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Interventional and Endoscopic therapy of chronic pancreatitis

Julia Mayerle[1], Rupjyoti Talukdar[2,3], Georg Beyer[1] and D. Nageshwar Reddy[2]

1) Department of Medicine A, University Medicine, Ernst-Moritz-Arndt University Greifswald, Germany
2) Asian Institute of Gastroenterology
3) Asian Healthcare Foundation, Hyderabad India
Email: mayerle@uni-greifswald.de

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1. Introduction

With an increasing number of hospital admissions, an average of 16 to 20 days in hospital per year, with 34 % of patients constantly taking pain medication, 57% in need for enzyme supplementation and 29% with diabetes mellitus, chronic pancreatitis is a debilitating disease with high socio-economic relevance. One third of all patients suffering from chronic pancreatitis can no longer practice in their original profession. The number of unemployed patients with chronic pancreatitis due to prolonged stays in hospital or continued alcohol abuse is known to be as high as 40%. Continued alcohol abuse with a Hazard Ratio of 1.6, smoking with a HR of 1.4 and the presence of liver cirrhosis with a HR of 2.5 negatively affects the prognosis of chronic pancreatitis. Belt-like upper abdominal pain is regarded as a cardinal symptom of chronic pancreatitis, together with weight loss, steatorrhea and diabetes mellitus. 30 - 60% of patients develop complications of their disease such as strictures of the common bile duct, inflammatory space-occupying masses, pancreatic pseudocysts, or pancreatic ductal stones, which require interventional or surgical treatment. In the absence of causal therapeutic options, treatment is restricted to symptom control by means of pain therapy, enzyme replacement, treatment of jaundice, strictures, fluid collections and optimal control of endocrine insufficiency. We will discuss the indications for and options of treatment. The evidence presented is graded according to the Oxford grading system (www.cebm.net) as displayed in **Table 1**.

2. Indication for Endoscopic therapy

Interventional or surgical treatment should be undertaken for long-lasting severe pain requiring analgesics [Evidence 2b]. Severe pain in chronic pancreatitis which requires analgesics can be dependent on its pathogenic causes effectively treated by both endoscopic as well as surgical procedures [Evidence 2b / 3b] (27). Surgical procedures (drainage) are superior to endoscopic procedures with regard to long-term pain reduction; they are, however, associated with higher mortality but lower morbidity. There are several studies with a level of evidence grade 2b or 3a available dealing with the treatment of pain from chronic pancreatitis by endoscopy, ESWL (extracorporeal shockwave lithotripsy), thoracoscopic splanchnicectomy, surgical resection and draining procedures. A direct comparison between surgery and endoscopy was carried out in only two studies with level of evidence grade 1b (22, 23, 33). Both studies demonstrated an advantage for the surgical

Table 1: Oxford grading system for level of evidence

Level of evidence grade	Description
1a	“evidence” from a systematic review of randomized controlled trials (RCT
1b	“evidence” from suitably planned RCTs
1c	all-or-none principle studies
2a	“evidence” from a systematic review of well-planned cohort studies
2b	“evidence” from a well-planned cohort study/low-quality RCT [e.g., <80% follow-up)
2c	“evidence” from outcome research studies
3a	“evidence” from a systematic review of well-planned case-control studies
3b	“evidence” from an individual case-control study
4	“evidence” from case series / poor quality cohort and moderate case-control studies
5	expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

procedure in the long term.

If a resectable pancreatic carcinoma is suspected, then surgery should be performed. [Evidence 2b]. If a space-occupying lesion of the pancreas is present and suspected (resectable) pancreatic carcinoma cannot be excluded, then surgical resection should be performed. Without surgery, life expectancy for patients with pancreatic carcinoma is less than one year; after successful resection it may be more than five years in 20 – 25%. [Evidence 1a] (20, 65, 66).

Surgical or interventional treatment should be carried out for persistent clinical symptoms of gastric outlet obstruction or duodenal stenosis secondary to chronic pancreatitis. Unfortunately, there are no comparative studies available which could answer whether resection surgery, bypass surgery, or endoscopic insertion of self-expanding metal stents are superior against each other (94).

In chronic pancreatitis the natural course predicts that sooner or later between 30 and 60% of all patients will require some interventions. In at least 30% of cases, conservative management, supplemented by endoscopic therapeutic interventions, appears to be sufficient to allow for an adequate quality of life. In 10 to 40% of cases, stenosis of the common bile duct (CBD) will develop which requires intervention. In the presence of an inflammatory tumor of the pancreatic head, primary endoscopy for bile duct obstruction with insertion of a stent into the bile duct should be performed followed by duct dilatation. However, if after temporary endoscopic therapy symptoms or cholestasis persist, then surgical resection should be performed [Evidence 2b]. A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for bile duct obstruction due to chronic pancreatitis does not produce a lasting long-term effect beyond one

year (24). A prospective study showed a clearly poorer long-term effect of stent management of distal bile duct obstruction if calcifications were associated with chronic pancreatitis (49, 50). A clinical example of patient with calcifying chronic pancreatitis in the head of the pancreas and subsequent bile duct obstruction that was managed by temporary stent insertion is shown in **Figure 1 A-C**.

A further complication is the development of stenosis of the pancreatic duct **(Figure 1 D-F)**. For this complication, the indication for the insertion of an endoprosthesis (stent) has so far not been fully clarified. There is only one prospective controlled study available which have demonstrated a positive effect of stent drainage of a dominant stenosis in the duct of Wirsung. Some studies suggest that the insertion of a stent into the pancreatic duct can induce secondary changes due to the stent with subsequent fibrosis and stricture (51, 55, 81). However, removal of the obstruction of the main pancreatic duct is often effective for pain management in shorter terms, and success rates of between 37 and 94% have been reported (67). Metabolic side effects of stenting the pancreatic duct over a longer period of time have not been reported yet.

A further endoscopic / interventional procedure for treating chronic pancreatitis is extracorporeal shock wave lithotripsy (ESWL) for stones of the pancreatic duct. Before the introduction of ESWL in 1989, surgery was often the only option for removing pancreatic duct stones which could not be removed by endoscopic means. Several retrospective studies have addressed the question of the clinical benefit of ESWL for pancreatic duct stones.

In the following sections we will discuss the benefits and drawbacks of interventional endoscopic options in more detail. For further reading see reference (58).

3. Endotherapy for pseudocysts

The prevalence of pancreatic pseudocysts in chronic pancreatitis lies between 20 and 40% (8). Pancreatic pseudocysts occur most often in patients with alcoholic chronic pancreatitis (70 – 78%) (2). The second most common cause is idiopathic chronic pancreatitis (6 – 16%), followed by biliary pancreatitis (6 – 8%) (8). Within the first six weeks after an acute bout of pancreatitis, 40% of the pseudocysts resolve spontaneously, while in 20% complications such as infection, obstruction of adjacent organs, cystic rupture or persistent pancreatitis render an intervention necessary. Spontaneous remission of pseudocysts after 12 weeks is very rare, and complications are observed in up to 2 / 3 of such cases. The increase in size of pseudocysts to over 5 cm in diameter is associated with an increased risk of complications. Pseudocysts which have resulted in complications such as gastric outlet obstruction, hemorrhage, pain, cholestasis or vascular stenosis, should undergo endoscopic or surgical treatment regardless of size [**Evidence 2a**]. The surgical procedures to treat pseudocysts tend to have higher success rates, but are marked with a somewhat higher mortality rate than the endoscopic pseudocyst drainage into either the duodenum or more usually the stomach. The decision on whom, when and by which procedure pancreatic pseudocysts should be treated had been very controversial in the past. In symptomatic pseudocysts either surgery or percutaneous or endoscopic drainage can be performed.

The literature on interventional therapy of pancreatic pseudocysts as a form of pain management is very limited. Most of the data are based on retrospective case series (3, 11, 28, 64, 87, 89). Despite the limited data available there are three systematic reviews (1, 5, 43, 46, 60). Pain relief will be achieved in a large number of patients either by surgical, endoscopic, or percutaneous drainage techniques. Given that a high rate of pain relief was achieved in these retrospective series (about 80%), all three

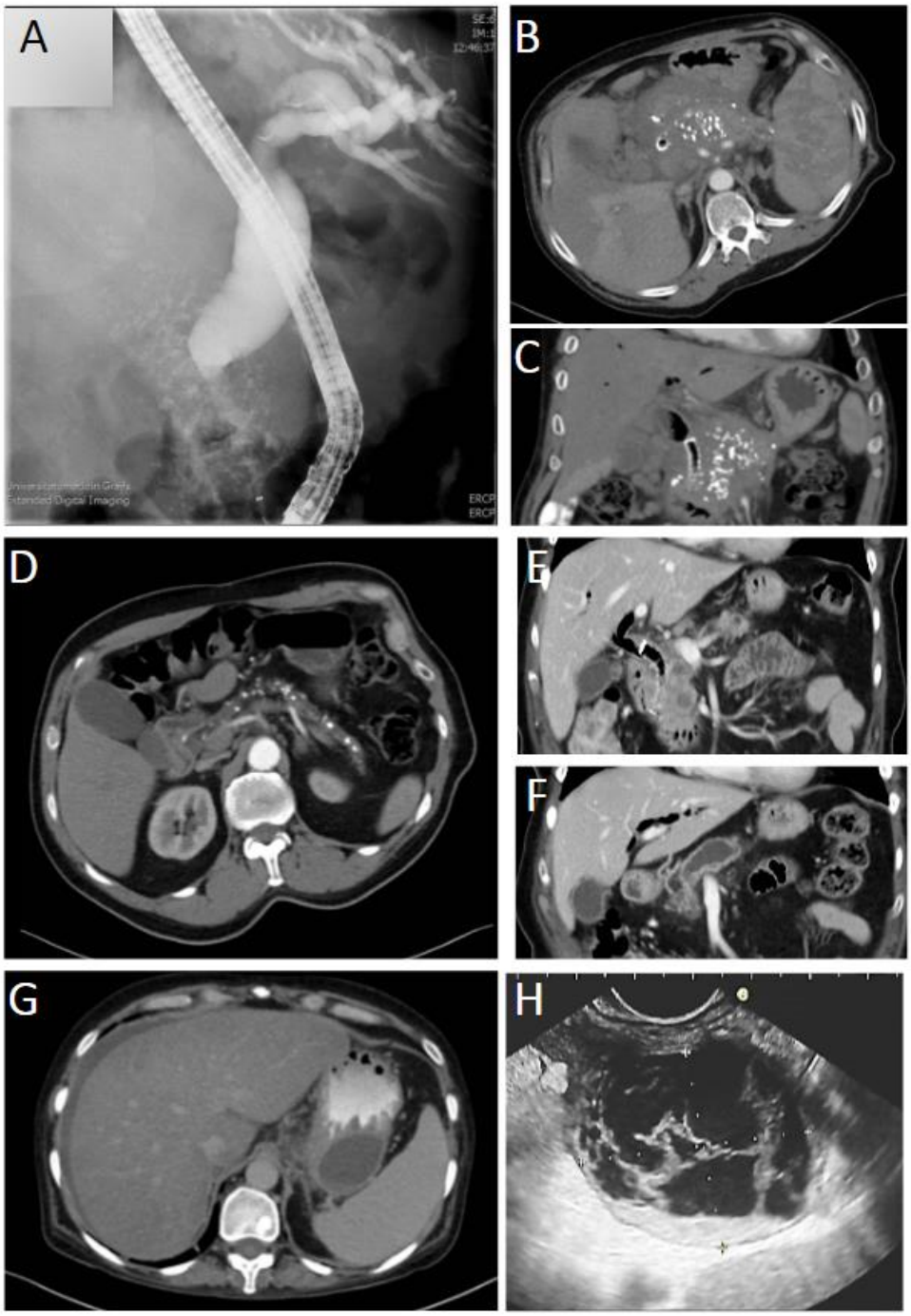

Figure 1: Complications of chronic pancreatitis which could warrant endotherapy are stenosis of the common bile duct, stricture and subsequent upstream dilatation of the pancreatic duct and pancreatic pseudocysts. **A)** ERC picture of patient with alcoholic calcifying groove pancreatitis and initial endoscopic therapy for cholangitis and jaundice**.** The patient is known to be a heavy smoker **B)** Native CT-scan with enlarged pancreatic head and calcifications. **C)** Sagittal view with a fully covered self-expandable metal stent (FCSEM) in the same patient **D)** Atrophic pancreas in a patient with alcoholic chronic pancreatitis and dilated pancreatic duct as well as calcifications. **E and F**) Patient with idiopathic chronic pancreatitis due to a chymotrypsin C mutation, jaundice, FCSEM and grossly dilated and atrophic pancreatic duct, no calcification. **G)** CT-Scan with oral contrast media of female patient at the age of 45 depicting a cystic lesion in the tail of the pancreas. **H)** EUS picture of the same patients illustrating the differential diagnosis between an MCN and a pancreatic pseudocyst in the absence of EUS guided FNA for cyst fluid analysis. Lipase levels were grossly increased while CEA level was normal in this patient.

systematic reviews came to the conclusion that, although conservative management of chronic pancreatitis also results in pain relief, in a certain percentage of patients, percutaneous, endoscopic or surgical drainage is still the more effective form of pain management. It is not possible to derive a significant difference in the comparison of the three procedures from the published data. In cases of obstruction of the bile duct or pancreatic duct by pancreatic pseudocysts, they should be treated. When cholestasis does not improve after drainage of the pseudocyst alone, stent placement into the bile duct or a resection procedure may be indicated.

Further complications, which render endoscopic or surgical treatment of the pseudocyst necessary, include compression of large abdominal vessels, clinically relevant gastric outlet obstruction or duodenal stenosis, infection of the pseudocyst, pancreatico-pleural fistula formation. Nausea and vomiting are quite common symptoms of pancreatic pseudocysts. Endoscopic interventional therapy of a hemorrhagic pseudocyst is associated with a high risk of bleeding. Thus, these pseudocysts should be treated surgically.

Initial therapy for symptomatic pancreatic pseudocysts can be endoscopic drainage of the pseudocyst, followed by surgery should the pseudocyst recur [Evidence 3a]. The choice between endoscopic and operative pseudocyst drainage should be decided by the location of the cyst and the type of additional pathomorphological changes [Evidence 3b]. Endoscopic procedures of draining a pancreatic pseudocyst are less prone to complications than surgical procedures. However, in the long term not all pseudocysts are successfully treated by endoscopic drainage alone. Studies comparing endoscopy with surgery are not available. An interdisciplinary therapeutic concept is intended (9) (**Table 2**).

Asymptomatic pancreatic pseudocysts, which have reached the size of more than 5 cm in diameter and which do not resolve within six weeks, can be treated [Evidence 2a]. Pancreatic pseudocysts which show already a fibrous wall of more than 5 mm on imaging are particularly suited for endoscopic or surgical drainage. In a multivariate analysis a pseudocyst size < 4 cm in diameter was the only favorable factor for spontaneous resolution (39). Untreated cysts larger than 5 cm may have a higher risk of complications such as rupture, infection, jaundice, or hemorrhage (18).

Drainage of pseudocysts can be carried out by transgastric, transduodenal or transpapillary approaches (9, 93). Percutaneous drainage is also possible, but is associated with the risk of external fistula formation [Evidence 4]. One should select the access route for endoscopic transmural drainage of pseudocysts by endoscopic ultrasound assessment. It depends on the size, vessels in the vicinity and location of the pseudocyst. Comparative studies showing superiority of the endoscopic access route, either through the stomach or duodenal wall, are not available. Transcutaneous drainage carries the risk of persistent cutaneous fistula formation. Furthermore, an existing transcutaneous drain can adversely affect the patient's quality of life. Thus, the endoscopic transmural drainage is preferred (9).

Transmural drainage should be done under endoscopic ultrasound guidance [Evidence 3]. Endoscopic ultrasound is a procedure which can best assess the appearance of the pseudocyst wall, content, location and relationship to adjacent blood vessels. Endoscopic ultrasound guidance will possibly reduce the rate of failed puncture attempts and complications (9, 93). A direct comparison of the complication rate for transmural needle drainage without ultrasound guidance is not available. The success rate in the 1,213 published patients with transmural drainage of a pancreatic pseudocyst is

Table 2 Summary of endoscopic pseudocysts/WOPN drainage

	number of patients	success rate	complete cyst drainage	recurrence rate	complications
Kozarek et al. 1985 (53)	4	2 (50%)	2 (50%)	0 (0%)	1 (25%) dead
Cremer et al. 1989 (30)	33	28 (85%)	30 (91%)	4 (12%)	3 (9%)
Sahel et al. 1991 (76)	37	31 (86%)	36 (97%)	2 (5%)	5(14%)
Kozarek et al. 1991 (52)	14	11 (79%)	n.a.	2 (14%)	3 (21%)
Benjamin et al. 1993 (13)	26	19 (73%)	n.a.	4 (15%)	4 (15%)
Funnel et al. 1994 (35)	5	5 (100%)	5 (100%)	0 (0%)	0 (0%)
Deviere et al. 1995 (31)	12	10 (87%)	10 (87%)	0 (0%)	0 (0%)
Vitale et al. 1999 (95)	36	31 (86%)	31 (86%)	5 (14%)	1 (3%)
White et al. 2000 (97)	20	20 (100%)	20 (100%)	0 (0%)	2 (10%)
Giovannini et al. 2001 (38)	15	15 (100%)	15 (100%)	0 (0%)	1 (6,6%)
Libera et al. 2000 (59)	25	21 (84%)	20 (80%)	1 (4%)	6 (28%)
Norton et al. 2001 (68)	17	14 (82,4%)	13 (76,5%)	1 (7,1%)	3 (17,6%)
Sharma et al. 2002 (79)	38	37 (97%)	37 (97%)	7 (16%)	5 (13%)
Binmollet et al. 1995 (14-16)	53	43 (81%)	47 (89%)	11 (23%)	6 (11%)
Smits et al. 1995 (82)	37	24 (65%)	24 (65%)	3 (12,5%)	6 (16%)
Barthet et al. 1995 (10)	30	23 (77%)	26 (87%)	3 (11,5%)	4 (13%)
Baron et al. 2002 (6)	64	52 (81%)	59 (92%)	7 (12%)	11 (17%)
Catalano et al. 1995 (25)	21	16 (76%)	17 (81%)	1 (6%)	1 (5%)
Antillon et al. 2006 (4)	33	31 (94%)	24 (82%)	1 (3%)	2 (6%)
Hookey et al. 2006 (44)	116	102 (87,9%)	108 (93,1%)	19 (16,4%)	13 (11%) 6 (5,2%) dead
Kruger et al. 2006 (56)	35	33 (94%)	30 (88%)	4 (12%)	0 (0%)
Weckman et al. 2006 (96)	165	142 (86,1%)	142 (86,1%)	8 (5,3%)	16 (10%)
Kahaleh et al. 2006(48)	99	93 (94%)	n.a.	n.a.	19 (19%)
Cahen 35 al. 2005 (21)	92	89 (97%)	79 (86%)	4 (5%)	31 (35%) 1 (1%) dead
Varadarajul et al. 2011(92)	154	154 (100%)	144 (93,5%)	1 (1,5%)	8 (5,2%)
Will et al. 2012 (99)	32	31 (97%)	k.A.	5 (15,4%)	3 (9,6%)
Total	**1213**	**1077 (88,8%)**	**919 (70%)**	**93 (7,7%)**	**161 (13,3%)**

reported to be 82.2%, with the more recent studies reporting success rates of significantly over 85%. These results are comparable with surgery. The mortality rate in larger series involving over 30 patients was 0.2%. The recurrence rate is reported to be around 8.5% and the complication rate 14.4% (69). **Figure 2** illustrates a case of a pancreatic pseudocyst in the tail of the pancreas due to pancreatic duct leak, which was managed by using a modern fully covered self-expandable metal stent (FCSEM) system which is mounted on an electrocautery-enhanced delivery system in addition to conventional pancreatic duct stenting.

A diagnostic needle aspiration of the cyst may be performed for suspected infection or for suspected neoplasm [Evidence 4]. If diagnostic needle aspiration of the cyst confirms an infection of its content, then drainage is indicated. Surgical treatment should be carried out if malignancy is suspected. Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between mucinous cystic tumours and pseudocysts, as those entities might be difficult to distinguish on modes of imaging alone **(Figure 1 G,H)**. When EUS-guided needle aspiration of a cyst reveals a CEA > 400 ng / ml, a variably increased or low amylase or lipase, high viscosity, mucin or epithelial cells in the cyst contents, then the presence of a mucinous neoplasm must be assumed (19, 85, 86). If a

connection to the pancreatic duct is excluded the final diagnosis of a mucinous cystic neoplasm (MCN) can be made.

Visualization of the pancreatic ducts can be performed before endoscopic or surgical drainage of a pseudocyst [Evidence 3b]. Whether an ERCP with the attempt of draining the pseudocyst via the papilla should be performed instead of a primarily transgastric or transduodenal drainage is still a matter of controversy. On one hand, drainage of the pseudocyst via a stent in the pancreatic duct is the “most physiological” form of drainage. According to one study, 22 – 57% of pancreatic pseudocysts have a connection with the pancreatic ductal system (64). Thus, an ERP can precede endoscopic transmural drainage in order to detect a connection with the duct or to exclude a rupture of pancreatic ducts (8% after acute necrotizing pancreatitis). Transmural drainage in the presence of an undetected rupture of the pancreatic duct or a connection of the pancreatic pseudocyst with an obstructed pancreatic duct is less promising with regard to the long-term outcome of therapy. On the other hand, the success rate of an attempted transpapillary drainage is usually less than 60%. Furthermore, these attempts impose a risk of ERCP-induced pancreatitis. Direct transgastric or transduodenal cyst drainage is very effective and usually associated with few complications (29, 76). Without antibiotic prophylaxis the procedure-related incidence of an infection of a pseudocyst and the risk of development of a pancreatic abscess increases (10). In patients with advanced pancreatic duct changes, especially pancreatolithiasis, any pseudocyst treatment should be part of a general therapeutic concept [Evidence 2b]. A relative indication to treat pseudocysts is the presence of chronic pancreatitis with respective pancreatic duct anomalies or pancreatic ductal stones, because in these cases the rate of spontaneous regressions, even of small cysts, is only at a maximum of 10 – 26% due to the constant inflammatory irritation (39). Treatment of pancreatic duct obstruction can be undertaken in patients with a pancreatic pseudocyst, prestenotic duct dilatation or fistula formation [Evidence 4]. Pancreatic pseudocysts are maintained by pancreatic duct obstruction in the presence of prestenotic duct dilatations or fistulae, if these stenoses are responsible for a blockade of drainage. In these cases removal of the pancreatic duct obstruction is recommended.

4. Therapy of pancreatic duct stenosis and ductal stones

In patients with chronic pancreatitis, the pressure in the pancreatic duct is initially increased, regardless of etiology or dilation of the duct of Wirsung is seen (98). An important role in the pathogenesis of pain is ascribed to ductal and interstitial hypertension and possible relative pancreatic ischemia. The aim of endoscopic and surgical decompression therapy in patients with chronic pancreatitis and pain and / or clinical episodes of acute pancreatitis is to remove the obstruction to the outflow of exocrine pancreatic juices. Techniques such as sphincterotomy, dilatation, ESWL and stent insertion have been modified for the pancreatic duct. Endoscopic decompression of the duct can precede a surgical procedure to predict whether surgical decompression of the pancreatic duct might alleviate pain or reduce acute bouts of chronic pancreatitis. Endoscopy represents an alternative to surgery and is associated with low morbidity and low mortality. Endoscopic interventions do not interfere with surgery that might still be necessary later in the course of the disease. Furthermore, clinical success after endoscopic reduction of the intraductal pressure does provide some indication of the later result of surgical drainage or a resection procedure.

Pancreatic ductal stones may cause pain by obstructing the outflow of pancreatic juice, induce recurrent exacerbations, maintain a pseudocyst or fistula or cause other complications. Stones can be treated by endoscopic or surgical means

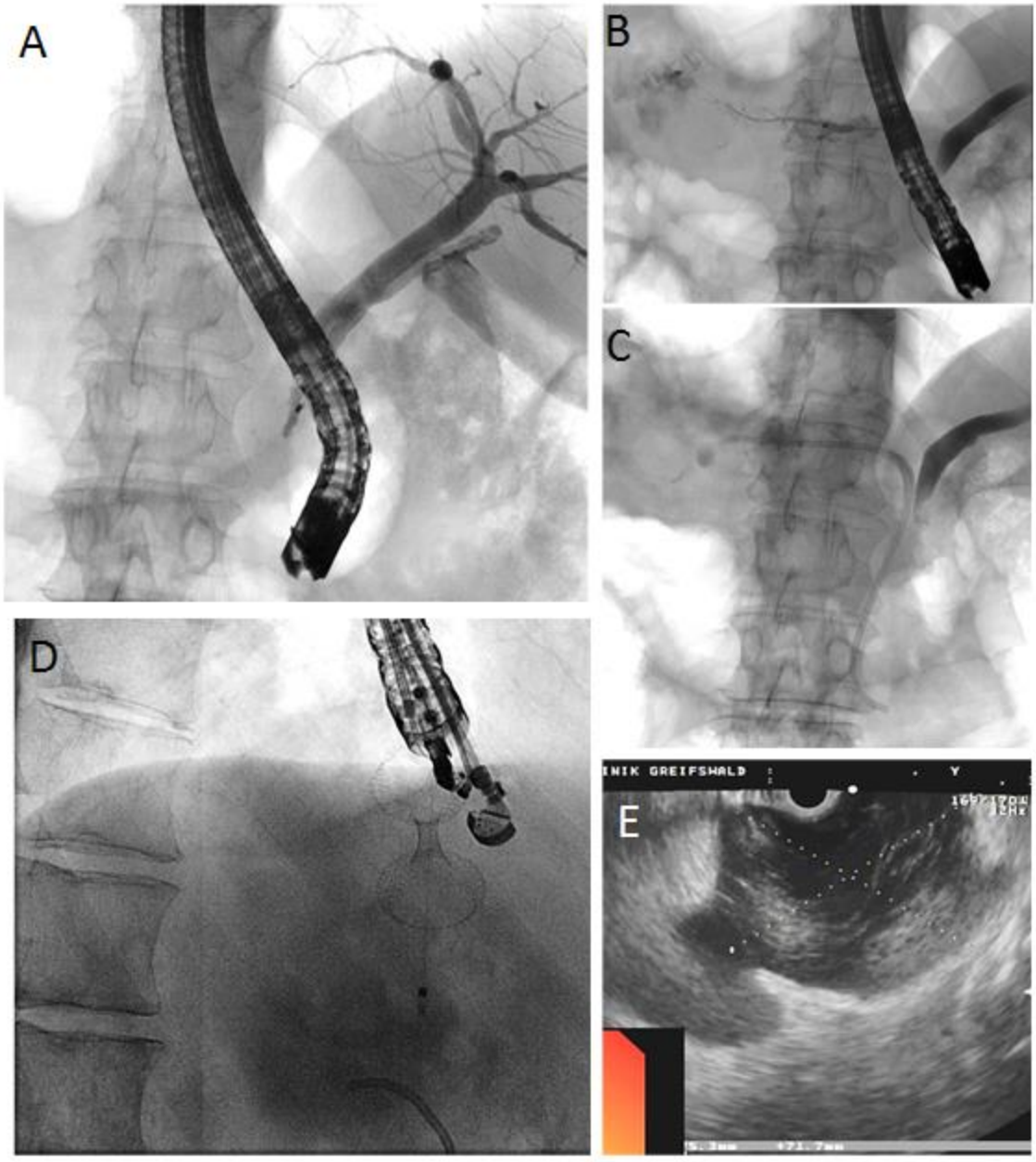

Figure 2: Endoscopic management of pancreatic fluid collection by a combined approach. **A)** ERC picture of a patient with recurrent acute pancreatitis due to alcohol abuse and a walled off pancreatic necrosis (WOPN) in the tail of the pancreas. ERC shows a normal cholangiogram and tailored distal common bile duct in the absence of cholestasis**. B)** ERP with distal leak of the main pancreatic duct classified as Cambridge IV. **C)** Treatment with a 15 cm 8.5 Fr stent reaching the leak. **D)** Radiograph of the subsequent EUS guided drainage of the collection in the tail employing a hot AXIOS Stent. **E**) EUS picture of the WOPN in the tail of the pancreas before drainage with a lumen opposing stent (hot AXIOS, Boston Scientific®).

[Evidence 4]. Pancreatic ductal stones are the result and not the cause of chronic pancreatitis. They can however lead to consecutive obstruction of the outflow of pancreatic secretions in the duct and duodenum and thus cause pseudocysts development or fistulae. They can also cause recurrent exacerbations or contribute to the pathogenesis of pain. Under these conditions, treatment of pancreatic ductal stones appears appropriate. There are, however, no studies available which have compared the treatment of pancreatic ductal stones with a sham intervention. Case series and one meta-analysis are available which show an improvement of pain after treatment of pancreatic ductal stones; comparative studies involving the spontaneous course or randomized studies, however, have not been published. Endoscopic treatment appears particularly suitable for treating solitary stones and obstructions close to the papilla. Surgical drainage procedures have been shown to be superior for distal obstructions. There are no comparative studies available comparing either endoscopic or surgical procedures with untreated cohorts or in direct comparison with the natural course of the disorder. In two studies, in which endoscopic treatment was compared with surgery, i.e. drainage operation, the results after surgery were significantly better with respect to long-term pain reduction (22, 23, 33).

Pancreatic duct strictures, which may be responsible for pain, recurrent exacerbations, maintenance of a pseudocyst, fistula, or other complications, can be treated by endoscopic dilatation and stent placement [Evidence 4]. In a prospective non-randomized study, rapid improvement of symptoms was achieved by insertion of a pancreatic stent in non-operable patients, although further interventions were frequently necessary (88). Some studies report that the insertion of a stent into the pancreatic duct can induce secondary changes due to the stent with subsequent fibrosis and strictures (55, 67, 81). Removal of the obstruction of the pancreatic duct is effective for the treatment of pain in the short term. Success rates between 37 and 94% have been reported. In the largest hitherto examined cohort of 1,021 patients, a long-term reduction of pancreas-related pain was achieved in 84% of cases (75). However, in 79% of the patients stent therapy for control of pain had to be repeated within one year and in 97% within two years. Metabolic side-effects have not been examined over the long term. The only randomized study recruited 41 consecutive patients with CP with a dominant stricture of the MPD to either receive pancreatic duct stenting or serve as control. Recurrence of pain and pancreatic function were recorded as outcome measures over a 3-year follow-up. In a mean follow-up period of 62.5 months pain recurred in 15% of patients with pancreatic duct stenting (3/20) and in 50.0% of control patients (11/22) ($p<0.05$). Progression of exocrine insufficiency in the stent group was significantly slower than in the control group ($p<0.05$), while endocrine function showed no difference between groups (78).

The endoscopic placement of a stent into the pancreatic duct may be performed if pancreatic ductal stones or stenosis of the pancreatic duct near the papilla causes obstruction to flow. No general recommendations can be made about the necessary duration of stent therapy [Evidence 4]. Benign strictures of the duct of Wirsung can develop as a complication of an impacted stone or as a result of acute inflammatory parenchymal changes with compression or stricture of the duct (29), examples of different etiology are displayed in **Figure 1, D-F**. The success rate of stent insertion was examined taking into consideration the rise in pressure due to the stone as a cause of pain development and of the exacerbations of chronic pancreatitis (15, 45, 51, 52, 54, 61, 73, 82-84). Pancreatic stent placement is technically successful in about 70% of patients. Those patients seem especially to profit in whom a pancreatic fistula or a pseudocyst are maintained by an obstruction. Endoscopic drainage with stone extraction and stent therapy is an effective

measure to control pain in some patients with a dilated duct of Wirsung (11). Better pain management, however, was achieved by pancreaticojejunostomy in two randomized controlled studies (22, 23, 33). Endoscopic therapy led to pain reduction or complete pain relief in 32% (33) and 65% (22, 23), respectively, whereas pancreaticojejunostomy led to pain reduction or relief in 75% (33) and 86% (22, 23), respectively. The different success rates of endoscopic therapy in both studies are possibly due to the longer duration of stent therapy in the study by Dité et al (33).

There are currently no reliable data available regarding the necessary duration of stent therapy. Some authors recommend treatment over one year with an exchange of the stent at least every three months.

When surgery is not possible a fully covered self-expandable metallic stent (FCSEMS) can be inserted into the duct of Wirsung for pain control [Evidence 4]. Some case reports and case series suggest that covered self-expandable metallic stents may be inserted into the pancreatic duct to treat pain. Their potential advantage versus plastic stents is due to their longer period of patency. Long-term results of their benefit are not available. Uncovered self-expandable metallic stents are not recommended due to the rapid proliferation of duct epithelium as a reaction to the metal mesh (17, 77).

Pancreatic ductal stones, which cause pain by obstruction may be treated by ESWL. There is some evidence that the subsequent endoscopic removal of the pancreatic ductal stones or their fragments is not a prerequisite for the effectiveness of the procedure (34). The treatment of pain in patients with diffuse calcifications by means of ESWL has not been substantiated in any studies [Evidence 2b]. A meta-analysis demonstrated a significant effect on pain reduction, but with a remarkable heterogeneity of the results (41). All the studies included in the meta-analysis were case studies without untreated or sham-operated control groups. So far only one randomized controlled study has been published comparing ESWL with and without subsequent ERP to remove fragments from the main pancreatic duct. In this study, the subsequent endoscopic stone extraction had no influence on pain relief after two years (34).

5. Endotherapy for biliary stricture

In 10 to 44.6% of cases, obstruction of the common bile duct (CBD) will develop in patients with chronic pancreatitis which requires intervention. Indications for endoscopic intervention include significant cholestasis, exacerbations of cholangitis, prevention of secondary biliary cirrhosis and for differentiation of the cause of pain (obstruction of the CBD vs. chronic pancreatitis). Several studies have assessed the efficacy and cost efficiency of endoscopic drainage of the CBD. A long term success rate was achieved in only one third of the patients. Thus endoscopic therapy is in most patients only indicated as an interim procedure until definitive surgery, e.g. as an acute intervention in septic patients, or in non-operable patients or in those unwilling to undergo surgery. In principle, there is a risk of developing cholangitis after endoscopic drain placement. The administration of prophylactic antibiotics together with ursodeoxycholic acid has not been proven effective in various clinical studies (7, 36, 37, 40, 42, 80). The commonly occurring complications include stent occlusion by cellular detritus, microcolonies of bacteria or extracellular, fibrillar material.

If chronic pancreatitis causes bile duct obstruction and if there are clinical signs of cholangitis, then an immediate endoscopic drainage of the obstruction should be carried out. There are no published studies comparing endoscopic therapy of cholangitis secondary to mechanical cholestasis to observation without therapy.

Treatment of mechanical cholestasis as part of the therapy for cholangitis is important and well substantiated by clinical experience. If chronic pancreatitis causes distal obstruction of the bile duct with cholestasis or jaundice, then either surgical treatment or endoscopic stent therapy should be performed, the later is illustrated in **Figure 1**). If calcifications are present in the pancreas, then surgical treatment should be favored [Evidence 4]. Cholestasis due to obstruction may be treated by either endoscopic or surgical means, although endoscopic stent therapy has lasting success beyond 12 months in only one third of patients. A prospective study showed an even worse long-term effect of stent management of distal bile duct obstruction in patients with calcifying pancreatitis (long-term effect 9%) (49, 50). In these cases, therefore, surgical treatment is clearly preferred. A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for obstruction of the CBD in patients with chronic pancreatitis has no additional effect beyond one year (24). Surgical treatment should therefore be pursued for recurrence of CBD obstruction after one year of stent therapy.

Treatment by insertion of several plastic stents for distal bile duct obstruction can be recommended [Evidence 3b]. The placement of multiple plastic stents into the bile duct to treat bile duct obstruction in patients with chronic pancreatitis is superior to both insertion of solitary plastic stents and that of uncovered metal stents. In a prospective, non-randomized single centre study the long-term success rate after insertion of 4 – 5 stents into the CBD was higher than after one single stent (26). The insertion of FCSEMS can be undertaken for distal bile duct obstruction [Evidence 4]. The insertion of covered metal stents has demonstrated good results in case series. A recent non-randomized study at 13 centers in 11 countries treated 187 patients with benign biliary strictures by fully covered self-expandable metal stents (FCSEMS). Removal was scheduled at 10-12 months. The rate of stricture recurrence was 14.8% (95% CI, 8.2%-20.9%). In a large prospective multinational study, removal success of FCSEMS after extended indwell and stricture resolution were achieved for approximately 75% of patients. While FCSEMS might be an attractive option to treat CBD stenosis in patients less fit for surgery, what remains unsolved is the role of calcifications on the long term treatment effect as well as a randomized head to head comparison between plastic stents versus FCSEMS in benign strictures (32, 70-72).

There are no randomized studies comparing FCSEMS with single or multiple plastic stents (12, 47, 90). Endoscopic treatment for distal common bile duct obstruction should not be pursued longer than 12 months. Stent exchange should be undertaken every three months at the latest [Evidence 4]. Stent exchange should be undertaken at least every three months because otherwise occlusion of the stent may cause cholangitis. The exchange interval is less critical with the insertion of multiple stents and is unnecessary if fully coated metal stents are used. Those are patent for up to 9 months (57).

Management of chronic bile duct obstruction after unsuccessful attempts of endoscopic treatment should be surgical [Evidence 1b]. Resecting surgical procedures to treat bile duct obstruction in patients with chronic pancreatitis are effective and of lasting success. The long-term results of the various surgical procedures such as “Beger”, “Büchler”, “Kausch-Whipple”, and “Frey” do not differ from each other with regard to quality of life, exocrine pancreatic insufficiency, endocrine pancreatic insufficiency, pain and recurrence rate (62, 63, 74, 91). If there is an indication to treat cholestasis by surgery, a preoperative endoscopic insertion of a stent into the bile duct should only be undertaken if 1) surgery cannot be done promptly or 2) cholangitis is present [Evidence 2a]. A multicentre prospective randomized study examined the effect of

preoperative endoscopic stent insertion into the CBD for mechanical cholestasis secondary to carcinoma of the head of the pancreas before pancreas resection. Preoperative drainage significantly increased the rate of complications (91). A short individual life expectancy of a patient, a high comorbidity, and a difficult, foreseeable technical feasibility of an operation (e.g. marked collateral circulation secondary to portal hypertension), all favor an endoscopic treatment of bile duct obstruction.

6. Summary

In a patient cohort burdened with a high co-morbidity, endoscopic therapy can provide short term relief of symptoms. In many instances the benefit of endoscopy therapy is transient and repeated interventions are necessary. Endotherapy is the first line of management in chronic pancreatitis with symptomatic pancreatobiliary ductal obstruction. Further studies are required in certain key areas such as use of fully covered self-expanding metallic stents for pancreatic ductal and biliary strictures and endoscopic ultrasonography guided pancreatobiliary drainage after failed endoscopic retrograde cholangiopancreatography. However, as endoscopic therapy puts the patient at minimal risk for long term morbidity or mortality and it plays a major role in an interdisciplinary treatment concept.

7. Funding

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