Pancreas

Digestive Diseases

Dig Dis 2013;31:43–50
DOI: 10.1159/000345720

Conservative Treatment of Chronic Pancreatitis

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Key Words
Chronic pancreatitis · Endoscopic therapy · Enzyme therapy · Guidelines · Cochrane reviews

Abstract
Background: Chronic pancreatitis is a progressive inflammatory disease giving rise to several complications that need to be treated accordingly. Because pancreatic surgery has significant morbidity and mortality, less invasive therapy seems to be an attractive option. ***Aim:*** This paper reviews current state-of-the-art strategies to treat chronic pancreatitis without surgery and the current guidelines for the medical therapy of chronic pancreatitis. ***Results:*** Endoscopic therapy of complications of chronic pancreatitis such as pain, main pancreatic duct strictures and stones as well as pseudocysts is technically feasible and safe. The long-term outcome, however, is inferior to definitive surgical procedures such as resection or drainage. On the other hand, the medical therapy of pancreatic endocrine and exocrine insufficiency is well established and evidence based. ***Conclusions:*** Endoscopic therapy may be an option to bridge for surgery and in children/young adolescents and those unfit for surgery. Pain in chronic pancreatitis as well as treatment of pancreatic exocrine insufficiency follows established guidelines.

Background

Chronic pancreatitis is a long-standing disease leading to impairment of both the endocrine and the exocrine pancreas. During the course of the disease, several symptoms and complications may develop requiring therapeutic actions (fig. 1). Modern state-of-the art pancreatic surgery in conjunction with the best intensive care still has a significant morbidity and mortality rate even in large referral centers, ranging between 5 and 14% and 1 and 2%, respectively [1–3]. Chronic pancreatitis is characterized by a deteriorating functional capacity of the pancreas, coinciding with a loss of endocrine and exocrine function. Consequently, nonsurgical procedures appear to be very attractive. Nonsurgical organ-preserving therapy is characterized by the medical treatment of pain and endocrine (diabetes mellitus) and exocrine insufficiency (PEI) as

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0257–2753/13/0311–0043$38.00/0

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well as addressing some of the symptoms and problems associated with interventional endoscopy.

This paper provides an overview of the range of current endoscopic therapies in chronic pancreatitis and their outcomes, also taking into account a recent Cochrane review [4]. Regarding medical therapy, it is not intended to provide an extensive review on chronic pancreatitis, but rather highlights the consensus of recent guidelines from Australia, Germany and Italy, including recent Cochrane reviews [5–8].

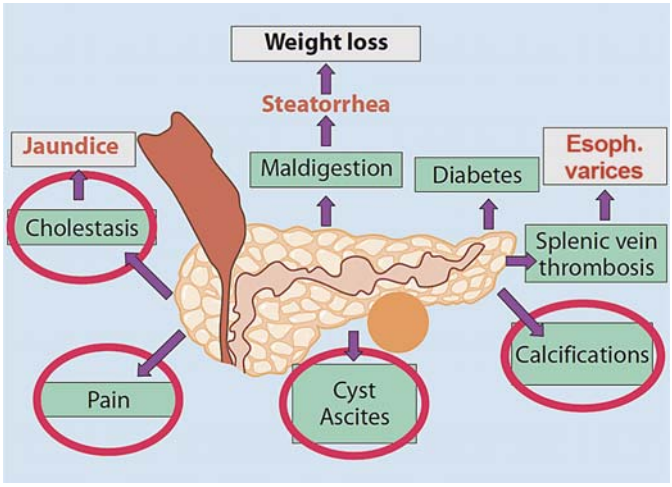

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Fig. 1. Symptoms and complications in chronic pancreatitis. Those in circles can be treated endoscopically. Adapted from [18].

Endoscopic Therapy of Complications in Chronic Pancreatitis

Endoscopic therapy represents the mainstay to treat four major symptoms in patients with chronic pancreatitis: obstructive jaundice (cholestasis), pain, pancreatic cysts and pancreatic duct stenosis/calcifications (stones; fig. 1).

Obstructive Jaundice

A common bile duct stricture occurs in 3–10% of all patients with chronic pancreatitis. Often an inflammatory pancreatic head tumor is the underlying reason. It can be treated successfully with endoscopic placement of a plastic stent via ERCP with previous endoscopic sphincterotomy (evidence 2b, recommendation B). However, these plastic stents are prone to occlusion. If the common bile duct stricture is occurring as a consequence of an acute inflammatory episode of chronic pancreatitis, it may resolve under appropriate therapy encompassing alcohol abstinence and pain medication (NSAID), having not only an analgetic but moreover an anti-inflammatory effect. However, a large inflammatory pancreatic head tumor usually persists. Therefore, insertion of self-expanding metal stents may be an option. Their occlusion rates are significantly lower – between 10 and 62% during a 5-year observation period compared to 100% of plastic stents over time [9]. In addition, self-expanding metal stents do not require regular exchange. This approach may represent an alternative for patients unfit for surgery (fig. 2).

Pancreatic Duct Stenosis and Calcifications

It is tempting to consider a main pancreatic duct stenosis as a target for endoscopic therapy, particularly if this stenosis is prominent and located in the pancreatic head. An endoscopic approach might be even more favorable in the presence of stones in the main pancreatic duct (fig. 3). The technical feasibility of these interventions has been demonstrated for a long time [10]. The technical success rate and the initial pain relief is high [9]. In addition, the procedure is very safe. However, there are only very few large and/or prospective studies which have systematically investigated this topic which is reflected by a low evidence level (grade 4) and low level of recommendation (grade D).

The largest study represents a collection of more than 1,000 cases demonstrating that endoscopic ductal decompression therapy offers pain relief in two thirds of all patients when it is used as the only form of treatment. However, one quarter of the patients eventually have to undergo surgery [11].

In treating chronic pancreatitis patients with pain, extracorporeal shock wave lithotripsy in conjunction with endoscopy resulted in additional costs without improving outcome [12]. Extracorporeal shock wave lithotripsy can be applied with or without ERCP with no difference regarding pain control [12].

In two prospective randomized clinical trials comparing endoscopic versus surgical therapy for the treatment of pain, the long-term outcome was markedly in favor of the surgical procedure (32 vs. 75%, p = 0.007) [13, 14]. In addition, surgery is more cost-effective [15].

Pancreatic Cysts

Pancreatic pseudocysts that cause complications should be treated (evidence 2a, recommendation B), which can be done initially with interventional endos-

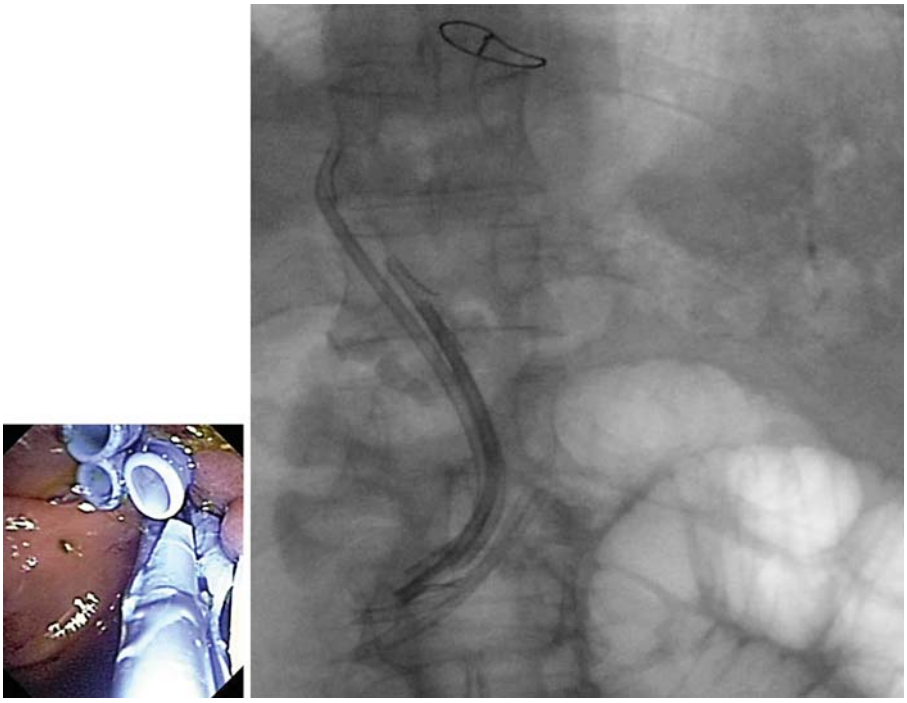

Fig. 2. Stenting of both the common bile duct stenosis and the main pancreatic duct in a patient with chronic pancreatitis unfit for surgery (see wiring from coronary artery bypass graft).

copy (evidence 3a, recommendation C; fig. 4). Pseudocysts need to be seen in the context of other complications of chronic pancreatitis, namely main pancreatic duct stenosis that could make ERCP with sphincterotomy necessary. Drainage can be done transpapillarily, especially if a connection between the main pancreatic duct and the cyst can be demonstrated. Otherwise, the endoscopic ultrasound-guided drainage is the method of choice. Applying modern therapeutic endoscopic ultrasound devices, this can be done as a single instrument/single-step procedure with fistulotome puncture, dilatation and insertion of (two) double pigtails during one session.

Pancreatic Fistulas

Treatment of pancreatic fistulas can be done via endoscopic transpapillary stenting with a good success rate (fistula control of 71% on average) [16]. However, this is a rare complication mostly seen in acute pancreatitis and seldom in chronic pancreatitis (fig. 5).

In conclusion, when considering interventional therapy for a patient with chronic pancreatitis, an individually tailored and multidisciplinary therapeutic approach should be chosen [9, 17]. Endoscopic interventions should be considered particularly in those patients unfit for surgery. Furthermore, young patients with hereditary

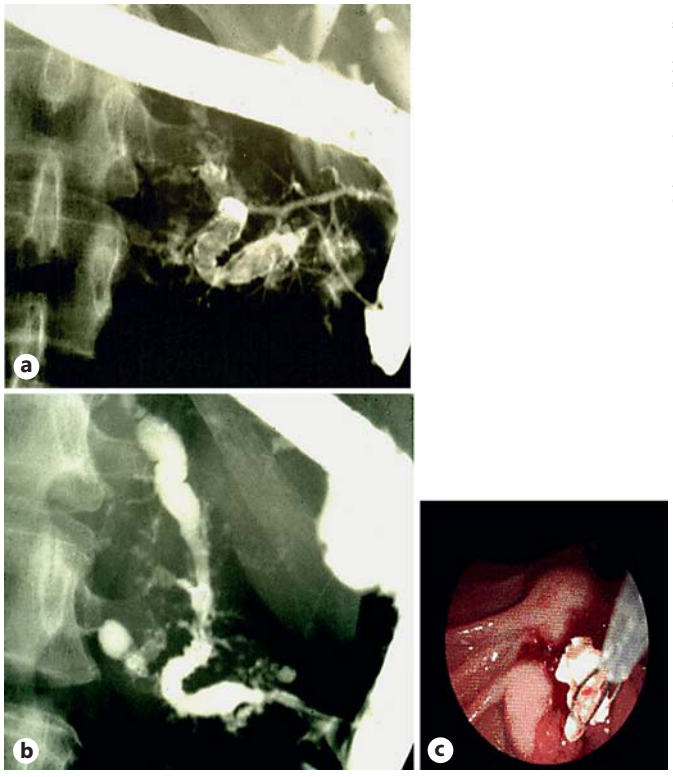

Fig. 3. Juvenile patient with hereditary pancreatitis, pancreatolithiasis. Pancreatogram before (**a**) and after (**b**) extraction of a typical stone from the main pancreatic duct with a basket (**c**).

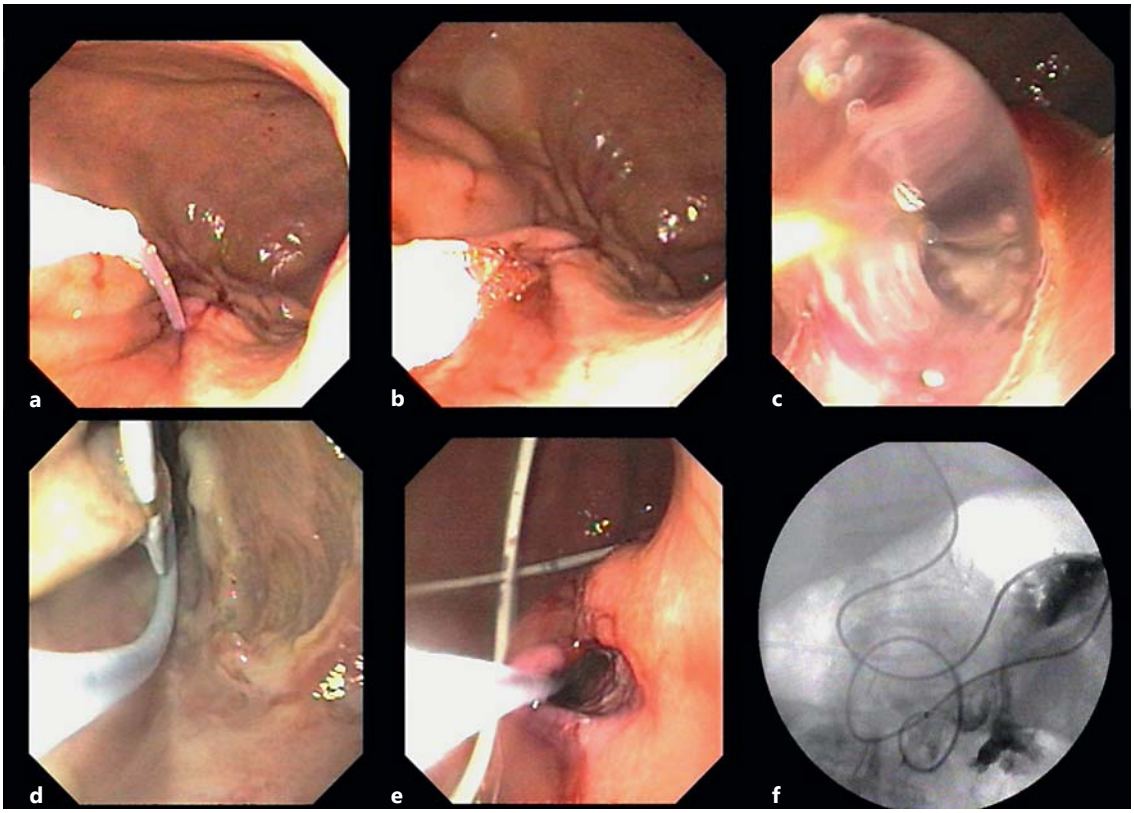

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Fig. 4. Pancreatic pseudocyst drainage. Puncture (**a**), insertion of a balloon dilatation catheter (**b**), inflated dilatation balloon catheter (**c**), view into the pseudocyst already without content (**d**), placement of a nasocystic drainage (**e**) and final fluoroscopic picture (**f**).

pancreatitis represent another group of patients who may profit from nonsurgical approaches during an extended period of time. Invariably, those patients should be discussed in a multidisciplinary conference encompassing surgical, gastroenterological, endoscopic and pain experts [18]. A recent Cochrane review [4] demonstrated that surgical intervention in the early course of the disease may be most beneficial. Of note, presumably due to the small number of prospective trials, there is no significant difference in morbidity and mortality between endoscopy and surgery [4].

Medical Therapy of Chronic Pancreatitis

Medical therapy has to address pain as well as functional and nutritional deficits. Furthermore, there are general measures that need to be taken, e.g. a change in lifestyle.

General Measurements

With regard to the most prominent known factor in chronic pancreatitis, alcohol should be avoided (evidence 2b, recommendation A) and this can reduce the pain in chronic pancreatitis (evidence 2b, recommendation B). There is no evidence and hence no recommendation for smoking cessation in chronic pancreatitis and pancreatic exocrine insufficiency (PEI) despite some reports [8, 19], even in acute pancreatitis [5–8, 20]. Smoking cessation is recommended (evidence 3b, recommendation A). Smoking withdrawal is moderately effective in reducing pain relapses in chronic pancreatitis (evidence 4, recommendation C).

Therapy of Pancreatic Pain

Patients with chronic pancreatitis suffer from severe visceral pain. Therefore, adequate pain therapy is mandatory (evidence 2b, recommendation A). The pain therapy follows the established WHO scheme with NSAID as an initial therapy, ultimately stepping up to opioids. Avoid-

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ing morphine, even during an acute attack, is obsolete in the presence of severe pain (evidence 2b). Continuous pain should be considered as an indication for interventional or surgical therapy (evidence 2b/2c).

Pancreatic Exocrine Insufficiency

As a definition, PEI is described as inadequate pancreatic enzyme activity, either due to insufficient enzyme production, insufficient enzyme activation or early enzyme degradation [21]. There is primary PEI due to a lack of exocrine pancreatic tissue or altered innervation. In secondary PEI, pancreatic enzymes are released but cannot work appropriately due to anatomical changes after surgery, inappropriate activation or inactivation.

Before treatment, the underlying cause of PEI should be established. Pancreatic function tests may be used to diagnose chronic pancreatitis (evidence 1c, recommendation B) [22]. Symptoms of PEI can be anticipated after 10 years of disease duration [evidence 1b, recommendation GCP (good clinical practice, i.e. expert consensus)].

A typical symptom of advanced PEI is steatorrhea, which is not present in all cases of advanced chronic pancreatitis and is furthermore not specific for chronic pancreatitis. Finally, no symptom definitively proves or excludes PEI (evidence 1b). Control intervals to meet patients should be between 6 and 12 months in order to pick up complications (deterioration of PEI, pain, diabetes or cancer; evidence 5, recommendation D). For instance, patients with diabetes mellitus have an increased risk to develop PEI (evidence 2B) because of atrophy of the exocrine acinar tissue [23].

Before treating a patient with PEI, the diagnosis should be established, e.g. via fecal elastase-1 or a breath test (evidence 2b, recommendation B). The secretin-pancreozymin test is still considered the gold standard (evidence 1, recommendation A), but is no longer in routine clinical use. There is also a recommendation to test the endocrine function before starting the therapy, e.g. with fasting blood glucose (evidence 4, recommendation C), as many patients with chronic pancreatitis may already have impaired glucose tolerance but no overt diabetes mellitus. This is called type 3c diabetes mellitus [7, 24]. A patient's compliance regarding diet and intake of medication should be assumed (recommendation A). According to some guidelines, a dietician should be involved (GCP/recommendation D).

There is no doubt that pancreatic enzyme replacement therapy (PERT) is indicated in patients with chronic pancreatitis and PEI (evidence 1a, recommendation A). Beside the clinical improvement, there is also some evidence

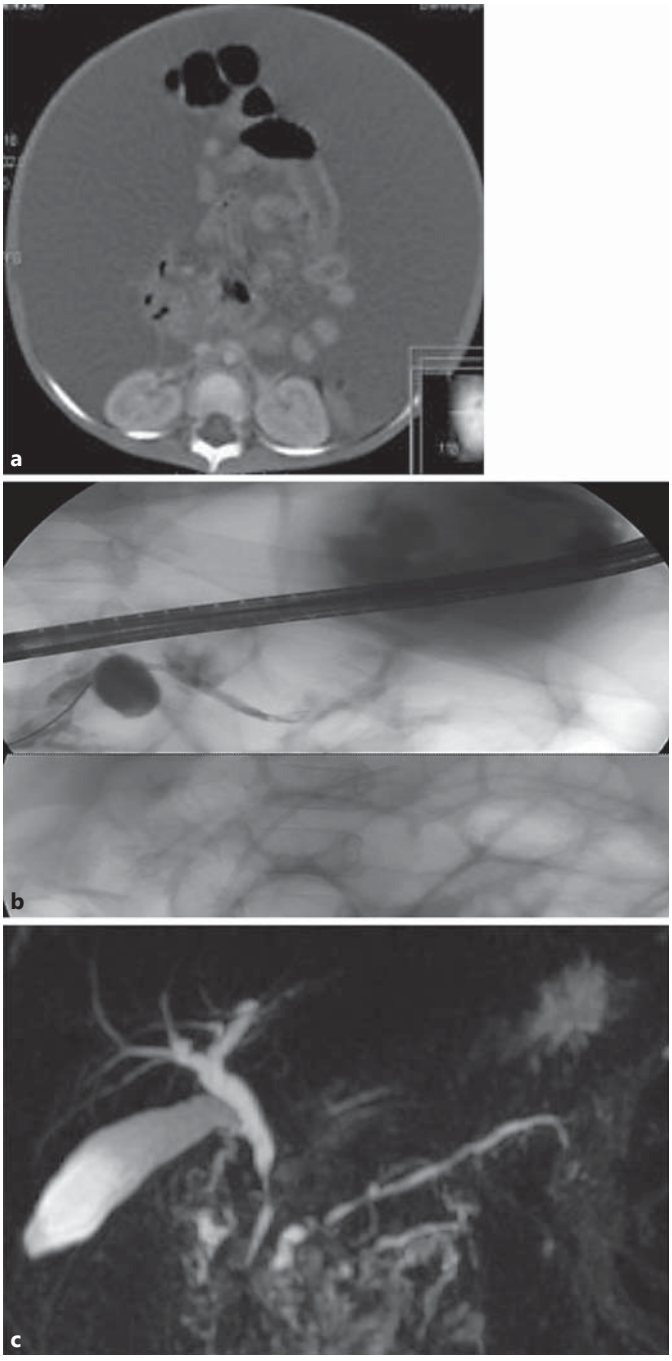

Fig. 5. a Pancreatic ascites after spontaneous main pancreatic duct rupture in a child with hereditary pancreatitis. **b** ERCP demonstrating the leakage and placement of a long plastic stent bridging the rupture. **c** Final MRCP after 5 years with seven ERCPs in total.

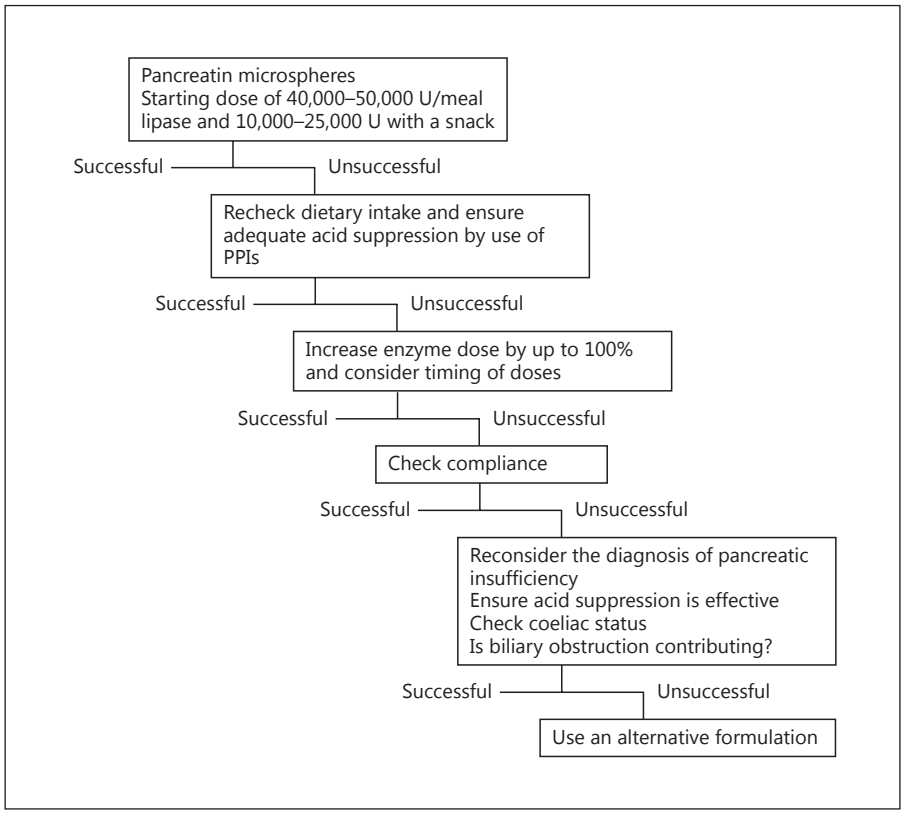

Fig. 6. Algorithm summarizing the rationale on how to conduct PERT in patients with PEI. PPIs = Proton pump inhibitors. Adapted from [27].

that PERT improves the quality of life (evidence 4, recommendation D).

There is some evidence and therefore a recommendation that small meals are often better tolerated (recommendation D). If PERT is conducted properly, no fat restrictions are necessary (recommendation D). Patients should take pancreatin along with a normal diet instead of changing their diet. If deficits in vitamins and trace elements are recorded, they should be substituted accordingly (evidence 1c, recommendation A/B). Antioxidants can be helpful in pain management in chronic pancreatitis (evidence 1b, recommendation C).

Pancreatin for PERT should contain sufficient lipase units (recommendation A), with 20,000–40,000 units as a starting dose for a meal and 10,000–20,000 lipase units for a snack (evidence 1b, recommendation B). In contrast to the consensus of all these guidelines, recent evidence suggests that this may not be sufficient: when probing with the ^{13}C breath test, this dose may not be sufficient to normalize maldigestion [21, 25]. Therefore, we might consider higher doses when initiating PERT [26, 27] (fig. 6). The only side effect of PERT is constipation; nevertheless, one of the guidelines presents an upper dose limit of 80,000 units/day (evidence 2b), but without a recommendation. Pancreatin should be given with every meal (recommendation A) and enzymes should be administered during the meal (evidence 1b, recommendation A).

In case of insufficient response to PERT, the pancreatin dose should be doubled or tripled (evidence 5, recommendation B) and/or a proton pump inhibitor should be administered (evidence 1b, recommendation B; fig. 6). Depending on prior surgical interventions [e.g. (partial) gastrectomy, Roux-en-Y], pancreatin can be given as a granulate.

There is no indication whatsoever to use PERT for treatment of pain in chronic pancreatitis (evidence 1a, recommendation A) [8, 28].

Although a transient PEI may be present in acute pancreatitis due to various reasons, patients with acute pancreatitis should not be treated with enzymes (evidence 1a, recommendation A). As an episode of acute pancreatitis sometimes represents the first manifestation of a hitherto undiagnosed chronic pancreatitis, patients should be reassessed and followed up between 6 and 18 months in order to detect PEI (evidence 2b).

Patients with chronic pancreatitis and diabetes mellitus have a pronounced acinar atrophy [23], hence an increased risk to develop PEI (evidence 2B), as evident from reduced fecal elastase-1 both in type 1 and type 2 diabetes mellitus [29]. These patients should also be treated (GCP).

Monitoring Treatment Success

The success of PERT and/or compliance can be monitored by several ways. In the normal clinical setting, the clinical improvement of the patient is a sufficient criterion to assess response (evidence 2a, recommendation B). There is good evidence that both the fecal fat excretion (CFA) and the ^{13}C MCT breath test are reliable instruments to evaluate success and compliance (evidence 1b/2b). The ^{13}C MCT breath test is even recommended in nonresponders (evidence 2b, recommendation B).

Conclusions

There is a good consensus among all guidelines on how to treat patients with PEI, as demonstrated here, especially on the starting dose and how to proceed in case of insufficient response to therapy (fig. 6). Recent evidence suggests that the starting dose may be too low if only clinical symptoms are taken as a surrogate marker of successful treatment. Following this concept, treatment of malnutrition represents the main focus, in contrast to the mere correction of symptoms associated with PEI.

Acknowledgements

This work is dedicated to Åke Andrén-Sandberg on the occasion of his 65th birthday.

Disclosure Statement

J.-M.L., F.L., R.S. and U.A. have received honoraria from Abbott; U.A. has received support from Boston Scientific.

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