history^[6], cross-sectional imaging^[7], and endosonography-guided sampling of the fluid content and of the wall of the lesion^[8,9]. Research has recently focused on the identification of new biomarkers and on *in vivo* confocal microscopic examination of the cyst wall through a needle inserted under endosonographic guidance^[10,11].

Indications for treatment

Widely accepted indications for PPC treatment include the presence of symptoms such as abdominal pain, gastric outlet obstruction, early satiety, weight loss, jaundice, and infected or enlarging PPC^[12]. Some authors also recommend treating PPCs in asymptomatic patients to prevent potential PPC-related complications, although these occur only in a minority of patients^[13,14]. Other such debated indications include compression of major vessels, intracystic hemorrhage, pancreaticopleural fistula, and PPCs with a diameter greater than 5 cm without any regression after more than 6 wk and a cyst wall thickness larger than 5 mm^[15]. In patients with CP, PPCs rarely resolve spontaneously, particularly if their diameter is greater than 4 cm or if they have developed outside of the pancreas^[16].

Results: Choosing endoscopic vs surgical treatment

Endoscopic drainage is recommended as a first-line treatment of accessible uncomplicated PPCs because it provides significantly better results compared to surgery in terms of cost, duration of hospital stay and quality of life up to three months post-procedure, as demonstrated in a small randomized controlled trial (RCT)^[17]. Reviews of non-comparative historical series of endoscopic and of surgical treatments of PPCs have reported similar results for both modalities in terms of morbidity, with 13% for endoscopic treatments and 16% for surgical treatments. A PPC recurrence rate during long-term follow-up has also been reported of 11% *vs* 10%, respectively, for endoscopic and surgical treatments. An advantage was found in favor of the endoscopic method in terms of mortality (0.2% *vs* 2.5%)^[15,18].

Some, but not all, authors have reported that endoscopic PPC drainage yielded higher success rates in the setting of CP *vs* acute pancreatitis. For example, Baron *et al*^[19] reported resolution of 92% of chronic pseudocysts *vs* 74% of acute pseudocysts in a series of 138 patients while Hookey *et al*^[20] reported resolution of 94% of chronic pseudocysts *vs* 92% of acute pseudocysts in a series of 116 patients.

A first-line surgical approach is usually adopted if necrosis has not yet liquefied and if treatment cannot be delayed. Endoscopy carries a lower success rate and higher morbidity rate in such instances; the reader is referred to a recent review for the comparison of currently available techniques in this particular indication^[21]. Pancreatic necrosectomy requires expert endoscopic skill, dedication and adequate patient selection.

Endoscopic technique

Access route: A direct communication between the PPC and the main pancreatic duct (MPD) may be demonstrated in 40%-66% of all PPCs^[22]. Such a communication allows drainage of the PPC *via* a stent inserted into the PPC through the papilla ("transpapillary drainage") as opposed to a stent being inserted into the PPC through the digestive wall ("transmural drainage").

No RCT has compared the transpapillary *vs* the transmural drainage route but, in nonrandomized comparative studies, procedure-related morbidity was lower with the transpapillary route (2% *vs* 15%) and long-term success was similar^[20,22,23]. The transpapillary route is usually reserved for relatively small (diameter < 5 cm) PPCs located in the head or the body of the pancreas.

"Conventional" endoscopic-guided vs endosonography-guided technique

Endosonography-guided PPC drainage tends to replace the "conventional" endoscopic approach that uses a duodenoscope or, in some cases, a gastroscope. A recent meta-analysis found that the single demonstrated advantage of the endosonography-guided technique is the possibility to drain non-bulging PPCs^[24], which represent approximately half of all PPCs^[22]. The most important limitations of the endosonography-guided technique reside in the thinner diameter of the working channel of the echoendoscope and in the lower maneuverability of the elevator. While the "conventional" approach is relatively standardized, new material is constantly being tested to make endosonography-guided PPC drainage a single-step, reliable procedure. One of the most recent devices allows puncturing, dilating the puncture tract and inserting two guidewires into the PPC without any device exchange. The device is made of a catheter with two balloons, one to anchor it to inside the PPC and the other one to dilate the puncture tract^[25].

Transgastric vs transduodenal transmural route

Some PPCs may be accessed through either the gastric or the duodenal wall. In such cases, the transduodenal route may be preferable as long-term success has been reported more frequently with the transduodenal *vs* the transgastric route (83% *vs* 64%); procedure-related morbidity was 10% with both routes^[26]. The difference in long-term success may be related to the longer durability of cystoduodenal compared with cystogastric fistulas (the latter ones typically close a few days after stent removal).

Number and type of stents

Two double pigtail stents are usually inserted for transmural drainage; a naso-cystic catheter may be left in place to rinse the PPC cavity with saline if debris is present. In a large retrospective series, the insertion of a single *vs* multiple stent was independently associated with the failure of endoscopic PPC drainage, defined as severe procedure-related complication or need for another treatment modality^[27]. In that series, straight stents were used

and they were associated with frequent bleeding (7% of patients, with surgery required in two thirds of them) and stent migration.

Stenting duration

Enterocystic transmural stents should not be retrieved before PPC resolution and not before at least 2 mo of stenting. This recommendation is mostly based on a RCT that allocated 28 patients (including 15 with CP) who had PPC resolution after transmural drainage to either stent maintenance or early stent retrieval; in the latter allocation group, stent retrieval was performed at a median of 2 mo post stent insertion^[28]. PPC recurrence was more frequent in the early stent retrieval group (38% *vs* 0%) and, in another, retrospective, series, a stenting duration of 6 wk or less was independently associated with the failure of endoscopic PPC drainage^[27].

Procedure-related complications

Reported figures largely vary from center to center with average morbidity rates of 13% and average mortality rates of 0.3%^[15,29]. Major complications include hemorrhage, perforation and infection. Most of these can be managed by non-operative means, including endoscopic coagulation, arterial embolization, repeat endoscopic drainage in the case of secondary infection and antibiotics in the case of retroperitoneal perforation. The following measures may help in preventing procedure-related complications:

Secondary infection: Although no data on the efficacy of antibiotic prophylaxis for endoscopic PPC drainage are available, antibiotic administration has been recommended immediately before transmural or transpapillary PPC drainage^[30]. The decision whether to continue antibiotics or not after the procedure should be based on drainage adequacy and on the presence or absence of necrosis^[12].

Bleeding: Severe bleeding usually arises from dilated arteries or veins. Pseudoaneurysms of the splenic artery may develop in the vicinity of PPCs. Imaging preceding the endoscopic drainage of PPCs should look for pseudoaneurysms and, in the case that one is discovered, have its prophylactic embolization discussed if the transmural route is elected. Extrahepatic portal hypertension develops during the course of CP in 15% or more of patients. It is frequently associated with PPC as well as leading to higher morbidity in patients who undergo pancreatic surgery^[31]. The endosonography-guided technique of PPC drainage has been recommended in such patients although it has not been demonstrated to decrease the risk of bleeding^[32].

In the case of infected PPC, should the strategy be different?

Primary infection is a rare complication of CP-related PPCs; secondary infection following stent occlusion or

endoscopic attempt at draining pancreatic necrosis is more frequent^[33].

Infected PPCs present a thick content that may not drain adequately through one or two thin plastic stents. Traditionally, in such cases, more large-bore stents are inserted together with a nasocystic catheter that is used for PPC irrigation. These additional interventions have resulted in similarly high success rates in patients with infected PPCs as compared with those who present uncomplicated PPC^[20,34]. As inserting multiple stents plus a nasocystic catheter requires time and may be technically challenging, fully covered self-expandable metal stents (FCSEMSs) seem to be a promising alternative for draining PPCs with a thick content. In a series of 20 patients with an infected PPC that was drained by endosonography-guided FCSEMS transmural insertion alone, clinical success was achieved in 17 patients^[35]. The authors suggested that using FCSEMSs rather than plastic stents plus nasocystic drains in patients with infected PPCs may decrease the number of endoscopic procedures, increase the final success rate, and reduce the time required for PPC resolution. FCSEMSs specifically designed for PPC drainage have become available from various manufacturers; they present a short length, a large lumen, and a diabolo shape aimed at preventing stent migration^[25,36].

In the case of complete MPD rupture, should the strategy be different?

If complete MPD rupture occurs, the disconnected pancreatic tail may keep secreting pancreatic juice that, in the absence of effective drainage, will lead to prolonged fluid accumulation. Bridging of complete MPD ruptures should be attempted and a combination of transmural PPC drainage plus a transpapillary stent bridging the MPD rupture should be considered^[37,38]. The stent should be left in place for a long duration, at least as long as secretin-enhanced magnetic resonance pancreatography demonstrates juice outflow from the disconnected pancreatic tail^[39].

BILIARY STRICTURES

Differential diagnosis

It is of paramount importance to reasonably rule out malignancy before embarking on the endoscopic treatment of presumed CP-related biliary strictures, as such a treatment usually lasts for one year and the course of pancreatic cancer is rapid. Particular attention should be paid to patients who present risk factors for pancreatic cancer; these include patients over 50 years of age, female gender, white race, or an absence of pancreatic calcifications and presence of exocrine insufficiency^[40,41]. Patients with hereditary pancreatitis present a very high risk of pancreatic cancer.

The accuracy of standard CT scanning and of endosonography for disclosing pancreatic cancer is limited in patients with CP^[42,43]. Endosonography, supplemented by fine needle aspiration (FNA) plus biliary endoluminal

sampling and assessment of malignancy biomarkers, is part of the standard work-up of a biliary stricture detected in the setting of CP. Other examination modalities such as probe-based endoluminal real-time microscopy are investigational. It should be kept in mind that endosonography-guided FNA is less accurate in the presence than in the absence of CP^[41,44], although this decrease in accuracy has been suggested to be confined to a subset of patients who present with obstructive jaundice and a biliary stent^[45]. Furthermore, in the community, the accuracy of endosonography-guided FNA for diagnosing pancreatic cancer is likely to be much lower than the 90% figure that is widely reported in the literature (latter reports originate from tertiary centers and use per-protocol analysis)^[46,47]. The technical details of the sampling procedure and of the sample processing are extremely important to reach a high diagnostic accuracy; they have recently been reviewed elsewhere for endosonography-guided FNA and for endoluminal biliary sampling^[48-50]. Recent improvements in the field of endoluminal biliary sampling include the development of more effective sampling devices and the use of rapid on-site examination for smears as well as for tissue biopsies^[48,51,52].

Indications for treatment

Generally accepted indications for the treatment of CP-related biliary strictures include symptoms such as secondary biliary cirrhosis, biliary stones, progression of biliary stricture, and asymptomatic elevation of serum alkaline phosphatase (greater than 2 or 3 times the upper limit of normal values) or of serum bilirubin or both for longer than one month.

Results: Choosing endoscopic vs surgical treatment

Guidelines recently issued by the European Society of Gastrointestinal Endoscopy propose that the choice between endoscopic and surgical treatment should rely on local expertise, loco-regional or systemic patient comorbidities and expected patient compliance with repeat endoscopic procedures^[53]. No strong recommendation could be made about the choice between the endoscopic and the surgical approach to CP-related biliary strictures due to the lack of comparative studies. In conditions different from CP, two comparative nonrandomized studies that included 143 patients with biliary strictures related to a traumatism have found that long-term success was similar (77%-83%) with the endoscopic and the surgical approaches^[54,55]. However, the endoscopic techniques used in these studies are not current anymore and the endoscopic treatment is more effective in post-traumatic compared with CP-related biliary strictures^[29]. Another study has compared the endoscopic vs the surgical drainage of CP-related biliary strictures; however, surgery was performed in only 6 patients, of whom five also had a pancreatic resection^[56].

Patient complications such as portal cavernoma or cirrhosis are often decisive factors in the selection of the endoscopic vs the surgical modality. Other factors that

may influence this selection include the expected patient compliance with endoscopic stent exchanges and, less importantly, the presence or absence of pancreatic calcifications. In a retrospective series of 14 patients, only two patients presented for elective stent exchanges scheduled at 3-mo intervals^[57]. Most patients were admitted with biliary infection due to stent occlusion after the scheduled stent exchange date. Another series that included 29 patients treated with multiple, side-by-side, plastic biliary stents reported the occurrence of at least 20 episodes of cholangitis (in this latter series, stents were exchanged when symptoms of clogging developed). The mean interval between stent exchanges was 6 mo in patients who were alive at the end of follow-up as compared to 22 mo ($P < 0.05$) in the three patients who died during follow-up (two of them from cholangitis)^[58]. The presence of pancreatic calcifications has been associated with long-term failure of single plastic biliary stenting^[59] but this factor may be less relevant if simultaneous multiple, side-by-side, plastic stents are used^[60].

Endoscopic technique

Plastic stents: If the endoscopic treatment modality is selected, temporary placement of simultaneous multiple, side-by-side, plastic stents is the gold standard amongst the various techniques available. A single nonrandomized series has compared long-term results after temporary placement of single *vs* multiple simultaneous plastic stents; clinical success was reported in 24% *vs* 92% of patients, respectively^[60].

From a practical point of view, amongst plastic biliary stents, polyethylene models are recommended because they allow obstruction relief more frequently than Teflon models^[61], and the exchange of plastic stents with an increasing number of stents is usually scheduled at 3-mo intervals for a total stenting duration of 12 mo^[58,60,62]. It has recently been suggested that with multiple, side-by-side, plastic stents, the interval between stent exchanges could be extended^[63]. However, as mentioned above, special care should be taken regarding the generally poor compliance and poor physical status of patients with alcoholic CP. It is recommended to implement a recall system to care for patients who do not turn up for stent exchanges at scheduled dates.

Self-expandable metal stents: “Definitive” insertion of self-expandable metal stents (SEMSs) (*i.e.*, with no intended SEMS removal) for benign biliary strictures has almost been abandoned due to the development of biliary epithelial hyperplasia that leads to late biliary obstruction^[64]. Recent studies of the endoscopic treatment of CP-related biliary strictures have focused on the temporary placement of covered SEMS with a shift of interest from partially covered to fully covered SEMS designs^[65,66]. Spontaneous SEMS migration has been the main drawback with FCSEMSs; new stent designs aiming to prevent migration include the adjunction of anchoring fins, the positioning of the stent covering on the internal

side of the SEMS and a flared-ends design. Such SEMSs remain investigational for the treatment of benign biliary strictures.

If FCSEMSs are used to treat benign biliary strictures, a stenting duration > 90 d is recommended as this was independently associated with stricture resolution in a multicenter trial that included 133 patients with benign biliary strictures, 44 of these being CP-related^[67]. In this trial, stricture resolution at the time of stent removal was reported in 26 (59%, intention-to-treat analysis) patients with CP. Other studies that included more than 10 patients followed up for at least one year after FCSEMS removal showed a success rate of approximately 50%: (1) Perri *et al*^[66] inserted a Niti-S stent with either a straight or a flared-ends design in 17 patients who had previously received a single plastic stent. Two years following FCSEMS removal, 56% of patients had presented no stricture relapse and had normal liver function tests. The flared-ends design partially prevented FCSEMS migration while all straight FCSEMSs migrated; and (2) Poley *et al*^[68] inserted a Hanaro prototype FCSEMS in 13 patients who had previously received a single plastic stent; success was reported in 6 (43%) of them.

FCSEMSs currently are the most promising alternative to multiple, side-by-side, plastic biliary stents. Despite their main advantages, *i.e.*, a reduced number of endoscopy procedures and a lower incidence of stent obstruction, FCSEMSs need improvements in their design as well as additional large multicenter trials before they can possibly be recommended as a first-line option for the endoscopic treatment of CP-related biliary strictures.

OTHER COMPLICATIONS

Other complications of CP include splenic vein thrombosis, pancreatic adenocarcinoma, pancreatic ascites and pleural effusion.

Splenic vein thrombosis is present in approximately 12% of patients with CP and it is usually asymptomatic but may cause bleeding in 7% of patients^[69]. In the case of bleeding, endoscopic variceal obturation using *N*-butylcyanoacrylate is effective in achieving hemostasis, and a splenectomy is an effective way to prevent recurrent bleeding^[70].

For the treatment of pancreatic adenocarcinoma, the endosonography-guided delivery of various cytotoxic agents is a rapidly evolving field that remains investigational^[71].

Pancreatic ascites and pleural effusion are rare complications of CP; they may or may not be associated with PPC and they present a high morbidity. The aim of endoscopic therapy in such patients is to insert a stent to bridge the MPD rupture that is responsible for pancreatic juice leakage; high success rates have been reported^[72].

CONCLUSION

Progress has recently been made in the field of the endo-

scopic treatment of CP-related complications.

With regard to uncomplicated PPCs, endoscopic drainage has been shown to be feasible in almost all cases and to be superior to surgical drainage. Techniques associated with the best clinical outcome have been identified. With regard to CP-related biliary obstructions, improvements in the design of FCSEMSs are challenging the standard technique and have the potential to improve patient acceptability.

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