

Belgian consensus on chronic pancreatitis in adults and children : statements on diagnosis and nutritional, medical, and surgical treatment

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Abstract

Chronic pancreatitis (CP) is an inflammatory disorder characterized by inflammation and fibrosis, resulting in a progressive and irreversible destruction of exocrine and endocrine pancreatic tissue. Clinicians should attempt to classify patients into one of the six etiologic groups according to the TIGARO classification system. MRI/MRCP, if possible with secretin enhancement, is considered the imaging modality of choice for the diagnosis of early-stage disease. In CP, pain is the most disabling symptom, with a significant impact on quality of life. Pain should be assessed using the Izbicki score and preferably treated using the “pain ladder” approach. In painful CP, endoscopic therapy (ET) can be considered as early as possible. This procedure can be combined with extracorporeal shock-wave lithotripsy (ESWL) in the presence of large (> 4 mm), obstructive stone(s) in the pancreatic head, and with ductal stenting in the presence of a single main pancreatic duct (MPD) stricture in the pancreatic head with a markedly dilated MPD. Pancreatic stenting should be pursued for at least 12 months in patients with persistent pain relief. On-demand stent exchange should be the preferred strategy. The simultaneous placement of multiple, side-by-side, pancreatic stents can be recommended in patients with MPD strictures persisting after 12 months of single plastic stenting.

We recommend surgery in the following cases : a) technical failure of ET ; b) early (6 to 8 weeks) clinical failure ; c) definitive biliary drainage at a later time point ; d) pancreatic ductal drainage when repetitive ET is considered unsuitable for young patients ; e) resection of an inflammatory pancreatic head when pancreatic cancer cannot be ruled out ; f) duodenal obstruction. Duodenopancreatectomy or oncological distal pancreatectomy should be considered for patients with suspected malignancy. Pediatricians should be aware of and systematically search for CP in the differential diagnosis of chronic abdominal pain. As malnutrition is highly prevalent in CP patients, patients at nutritional risk should be identified in order to allow for dietary counseling and nutritional intervention using oral supplements. Patients should follow a healthy balanced diet taken in small meals and snacks, with normal fat content. Enzyme replacement therapy is beneficial to symptomatic patients, but also in cases of subclinical insufficiency. Regular follow-up should be considered in CP patients, primarily to detect subclinical maldigestion and the development of pancreatogenic diabetes. Screening for pancreatic cancer is not recommended in CP patients, except in those with the hereditary form. (*Acta gastroenterol. belg.*, 2014, 77, 47-65).

Chronic pancreatitis (CP) is an inflammatory disorder characterized by inflammation and fibrosis, resulting in a progressive and irreversible destruction of exocrine and endocrine pancreatic tissue, with pain often a predominant clinical symptom. Population-based epidemiologi-

cal data on CP is scarce, which is probably due to the difficulty in establishing a firm diagnosis at the early stage of the disease. Prevalence rates of about 26 to 28 per 100,000 people have been reported in France and Japan (1,2). Time course data suggests that CP incidence is rising, most likely on account of increased alcohol consumption and improved diagnostic techniques (3-5). No data on CP epidemiology and etiology in Belgium is available yet.

I. Etiology and risk factors of chronic pancreatitis

Statement : In every CP case, clinicians should attempt to classify the patient – after a thorough patient anamnesis covering environmental factors, and personal and family history, and after standardized biochemical, immunological, and genetic testing, if appropriate, as well as detailed imaging studies – into one of the six etiologic groups of the TIGARO classification

In earlier studies, alcohol was considered the main etiologic factor in calcifying CP. These older studies concluded that most CP patients were men (70-90%), with heavy drinking being the most common etiology in 70-80% of patients (5,6). During recent years, it has become apparent that a number of other risk factors, including hereditary and immunological factors, as well as interactions between these risk factors, are crucial in CP pathogenesis. Major risk factors for CP can be classified into systems such as the TIGAR-O (7) classification, allowing patients to be categorized into one of six groups

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Submission date : 15/01/2014

Acceptance date : 16/01/2014

Table 1. — Etiologic groups of chronic pancreatitis according to the TIGAR-O classification system

Toxic	Alcohol
	Cigarette smoking
	Hypercalcemia, hyperparathyroidism
	Hypertriglyceridemia
	Chronic renal failure
Idiopathic	Early onset < 35 years
	Late onset > 35 years
Genetic	PRSS1, CFTR, and SPINK1 mutations
Autoimmune	Type I: IgG4-related disease
	Type II: IgG4-negative
Severe acute pancreatitis-associated	
Obstructive	Pancreas divisum
	Pancreatic duct scars
	Groove pancreatitis

according to the factor most strongly associated with their pancreatic disease (Table 1). The etiological classification of every individual CP patient undoubtedly requires a thorough anamnesis covering environmental factors, as well as personal and family history, along with standardized laboratory evaluation, genetic testing, and detailed radiological studies, along with MRCP, CT, and ERCP (8-9).

For inclusion into the toxic alcohol abuse group, patients must exhibit a “heavy” alcohol drinking-pattern, consisting of at least four to five consumptions or 48 to 60g of alcohol per day over several years. This alcohol amount is considered a threshold for developing alcoholic CP (6,10,11). However, less than 10% of people who drink alcohol in excess develop the disease, suggesting that other environmental and genetic factors interact with alcohol to amplify its toxicity. Smoking is considered an independent risk factor for CP pathogenesis and progression rate (5,6,10,11).

A diagnosis of idiopathic CP is established when no other clear etiology is identified, such as alcoholism, hereditary or familial, autoimmune pancreatitis, obstructive causes, or acute pancreatitis-associated CP.

Hereditary CP is considered when pancreatitis occurs in an individual from a family with a pancreatitis phenotype inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern (12).

The diagnosis of autoimmune pancreatitis requires clinical and radiologic characteristics, as well as distinct serological/immunohistochemical IgG4 features. The Type 1 group is mainly characterized by high IgG4 concentrations and histological findings designated as lymphoplasmocytic sclerosing pancreatitis (LPSP). The Type 2 group is distinguished by a normal IgG4 concentration and histological findings of idiopathic duct-centric pancreatitis (IDCP). Type 1 CP is part of the IgG4-related spectrum, and may be accompanied by other IgG4-related diseases, whereas Type 2 is associated with ulcerative colitis (13,14).

Groove pancreatitis or cystic dystrophy of the duodenal wall is considered when a typical clinical, endoscopic, and radiologic pattern is observed, with significant thickening and cystic changes of the duodenal wall, along with a mass lesion between the duodenum and pancreatic head (15).

Genetic analysis for mutations in the cationic trypsinogen gene (PRSS1) is only conducted in patients with hereditary pancreatitis or a family history of pancreatitis. The PRSS1-gene is considered a disease-causing gene. Yet other genes such as the cystic fibrosis transmembrane conductance regulator (CFTR) and serine protease inhibitor Kazal Type 1 (SPINK1) are considered disease-modifying genes that may, together with other environmental and genetic factors, play a role in the pathogenesis of distinct CP types, such as alcoholic and idiopathic CP (7,8,13).

II. Diagnosis of chronic pancreatitis

1. How should a diagnosis of early chronic pancreatitis be established ?

Statement : MRI/MRCP, if possible combined with secretin enhancement, is the imaging modality of choice for diagnosing early chronic pancreatitis

Diagnosis of CP is usually made using imaging techniques. Yet, in early stage CP, diagnosis by these means may be difficult as the morphological changes are minimal (16,17). Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for detecting early CP stages, as signal changes can be picked up prior to morphological changes. Magnetic resonance cholangiopancreatography (MRCP) allows for excellent visualization of the pancreatic ducts, with secretin enhancement providing an even better visualization of abnormalities of the pancreatic duct and its branches. MRI/MRCP, if possible combined with secretin enhancement,

are thus the imaging modalities of choice to detect less advanced disease with the greatest reliability and minimal invasiveness (18). Endoscopic ultrasound (EUS), which is more invasive, is the most sensitive imaging method for detecting minimal structural changes indicative of CP, and may provide add-on value in uncertain cases (19). To standardize EUS features and thresholds for CP diagnosis, a consensus-based scoring system has been proposed (20). The so-called Rosemont classification does not specifically address early-stage CP, and it is still unresolved whether 'indeterminate for CP' according to this classification represents early-stage CP (21). In addition to low interobserver agreement amongst endosonographers, it should also be mentioned that subtle abnormalities detected by EUS are not specific, as they have also been reported in the context of alcoholism, advanced age, male gender, obesity, and cigarette smoking (22). Early-stage CP tends to be a focal, patchy disease that can be missed by image-guided biopsies, and tissue sampling (FNA or biopsy) is thus not recommended (23,24).

2. How should chronic pancreatitis be classified ?

Statement : There is no consensus on which clinical classification system is to be proposed for daily practice

The main reason for the lack of guided strategies in CP management is the absence of a clinically applicable classification. In recent years, it has become clear that clinical decisions cannot be made solely on the type and degree of morphological abnormalities, but need to be based on clinical, functional, and imaging findings. Multiple classification systems have been proposed, however none of them have been extended to clinical practice or used as a standard for comparative studies (9, 25-27). In one of the more simple classifications (27), CP is separated into four different stages :

- I. Pre-clinical stage with absent or uncharacteristic symptoms ;
- II. Recurrent acute episodes of pancreatitis without definite signs of CP ;
- III. Further recurrent episodes with intermittent or constant pain in between and signs of CP, such as duct dilatation and pancreatic calcification on imaging ;
- IV. Final stage, mostly without acute flares and absence or decreased frequency of pain, possibly associated with evidence of endocrine and exocrine insufficiency (burnout).

This classification is easily reproducible in clinical practice and more suitable for treatment purposes.

3. Utility of pancreatic function testing for diagnosis

Statement : Pancreatic function tests have only a limited value in the diagnosis of CP

While CP diagnosis is mainly based on imaging studies, functional pancreatic assessment is principally aimed at detecting gland insufficiency in patients with known pancreatic disease or after pancreatic surgery, assisting in the indication of enzyme substitution therapy, and overseeing the efficacy of this therapy (28). At present, there is only a limited role for function tests in the diagnosis of CP. These tests can, however, be of some help for CP diagnosis in cases with inconclusive morphological findings associated with high clinical suspicion. MRCP after intravenous secretin (s-MRCP) administration enables assessment of exocrine pancreatic function based on quantification of duodenal filling, which is reduced in patients with exocrine insufficiency. This study is less invasive than other direct function tests, yet appears to be sufficiently sensitive to identify patients with mild exocrine pancreatic insufficiency (29-31).

4. Differential diagnosis

Statement : MRI and EUS are essential for the differential diagnosis of chronic pancreatitis with other pancreatic masses or cystic lesions

Differentiation between mass-forming CP and other pancreatic lesions remains a challenge (31,32). MRI is superior to CT in visualizing tumors within pancreatic inflammation areas. While EUS produces high resolution images, this procedure cannot reliably differentiate malignant from inflammatory lesions due to the similar EUS appearance of adenocarcinoma and focal pancreatitis. Even when FNA is used in conjunction with EUS, a cytological evaluation of pancreatic tissue in the setting of chronic inflammation proves highly difficult, as inflammatory infiltrates may obscure or simulate pancreatic malignancy. EUS-FNA sensitivity is therefore much lower in the CP setting (54%-73%) (33). New EUS imaging techniques, such as elastography and contrast-enhanced harmonic EUS (CEH-EUS), have been proposed so as to overcome these limitations. Recent meta-analyses have shown high accuracy with both techniques, but their true diagnostic value for patients where FNA has failed, or in those with underlying CP, has not been consistently proven (34,35).

Groove pancreatitis is a rare CP form affecting the duodenopancreatic groove. Its principal feature is the presence of cysts surrounded by inflammation and fibrosis in the intestinal wall. Differentiating this entity from infiltration by a pancreatic carcinoma may prove highly difficult. Diagnosis should rely on CT, MRI, the duodenum's endoscopic appearance, as well as EUS with FNA (36).

Auto-immune pancreatitis (AIP) may be difficult to differentiate from pancreatic adenocarcinoma. There is no single test that can reliably diagnose AIP. The diagnosis is based on a combination of imaging findings, serology, other organ involvement, histology, and response to corticosteroids (37). Intraductal papillary

mucinous neoplasms (IPMN) can be misdiagnosed for CP, as both conditions share similar features, such as dilated pancreatic ducts, cystic lesions, and even extensive calcifications. In rare cases, focal CP can also present as IPMN due to cystic dilatations of the branch ducts (38, 39). In this context, CT, MRI/MRCP, and EUS are indicated for diagnosis and differentiation of IPMN and CP (40). EUS-guided FNA enables sampling of cyst fluid contents for cytology and tumor markers. Cytology is usually non-contributive due to its low sensitivity and insufficient sample volumes (41). ERCP and per oral pancreatoscopy can be useful in the evaluation of main duct type IPMN lesions and differentiation from CP (42).

III. Assessment of pain, complications, and malnutrition in chronic pancreatitis

A. Pain in chronic pancreatitis

1. Which type and mechanism of pain is suspected ?

Most CP patients experience pain as one of the most dominant and disabling symptoms of their disease. However, some CP patients do not display any nociceptive symptoms at all. In a certain number, the pain wears off with time and tends to disappear at the stage of full sclerosis of the pancreas (43).

The pathophysiology of the different types of pain observed in CP is probably multifactorial. A more visceral type of pain occurs when nociceptive receptors become sensitized due to high pressure in the pancreatic ducts or parenchyma. It has also been postulated that visceral pain can be induced by the secretion of pancreas enzymes or tissue ischemia (8,44-48). The various surgical and endoscopic drainage procedures performed in clinical practice are based on this principle. Although a large proportion of patients are (partly) relieved from pain after such procedures, there is also a group of patients suffering from CP and chronic pain who do not display significant changes in ductal or parenchymal pressure (8,47). The hypothesis that alcohol could have a direct nociceptive (pain inducing) effect is contradicted by the fact that a direct correlation between alcohol and pain has never been proven (48).

A peripheral neuropathic syndrome is also considered as playing a role. There is, indeed, evidence that the receptors involved in visceral sensitivity, such as TRPV1, GAP-43, and NGF, are increasingly expressed in the nerve endings within the pancreas of CP patients (8,45,46,48).

The current consensus clearly indicates that many of these patients suffer from a chronic pain syndrome due to the development of central nervous system sensitization and wind-up. In such cases, the pain syndrome should be treated as a disease entity, rather than a symptom arising from tissue injury (8,46).

In a broader sense, the temporal features of the pain syndrome in CP patients can be divided into two categories

(43,49). Firstly, most patients exhibit an intermittent pain pattern that is characterized by pain-free intervals alternating with pain attacks. These attacks can range from mild and responding well to systemic analgesics to a more severe form requiring hospitalization and more invasive treatment options. On the other hand, other patients experience more continuous pain, which is at times complicated by acute flares. The second pattern often correlates with continued alcohol intake and is more frequently observed in smokers. This latter patient group is more frequently hospitalized, with a significant higher number of sick days (49).

2. How should pain be objectively assessed ?

No objective instruments have been validated to estimate the intensity of pain in CP patients. Numerical scales, such as the visual analog scale (VAS), are commonly applied. In recent studies, the Izbicki score (Table 2) has been used. This specific score is based on the pain attack frequency, VAS-score, analgesic use, and duration of disease-related inability to work (50).

Pain obviously affects overall quality of life (QOL). Various questionnaires have been used to assess the impact of pain on patient QOL (SF-12, SF-36, EORTC QLQ C-30, and GIQLY). The easiest evaluation tool in this respect is undoubtedly the SF-12, for this scale provides the same information as more extensive questionnaires, while being far less complicated (51).

3. How should pain be treated in chronic pancreatitis ?

Statement : Pain is the most disabling symptom in chronic pancreatitis, which significantly impacts QOL, and is caused by several pathophysiological mechanisms. It should be assessed using the Izbicki score. The “pain ladder” approach is recommended for pain treatment. In refractory cases, alternative treatments are available

As with all chronic pain syndromes, treating pain associated with CP may prove challenging. The WHO 3-step (52) approach is used as standard when prescribing analgesics (the so-called “pain ladder”), yet paracetamol alone or in combination with non-steroidal anti-inflammatory drugs (NSAID) is rarely sufficient. A weak opioid may be added in the next step. Tramadol appears to be a logical choice, as this drug exhibits less opioid-induced side-effects like obstipation and sedation. However, a large percentage of patients experience nausea and vomiting due to tramadol’s serotonergic activity (53). Anti-oxidants may be beneficial, yet clinical studies have shown mixed results (52,54).

Endoscopic approaches, aimed at decompressing an obstructed pancreatic duct, are performed in the presence of stones or strictures. Short-term pain relief is readily achieved with such procedures, although more definite surgical interventions appear more effective for sustained analgesia (56-59). Celiac plexus infiltration with local

Table 2. — IZBICKI pain score

	Points
Frequency of pain attacks	
Daily	100
Several times a week	75
Several times a month	50
Several times a year	25
None	0
Visual analog scale (VAS)	
No pain	Imaginative maximum of pain
1-----1	
0 points	100 points
Analgesic medication*	
Morphine	100
Buprenorphine	80
Pethidine	20
Tramadol	15
Metamizole	3
Acetylsalicyl acid	1
Duration of disease-related inability to work	
Permanent	100
> 1 year	75
> 1 month	50
> 1 week	25
No inability to work during the last year	0

* When drug combinations were used, the most potent analgesic was taken into account.

anesthetics or radiofrequency-induced denervation can also be applied in therapy-resistant pain syndromes. The use of neurodestructive methods with alcohol or phenol is contraindicated in CP on account of the high risk of severe deafferentation syndromes after such procedures.

Recently, spinal cord stimulation via epidurally-placed leads at the T6-T7 level has resulted in therapeutic benefits in CP-associated pain (60).

B. Complications other than endocrine/exocrine pancreatic failure

The main complications of chronic pancreatitis are pseudocyst formation, common bile duct (CBD) obstruction, duodenal obstruction, cancer development, splenoporto-mesenteric thrombosis, and gastrointestinal bleeding.

1. Pseudocysts

Statement : Endoscopic therapy, in particular EUS-guided TM drainage, is the first-line therapy for uncomplicated chronic pseudocysts, for which treatment is indicated and which are within endoscopic reach

Pseudocyst formation is a common complication of CP, with a reported incidence of 20%-40%. Less than 10% of these pseudocysts resolve spontaneously (61). Treatment is indicated for pseudocysts that cause symptoms (abdominal pain or early satiety), complications (infection, bleeding, or rupture), or compression of surrounding organs (gastric, duodenal, or biliary obstruction).

The size, number, content, and location of pseudocyst(s), the MPD anatomy and presence of associated ductal lesions (stones, strictures, or rupture), the communication of the pseudocyst with the pancreatic duct, the presence of associated vascular lesions like pseudoaneurysm or venous thrombosis, and any compression of adjacent organs are all best delineated by means of magnetic resonance imaging (MRI and MRCP). These procedures are therefore recommended as essential tools in therapy planning (62).

Chronic pseudocyst(s) can be treated by endoscopic, percutaneous, or surgical drainage. Two endoscopic approaches have been described for pseudocyst drainage, namely through the papilla (transpapillary [TP] drainage) or gastrointestinal wall by creating a cystogastrostomy or cystoduodenostomy (transmural [TM] drainage), followed in both cases by the insertion of one or more plastic stents. TP drainage may be recommended if TM drainage is contraindicated or not feasible (*e.g.*, significant coagulopathy or no safe window due to intervening blood vessels secondary to portal hypertension), for small (< 6 cm) pseudocysts communicating with the pancreatic duct on pancreatography, for preprocedural MRCP, and when pancreatic duct obstruction (stricture or stone) or leaks must be addressed (63). When both TM and TP drainage are technically feasible, we currently favor TM drainage with the insertion of at least two double-pigtail plastic stents, which should be left in place for at least 2 months or longer if MPD rupture (disconnected duct syndrome) is observed. The technical success rate of TM drainage was reported to be significantly higher for EUS-guided TM drainage compared to non-EUS-guided

TM drainage in two randomized controlled trials (RCT) (64,65). Multivariate analysis identified three factors predictive of a more favorable outcome after pseudocyst TM drainage: pancreatic head localization of the cyst, drainage duration of more than 6 weeks, and insertion of multiple double-pigtail stents (66). A randomized clinical trial also showed that systematic stent retrieval within 2 weeks of pancreatic fluid collection resolution resulted in a higher recurrence rate, mostly in patients with PD rupture (62,63).

Percutaneous drainage should not be performed in chronic pseudocysts (67), excepting patients who are not candidates for other procedures (63). Compared with surgical cystogastrostomy, EUS-guided TM drainage of pseudocyst provided similar clinical results, at a lower cost, with shorter hospital stay, and improved quality of life (68,69).

2. Biliary stricture

Statement: CP-related biliary strictures can be treated with multiple 10F plastic stents for approximately 12 months. Uncovered or partially covered SEMS should not be used. Fully covered stents are currently in evaluation in this setting

Common bile duct (CBD) stenosis is a result of pancreatic head inflammatory or fibrotic changes, or may be related to compression by a pancreatic pseudocyst. Its prevalence rates range from 3% to 45% of CP patients, but only about 10% of these patients actually develop symptoms related to biliary obstruction (70). Conservative management is recommended in asymptomatic patients with CBD dilatation yet presenting normal liver function tests (67). MRCP is the preferred imaging procedure for delineating the bile duct stricture and pancreatic duct anatomy, while ERCP is favored when intervention is required. Endoscopic stenting of the CBD distal stricture is an effective approach for temporary biliary decompression in CP patients presenting with cholangitis, persistent cholestasis, or obstructive jaundice.

The only predictive risk factor for failure of endoscopic single plastic biliary stenting identified in CP patients was the presence of pancreatic head calcifications (71). On the other hand, concomitant acute pancreatitis at presentation was the only factor predictive of a successful outcome after biliary stenting (72). Long-term stricture resolution after stent removal in 350 patients treated with a single plastic stent (usually 10F) was reported in 10-80% of cases (mean 31%) during follow-up periods ranging from 14 to 58 months (73).

Long-term results were improved following the placement of multiple (≥ 3) plastic 10F stents, usually during 1 year, with stricture resolution observed in 44-92% of cases (mean 62%) in the 12 to 48 months after stent removal (67,73,74). Uncovered and partially covered self-expandable metal stents (SEMS) are currently not recommended. This is due to the early stent occlusion

caused by epithelial hyperplasia involving the uncovered portions, while these stents cannot be removed. In contrast, fully covered SEMS can be removed, and temporary treatment with covered SEMS has thus become an attractive option (74). In a proportion of CP patients with biliary strictures refractory to endoscopic stenting, bypass surgery (hepaticojejunostomy) is usually preferable to long-term stenting, especially for non-compliant patients with alcoholic CP. However, in non-operative candidates with high operative risk due to local (*e.g.*, portal cavernous) or general conditions, fully covered SEMS are a therapeutic option.

3. Other rare complications

Vascular complications in the CP setting include pseudoaneurysm. In patients with both pseudoaneurysm and pseudocyst (75), the former should be treated using selective angiographic embolization prior to any pseudocyst drainage attempt.

In patients with left-sided portal hypertension due to splenic vein thrombosis, splenectomy or interventional radiology should only be performed in cases of proven variceal bleeding (67,73).

Duodenal obstruction, which occurs rarely (in approximately 1% of CP cases), should be treated by surgery (bypass or resection in cases of inflammatory mass in the pancreatic head) (76).

For pancreatic ascites or pancreatic pleural effusion, conventional treatment strategies comprise bed rest with nutritional support using parenteral or enteral feeding, paracentesis, and somatostatin analogues. When supportive management fails, endoscopic intervention (pancreatic sphincterotomy or stenting) should be considered, with the aim of sealing off the leak and overcoming a distal ductal obstruction (76).

4. Inflammatory masses

Statement: In patients with a pancreatic mass or main pancreatic duct/common bile duct stricture, adequate work-up should be performed to reasonably rule out pancreatic cancer

Approximately one-third of CP patients undergoing surgery present with an inflammatory mass in the pancreatic head. We do not know the exact prevalence of such a mass in the entire CP population. From a radiological perspective, the pancreatic head is considered enlarged when the antero-posterior diameter exceeds 4 cm. This enlargement may cause local complications, such as duodenal compression, vascular thrombosis, and biliary strictures. Nearly 50% of the patients with an enlarged pancreatic head experience episodes of jaundice due to common bile duct stenosis. Other local complications are listed in Table 3. Surgery is key in the treatment of complications due to an inflammatory mass of the pancreatic head. As preferred techniques, we consider the Frey or Beger drainage-resection intervention (77).

Table 3. — Local complications associated with an inflammatory mass in the pancreatic head

N = 380 patients	%
Main pancreatic duct stenosis	39
Common bile duct stenosis	48
Severe duodenal compression	7
Portal vein compression	13

C. Malnutrition

Statement : As malnutrition is highly prevalent in CP, patients at nutritional risk should be identified to allow for dietary counseling and nutritional intervention using oral supplements

CP results in exocrine and endocrine dysfunction, with negative effects on digestion and absorption of nutrients. In CP patients, nutrition status may be further affected by poor dietary intake, often related to alcoholism.

It is widely accepted that CP patients are often undernourished, although only a few well-conducted clinical studies have confirmed this assumption. In a study conducted in a medical rehabilitation clinic setting, low BMI (< 20 kg/m²) and ongoing maldigestion were prevalent in 32% of patients (78). A cross-sectional cohort study involving 60 patients admitted to a Danish university gastroenterology department reported that 28% exhibited nutritional risk (NRS-2002 screening tool), despite still presenting with a normal BMI. Patients at nutritional risk had lower muscle mass (low fat-free mass index FFMi) and muscle strength (hand grip strength). A very low BMI (< 20) was associated with higher resting energy expenditure (79). Evaluation of body composition showed a decrease in lean body mass, reduced functional capacity, and reduced fat mass (energy store), which was significantly more pronounced in patients with severe exocrine pancreatic insufficiency compared to those with residual pancreatic function (80). Poor nutritional status clearly affected quality of life, as almost half of the patients suffered from moderate to severe fatigue (81). Furthermore, specific deficiencies resulting in nutrition-related problems, such as diminished bone health, may be overlooked (82).

These findings raise questions about what measures should be implemented for improving CP patient quality of life. A thorough nutritional assessment is undoubtedly necessary to establish a targeted nutrition and rehabilitation plan. A randomized controlled trial compared dietary counselling to commercial dietary supplementation in undernourished (BMI of < 18.5kg/m² or >10% loss of body weight in the previous 6 months) CP patients receiving PERT. In this trial, body weight, BMI, and energy intake increased, with fecal fat decreasing to a similar extent in both groups (83). This data clearly shows that adequate nutritional management, together with PERT,

has the potential to improve both nutritional status and maldigestion. Parenteral nutrition should only be used in cases of GI-tract obstruction or as a supplement to enteral nutrition (78).

IV. Medical treatment of chronic pancreatitis

Statement : There is no specific medical treatment for chronic pancreatitis, apart from measures aimed at compensating exocrine and endocrine insufficiency. Every effort should be focused on supporting the patient in stopping drinking and smoking

There is no specific medical treatment for CP, apart from treating pain and managing exocrine and endocrine insufficiency. First-line medical options mainly comprise appropriate dietary counseling, abstinence from alcohol and tobacco, adjunctive agents and pancreatic enzymes, as well as analgesic agents.

Every effort should be focused on supporting the patient in stopping drinking and smoking. Abstinence from alcohol has a crucial impact on pain alleviation in patients with alcoholic pancreatitis. Abstainers exhibit a slower rate of pancreatic function deterioration and a better response to therapeutic pain control than non-abstainers (84,85). It is difficult to distinguish the role of smoking from that of alcohol consumption in terms of CP etiology and clinical evolution, as cigarette smoking and alcoholic consumption are most often mutually inclusive (86,87). Moreover, alcohol withdrawal is rarely accompanied by smoking withdrawal. Combined withdrawal of both toxic habits should perhaps be considered, rather than initially prioritizing alcohol withdrawal. Retrospective data indicating a beneficial effect of smoking withdrawal in reducing pain and CP-related complications has led to the recommendation of smoking withdrawal for CP patients (28).

Increased oxidative stress has been implicated as a potential mechanism in CP etiology and pathology. A number of studies have demonstrated that CP patients display a compromised antioxidant status, which may contribute to the enhanced oxidative state associated with the disease. Exocrine insufficiency leads to further deficiencies and impaired antioxidant status. Chronic use of oral antioxidant supplements could help prevent painful CP recurrences. The overall effectiveness of antioxidants has not however, been proven, and the best combination of agents and dosages is not yet clear (8,54,55, 88-90).

The exogenous pancreatic protease replacement for pain relief is based on the concept of the feedback inhibition of pancreatic exocrine secretion. In addition, it has been proposed that PERT can stimulate receptors in the proximal small intestine and trigger a negative feedback loop that suppresses baseline pancreatic secretion, decreasing ductal pressures and therefore pain. A meta-analysis conducted on published studies concluded that there was no significant benefit provided by pancreatic enzymes for pain relief in painful CP. Although

administering enzymes appears an attractive option, there is no evidence that these are effective in reducing pain (91-93).

Medical and nutritional treatment make up the first, yet essential, step before any endoscopic or surgical therapy can be considered (83). Conservative management may, however, be the only step for patients with no ductal abnormalities, and those with end-stage or asymptomatic disease, in whom endoscopy and surgery are not indicated, and may even increase associated morbidity and mortality.

V. Endoscopic treatment of chronic pancreatitis

Pain is the CP symptom that most commonly requires treatment. It may be related to increased pressure within the ductal system or parenchyma secondary to outflow obstruction of the main pancreatic duct (MPD).

1. How should the best candidates for initial endoscopic treatment be selected ?

Statement : Endoscopic therapy can be considered as early as possible in the course of painful CP ; it can be combined with extracorporeal shock-wave lithotripsy (ESWL) in the presence of large (> 4 mm), obstructive stone(s) located in the pancreatic head, and with ductal stenting in the presence of a single MPD stricture that induces a markedly dilated MPD

The best candidates for endoscopic treatment (ET) are symptomatic patients presenting with appropriate morphological features, such as obstructive ductal stone(s), ductal stricture(s), or MPD dilatation (94).

Factors independently associated with long-term (≥ 2 years) pain relief following ET include : (a) location of obstructive calcifications in the pancreatic head ; (b) short disease duration ; (c) low frequency of pain attacks before ET ; (d) complete MPD stone clearance ; (e) absence of MPD stricture at initial ET ; (f) alcohol and smoking withdrawal during follow-up (73,94-99).

2. How should the best candidates for ESWL alone be selected ?

Statement : In uncomplicated CP with radiopaque stones ≥ 5 mm obstructing the MPD, ESWL alone could be recommended as the first-line procedure in centers with ESWL experience

Patients selected for treatment using ESWL alone are those who present with uncomplicated painful CP associated with at least one calcification ≥ 5 mm located in the pancreatic head or body, with upstream MPD dilatation. (95). Two uncontrolled series involving 350 patients have reported on ESWL used alone in painful CP. Spontaneous MPD stone clearance was reported in 70%-88% of patients, with pain relief observed in 78% of patients over a mean follow-up of 44 months (100,101).

A bicentric randomized control trial compared ESWL alone versus ESWL followed by endoscopic MPD drainage in 55 patients (95). Two years after trial intervention, a similar proportion of patients experienced complete pain relief in both groups. The only significant between-group differences were a longer hospital stay duration and higher treatment cost in the ESWL plus ERCP vs. the ESWL alone group (96). The location of obstructive calcifications in the pancreatic head was the only factor independently associated with absence of pain relapse (95).

3. Pancreatic duct stenting

Pancreatic duct stenting is recommended for treating painful CP associated with a dominant MPD stricture (73).

a) What should be the total duration of stenting ?

Statement : Pancreatic stenting should be pursued for at least 12 months in patients with persistent pain relief

Criteria used for “definitively” removing a stent are : 1) adequate contrast medium outflow into the duodenum, occurring within 1-2min following ductal filling upstream from the dilated stricture, immediately after stent removal ; 2) easy passage of a 6Fr catheter through the dilated stricture (73). MPD stenting for a short, pre-defined duration (6 months) has been shown to be poorly effective (102). After a 23-month median total duration of stenting prior to removal, 62% of patients maintained satisfactory pain control without pancreatic stent replacement during a median time of 27 months (103). The majority of patients with pain recurrence after attempted “definitive” stent removal relapsed during the first year following stent removal (79%), with almost all (97%) having relapsed by 24 months (103). Consequently, if a patient remains stable during the first year after stent removal, subsequent relapse and need for re-stenting are less likely.

b) How should stent exchange be managed : on-demand or systematic ?

Statement : On-demand stent exchange should be the preferred strategy

Stent occlusion, the most frequent complication of MPD stenting, is treated by stent exchange. This may be performed either at regular intervals (*i.e.*, 3 months) or “on-demand”, such as in patients with pain recurrence and recurrent MPD dilatation (103).

On-demand stent exchange is the preferred strategy, as the length of the stent’s clinical effect is rather unpredictable : even when clogged, the stent may remain clinically effective (104). Stent replacement was reported to be required after a mean period of 8-12 months using this on-demand strategy (105). Longer stent placement

without exchange should be avoided in order to prevent complications related to long-standing pancreatic stent occlusion.

c) *Should single or multiple stents be used ?*

Statement : The simultaneous placement of multiple, side-by-side, pancreatic stents can be recommended in patients with MPD strictures persisting after 12 months of single plastic stenting

The theoretical advantages of multiple stents consist of the following : greater stricture dilatation, lower frequency of simultaneous stent occlusion, possible drainage of pancreatic secretions alongside the stents even if all stents occlude, potential longer interval between stents replacements, and potential higher rate of stricture calibration.

In one study (106), the calibration of a single distal MPD stricture with multiple stent insertion was observed in 95% of 19 patients over a mean 7-month period. After a mean 38-month follow-up, 84% remained free of pain.

4. *When should surgical options be considered after endoscopic treatment ?*

Statement : We recommend surgery in the following cases : a) technical failure of ET ; b) early (6 to 8 weeks) clinical failure ; c) definitive biliary drainage at a later time ; d) pancreatic ductal drainage when repetitive ET is considered unsuitable in young patients ; e) resection of a pancreatic inflammatory head where pancreatic cancer cannot be ruled out ; f) duodenal obstruction. Pancreatic resection may also be indicated when the disease (isolated ductal obstruction) is confined to the pancreatic tail

Current guidelines recommend performing ET as initial approach, with surgery only considered for cases where all other measures have failed or when symptoms recur (67,73). However, the clinical response to ET should be evaluated at 6-8 weeks. If the response is deemed unsatisfactory, the patient's case should be discussed in a multidisciplinary team involving endoscopists, surgeons, and radiologists. Surgical options should

be considered, particularly for patients with a poor predicted outcome following ET (see above) (67). We highly agree with this recommendation (Table 4).

In addition, ET could be performed as a bridge to surgery in the following cases : for patients where surgery is the optimal approach but should be delayed until inflammatory changes in the pancreatic or peripancreatic area have resolved ; to assess response to ductal decompression as a response predictor of surgery ; for patients who initially refused surgery in favor of ET (94).

VI. Surgical treatment of chronic pancreatitis

Indications for surgery are described in Table 4.

1. *Types of surgical interventions*

Surgical therapy for CP consists of :

- a) surgical drainage of obstructed pancreatic body and tail (longitudinal pancreatico-jejunostomy) ;
- b) resection of pancreatic head or tail (pancreatico-duodenectomy or distal pancreatectomy) ;
- c) combination technique to drain pancreatic body and tail with resection of the inflammatory pancreatic head (duodenum preserving pancreatic head resection according to Frey or Beger) ;
- d) total pancreatectomy with islet transplantation, the most aggressive, though seldomly performed, surgical approach.

Drainage-surgery : longitudinal pancreatico-jejunostomy

In earlier years, the most common drainage surgery was longitudinal pancreatico-jejunostomy (LPJ). In this procedure, the dilated pancreatic duct is incised over its entire length, and a jejunal loop is sutured to the anterior surface of the pancreas. This constitutes a rather simple procedure with low risk of postoperative complications and of exocrine and endocrine insufficiency. In most cases, however, this approach has proven insufficient to relieve pain, especially when the pancreatic head is not adequately drained (107).

Table 4. — **Surgical intervention after initial endoscopic therapy should be discussed in a multidisciplinary approach in the following cases**

<ul style="list-style-type: none"> • Technical or early clinical failure of endoscopic therapy <ul style="list-style-type: none"> – Failure of adequate drainage of the main pancreatic duct – Unsatisfactory clinical response evaluated after 6-8 weeks following initial endoscopic therapy – When repetitive endoscopic therapy is considered too frequent in young patients – Disease confined to the tail (isolated duct obstruction)
<ul style="list-style-type: none"> • Complications at nearby organs <ul style="list-style-type: none"> – Persistent obstruction of duodenum or bile duct due to an enlarged mass in the pancreatic head – Inflammatory erosion of arteries surrounding the pancreas unsuccessfully treated by interventional radiologist
<ul style="list-style-type: none"> • Symptomatic inflammatory mass in the pancreatic head
<ul style="list-style-type: none"> • Recurrent complaints after initial successful endoscopic therapy <ul style="list-style-type: none"> – When stents are removed definitively after 12-24 months

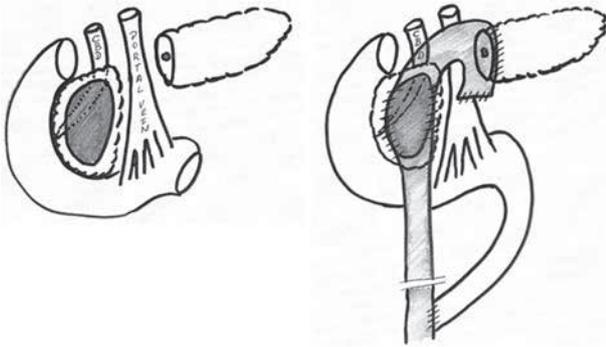


Fig. 1. — Duodenum and bile duct preserving pancreatic head resection according to Beger (CBD : common bile duct).

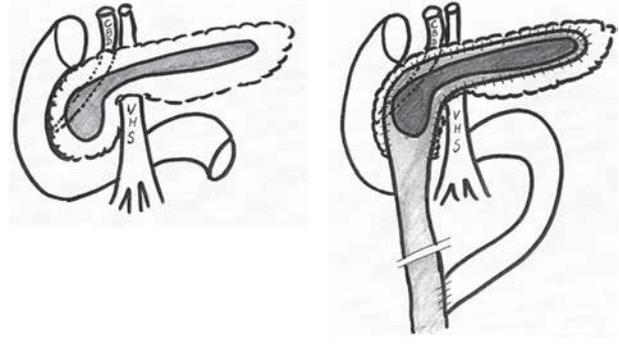


Fig. 2. — Duodenum and bile duct preserving pancreatic head resection according to Frey (CBD : common bile duct, VMS : superior mesenteric vein).

Resection : pancreatico-duodenectomy and distal pancreatectomy

When performing a pancreatico-duodenectomy (PD), the diseased pancreatic head and surrounding duodenum are removed along with the inflamed neural tissue and mesoduodenum. This approach, which has been shown to be effective in treating chronic pain, is certainly indicated in cases of suspected malignancy or groove pancreatitis. Yet long-term postoperative morbidity after PD is significant, involving up to 20% of cases (108).

When performing a distal pancreatectomy (DP), the diseased distal pancreas is removed. As this technique often results in exocrine and endocrine insufficiency, it is only indicated in cases of suspected malignancy or in the presence of pancreatic tail obstruction.

Drainage-resection-technique : duodenum preserving pancreatic head resection (DPHR)

In duodenal-preserving pancreatic head resection (DPHR), two techniques are described in the surgical literature : Beger technique (Fig. 1) and Frey technique (Fig. 2). In both techniques, the diseased pancreatic head is partially excised, with the duodenum and intrapancreatic bile duct left intact. On the cut surface and pancreatic tail, a jejunal loop is sutured so as to drain the entire pancreas (109,110).

The technique's advantages are as follows :

- Only one single anastomosis has to be performed to drain the entire pancreas ;
- Duodenum and intrapancreatic bile duct remain untouched, with advantageous consequences on postoperative nutritional status and gastric emptying ;
- Superior results in resolving chronic pain as compared to PD ;
- Improved exocrine and endocrine function preservation as compared to PD (111) ;

- Better postoperative quality of life as compared to PD (50).

These techniques are currently considered first-choice surgical interventions when dealing with CP.

In a recent meta-analysis, both DPHR techniques were shown to be equally safe and effective compared to PD. With the Beger procedure, complete pain relief could be achieved in a large percentage of patients, yet with a possibly higher postoperative morbidity. With the Frey procedure, a significantly lower postoperative morbidity was demonstrated, though complete pain relief was less commonly achieved when compared to the Beger procedure. Conclusively, both new strategies should be recommended in preference to PD. In terms of quality of life, pancreatic exocrine function, and delayed gastric emptying, the published results were also in favor of duodenum-preserving strategies (112,113).

Total pancreatectomy and islet transplantation

A recent review covering total pancreatectomy followed by islet transplantation was based on five subject-related studies with poor evidence and obvious procedure selection bias. For this rather aggressive approach, the indication was shown to rely on small duct chronic pancreatitis and recurrent pain following celiac plexus block or splanchnicectomy. Insulin independence rates ranged from 46% to 64% at 5 years and up to 28% at 10 years of follow-up. There was a significant reduction in morphine requirements and, based on a questionnaire, 79% of patients felt that surgery had improved their quality of life. Results observed concerning pain reduction were equal to those noted with other surgical interventions. Factors associated with insulin independency were female gender, low body weight, and higher islet equivalents per kg of body weight, which, according to the authors, was an argument in favor of early referral for this procedure (114).

Table 5. — Comparison of endoscopic and surgical results in chronic pancreatitis based on two randomized trials (56,57)

		Endoscopy	Surgery
Izbicki pain score	P < 0.001	51 ± 23	25 ± 15
Technical success	P < 0.001	53%	100%
Complications	P = 0.15	58%	35%
Procedures	P = < 0.001	8 (1-21)	3 (1-9)
	Diagnostic	3 (0-11)	2 (0-8)
	Therapeutic	5 (1-11)	1 (1-5)

2. Endoscopic or surgical treatment

Statements : Duodenopancreatectomy or oncological distal pancreatectomy should be considered in cases of suspected malignancy

Drainage surgery in combination with limited pancreatic head resection (duodenum preserving) appears to be the best surgical strategy in most chronic pancreatitis patients exhibiting early complications or recurrent complaints after endoscopic therapy

Two prospective randomized studies have addressed the longstanding dispute whether either endoscopic or surgical intervention should be the preferred approach in CP treatment. According to Dite *et al.* (56), 34% of the surgically-treated patients were pain-free after 5 years, as compared to 15% of the endoscopically-treated patients. Nutritional status was shown to be superior in the surgically-treated group, with new onset diabetes being comparable in both groups. A second report from Cahen *et al.* (57) showed that 32% of the endoscopically-treated patients exhibited improved pain complaints versus 75% of the surgically-treated patients. Complication ratio, length of hospital stay, and pancreatic function were similar in both groups, though the endoscopically-treated patients underwent more procedures (Table 5).

These studies underline the role of the surgical approach in CP treatment. Correct patient selection in a multidisciplinary approach and appropriate timing for referral to surgery are key to a successful outcome (115).

VII. Chronic pancreatitis in children

1. What are the specificities of chronic childhood pancreatitis ?

Statement : Pediatricians should be aware of and systematically search for CP in the differential diagnosis of chronic abdominal pain. Clinicians should attempt to determine CP etiology

Pancreatitis is a rare clinical entity in children, with an estimated incidence of approximately 4-13/100,000 (116). Recurrence likely occurs in 10% of these patients (117).

Until recently, the causes of CP in children were thought to be idiopathic (51-73.8%), traumatic (10-35%), biliary including congenital malformations like choledochal cyst or anomalous pancreatobiliary junction (14-19%), drug-related (< 10%), hereditary (5-8%), metabolic (2-7%), and other (< 2%). There has been growing evidence that the contribution of genetic or hereditary causes has been underestimated. These etiological factors may, in fact, be responsible for a significant proportion of cases previously diagnosed as idiopathic [118,119]. Pediatric onset CP with a contributory genetic etiology is primarily related to CFTR (14-69%), SPINK (27-57.3%), and PRSS 1 (9.3-24%) mutations. CTRC may also be a putative gene, yet given that screening for this gene has only been routinely available for a short time, this association frequency remains unknown. Moreover, different studies highlight that heterozygous mutations in CFTR with SPINK or PRSS1 may have an additive effect in its contributory role in genetically-determined CP. In this context, systematic screening for mutations in all four of these genes should be performed in children with CP, irrespective of family history (118,119). Furthermore, the systematic search for sensitizing factors, such as passive tobacco exposure, should be performed.

Clinical presentation of pancreatitis in children is similar to that of adults. However, young children cannot verbalize their complaints, which often results in a delayed diagnosis. Pediatricians should therefore be aware of the possibility of pancreatic pathologies in this specific population (117,120). To date, only scarce data has been available that determines the best imaging modality for CP diagnosis in children. However, ultrasonography remains the preferred first-line imaging technique, though the technique is operator-dependent. MRCP after secretin administration seems to be the technique of choice for further imaging in CP. It is worth noting that MRCP needs to be performed under narcosis in children under 6 years, as movement or anatomical particularities (small caliber of non-dilated ducts and poor parenchymal signal) may render the examination poorly contributive. CT scan is not routinely recommended to evaluate pancreatitis in children, as it is associated with high-radiation exposure. The role of EUS or ERCP in CP diagnosis must

particularly be discussed in young children, as other techniques may be less invasive and thus favored for establishing the diagnosis (120).

2. What are the childhood-specific therapeutic options ?

Statement : There is a lack of specific treatment guidelines for CP in the pediatric population. First-line medical treatment should be conservative, while ERCP can be considered for ductal drainage

The medical treatment of CP in children is initially conservative, consisting of withholding fatty food and controlling pain. Based on expert opinion, non-steroidal anti-inflammatory drugs and acetaminophen are first-line agents for pain control. Narcotics can be considered as second-line drugs. Pancreatic enzyme supplementation to reduce the feed-back loop of exocrine pancreatic activation is a controversial technique. The usefulness of antioxidants in pediatric CP has not yet been evaluated. ERCP is indicated in the treatment of symptomatic ductal strictures and pancreatic stones. Ductal decompression can be obtained by performing sphincterotomy or stone extraction with stent placement (120,121). Pancreatic surgery is rarely indicated for childhood CP and is reserved for patients that do not respond to medical or endoscopic therapy (120).

VIII. Complications : pancreatic exocrine insufficiency

1. How should we assess mild/moderate/severe pancreatic exocrine insufficiency ?

Statement : There is no optimal test to assess pancreatic exocrine insufficiency. The 3-day fecal fat test, though unpopular, is considered the gold standard. Suitable alternatives are fecal acid steatocrit or fecal elastase tests

There are numerous available procedures to evaluate pancreatic exocrine insufficiency (PEI), but the fact that so many exist indicates that none reliably detect PEI. In clinical practice, PEI diagnosis is usually based on patient's clinical state assessment, self-reporting of bowel movements, as well as weight loss in adults and failure to thrive in children. A trial with pancreatic enzyme replacement resulting in symptom improvement would support a PEI diagnosis (122,123). In Belgium, however, reimbursement for pancreatic enzymes requires proof of PEI.

The 3-day fecal fat test is considered the gold standard for diagnosing and quantifying steatorrhea, but this procedure is unpopular with patients and laboratory technicians (122). A suitable alternative is the stool acid steatocrit determined on spot samples from a 24-hour stool collection, a reliable, easy, and inexpensive test, which, when compared with 72-hour stool quantitative fecal fat,

displayed a sensitivity of 100% and specificity of 95% (124,125). The ¹³C-MTG is a sensitive (89%) and specific (81%) test to evaluate steatorrhea in mild to moderate disease, and to assess the efficacy of pancreatic enzyme replacement therapy (PERT) (126). This investigation, however, requires local validation and is time-consuming. Of the remaining indirect function tests, fecal elastase-1 (<200µg/g stool) is more accurate in moderate to severe insufficiency, and its simplicity and convenience make it a useful test. In addition, fecal elastase results are independent of PERT (122,67).

2. In which chronic pancreatitis patients is it recommended to screen for pancreatic exocrine insufficiency ?

Statement : Every patient with a diagnosis of chronic pancreatitis should be screened for PEI

In recent guidelines, there is no consensus on the precise timing for PEI screening in PC patients. It seems, however, crucial to assess the patient's nutritional status, as the severity of a pre-existing or developing malnutrition likely affects outcome and vital prognosis.

Clinical symptoms of steatorrhea are observed relatively late in the course of CP, and even in late stages, steatorrhea may be much more common than based only on clinical grounds (67). Due to symptoms being potentially absent or mimicking other diseases, a routine blood test with serum nutritional markers is often helpful as an initial step when malabsorption is suspected, although blood tests alone should not be considered as sufficient to establish a diagnosis (123).

3. What are the clinical/nutritional consequences of pancreatic exocrine insufficiency ?

Statement : Subclinical or clinical steatorrhea may lead to micronutrient deficiencies and malnutrition

Maldigestion of dietary macronutrients (fat, proteins, and carbohydrates) leads to malnutrition. The main clinical manifestations of PEI are fat malabsorption (commonly manifesting as steatorrhea), weight loss, abdominal discomfort, and distension. Overt steatorrhea (characterized by voluminous, yellowish, and foul-smelling stool) occurs in approximately one-third of CP patients (127). Steatorrhea is usually observed prior to protein deficiencies, as lipolytic activity decreases faster than proteolysis (128). Steatorrhea is distressing, socially embarrassing, and may facilitate the occurrence of hyperoxaluria, urinary oxalate stones, and renal insufficiency (8). This condition may also impact working ability, cognitive functioning, financial strain, and overall QoL (129).

In addition, malabsorption of fat-liposoluble vitamins (A, D, E, and K) may occur, yet clinically-symptomatic vitamin deficiencies are rare (82,130,131). Nevertheless, almost one in four CP patients exhibit osteoporosis, while almost two-thirds have either osteoporosis or

osteopenia due to vitamin D deficiency (132), malabsorption of calcium, poor dietary intake, or other factors like smoking. Therefore, calcium and vitamin D supplementation, as well as regular monitoring of bone health, should be an integral part of CP nutrition management (81). Vitamin E deficiency may occur more often than that of vitamin A, D, and K, potentially affecting as many as 75% of cases. This deficiency may be more prevalent in the presence of steatorrhea, malnutrition, and alcoholic CP, regardless of dietary intake. Impaired night vision has also been observed (133).

Specific deficiencies in calcium, magnesium, zinc, prealbumin, iron, thiamine, vitamin B12, folic acid, and essential fatty and amino acids have also been reported (134). These may lead to tetany, glossitis, and cheilosis, and even to peripheral neuropathy in a more progressive stage. Furthermore, reduced plasma lipoprotein levels can increase the risk of cardiovascular events (arterial involvement, coronary heart disease, and aortic calcifications), independently of lifestyle factors (135). Moreover, qualitative fat maldigestion might clinically impact glucose metabolism, and exocrine disease might enhance the risk of diabetes mellitus (136).

4. Which dietary management should be used for pancreatic exocrine insufficiency ?

Statement : Patients should follow a healthy balanced diet taken in short meals and snacks, with a normal fat content. Medium-chain triglycerides are not recommended in first intention

Although there is no specific diet to follow, patients should be advised to pursue a well-balanced diet in line with the "food pyramid chart". Fat restriction is no longer advocated (16,67,82,83). Low-fat diets are inferior in terms of total energy, and restricting fat intake also reduces the intake of fat-soluble vitamins. Patients should be advised to consume an at least normal fat intake (*e.g.*, 30% energy from fat). All meals and snacks should contain some fat in order to spread the recommended fat intake over the whole day.

Frequent small meals should be preferred and alcohol stopped. Six or more smaller meals throughout the day, combined with suitable enzyme therapy, likely reduce the risk of residual fat malabsorption. Smaller meals and snacks exhibit better tolerance (less anorexia and nausea), along with more efficient gastric mixing, as well as simultaneous gastric emptying of the chyme with enzymes.

Medium-chain triglycerides are not recommended in the first stages (137). Despite theoretical benefits (pancreatic enzymes or bile unnecessary for absorption), they do not provide any clear nutritional advantage over the usual long-chain triglycerides in patients using pancreatic enzymes. Moreover, they are poorly tolerated in many patients, as they are associated with side-effects such as abdominal pain, nausea, and diarrhea. Medium-chain triglycerides are, therefore, rarely used.

Diet counseling is best achieved with the involvement of a specialized dietician (83). Her/his role is to make a full assessment of the patient's nutritional habits, including total energy, fat, and protein intake, as well as to advise improvements and monitor compliance and results.

5. How should pancreatic exocrine insufficiency be treated ?

Statement : Enzyme replacement therapy is beneficial for symptomatic patients, but also in cases of subclinical insufficiency. Enteric-coated preparations should be taken with each meal or snack containing fat, and dosage should be adapted to the meal's fat content. Weight gain and symptom improvement correlate with adequate enzyme use

Pancreatic enzyme replacement therapy is recommended for patients with clinical features of exocrine insufficiency or with proven pancreatic insufficiency (138,139). Enzyme supplementation should certainly be started in symptomatic patients with steatorrhea, diarrhea, and weight loss, with the aim of suppressing maldigestion and malabsorption and restoring adequate nutrition and weight gain. In cases of subclinical exocrine insufficiency (symptom-free but abnormal testing), treatment is also recommended.

The only pancreatic enzyme preparation is a porcine extract encapsulated in enteric-coated mini-microspheres (140). The preparation is available in capsules of three different strengths : Creon 10,000, 25,000, and 40,000 lipase U.

In adults, the initial dosage recommended is 25,000-40,000 units of lipase with every meal, and 10-25,000 units of lipase with snacks. Dosage can then be titrated up to a maximum of 10,000 units/Kg/day (141,142). In children, the initial recommended dosage is 1000 units/Kg/meal.

Pancreatic enzymes should be taken during all meals or snacks containing fat. Fat-free snacks like fruits, jelly, or juices do not require enzyme intake (143). Patients should be educated to modulate pancreatic enzyme dosage according to the meals' fat content. Self-dosing of pancreatic enzymes correlates with improved symptom relief (144).

The treatment response is measured clinically by weight gain and improvement in symptoms like steatorrhea. When symptoms of exocrine insufficiency persist in spite of adequate PERT, function tests (mixed triglycerides breath, acid steatocrit, and quantitative fecal fat) are indicated in order to evaluate treatment efficacy (126,145,146).

6. What should be done in cases of unsatisfactory clinical response ?

Statement : In cases of unsatisfactory clinical response, compliance and adequate use of enzymes should be checked, proton pump inhibitors added, and other malabsorption syndromes ruled out

In cases of unsatisfactory clinical response, dosage of pancreatic enzymes should be optimized, and compliance and adequate use of pancreatic enzymes checked. Otherwise, acid-suppressing agents (proton pump inhibitors) should be added at a standard dose (145).

If the patient is still not responding to treatment, other malabsorption syndromes (such as *Giardia* infestation, coeliac disease, bacterial overgrowth, and cholestasis) must be ruled out (146).

IX. Complications : pancreatogenic diabetes

1. What are the specificities of diabetes secondary to chronic pancreatitis ?

Patients with pancreatic endocrine insufficiency, abnormal pancreatic imaging, and absence of diabetes-associated antibodies are classified as pancreatogenic or Type 3c diabetes (T3cDM) according to the American Diabetes Association classification (147). Diabetes mellitus has been observed in 26-80% of CP patients (148). Hyperglycemia is typically relatively mild, yet blood glucose control may be labile due to the loss of glucagon response to hypoglycemia, carbohydrate malabsorption, and inconsistent eating patterns associated with pain or nausea. T3cDM often presents as brittle diabetes (149-151). In these cases, complications like macro- or microangiopathy, nephropathy, neuropathy, and retinopathy are as common as in Type 1 diabetes patients. CP and diabetes are both risk factors for developing pancreatic cancer (152).

2. What is the recommended treatment for pancreatogenic diabetes ?

There is a lack of data for evidence-based practice in these patients. As the principal endocrine defect is insulin deficiency, insulin therapy is the preferred treatment for most patients, in compliance with general insulin dosing and regimen guidelines for Type 1 diabetes. Given that the degree of insulin deficiency is dependent on disease severity and duration, controlling mild hyperglycemia using oral hypoglycemic agents early in the disease course may be a valid approach. Many T3cDM patients are initially treated with metformin as drug of first choice (151,152). In a retrospective study, metformin has been shown to reduce the risk of pancreatic cancer by 70% (153). In addition, this drug was reported to be associated with a significant reduction in cancer-related mortality (154,155). However, more studies are warranted before a definite conclusion can be made as to the recommendation of metformin for oncologic considerations.

X. Follow-up

1. How should a patient with chronic pancreatitis treated by medical, endoscopic, or surgical therapy be followed up ?

Statement : Follow-up should be implemented in patients with chronic pancreatitis, primarily in order to detect subclinical maldigestion and the development of pancreatogenic diabetes

Patient follow-up should be concerned with the development of endocrine and exocrine insufficiency, effectiveness of ductal drainage, detection of local complications, and screening for cancer (for specific etiologies, such as hereditary pancreatitis) (67,73,76,81,157,131). CP is an ongoing process that may not be altered by any treatment except total pancreatectomy. Follow-up is therefore mandatory and should include clinical features (weight loss and steatorrhea), nutritional parameters, and metabolic abnormalities (diabetes, osteopenia, and hyperoxaluria). Clinical check-up (including body weight and BMI) and laboratory follow-up (including glycemia, complete blood count, comprehensive metabolic panel, international normalized ratio, as well as levels of albumin, prealbumin, vitamin D, and carotene or other fat-liposoluble vitamins) every 6-12 months seem reasonable (157). Patients with exocrine insufficiency and risk factors (frail patients and smokers) should undergo bone densitometry, on a case-by-case basis, because of the risk of osteopenia or osteoporosis due to vitamin D deficiency.

Should we consider differences in the follow-up between medical, endoscopic, or surgical treatments ? Differences may first relate to the disease severity when treatment is undertaken, type of surgery (drainage vs. resection) used, as well as completeness of endoscopic drainage and stone extraction. Surgery may induce deterioration of endocrine function resulting in a more unstable form of pancreatogenic diabetes. The placement of stents via endoscopy induces a need for stent patency control by means of regular CT scan or MRI. This should equally be a good opportunity for further dietary counseling and advising patients to stop smoking.

2. What are the effects of ductal drainage (by endoscopic or surgical means) on the natural history of chronic pancreatitis, especially regarding endocrine and exocrine pancreatic functions ?

Statement : There is no evidence for treating asymptomatic patients with morphological features of chronic pancreatitis

There are only a few studies reporting long-term effects on pancreatic function following endoscopic or surgical therapy, and the results are conflicting (96,98,158-160). Currently, therefore, there is no consensus on the long-term effects of surgery and endoscopy on pancreatic endocrine and exocrine function. The natural disease history remains related to the factors leading to inflammation and fibrosis, and particularly alcohol and smoking continuation.

The question of whether to treat painless CP with ductal obstruction in order to avoid or postpone pancreatic endocrine or exocrine insufficiency remains unanswered. Several surgical and endoscopic trials reported improved function after ductal decompression, yet this procedure is not recommended outside of the clinical trial setting (161,162).

3. How should the risk of cancer be dealt with in chronic pancreatitis patients ?

Statement : Screening for pancreatic cancer is not recommended in patients with chronic pancreatitis, except in hereditary pancreatitis

The incidence of pancreatic cancer is increased in long-lasting CP, and the relation of CP to pancreatic cancer has been addressed in several epidemiological case-control and cohort studies (4,151,163-169). Given the wide variability in relative risk of developing pancreatic cancer found in CP studies compared to the general population, a panel of experts classified this disease as carrying a moderate risk (*i.e.*, 5- to 10-fold) (170). This moderate risk does not justify screening for pancreatic cancer, as screening is only recommended for patients with a relative risk of pancreatic cancer higher than 10. Yet screening is indicated in patients with hereditary pancreatitis who have a higher relative risk of developing cancer (> 50-fold) (170).

In addition, more attention should be paid in order to detect pancreatic cancer in patients over 50 years of age presenting with diabetes, loss of weight, and jaundice, and this in the absence of pancreatic calcifications. Routine testing of CA 19-9 is not recommended during CP follow-up. Triple-phase CT scan with time-attenuation curves has been recommended as first-choice procedure to detect cancer, followed by MRCP, EUS-FNA, and PET-CT scan (73).

4. What is the late mortality related to chronic pancreatitis ?

Statement : The mortality of patients with chronic pancreatitis is higher than that of the general population, with malnutrition, cardiovascular events, and cancer being the leading causative factors

The mortality of CP patients is higher than that of the general population (171-174), though mortality predictors are not easy to determine. There are only a few studies available, with conflicting outcome data. However, some causes have been clearly established, such as pancreatic cancer and being underweight. Maldigestion may result in low circulating levels of fat-soluble vitamins, lipoproteins, and micronutrients, which have been associated with high morbidity and mortality rates secondary to malnutrition-related complications and cardiovascular events (175). On the other hand, endocrine insufficiency is not a well-established risk factor of mortality (176). In

addition, late mortality may be related to other cancers, such as oropharyngeal, lung, and esophageal tumors, which are also linked to alcohol use and smoking behavior.

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