Endoscopic and Conservative Management of Chronic Pancreatitis and Its Complications

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Keywords

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Abstract

Chronic pancreatitis is a progressive inflammatory disease of the pancreas potentially giving rise to several complications. For this reason, patients need long-term care and treatment by medical, interventional, and sometimes surgical measures. This article reviews current state-of-the-art strategies and guidelines for treating chronic pancreatitis with conventional and endoscopic measures.

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Definition, Epidemiology, Causes, and Manifestation

Chronic pancreatitis (CP) is a chronic inflammatory reaction of the pancreas, often arising as a consequence of long-term exposure to toxic agents, autoimmune or genetically induced inflammatory processes, obstructions to the flow of pancreatic juice, or repeated episodes of acute pancreatitis, eventually leading to changes in the organ's form, structure, and function [1, 2]. Additionally, secondary complications like pseudocysts, stenoses of the pancreatic or biliary duct or duodenum, and nutritional problems and pain may occur [1, 3–6]. CP is also a risk factor for pancreatic carcinoma and can have a severe impact on quality of life and life expectancy [7, 8].

Although its exact prevalence is almost unknown and has been poorly investigated so far, the incidence of CP is increasing worldwide in a range between 4/100,000 in the UK and the USA and 13.4/100,000 in Finland, correlating with the average alcohol intake [9]. The majority of patients is male and usually aged between 30 and 45 years at disease manifestation [9–11]. In Europe, the most common etiology of CP is excessive alcohol consumption over a course of several years, in most cases exceeding 80 g of pure alcohol intake per day over a time of 6–12 years [12]. Cigarette-smoking is a second, independent risk factor that potentiates disease progression in combination with excessive alcohol intake [13]. Genetic causes are less frequent and include mutations in cationic trypsinogen 1 and 2 (PRSS1/2), serine protease inhibitor Kazal-type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsin C (CTRC), carboxypeptidase A1 (CPA1), carboxyl ester lipase (CEL), and calcium-sensing receptor (CASR) [14–16]. In their pangenetic association study, Rosendahl et al. [17] identified a variety of other genetic loci that alter susceptibility to CP, supporting the concept of multiple factors engaging in promoting the disease with a clinically almost stochastically appearing risk. Rare causes include primary hyperparathyroidism as well as posttraumatic states. Pancreas divisum is an independent risk factor for development of CP, but this might have been overestimated in its significance [18]. A biliary etiology of CP has been debated in the past, especially in Anglo-Saxon countries, but newer concepts of the disease accept the model of repeti-

Fig. 1. Complications of chronic pancreatitis (with permission from Löhner et al. [62]).

tive acute episodes of pancreatitis, independently of the underlying stimulus [19].

In summary, CP is considered a multifactorial disease today; 10–30% of patients develop a chronic inflammatory mass at the pancreatic head that can lead to secondary problems such as compression of blood vessels, of the bowel, and of the biliary and pancreatic ducts [20]. In patients with portal vein thrombosis, portal hypertension and ascites can arise. Other common secondary changes include the development of pseudocysts and calcifications [2, 21, 22]. Complications of CP are illustrated in Figure 1.

Basic Approach

To offer the best clinical care to patients with CP, a comprehensive knowledge of the medical history, symptoms, lifestyle, and imaging and laboratory data is mandatory. Therefore, a complete anamnesis and detailed documentation of a patient's medical history should be obtained. All known risk factors, including alcohol consumption, smoking, and the family history, should be investigated by a systematic approach and a quantitative assessment [23]. Patients who smoke should be advised to stop smoking, patients with alcoholic CP should be advised to stop consuming alcohol, and professional addiction counselling should be offered to increase the chances of long-term abstinence [24]. This process is critical, since it should contain all important information on the positive effects on long-term disease progression and pain, but it should also not damage the relationship between doctor and patient or stop the patient from visiting a doctor because of symptoms of CP even if he does not manage to stop drinking or smoking. For these reasons, long-term care by a single physician specialized in the treatment of CP patients should be aimed at to increase adherence and compliance.

Diagnosis

A laboratory work-up should include Ca^{++} (primary hyperparathyroidism), triglycerides, and functional testing of the exocrine and endocrine pancreatic function. In cases with reasonable doubt about the sincerity of a patient concerning alcohol anamnesis, quantification of carbohydrate-deficient transferrin in blood, or ethyl glucuronide in urine or hair, can be useful [24, 25]. A disease manifestation before 20 years of age, as well as the occurrence of CP in the setting of recurrent idiopathic pancreatitis, should lead to exclusion of genetic causes, which are reported in up to 63% in this patient collective [26, 27]. In all patients with so-called idiopathic CP, autoimmune pancreatitis should be ruled out. EUS is considered the most sensitive method for diagnosing early changes in CP [28], and it is an essential tool for differential diagnosis in CP – that is, for obtaining histologic diagnoses in cases of a possible malignant or autoimmune disease [23].

A meta-analysis comparing image modalities for diagnosing CP revealed a similar accuracy for EUS, MRI, CT, and ERCP and a lower accuracy for transabdominal ultrasound [29]. Since diagnostic ERCP is not the state of the art anymore, EUS, MRI, and CT may be performed, depending on local resources and individual factors such as kidney or thyroid disease, age, comorbidities, and claustrophobia. CT, especially in the sequences without contrast enhancement, has advances over the other modalities for detecting small calcifications. MRI with heavily T2-weighted MR cholangiopancreatography is better in diagnosing the ductal anatomy and can be further optimized in combination with intravenous application of secretin [23].

Nutrition

Patients with CP have a lower body mass index than healthy individuals, due to several factors. Abdominal pain and a high stool frequency after food intake often lead [30] to smaller meals [31] despite the fact that such patients would need a higher-than-average calorie intake of around 35 kcal/kg/day [32]. Fat resorption is impaired, most dramatically in patients with pancreatic exocrine insufficiency [33], which can lead to nutritional hypovitaminosis with regard to fat-soluble vitamins [6, 34].

In patients with an initial diagnosis of CP, a complete laboratory evaluation including nutritional parameters such as vitamins A, D, B6, and B12 and albumin, electrolyte status, liver function tests, fasting plasma glucose, and HbA_{1c} should be performed. United European Gastroenterology (UEG) recommends screening for malnutrition with nutritional parameters such as prealbumin, retinol-binding protein, vitamin D, and minerals/trace elements [23].

In patients with alcohol abuse, deficiencies in vitamins B1, B2, and B6 should be ruled out or substituted if necessary, while deficiencies in vitamin B12 and folic acid are rare [32, 35]. Patients with CP have a pathological bone metabolism with a 3-fold-higher risk of osteoporosis, which is associated with deficiencies in vitamin D, and in men also in vitamin K [34, 36–38].

Diabetes Mellitus Type 3c

Diabetes in CP usually refers to pancreoprivic diabetes mellitus (DM). Similar to DM1, it is caused by a dramatic reduction in insulin-producing tissue, and the therapy consists of replacement of the lacking insulin. When treating CP patients with insulin, one should be aware of the higher-than-average risk of hypoglycemia: tissues are highly sensitive to glucose uptake when exposed to insulin. At the same time, synthesis of glucagon by the pancreas is impaired, leading to decreased gluconeogenesis from glycogen in the liver. Ongoing alcohol abuse further increases the risk of hypoglycemia, which is because of the alcohol itself, as well as due to worse therapy compliance and less regular food intake [23]. To rule out a possible overlap with DM2, quantification of C peptide or, in some cases, even the pancreatic polypeptide response may be helpful [23]. Since patients with CP in general are rather young but the 10-year mortality after primary diagnosis is about 50%, the first aim in diabetes therapy should be avoidance of extreme blood sugar swings. Depending on individual patients' characteristics, a more stringent blood sugar management, similar to type 1 management, may be evaluated [39].

Acid Suppression

In patients with exocrine pancreatic insufficiency, not only the secretion of pancreatic enzymes, but also secretion-induced secretion of bicarbonate by ductal epithelial cells, as well as the negative feedback mechanism for gastric acid production, are impaired [40, 41]. Furthermore, acid neutralization can be reduced and delayed in the small intestine. As a result, the duodenal pH may fall below 4. This leads to a delayed activation of lipase with less activity in the proximal small intestine, causing suboptimal utilization of enzyme activity and resorption capacity [40, 42, 43]. Additionally, bile acid precipitation may affect the enterohepatic cycling of bile [44]. Proton pump inhibitors (PPI) do not have a direct inhibitory effect on pancreatic acinar cells. Therefore, PPI prescription and dose escalation should be evaluated generously in CP patients in case of dyspeptic but also maldigestive symptoms.

Small Bowel Bacterial Overgrowth

Small bowel bacterial overgrowth (SIBO) is common in CP patients (30–90%), but this is not related to PPI therapy [45–47]. Therefore, with burping, flatulence, dyspepsia, and other symptoms related to food intake, SIBO should be considered, especially in patients after pancreatic surgery or antibiotic therapy or in those with DM [46].

Pancreatic Enzyme Replacement Therapy

Pancreatic exocrine insufficiency should be treated with pancreatic enzyme replacement therapy (PERT) with pancreatin in case of clinical or laboratory signs of malabsorption. In most cases, a meal should be accompanied with 40,000–50,000 units of lipase, a snack by half the dose [23, 48]. Modern pancreatic enzyme preparations consist of capsules filled with so-called microspheres that have an acid-resistant coating. Patients should be instructed to take PERT during their meal. The microspheres mix with the food, pass the pylorus together with the food, and are activated by dissolving their acid-resistant coating in a pH of 5–6, matching the acidity of a healthy individual's duodenum [49–51]. The effect of PERT on pain has been extensively discussed, but a meta-analysis showed no significant effect [52].

Currently, all pancreatic enzyme preparations are produced from pork-derived ingredients. Therefore, they do not interfere with quantitative stool tests specific for human elastase 1. It is widely accepted that they can be consumed by patients of Muslim faith (verse 139 of surah al-Baqarah) and Jewish patients (approval from the Chief Rabbi), since no alternatives are available [53].

If PERT is clinically insufficient, several steps may be considered:

- Ensure that the patient knows for which food, when, and how PERT should be taken
- Check if the patient takes PPI; consider PPI dose escalation
- There are considerable variations in the number (100–800 per capsule), size (1–3 mm) [50, 51], and consistency [51, 54] of preparations; try switching to another product
- PERT is often underdosed [55]; the exact dose recommendation is 2,000 units of lipase per gram of ingested fat [56]; if in doubt, try dose escalation
- Consider if persistent symptoms are compatible with SIBO or other causes of maldigestion rather than exocrine pancreatic insufficiency

The steps are illustrated in Figure 2.

Fig. 2. Stepwise approach to an insufficient response to pancreatic enzyme replacement therapy (PERT) for chronic pancreatitis patients with pancreatic exocrine insufficiency and maldigestive symptoms. PPI, proton pump inhibitor; SIBO, small bowel bacterial overgrowth.

Pain Management

Pain affects about 80% of CP patients, constantly or intermittently [4]. The etiology of pain in CP is thought to be multifactorial, with obstructive, hypertensive, ischemic, and inflammatory components. Usually, the pain decreases over the course of the disease [20].

Other causes of abdominal pain, such as peptic disease and synchronous malignancies, should be ruled out, considering that such patients are often exposed to risk factors overlapping between CP, cancer, and peptic disease [57]. Exacerbation of pain can be associated with food intake or an acute bout of pancreatitis and has a significant impact on patients' quality of life and behavior [4, 58]. In general, conservative pain management in CP follows the WHO stepladder recommendation. Special attention must be given to patients who have issues with alcohol abuse, since they are at higher risk of developing substance addictions [59]. Abstinence from alcohol can have a positive effect on pain [60], and a thorough joint evaluation and intervention by pancreatologists and addiction and pain specialists seems to have the potential for providing a sustainable effect on alcohol use disorders among patients with CP and alcohol addiction [24]. If opiates are used, preference should be given to preparations with lower potency, in order to avoid not only addictions but also other side effects like loss of appetite and nausea [61]. NSAIDs should not be used due to their gastrointestinal toxicity [23].

Endoscopic Therapy

Endoscopic therapy (ET) for CP has become a wider research field over the last decades, but it also has been kept under scrutiny. In 2007, a randomized controlled trial was published in *The New England Journal of Medicine*, stating a clear long-term inferiority of ET to surgery for drainage of the pancreatic duct [63]. This study and its follow-up study [64] were heavily criticized for their weaknesses in methodology. Anyhow, possibly also due to the lack of sufficient data and uniform concepts for ET, the study still had an impact on treatment practice, increasing the importance of surgical therapy in CP. The indication for ET in CP is long-lasting, since severe pain requires treatment with analgesics [23]. Beneficial effects of ET regarding preservation of pancreatic endocrine and exocrine function have not been demonstrated, and the same applies to surgical drainage procedures [23]. Most of the patients with an indication for ET suffer from pancreatic stones, while about 18% have ductal strictures only [3]. ET is successful in the majority of patients and may be attempted as the first approach for patients with pain in CP and a dilated main pancreatic duct (MPD) [23]. Patients who smoke or drink alcohol should be informed on the positive predictive value of discontinuation of alcohol and nicotine consumption for successful ET [65, 66]. ET is more likely to succeed for ductal obstruction by stones than for strictures [67], as well as for patients with a short disease duration and of a younger age [23, 68].

MPD Strictures

Pain of the “obstructive type” caused by pancreatic duct obstruction is an established concept in CP that can be treated by decompression [23, 69]. Dilation of the MPD of more than 6 mm is considered an indicator of increased ductal and parenchymal pressure causative of pain. A ductal stricture in the pancreatic head with ductal dilatation equal to or more than 6 mm is defined as dominant stricture [23]. Endoscopic dilatation of an MPD stricture alone has no sufficient long-term effect. Instead, the most ample evidence exists for treatment with a single plastic stent [70–75]. Special modifications of plastic stents described for the MPD include a 10-Fr S-shaped plastic stent that has been evaluated with good results in long indwelling times [71, 72, 76]. The majority of patients respond to treatment with single plastic stents, and patients who receive a larger stent have less frequent hospitalizations [77]. There is only one prospective study on multiple plastic stents (MPS) in the pancreatic duct by Costamagna et al. [78], describing the insertion of an increasing number of stents in the pancreatic duct in 19 patients who had previously failed in single-stent therapy and were alternatively considered candidates for surgery. Good treatment success after 6–12 months of ET (94.5%) and long-term success after a mean follow-up of 38 months (84%) were reported. This technique with repeated cannulation and balloon dilatation is technically more challenging than implantation of a single stent and requires more procedures. However, it seems to be able to spare almost all patients who do not respond to single-stent therapy from undergoing surgery. A trial from the same center on the same patient group using fully covered self-expanding metal stents (fcSEMS) in the MPD showed a high frequency of stent migrations as well as de novo strictures arising at the proximal end of the SEMS [79]. Therefore, MPS should be preferred over SEMS treatment in the MPD in CP. UEG mentions pancreatic fcSEMS as an alternative to MPS in patients that fail in single-stent therapy [23].

The consequences of pancreatic plastic stent occlusion are less dramatic than those of the occlusion of biliary stents [75]. Given this background, UEG recommends the treatment of dominant pancreatic duct strictures in CP with a single plastic stent, preferably 8.5 Fr or larger, with preferred stent exchange “on demand” [75] and/or extraction of the stent after 12 months, alternatively after regular stent exchange intervals [23]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends inserting a single 10-Fr plastic stent, with stent exchange planned within 1 year [80]. Criteria for treatment discontinuation are an adequate outflow of contrast medium and passage through the stricture of a 6-Fr catheter [23]. The total duration of ET should not be shorter than 12 months, and MPS can be applied if stricture resolution is

not achieved by single-stent treatment. Alternatively, surgery should be discussed [23, 80].

At our center, we follow these recommendations for the most part, but prefer 3 months of elective controls and exchanges of plastic stents in the MPD over long indwelling durations or “on-demand” strategies, with the aim of avoiding symptomatic stent dysfunctions and allowing an earlier switch from single stents to MPS in case of an insufficient response to ET.

Pancreatic Stones

Stone treatment in the MPD is an effective treatment: the best predicting factor for successful ET of symptomatic CP in a randomized controlled trial was the presence of ductal stones in the pancreatic head [67]. UEG discourages basket stone extraction attempts with stones larger than 5 mm without prior extracorporeal shock wave lithotripsy (ESWL) because of the higher risk of therapy failure and complications [23]. In expert centers, ESWL is successful in fragmenting most larger radiopaque stones and therefore can be considered as first-step treatment for radiopaque stones greater than 4 mm in size obstructing the MPD before endoscopic extraction of stone fragments [81]. ESWL alone can be as effective as ESWL with endoscopic stone fragment extraction [67], but it can lead to complications. A newer approach is the use of peroral pancreatoscopy (POP) with lithotripsy for stone clearance. Howell et al. [82] first described MPD stone removal under direct visualization using an electrohydraulic lithotripsy (EHL) probe in 1999. A systematic review from 2017 including 88 patients from 10 publications, among them 2 prospective studies, showed high treatment success rates with acceptable complication rates [83]: 5 studies used EHL, 4 studies used laser, 1 study used a basket for stone extraction, 1 study compared laser with EHL, and 1 study used a combination of ESWL first, followed by EHL during POP. The study in which ESWL had been performed before POP described an exceptionally low treatment success (43%) and the highest complication rate (28%) [84]. In a recent retrospective study using EHL in 21 patients, a high rate of stone clearance (88.2%) after a mean of 1.29 sessions and a low rate of complications (1 mild case of pancreatitis) were reported [85]. Figure 2 shows treatment with direct visualization of the stone and EHL via POP in CP. Laser lithotripsy may be more powerful than EHL, while EHL treatment is less expensive, but there are very limited data. Overall, there is no clear evidence of one method being superior to the other.

Biliary Stenosis

Jaundice in CP arises due to compression of the intra-pancreatic portion of the common bile duct by an inflammatory mass in the pancreatic head [2, 21, 22]. In this

case, drainage of the obstructed biliary tract is indicated to avoid secondary problems like cholangitis, liver damage, or secondary biliary cirrhosis [86]. Interventional endoscopic treatment with implantation of plastic stents for patients with CP is almost always technically successful and achieves good short-term clinical outcomes [22, 87, 88]. Nevertheless, biliary strictures caused by CP have the worst chance of long-term success after ET of all benign causes [89, 90]. If an acute inflammatory episode is ongoing at the time of stricture development, chances are better. On the other hand, in the presence of calcifications of the pancreatic head as a sign of a long-lasting inflammatory situation, chances for long-term stricture resolution by ET are worse [91, 92]. Therefore, endoscopic treatment of CP patients with benign biliary strictures (BBS) consists of repeated ERCP interventions that can lead to a considerable cumulative risk of procedure-related complications as well as patient stress, radiation exposure, and costs [91] with uncertain long-term success.

Treatment of BBS with a single plastic stent has been abandoned because of poor long-term results [93]. Biliary MPS implantation in patients with calcifying CP showed persistent stricture resolution in 60% of patients after a medium therapy duration of 21.1 months with 3-month stent exchange intervals [94]. This would imply an average number of 8 ERCP per patient. Since chances for further long-term improvement after an ET duration of more than 12 months are slim, a threshold of 12 months of ET duration is widely accepted [91]. Still, this requires 4–5 procedures with stent exchange intervals of 3–4 months. If plastic stent exchanges are not performed regularly, there is a high risk of secondary complications, such as stent occlusion and cholangitis [95].

SEMS are an alternative to plastic stents. The use of uncovered SEMS in CP patients with biliary stricture was first described in 1994 by Deviere et al. [96]. Today, uncovered or partially covered SEMS should not be used in BBS because of the risk of stent ingrowth and secondary strictures caused by irritation by the uncovered portion, even if long patency rates and few problems with dislocations have been described [23, 96–98]. fcSEMS appear to be as effective as MPS, but they require fewer ERCP to achieve clinical success [89, 99]. A randomized controlled trial on 60 patients with CP using MPS versus fcSEMS over a period of 6 months resulted in 92 and 90% stricture resolution, respectively, 2 years after stent removal, with similar complication rates [100]. A second randomized study comparing MPS versus SEMS in BBS mostly included post-liver transplant strictures, and only about one-third of the patients had CP [89]. In that study, the SEMS were removed after 6 months, but exchanged for new SEMS if necessary. All strictures had resolved after 12 months. A systematic review concluded that covered SEMS provided better results than MPS in BBS caused by

CP. It is noteworthy that 3 studies were included in the review that actually only used single-stent implantation [101], which may have had an impact on the conclusion.

Common concerns when implanting fcSEMS are stent dislocations and cholecystitis. To prevent stent dislocations, anchoring devices and flares have been developed, with a positive effect on migration events [102]. On the other hand, in a small portion of patients, de novo biliary strictures from irritations caused by anchoring devices have been described [103, 104].

Studies comparing the risk of cholecystitis when using covered versus uncovered SEMS have been carried out solely on patients with malignant biliary obstructions. Meta-analyses yielded heterogeneous results for these patients [105–107]. Tumor properties, such as invasion of the feeding artery of the gallbladder and the orifice of the cystic duct, rather than stent choice have been identified as influencing the cholecystitis rate [108, 109]. In conclusion, even if there is a small risk of cholecystitis, it is so small that it should not adversely influence the endoscopist's stent choice.

Critical questions when discussing pros and cons of SEMS over MPS are the ideal indwelling time and the total therapy duration with fcSEMS. A meta-analysis including 37 studies and 1,677 patients found a median stenting duration of 4.4 months [110], while another meta-analysis of 22 studies with 1,298 patients found a lower stricture recurrence with 6 months than with 3 months or less of stent therapy [99]. A prospective multicenter study used fcSEMS with a stent indwelling duration of 10–12 months in 177 patients with BBS; among those 127 with CP, it showed that all attempted fcSEMS removals were successful after a mean period of 11.3 months, even though fcSEMS could not be removed in the first attempt from 6 patients [111]. Stent migration increased from 5% at 6 months to 18.3% at 12 months, and stricture resolution was observed in 90.5% of the CP cases. The maximum recommended indwelling time for the fcSEMS type used in that study is 12 months, while other manufacturers mostly set a limit of 6 months.

Probably also due to this, the ESGE and UEG recommend 6 months of fcSEMS therapy. In theory, an indwelling time of 12 months could be attempted to increase the effectivity of ET in BBS without additional stent exchanges. This could be done either by using the fcSEMS according to the manufacturer, which allows a 12-month indwelling time, or by off-label use of other fcSEMS on the market, possibly with antimigration properties to reduce the fairly high incidence of dislocations during a 12-month indwelling time.

In selected CP patients not achieving stricture resolution and not suitable for surgery, 12-month exchange intervals make long-term ET more efficient, but further studies are required to prove this concept. With such long

Fig. 3. Direct visualization of wide pancreatic side branches and fragmentation of a pancreatic stone by electrohydraulic lithotripsy via peroral pancreatoscopy.

intervals between ERCP, a save recall system should be established to avoid complications from missed follow-up ERCP.

In summary, if correctly applied, MPS as well as fcSEMS regimes can be efficient in the majority of patients with BBS associated with CP. Surgery should be applied in nonresolving cases. In the future, stretching the fcSEMS indwelling times to 12 months may dramatically reduce the need for ERCP procedures compared to the 3-month exchange intervals with plastic stents (Fig. 3).

Pancreatic Pseudocysts

Pancreatic pseudocysts (PPC) are common in CP (20–40%) and often arise as a consequence of an acute bout of pancreatitis. Spontaneous resolution can be expected within the first 6 weeks, but rarely later than after 12 weeks [112]. In a multivariate analysis, a pseudocyst size smaller than 4 cm in diameter was the only favorable factor for spontaneous resolution [113]. Indications for PPC treatment include the presence of symptoms, complications (infection, bleeding, or rupture), or compression of surrounding structures with present or immanent secondary problems such as cholestasis, thrombosis, and duodenal obstruction. The interventional risk from drainage of pancreatic fluid collections is low, and they are suited best for EUS drainage if a fibrous wall more than 5 mm thick is present. EUS is superior to surgical drainage regarding costs, patient stress, and mortality, while long-term morbidity and success rates are comparable [114, 115].

Asymptomatic and uncomplicated PPC should not be drained, especially if small (<4 cm). The incidence of complications rises if a PPC is larger than 5 cm in size [116]. Therefore, UEG states that cysts that do not resolve and are larger than 5 cm may be drained even if asymptomatic [23]. Transpapillary drainage is preferred over transmural drainage if there is communication with the MPD and it is technically possible, since lower complication rates and similar long-term success rates have been observed [80].

It is not easy to predict whether a PPC can be reached transpapillarily, and cases in which an ERP should be attempted are not clearly defined. According to 1 study, PPC are connected to the pancreatic ductal system in 22–57% of cases [117]. ERP can also be useful to detect and treat a possible pancreatic duct rupture after an acute bout of pancreatitis, which decreases the chances of successful long-term treatment with EUS drainage. In most cases, MR cholangiopancreatography and/or EUS can provide clues about the ductal anatomy and help deciding whether or not to expose a patient to the interventional risk of an ERP [118]. If transpapillary drainage is not possible, EUS-guided drainage of PPC should be attempted [119]. This should be done under antibiotic prophylaxis to avoid secondary infection and abscess formation in PPC [120]. After access has been established, insertion of several double-pigtail stents should be performed [23]. A modern alternative to insertion of MPS approved by UEG is the use of lumen-apposing metal stents (LAMS).

Modern LAMS can be inserted in a single step without additional devices, minimizing the risk of loss of position during insertion. UEG suggests they may be favorable if a cyst's contents are suspected to be thicker than the thin pancreatic juice of a classic PPC, like in walled-off necrosis [23]. LAMS offer a greater lumen that in the further course may be passed with a gastroscope to mobilize the cyst's contents if necessary [121]. In contrast, a study on pancreatic necrosectomy using LAMS and a meta-analysis on PPC drainage with SEMS found higher costs but no clear advantage over plastic stent use [122, 123], while a recently published multicenter study found superiority of LAMS over plastic stenting concerning clinical success, complication rates, and procedure duration in PPC treatment [124]. The recommended maximal indwelling time for modern one-step insertion LAMS is 60 days, while UEG recommends that stents for PPC drainage be left for a minimum of 2 months. General practice at our center is LAMS extraction after about 2 months, although longer indwelling times did not lead to complications in our ex-

perience as well as according to multiple personal communications. Pigtail stents can be left in place for longer periods or until spontaneous dislocation.

Celiac Plexus Block

EUS-guided celiac plexus block is safer than previously used blind approaches. Neurodestructive methods with alcohol or phenol are not recommended, since they carry a high risk of serious complications such as severe deafferentation syndromes, while serious complications are rare if local anesthetics are used [125]. Local anesthetics, however, are only effective in half of the patients with a long-term pain relief for more than 24 weeks in only 10% of patients [126]. Acute adverse effects of celiac plexus block are reported for about 40% of patients, and they include transient worsening of pain, diarrhea, and hypotension [127]. For these reasons, celiac plexus block should be restricted to selected, severe cases of CP-related pain that are untreatable with other approaches [23].

EUS-Guided Ductal Drainage

Cannulation of the papilla of Vater is successful in a vast majority of ERCP attempts [128], but in some cases an alternative access has to be established. Several case reports have described EUS drainage of the MPD in benign conditions [129] and unresectable pancreatic cancer [130] as a salvage access route in patients with strong indication for ductal drainage because of recurrent pancreatitis. Access can be transduodenal or transgastric [131] depending on the position of the ductal obstruction. In the largest meta-analysis of EUS-guided biliary

drainage (EUS-BD) so far, higher complication rates compared to ERCP have been described [132]. However, an individually higher risk of complications from any procedure may be indicated by failed primary biliary cannulation in cases selected for EUS-BD. A retrospective study found a higher complication rate for endoscopic precut papillotomy than for the EUS-guided rendezvous procedure after failed primary biliary cannulation [133]. Complication rates in EUS-guided drainage procedures have been shown to decrease with growing experience of centers and single endoscopists [134, 135]. Only recently, 3 prospective randomized trials comparing ERCP and EUS-BD in patients with malignant biliary obstruction showed largely equivalent or better results in the EUS-BD group [136–138]. Interestingly, when transduodenal EUS-BD was performed, no complications arose from stent dislocation after a stable enterobiliary fistula had formed [137]. In theory, this may also be applied to patients with CP and BBS not responding to transpapillary stent therapy and not suitable for operation. Bypassing the inflammatory mass of the pancreatic head with a fistula may be a long-term concept for these patients, without foreign bodies facilitating bacterial colonization and obstruction. However, further evaluation is needed to validate this concept.

Disclosure Statement

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