Pancreatology 13 (2013) 18–28

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: Part 2 (treatment)

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ARTICLE INFO

Article history:
Received 12 July 2012
Received in revised form
11 November 2012
Accepted 20 November 2012

Keywords:
Pancreatitis, Chronic
Therapy
Diagnosis
Exocrine pancreatic insufficiency
Guidelines

ABSTRACT

Chronic pancreatitis (CP) is a complex disease with a wide range of clinical manifestations. This range comprises from asymptomatic patients to patients with disabling symptoms or complications. The management of CP is frequently different between geographic areas and even medical centers. This is due to the paucity of high quality studies and clinical practice guidelines regarding its diagnosis and treatment. The aim of the *Spanish Pancreatic Club* was to give current evidence-based recommendations for the management of CP. Two coordinators chose a multidisciplinary panel of 24 experts on this disease. These experts were selected according to clinical and research experience in CP. A list of questions was made and two experts reviewed each question. A draft was later produced and discussed with the entire panel of experts in a face-to-face meeting. The level of evidence was based on the ratings given by the Oxford Centre for Evidence-Based Medicine. In the second part of the consensus, recommendations were given regarding the management of pain, pseudocysts, duodenal and biliary stenosis, pancreatic fistula and ascites, left portal hypertension, diabetes mellitus, exocrine pancreatic insufficiency, and nutritional support in CP.

1. Introduction

The objective, justification and methodology of this consensus are explained in the first part of the consensus: "Spanish Pancreatic Club recommendations for the diagnosis and treatment of chronic pancreatitis: part 1 (diagnosis)". Briefly, two coordinators chose a multidisciplinary panel of 24 experts on this disease. These experts

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1424-3903/$ – see front matter
http://dx.doi.org/10.1016/j.pan.2012.11.310

were selected according to clinical and research experience in Chronic Pancreatitis (CP). A list of questions was made, and two experts reviewed each question. A draft was later produced and discussed with the entire panel of experts and in a face-to-face meeting. The degree of scientific evidence was based on the ratings given by the Oxford Centre for Evidence-Based Medicine [1].

2. Which is the optimal pharmacological treatment for pain in chronic pancreatitis?

Before addressing the treatment of CP-related pain, one must rule out other possible coexisting causes, such as the presence of pseudocysts, gastric or pancreatic neoplasms, peptic ulcer disease or biliary lithiasis. It is also desirable to eliminate the cause of CP, such as alcohol or tobacco use and ductal obstruction or to provide treatment for autoimmune pancreatitis. There are few high-quality studies on the treatment of CP-related pain. Pain-relieving drugs should be administered at effective doses and appropriate intervals with monitoring of renal, respiratory and liver function. Drug treatment should consider the nature of pain (continuous or episodic) and the treatment setting (inpatient or outpatient). Clinicians should promote adequate therapeutic compliance. The WHO method for pain relief may provide a basis for the medical management of pain in CP [2].

The first proposed step in the pharmacological treatment of pain is paracetamol (which has a notably safe profile) for acute or chronic pain and nonsteroidal anti-inflammatory drugs (NSAIDS), including metamizol for acute pain. Paracetamol seems to be safe in patients with chronic excessive alcohol intake [3–5]. Metamizol is not available in many countries due to safety concerns, however the real incidence of agranulocytosis seems to be very low [6-8]. In chronic pain NSAIDS and metamizol should be avoided due to undesirable long-term side effects. Pregabalin has been shown to decrease pain moderately in CP [9]. Pregabalin may be administered in chronic pain in combination with paracetamol.

If the above mentioned treatments do not control pain, the second recommended step is tramadol. This drug is effective in controlling CP-related pain and has fewer adverse effects than strong opioids, especially in terms of intestinal motility [10]. If pregabalin was not previously administered, it may be given in combination with tramadol.

The third step would be to use strong opioids, preferably in controlled-release formulations to avoid plasma peaks and reach the central nervous system slowly (thus preventing the euphoric effect) [11]. The dose should be adjusted according to the pain of the patient. In a clinical trial comparing transdermal fentanyl and oral morphine in a controlled-release preparation, the fentanyl group required a higher dose of immediate-release rescue morphine and had a higher incidence of local skin reactions [12]. Invasive treatment should be considered if treatment with strong opioids will extend longer than three months, in cases of adverse effects or lack of a real benefit. It should be considered in patients with moderate-to-severe pain to start directly in the second or third step respectively.

Some patients may benefit from an earlier invasive treatment, for example in obstructive chronic pancreatitis.

The use of pancreatic enzymes in CP pain remains controversial. Available studies have methodological and design flaws [13], and the results were heterogeneous. Some studies did not find a significant relief of pain [14–16], but others did [17–19]. Most of the studies with positive results used uncoated pancreatic enzymes [17,18], that are not available in many countries. Pancreatic enzyme use has not shown a clear effect on pain control in recent systematic reviews [13,20]. However, given the low toxicity profile of pancreatic enzymes and the above mentioned methodological flaws of published studies, a therapeutic trial may be attempted [13]. In such a case we recommend a 2-month trial. Antioxidants have shown a long-term mild pain reduction in two placebo-controlled double blind trials [21,22]. In the study with a better design and higher patient recruitment, a cocktail of antioxidants consisting on daily doses of organic selenium, ascorbic acid, beta-carotene, alpha-tocopherol and methionine was used [22]. The recommended steps for the medical treatment of pain are summarized in Fig. 1.

2.1. Recommendation

When a patient presents with CP-related pain, the clinician should attempt to eliminate the etiology of the disease and rule out complications and other diseases. Analgesic treatment with paracetamol (for acute or chronic pain) or NSAIDs/metamizol (for acute pain) is recommended (Level of evidence: 5. Recommendation grade: D). Combination treatment with pregabalin is an option (Level of evidence: 1b. Recommendation grade: A).

As a second step, tramadol is recommended (with or without pregabalin) (Level of evidence: 5. Recommendation grade: D). In cases of persistent pain, a short course of strong opioids may be attempted (Level of evidence: 2b. Recommendation grade: B). It is advisable to reconsider the use of strong opioids if the treatment extends beyond three months, in case of adverse effects or a lack of real benefit (Level of evidence: 5. Recommendation grade: D).

Antioxidants have shown a long-term mild pain reduction (Level of evidence: 1b. Recommendation grade: A).

The effectiveness of treatment with pancreatic enzymes has not been conclusively demonstrated (Level of evidence: 1a;

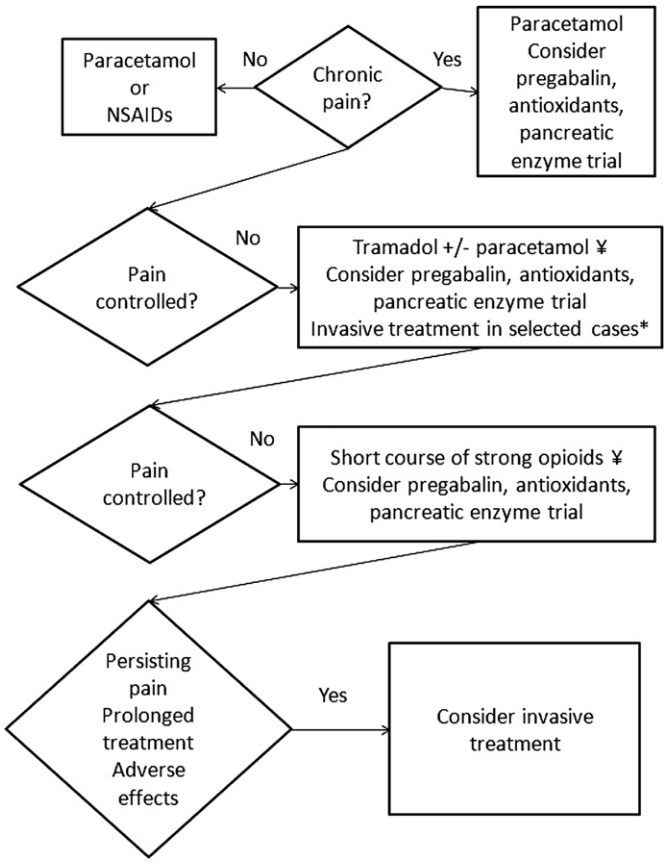

Fig. 1. Proposed steps for medical pain management in Chronic Pancreatitis. NSAIDs: nonsteroidal anti-inflammatory drugs. * Some patients may benefit an early invasive treatment, for example in obstructive chronic pancreatitis. ¥ Consider in patients with moderate-to-severe pain to start in the second or third step respectively.

Recommendation grade: A). Certain patients may benefit from a two-month trial period (Level of evidence: 5. Recommendation grade: D).

3. What kind of endoscopic treatment is available for CP-related pain? What is the role of extracorporeal shock wave lithotripsy in the treatment of patients with CP?

Invasive pain treatment for patients with CP is indicated when medical treatment fails or when it is necessary to resort to long-term opioid administration. Endoscopic decompression treatment (EDT) is an option for treating pain in patients with dilated main pancreatic duct (increased ductal pressure) and in patients with an obstructive stones or stenosis of the ductal system [23,24]. When recommending EDT for pain, the clinician must take into account a number of limitations: 1) Randomized clinical trials comparing EDT and surgical pain treatment in CP have shown better results for surgery [25,26]. Neither endoscopic nor surgical therapy have been tested in a randomized fashion against medical therapy; 2) it is difficult to determine the effectiveness of EDT for pain control in long-term studies without a control group, given the tendency of its effects to disappear over time [27]; 3) EDT for CP is technically difficult and therefore operator-dependent.

EDT using endoscopic retrograde cholangiopancreatography (ERCP) consists of the dilatation and placement of a stent across the stenosis and the extraction of calculi in the main pancreatic duct. With this approach, 70–94% of patients experience pain relief in the short-term, and 52–82% of patients experience pain relief in the long-term [28–33]. Calculi alone, stenosis alone or a combination of both can cause pancreatic duct obstruction; EDT provides similar results in patients with all three types of obstruction [29]. EDT appears to decrease the number of pain-related hospitalizations and the need for analgesic treatment [34,35]. However, EDT does not appear to modify patients' quality of life [26,36,37]. Dilation of the pancreatic duct stenosis is not a useful treatment unless it is accompanied by the placement of one or more stents to maintain the opening. In addition, stents should be kept in place for a long time (one to two years) and require replacement in cases of obstruction and recurring symptoms [38]. Multiple stents may improve the outcome of EDT [39]. One-third of patients experience a recurrence of pain after the stent is removed [28,30,31]; such pain often improves when a new stent is placed.

Extracorporeal shock wave lithotripsy (ESWL) was proven useful for treating CP-related pain in meta-analysis of various case series [40] and in a randomized study that compared ESWL alone with ESWL combined with endoscopy [41]. In that clinical trial, there was no evidence that the combination of endoscopy and ESWL was better than ESWL alone for the prevention of pain.

EUS-guided blocking/neurolysis of the celiac plexus through the use of corticosteroids and/or alcohol is one option for pain relief and life-quality improvement for patients with CP, and it can be used in patients with nondilated main pancreatic duct [42]. EUS-guided neurolysis appears to be associated with better outcomes and is more cost-effective than neurolysis under CT guidance, and it has a low incidence of side effects [43,44]. However, the efficacy of this therapy remains unclear. No randomized trials compared the usefulness of EUS-guided celiac plexus blocking/neurolysis with placebo in patients with CP, and few studies of the procedure included long-term follow-up results [45]. In general, 55–70% of patients experienced short-term pain relief [44–49], and less than 10% experienced pain relief that was long-lasting (more than 24 weeks) [44].

3.1. Recommendation

Endoscopic decompression treatment is less effective and has shorter-term effects compared with surgery (Level of evidence: 1b. Recommendation grade: B).

Endoscopic pain treatment for patients with CP has been shown to be effective for patients with a dilated main pancreatic duct, particularly when various endoscopic techniques are combined (Level of evidence: 3b. Recommendation grade: B).

Pancreatic stent placement is effective for treating short-term pain in patients with pancreatic duct stenosis, but it requires multiple ERCPs during follow-up (Level of evidence: 4. Recommendation grade: C). Pancreatic stents must be maintained for at least 12 months (Level of evidence: 3b. Recommendation grade: B).

Extracorporeal shock wave lithotripsy is effective for removing intraductal calculi and provides pain relief (Level of evidence: 2a. Recommendation grade: B).

EUS-guided celiac plexus block may be an option for CP-related pain treatment in some patients who do not respond to other treatment options (Level of evidence: 4. Recommendation grade: C).

4. Which are the surgical treatments for pain?

Surgery in patients with CP is indicated in three scenarios: disabling pain, when pancreatic cancer is suspected and in certain CP complications.

There is no validated threshold for indicating surgery for pain control [50]. Currently there is not any available randomized controlled trial comparing surgery with conservative treatment or different timing for surgery. As stated previously we recommend considering invasive treatment in patients with pain under treatment with strong opioids that will extend longer than three months, in cases of adverse effects or lack of a real benefit.

Briefly, the current pain surgery options are classified into three categories: decompression (focusing on ductal hypertension [51]), resection (focusing on inflammatory masses [52–54] and pancreatic head as a pain pacemaker [55,56]) and mixed techniques.

1. Decompression techniques. Decompression techniques should be applied in patients with dilated main pancreatic duct (>7–8 mm) [57] and an absence of inflammatory mass. The most commonly performed decompression technique is the one advocated by Partington and Rochelle in 1966 [58]. This technique achieves pain relief in 66–91% of patients, with a low morbidity and mortality (20% and 2%, respectively) [26,59–61]. However, the long-term results show that up to 50% of patients experience a recurrence of pain, and the painful manifestations persist in 15–30% of patients [61–63]. A prospective randomized trial compared the longitudinal pancreaticojejunostomy technique with endoscopic transampullary drainage [26]. At the end of the study (at 24 months), full or partial relief was achieved in 32% of patients with endoscopic drainage and in 75% of patients with surgical drainage.
2. Resection techniques are indicated in patients with inflammatory mass in the pancreatic head, particularly if pancreatic cancer is suspected. Distal pancreatic resection is indicated in case of inflammatory mass or post-obstructive CP affecting the pancreatic body or tail [64]. Several authors consider the pancreatic head as the trigger point for pancreatic pain in CP [55,56]; therefore, they advocate performing resections. In the three major surgical series, pancreaticoduodenectomy demonstrated pain relief at 4 and 6 years in 71% and 89% of patients, respectively [65–67]. Randomized controlled trials have shown short term pain relief in 70–100% of patient (Table 1) and long-term pain relief in 70–87% (Table 2) [53,68–71]. However morbidity associated with pancreatoduodenectomy [68–70] has favored the more conservative mixed techniques (Tables 1 and 2).

Table 1
Randomized controlled trials comparing different surgical techniques for the treatment of pain in chronic pancreatitis: follow-up 1–4 years.

First author	Procedure	*N*	Surgical mortality (%)	Perioperative morbidity (%)	Fistulae (%)	Hospital stay (days)	Pain relief (%)	Diabetes (%)	Exocrine insufficiency (%)	Weight gain (Kg)
Klempa [68]	Beger	22	1	54	0	16	100	12	20	6.4
	PD	21	0	51	5	22	70	38	100	4.9
Buchler [53]	Beger	20	0	15	0	13	94	–	100	4.1
	PD	20	0	20	5	14	77	–	100	1.9
Izbicki [69]	Frey	31	3	19	3	–	80	0	58	6.7
	PD	30	0	53	7	–	75	10	83	1.9
Farkas [70]	Beger	20	0	0	–	8	100	0	–	7.8
	PD	20	0	40	–	14	100	15	–	3.2
Izbicki [73]	Beger	20	0	20	5	–	70	0	50	6.7
	Frey	22	0	9	0	–	70	0	50	6.4
Koninger [74]	Beger	32	0	20	7	15	–	–	–	–
	Frey	33	0	21	3	11	–	–	–	–

PD: Pancreaticoduodenectomy. Beger: Beger technique. Frey: Frey technique. N: number of patients.

3. Mixed techniques. There are also mixed resection and drainage techniques. The basis of these techniques is the removal of the inflammatory mass in the pancreatic head and the drainage of the obstructed pancreatic region (body and tail). Currently, two techniques are most widely used: 1) partial resection of the pancreatic head with the duodenal preservation technique or the Beger technique [56] and 2) coring of the pancreatic head associated with a longitudinal pancreaticojejunostomy technique or the Frey technique [72]. In randomized controlled trials, the mixed interventions have shown short term pain relief in 70–100% of patients (Table 1) and long-term pain relief in 82–100% (Table 2) [53,68–71,73,74].

It has been described a surgical procedure that may be useful in small duct disease without inflammatory mass: a longitudinal V-shaped excision of the ventral aspect of the pancreas combined with a longitudinal pancreaticojejunostomy [75].

Table 1 lists the randomized and controlled prospective studies that compare two or more interventions [53,68–70,73,74]. Table 2 includes randomized controlled trials with long-term follow-up [68,69,71].

4.1. Recommendation

Resection, decompression or mixed techniques achieve pain relief that is maintained over time in approximately 80% of patients (Level of evidence: 1a. Recommendation grade: A).

5. Which are the other interventional treatment options for chronic pancreatitis-related pain?

In general, patients with a dilated duct are candidates for endoscopic or surgical decompression, which have been addressed previously in this consensus. However, the interventional techniques that are indicated in patients without duct dilation are discussed in this section. Celiac plexus blockade has been discussed previously. These interventional techniques may also be used when decompression treatments fail. The evidence for its use is scant. Published studies lack a control group.

Bilateral thoracoscopic ablation of the greater splanchnic nerves was studied prospectively in patients with CP [76] showing a 28% long term pain relief. In a systematic review it was concluded that this technique relieves pain and is associated with a quality of life improvement [77]. It has been described percutaneous radiofrequency splanchnic ablation [78].

Intrathecal morphine therapy by continuous infusion pumps has been described in case series [79] with good analgesic results. In all cases, the procedures were performed on patients for whom other standard techniques had failed. A published case series reported that patients with CP and refractory pain achieved improvement after the implantation of a posterior cord stimulator [80].

Radiation therapy has been studied as a treatment for CP pain [81,82]. In the most recently published study, a single dose of 8 Gy was administered to patients with repeated bouts of acute exacerbation of CP or chronic pain and resulted in a complete absence of symptoms in 13 out of 15 patients [82].

5.1. Recommendation

The ablation of the splanchnic nerves may relieve CP-related pain (Level of evidence: 4. Recommendation grade: C).

6. Treatment options for pancreatic pseudocyst and its complications

A pancreatic pseudocyst is a collection of fluid with high concentration of amylase, surrounded by fibrous tissue. Most studies do not distinguish between pseudocysts in acute and chronic pancreatitis and include few patients, making decision-

Table 2
Long-term results (7–10 years) of randomized controlled trials comparing different surgical techniques for the treatment of pain in chronic pancreatitis.

First author	Procedure	*N*	Pain relief (%)	Late mortality (%)	Diabetes (%)	Exocrine insufficiency (%)
Klempa [68]	Beger	22	100	5	25	20
	PD	21	70	5	20	100
Izbicki [69]	Frey	31	90	3	29	58
	PD	30	87	0	37	83
Strate [71]	Frey	31	82	20	61	86
	PD	30	81	13	65	96

PD: Pancreaticoduodenectomy. Beger: Beger technique. Frey: Frey technique. N: number of patients.

making guidelines difficult. Most pseudocysts are small and asymptomatic [83]. Pseudocysts associated with CP are less likely to resolve spontaneously than are those associated with other disorders.

Thirty-nine per cent of pseudocysts in CP evolve to spontaneous resolution [84]. The duration and size of the pseudocyst do not accurately predict the probability of spontaneous resolution or the development of complications; however, larger (>4 cm) and/or longer-lasting (>6 weeks) pseudocysts are generally the ones that require active treatment [85].

Invasive procedures for the management of pseudocysts include percutaneous or endoscopic drainage and surgery. The indications for invasive treatment are: vascular compression, symptomatic gastric or duodenal compression, biliary stenosis, infection, bleeding, pancreaticopleural fistula and pancreatitis-panniculitis-polyarthritis syndrome; in other words, it depends on the existence of symptoms attributable to the pseudocyst. Pseudocysts may grow progressively; in such cases, invasive treatment may be necessary, even in an asymptomatic patient to avoid pseudocyst rupture.

Percutaneous drainage is rarely indicated, only in the presence of infection [86] when endoscopic and surgical options are not available. This treatment should be considered if the patient's clinical situation forces rapid drainage and the surgical risks are very high. Percutaneous drainage should be used cautiously as the presence of proximal obstruction will ensure a pancreatic fistula [87].

If communication exists, most pseudocysts can be drained endoscopically through the papilla by placing a stent in the main pancreatic duct or by transmural drainage. Drainage via EUS is highly effective and has a low incidence of side effects and mortality [88]. In multiloculated pseudocysts with necrotic debris, surgical drainage is usually preferable [89].

Surgery is indicated for large cysts, multiple cysts and those accompanied by stenosis, calculi or ductal disruption. The surgical techniques used to treat pseudocysts include creating a communication to the gastrointestinal tract (stomach, duodenum or jejunum) and resecting the pseudocyst (sometimes in combination with pancreatic resection). In some cases drainage of the main pancreatic duct may be necessary. Surgery is a highly effective technique [90]. The success rate, complications and recurrence rate of surgical treatment are similar to those of EUS drainage; however, EUS drainage offers a shorter hospital stay and lower cost [91].

The most dangerous complication of a pseudocyst is the rupture of a pseudoaneurysm of any of the peripancreatic arteries, which may be associated with massive internal bleeding and a high risk of death. Angio-embolization is the treatment of choice for pseudoaneurysms in CP. Surgery should be reserved as a second-line treatment when embolization does not resolve the bleeding [92–94]. Hemorrhagic relapse and morbidity are more common after surgery than after angio-embolization [95].

6.1. Recommendation

Spontaneous resolution of pseudocysts in chronic pancreatitis is rare (Level of evidence: 4. Recommendation grade: C).

Active treatment should be reserved for symptomatic or complicated pseudocysts (Level of evidence: 4. Recommendation grade: C).

Endoscopic internal drainage is preferable to surgical drainage (Level of evidence: 2c. Recommendation grade: B).

It is preferable to treat a ruptured pseudoaneurysm with angiographic techniques that take advantage of diagnostic angiography; surgery should be reserved for situations in which angiography has been ineffective (Level of evidence: 4. Recommendation grade: C).

7. How should CP-related biliary stenosis and duodenal stenosis be treated?

The incidence of biliary stenosis in patients with CP is variable; it may affect up to 60% of patients with a pancreatic head mass [96]. Jaundice often resolves spontaneously within the first month in 20–50% of cases, but spontaneous resolution is more unlikely the longer the jaundice persists [97–101]. Cholangitis occurs in 10% of cases [96].

The following have been proposed as indications of biliary drainage in CP: cholangitis episodes, a progressive increase of biliary stenosis with bile duct dilatation, associated choledocholithiasis, jaundice or elevated bilirubin for over a month and persistent signs of cholestasis, such as elevated alkaline phosphatase, for more than one month [102].

Treatment of biliary stenosis can be performed endoscopically or surgically. No adequate comparative studies have been performed. Because stent treatment carries a high rate of recurrence and cholangitis in the medium- to long-term, surgical bypass is still considered the technique of choice, and stent is preferred for inoperable patients [103,104]. This approach can be used as a bridge to stabilize the patient or as a definitive treatment attempt in cases in which high surgical risks do not permit surgery or when patients refuse surgery. In such cases, the best results are obtained with the placement of multiple stents or metal-covered stents [105,106]. Regarding the selection of a particular type of biliary bypass surgery, patients with pancreatic mass or pancreatic pain and main pancreatic duct dilation should undergo biliary bypass in combination with the corresponding intervention. In cases of biliary obstruction alone, a hepaticojejunostomy or choledochoduodenostomy should be performed.

Duodenal obstruction is somewhat less common than biliary obstruction. It affects 1.2% patients admitted for CP, 12% of those who require intervention and 36% of those with an inflammatory mass [96]. Duodenal obstruction may be caused by either a pancreatic head mass or paraduodenal pancreatitis [107]. When the obstruction is partial and isolated, conservative management with bowel rest and parenteral nutrition for two to three weeks is an option. If this method fails, surgical intervention in the form of a gastrojejunostomy is indicated. In cases where the duodenal obstruction is associated with a pancreatic mass, pancreatic pain or biliary stenosis, treatment of the duodenal obstruction should be combined with the corresponding surgical technique (resection or bypass).

7.1. Recommendation

Surgery is the treatment of choice for symptomatic biliary stenosis. Stents should be reserved for patients with high surgical risk to temporarily stabilize or improve them for surgery or for patients who refuse surgical treatment (Level of evidence: 4. Recommendation grade: C).

Duodenal obstruction should be managed surgically when the obstruction is complete or in partial cases that have not improved after two or three weeks of conservative treatment (Level of evidence: 4. Recommendation grade: C).

8. The diagnosis and treatment of CP-related fistulae and ascites

The communication between the pancreatic ductal system (often after the rupture of a pseudocyst) and the abdominal cavity produces pancreatic ascites, and communication with the pleural cavity produces pleural effusion. The pancreatic origin can be confirmed by elevated levels of amylase (>1000 U/L). In these cases, ERCP or magnetic resonance cholangiopancreatography (MRCP) are

useful imaging techniques that sometimes help to determine the source of the leak [108,109].

In these situations, management is primarily based on case series and retrospective studies, there are no randomized trials and the response to treatment has not been compared with a control group. We recommend a step-up approach [108,110,111]: A) Medical treatment with enteral or parenteral nutrition. Somatostatin or its analogs may be added to reduce the volume of pancreatic secretion, although their efficacy is unproven [112]; B) Endoscopic treatment of the ductal system disruption [109,110,112]; C) Surgical treatment [110,112–114]. Sometimes after percutaneous puncture or surgery, external fistulae may occur; when they do, they can be managed in the same way as internal fistulae [115]. It is possible that the prophylactic use of somatostatin analogs in surgically treated patients may reduce the incidence of this complication [116].

8.1. Recommendation

CP-related fistulae and ascites are diagnosed when high levels of amylase are observed in the associated fluid. We recommend conservative initial management with enteral or parenteral nutrition to which somatostatin or its analogs may be added. If there is no improvement, endoscopic treatment of the ductal system disruption and surgery are recommended (Level of Evidence: 4. Recommendation grade: C).

9. How to manage left portal hypertension caused by thrombosis or splenic vein stenosis

Left portal hypertension (LPH) is a syndrome of which the most serious clinical consequence is gastrointestinal bleeding caused by gastric varices. This syndrome is secondary to splenic vein obstruction [117] in most cases, being caused by thrombosis that develops during the progression of CP [118].

In most cases, the diagnosis of gastric varices can be made using conventional endoscopy. EUS can increase the diagnostic sensitivity [119]. Little is known about the natural history of patients with LPH. According to the most recent studies, the risk of variceal bleeding in patients with LPH is nearly 5% [120,121]; this leads us to believe that prophylactic splenectomy should not be performed in patients who have never bled [118,121,122], although there are no controlled studies to support this assertion. Given the potential severity of fundic variceal bleeding [123] and the approximately 20% incidence of gastrointestinal bleeding among patients with LPH and gastric varices [124], it seems reasonable to evaluate its presence in patients with LPH who will need surgical treatment for pancreatic disease and then proceed to splenectomy if varices are present [118,125,126]. It is not known which therapeutic approach is preferable for patients with LPH and varicose veins who do not require surgery for their pancreatic disease. The role of beta-blockers in this context is not clear. Acute bleeding caused by gastric varices can be temporarily controlled by plugging with a Linton's tube or with cyanoacrylate via endoscopy [127–129]. Once a patient with CP and LPH has had a variceal bleeding, a curative splenectomy should be performed [117,118,125,126,129].

9.1. Recommendation

Patients with left portal hypertension should undergo an endoscopic examination to determine whether gastro-esophageal varices have developed (Level of evidence: 5. Recommendation grade: D).

Prophylactic splenectomy should be performed in patients with left portal hypertension and gastro-esophageal varices who will undergo surgery for chronic pancreatitis (Level of evidence: 5. Recommendation grade: D).

Patients with left portal hypertension who have had variceal bleeding should be treated with splenectomy (Level of evidence: 2b. Recommendation grade: B).

10. Which treatment peculiarities are particular to diabetes mellitus secondary to chronic pancreatitis?

Diabetes mellitus related to CP (DM-CP) differs from DM Types 1 and 2 because it carries a greater risk of hypoglycemia resulting from the altered secretion of glucagon, which is particularly problematic in patients with inadequate compliance, alcohol consumption or autonomic neuropathy [130]; however, it is also associated with a reduced risk of diabetic ketoacidosis. Management can be difficult, especially in the advanced stages of endocrine insufficiency and after pancreatic surgery [131]. Micro-and macroangiopathic complications are comparable with those found in DM Types 1 and 2.

The management strategy used for DM Type 2 might be appropriate with the initial use of metformin followed by insulin secretagogues (sulphonylureas, repaglinide) as the second step; however, it is necessary to individualize therapy according to the duration of DM, the body mass index and the presence of comorbidities [132,133]. The availability of self-injectable glucagon preparations is important for managing severe hypoglycemic episodes. The possible association between the use of incretin-mimetic therapies (DPP4 enzyme inhibitors and GLP-1 receptor agonists) and the appearance of low-grade pancreatitis in humans discourages the use of such treatments in this population until further information is available [134]. Symptomatic hyperglycemia, C-peptide basal levels <1 ng/ml, intolerance or failure of oral hypoglycemic treatment (HbA1c or HbA1c at diagnosis$>$ 9.5%) determine the need for insulin therapy. We recommend the use of basal insulin analogs (detemir, glargine) as monotherapy or in combination with pre-prandial insulin analogs (aspart, lispro, glulisine) because they carry a lower risk of hypoglycemia. In addition, treatment should include an educational program of DM-CP self-management (divided meals, alcohol intake suppression, regular physical activity and adherence to scheduled treatment with pancreatic enzymes).

The metabolic control goals for people with DM-CP must be individualized according to the prognosis and the presence of repeated hypoglycemia; however, the general goal is an HbA1c value of less than 7% [135].

10.1. Recommendation

The treatment of pancreatic diabetes is not different from the treatment of diabetes mellitus Types 1 and 2 and should avoid aggressive patterns that predispose the patient to hypoglycemia (Level of evidence: 5. Recommendation grade: D).

11. How to treat exocrine pancreatic insufficiency and how to monitor the treatment

Exocrine pancreatic insufficiency (EPI) treatment is based on the oral replacement of pancreatic enzymes to optimize the process of digesting and absorbing nutrients. Although fat, carbohydrate and protein maldigestion may occur during EPI, most authors have primarily addressed steatorrhea because it is considered an early and frequent occurrence in CP [136,137]. Initially, oral enzyme therapy should be recommended in patients who have exhibited frank steatorrhea ($>$15 g/day) [138] or malabsorption of lipids (13C-triglycerides breath test) [139] or those who have exhibited

diarrhea, weight loss or other clinical or laboratory signs of malnutrition [138,139]. The treatment for patients with mild steatorrhea (7–15 g/day) is of debatable benefit.

Among the enzyme preparations that have become available, only minimicrospheres or enteric-coated microspheres have shown adequate therapeutic efficacy in CP-related EPI [139] in randomized, double-blind studies [140,141]. Enzyme replacement therapy improves the digestion and absorption of nutrients and is associated with a significant improvement in quality of life in patients with CP [19]. The dose of administered enzymes must be sufficient to replace the pancreatic exocrine function. In general, although there are no randomized trials comparing different doses of enzymes, studies have shown that clinical efficacy is achieved with the administration of a minimum dose of 40,000–50,000 Ph.Eur.U (Pharmacopoeia European Units) of lipase at each main meal and half of that dose (20,000-25,0000 Ph.Eur.U.) with morning and afternoon snacks [139–142]. Enzymes should be distributed throughout the meal or given at the end of the meal [143].

Despite the use of enzyme preparations in enteric-coated minimicrospheres and the use of suitable doses with an optimal dosing regimen, enzyme replacement therapy fails to normalize fat digestion in approximately 40% of cases of EPI secondary to CP [139,144]. Inadequate patient compliance, the acid intestinal pH present in most patients with EPI and the presence of intestinal bacterial overgrowth are the main factors for treatment failure. Acid secretion inhibition with proton pump inhibitors significantly improves the effectiveness of enzyme replacement therapy with enteric-coated minimicrospheres in patients with EPI secondary to CP who have had an insufficient response to monotherapy with enzymes [144]. A symptomatic response to enzyme replacement therapy (i.e., the improvement or abolition of symptoms and such signs as diarrhea, bloating or weight loss) does not ensure that digestion and nutritional status have normalized in patients with EPI secondary to CP [139,142]. Therefore, treatment response monitoring should also be based on objective parameters – either digestion normalization, as measured by CFA or breath test, or standardization of the patient's nutritional status. Because of the limited availability of the diagnostic tests mentioned, the normalization of nutritional parameters and symptomatic improvement are sufficient to determine the effectiveness of enzyme replacement therapy in most cases.

11.1. Recommendation

Oral enzyme therapy is indicated in patients with frank steatorrhea or malabsorption of lipids or those who have exhibited diarrhea, weight loss or other clinical or laboratory signs of malnutrition (Level of evidence: 2b. Recommendation grade: B).

Minimicrospheres or enteric-coated microspheres have demonstrated efficacy in the treatment of exocrine pancreatic insufficiency secondary to CP. A minimum lipase dose of 40,000 to 50,000 Ph.Eur.U. is recommended at each main meal, with half that dose administered with the morning and afternoon snacks (Level of evidence: 5. Recommendation grade: D). It should be given in the middle or at the end of meals (Level of evidence: 1b. Recommendation grade: A).

The inhibition of acid secretion with proton pump inhibitors improves the efficacy of enzyme replacement therapy with enteric-coated minimicrospheres in patients who are insufficiently responsive to monotherapy with enzymes (Level of evidence: 1b. Recommendation grade: A). Other causes of poor response include poor compliance and bacterial overgrowth.

To evaluate the efficacy of enzyme replacement therapy, it is sufficient in most cases to verify the normalization of nutritional parameters and symptomatic improvement (Level of evidence: 2b. Recommendation grade: B).

12. Nutritional support in chronic pancreatitis: how to detect, prevent and treat the nutritional deficit

The most important underlying mechanism for malnutrition is EPI; other factors include the increase in basal energy expenditure, the coexistence of abdominal pain, diabetes and alcohol abuse [145]. Thus, it is common to find a deficit of liposoluble vitamins [146–150], calcium, zinc [151,152] and, occasionally, vitamin B12 [153].

Because of this high risk of malnutrition, it is imperative to perform a thorough nutritional status assessment that includes weight, symptoms that impede nutrition, alcohol habits, dietary assessment (by calculating energy), percentage of macronutrients and amount of consumed micronutrients, anthropometric data, assessment of lean and fat mass and the presence of ascites or edema, as well as a blood analysis that includes albumin, liposoluble vitamins and hydrocarbon and bone metabolism [154].

Before starting a specific nutritional therapy, it is important to control the abdominal pain and cease alcohol consumption. A diet that provides 35 kcal/kg/day, 1–1.5 g/kg/day of protein and 30% fat being rich in complex carbohydrates and low in fiber is usually sufficient to maintain the nutritional status [154]. Daily multivitamin with mineral supplements and a normocaloric diet are recommended to prevent nutritional deficits in well-nourished patients [155,156].

Classically, clinicians have recommended to reduce dietary fat intake to $<$20 g/day in patients with steatorrhea, although no evidence supports this recommendation [157]. In this context, enzyme replacement therapy for EPI should be optimized.

The insoluble fiber intake should be moderated to prevent possible interference with enzyme supplements [136]. In cases of weight loss in spite of an optimized EPI treatment, oral nutritional supplements should be introduced with polymeric norm/hypercaloric norm/hyperproteic formulas as needed. Intact protein formulas are generally well-tolerated; however, if they are not, it is possible to supplement with partially digested peptide formulas. Medium chain triglyceride (MCT) supplements have not demonstrated consistent benefits. A randomized controlled trial showed that MCT enriched commercial preparation offered no advantage over homemade balanced diet for improving nutritional status of patients with CP [158]. Furthermore MCT supplements have low adherence because of their low palatability and high cost [155,159].

Enteral nutrition is indicated in the following cases: 1) weight loss despite the above measures; 2) low intake because of abdominal pain; 3) acute complications for which artificial nutrition is indicated; and 4) prior to elective surgery in cases of moderate to severe malnutrition. Enteral nutrition with jejunal access (nasojejunal tube) should begin using diets with partially hydrolyzed peptides and medium chain triglycerides (MCTs), although there are no long-term studies demonstrating effectiveness. If this situation lasts longer than eight weeks, a definitive jejunostomy, either surgical or via percutaneous endoscopic/radiologic gastrostomy, should be considered [155,157,160]. Parenteral nutrition is indicated for patients with the following issues: 1) duodenal stenosis, 2) pancreatic fistula and 3) severe malnutrition prior to surgery when enteral nutrition is not possible. A clinical thiamine deficiency and the so-called refeeding syndrome can develop in severely malnourished patients who do not receive adequate nutritional support, especially in the early days of parenteral nutrition [159].

If there are vitamin deficiencies, they must be corrected. Deficits of liposoluble vitamins (A, D, E and K), calcium, magnesium, zinc, copper, thiamine, vitamin B12 and folic acid have been described. Although these deficiencies are often overlooked clinically, they can cause metabolic bone disease and fatigue. These deficits should be supplemented orally when they are observed, and parenteral administration should be used if oral supplementation does not normalize vitamin deficiencies. If there is deficiency of vitamin D, calcifediol supplementation is preferred for its higher polarity. Calcium levels should be monitored in patients treated with calcifediol because of the increased risk of hypercalcemia [155,157].

12.1. Recommendation

The high prevalence of malnutrition in chronic pancreatitis makes necessary to identify individuals who require nutritional support (Level of evidence: 2c. Recommendation grade: B).

Adequate dietary support, corrections of micronutrient deficits, pancreatic enzyme use and pain management has shown a positive impact on the nutritional status of patients with chronic pancreatitis (Level of evidence: 2c. Recommendation grade: B).

13. Conclusions

The Spanish Pancreatic Club has developed the present Consensus to guide the management of CP. The paucity of well-designed randomized controlled trials, the heterogeneity of available data, and the methodological flaws of published studies are reflected in the number of grade D recommendations: 8 out of 34 (23.5%), similar to previous consensus [161]. We recommend a step-up approach to medical management of CP-related pain, based in the WHO method for pain relief, detailed in Fig. 1. The most effective and long lasting invasive treatment for pain is surgery. Endoscopic decompression treatment may be useful in patients with dilated main pancreatic duct. Extracorporeal shock wave lithotripsy is effective for removing intraductal calculi and provides pain relief. EUS-guided celiac plexus block or ablation of the splanchnic nerves may be an option for CP-related pain treatment in patients with small duct CP. Endoscopic drainage is the treatment of choice for symptomatic or complicated pseudocysts. A ruptured pseudoaneurysm should be treated by means of angiographic embolization. Surgery is the treatment of choice for symptomatic biliary or duodenal stenosis. We recommend an initial medical treatment for CP-related fistulae and ascites. If there is no improvement, endoscopic treatment of the ductal system disruption should be attempted; surgery is indicated in refractory cases. Patients with left portal hypertension should undergo an endoscopic examination to rule-out gastro-esophageal varices. Splenectomy should be performed in patients with left portal hypertension and gastro-esophageal varices who will undergo surgery for chronic pancreatitis and in patients who had suffered variceal bleeding. The treatment for pancreatic diabetes is not different from the treatment for diabetes mellitus Types 1 and 2 and should avoid aggressive patterns that predispose the patient to hypoglycemia. Oral enzyme therapy is indicated in patients with frank steatorrhea or malabsorption of lipids or those who have exhibited diarrhea, weight loss or other clinical or laboratory signs of malnutrition. To assess the efficacy of enzyme replacement therapy, it is sufficient in most cases to verify the normalization of nutritional parameters and symptomatic improvement. Adequate dietary support, corrections of micronutrient deficits, pancreatic enzyme use and pain management have shown a positive impact on the nutritional status of patients with CP.

In loving memory of Luisa Guarner and Miguel Pérez-Mateo.

Conflicts of interest

Enrique de-Madaria, Enrique Domínguez-Muñoz, Julio Iglesias-García and José Lariño-Noia have been paid speakers for Abbott Laboratories. Enrique Domínguez-Muñoz is a consultant for Abbott Laboratories and Pentax. Julio Iglesias-García is a consultant for Cook Medical Company. Luis Gómez and Yolanda Sastre have been paid speakers for Mundipharma, Zambon, Ferrer Pharma and Grunenthal Pharma. José Ramón Aparicio is a consultant for Boston Scientific.

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