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Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis

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ABSTRACT

Background: In collaboration with United European Gastroenterology, the working group on 'Harmonizing diagnosis and treatment of chronic pancreatitis across Europe' (HaPanEU) developed European guidelines for the management of chronic pancreatitis using an evidence-based approach.
Methods: Recommendations of multidisciplinary review groups based on systematic literature reviews to answer predefined clinical questions are summarised. Recommendations are graded using the Grading of Recommendations Assessment, Development and Evaluation system.
Results: Recommendations covered topics related to the clinical management of chronic pancreatitis: aetiology, diagnosis of chronic pancreatitis with imaging, diagnosis of pancreatic exocrine insufficiency, surgical therapy, medical therapy, endoscopic therapy, treatment of pancreatic pseudocysts, pancreatic pain, nutrition and malnutrition, diabetes mellitus and the natural course of the disease and quality of life.
Conclusions: The HaPanEU/United European Gastroenterology guidelines provide evidence-based recommendations concerning key aspects of the medical and surgical management of chronic pancreatitis based on current available evidence. These recommendations should serve as a reference standard for existing management of the disease and as a guide for future clinical research. This article summarises the HaPanEU recommendations and statements.

Abbreviations: CEL, carboxyl ester lipase; CFA, coefficient of fat absorption; CFTR, cystic fibrosis transmembrane regulator; ^{13}C-MTG-BT, ^{13}C-mixed triglyceride breath test; CP, chronic pancreatitis; CPA1, carboxypeptidase A1; CPRD, chronic pancreatitis-related diabetes; CT, computed tomography; CTRC, chymotrypsin C; DPPHR, duodenum preserving pancreatic head resection; EUS, endoscopic ultrasound; FE-1, faecal elastase-1; GRADE, grading of recommendations assessment, development and evaluation; HaPanEU, harmonizing pancreatitis across Europe; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PD, pancreaticoduodenectomy; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; PRSS1, cationic trypsinogen; QoL, quality of life; SPINK1, serine protease inhibitor Kazal-type 1; UEG, United European Gastroenterology; US, ultrasound.

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Introduction

The Harmonizing diagnosis and treatment of chronic pancreatitis across Europe (HaPanEU) initiative of United European Gastroenterology (UEG) aims to provide the community with evidence-based, state-of-the-art clinical guidelines to help in the management of patients with chronic pancreatitis (CP) [1]. The statements are based on the recent guidelines and recommendations published by the Australian [2], Belgian [3], German [4], Hungarian [5], Italian [6], Romanian [7], and Spanish [8,9] Societies of Gastroenterology and Pancreatology, as well as pertinent new literature.

The recommendations format comprised the question, the statement, its level of evidence and strength of recommendation, and the percentage agreement of the global consensus group with the final version. With this aim, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was applied: strength of recommendation (1 = strong, 2 = weak) and quality of the evidence (A = high, B = moderate, C = low) [10,11]. Recommendations with ≥90%, 70–89%, 61–69% or ≤60% consensus were defined as strong agreement, moderate agreement, agreement and weak agreement, respectively.

The full document of the HaPanEU guidelines was published elsewhere [1]. This article summarises the recommendations and statements for a rapid overview and quick reference. New papers published after the HaPanEU guidelines do not contradict these recommendations.

Definition and aetiology

Definition of CP (regardless of the aetiology)

- CP is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of the pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganisation of the pancreas leads to progressive exocrine and endocrine pancreatic insufficiency. *(Strong agreement).*

What needs to be done to define the aetiology of CP patients?

- It is recommended that a comprehensive medical history (including alcohol abuse, smoking and family history), laboratory evaluation (including Ca^{2+} and triglyceride levels) and imaging studies (including abdominal ultrasound –US-, computed tomography –CT-scan or magnetic resonance cholangiopancreatography –MRCP-) are performed in patients with CP. *(GRADE* 2C, *strong agreement).*
- All patients with a family history or early onset disease (<20 years) should be offered genetic testing for associated variants. Testing should include PRSS1 (sequencing of exon 2 and 3 to cover mainly p.A16V, p.N29I and p.R122H), SPINK1 (all four exons, mainly p.N34S and c.194+2T > C in exon 3 and intron 3), CPA1 (several variants, mainly in exons 7, 8 and 10), CTRC (especially exon 7), CEL (hybrid allele only) and may include screening for variants in CFTR. *(GRADE* 2C, *strong agreement).*
- A diagnosis of cystic fibrosis needs to be ruled out in children and all patients with CP onset before the age of 20 years as well as in patients with so-called 'idiopathic' CP (regardless of the age of onset). *(GRADE* 1B, *strong agreement).*
- If no other aetiology of CP can be identified, then the diagnosis of autoimmune pancreatitis should be ruled out following current consensus guidelines [12]. *(GRADE* 2C, *strong agreement).*
- Classification systems like the TIGAR-O [13] and the M-ANNHEIM [14] can be used to classify the aetiology of CP. *(GRADE* 2C, *strong agreement).*

Diagnosis

- Endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and CT are the best imaging methods for establishing a diagnosis of CP. EUS outperforms MRI and CT. Abdominal ultrasound is the least accurate imaging technique for CP, whereas endoscopic retrograde cholangiopancreatography (ERCP) is not considered a diagnostic procedure due to its invasiveness. *(GRADE* 1C, *strong agreement).*
- CT examination is the most appropriate method for identifying pancreatic calcifications, while for very small calcifications non-enhanced CT is preferred. *(GRADE* 2C, *strong agreement).*

MRI/MRCP examination for the diagnosis of CP

- The presence of typical imaging findings for CP with MRI/MRCP is sufficient for diagnosis; however, a normal MRI/MRCP result cannot exclude the presence of mild forms of the disease. *(GRADE* 1C, *strong agreement).*
- The use of intravenous secretin (s-MRCP) increases the diagnostic potential of MRCP in the evaluation of patients with known/suspected CP since it enhances visualization of the main pancreatic duct and side branches, it reveals strictures or abnormal dilatations, and it may quantify exocrine secretion *(GRADE* 1C, *strong agreement).*
- Duodenal filling during s-MRCP does not help to evaluate the severity of CP, but it may assess the exocrine pancreatic functional reserve. *(GRADE* 2C, *moderate agreement).*

Abdominal US in patients with suspected or known CP

- Abdominal US can only be used to diagnose CP at an advanced stage due to its low accuracy. Additional limitations are operator-dependency and obscured visualization of the pancreas due to obesity or intestinal gas *(GRADE* 1A, *strong agreement).*
- In recognised CP, US can be used to visualise CP complications such as pseudocysts and pseudoaneurysms. *(GRADE2C, strong agreement).*
- Contrast-enhanced US can increase the diagnostic accuracy in CP patients with cystic and solid pancreatic lesions. *(GRADE* 1C, *strong agreement).*

EUS in patients with suspected or known CP

- EUS is the most sensitive imaging technique for the diagnosis of CP, mainly during the early stages of the disease, and its specificity increases with increasing diagnostic parenchymal and ductal criteria. *(GRADE* 1B, *strong agreement).*
- EUS has a potential role in the follow-up of patients with CP in the detection of complications, mainly due to its ability in detecting pancreatic malignancy. *(GRADE* 2B, *strong agreement).*
- EUS is an essential tool in the differential diagnosis of CP with other pancreatic masses or cystic lesions. EUS-guided fine needle biopsy can be considered as the most reliable procedure for detecting malignancy, however its sensitivity decreases in case of underlying CP. EUS-guided elastography and contrast enhancement may provide useful information, but their role in this setting needs to be assessed further in future clinical trials. *(GRADE* 2C, *strong disagreement).*

Diagnosis of pancreatic exocrine insufficiency (PEI)

- PEI refers to an insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function) to maintain a normal digestion. *(GRADE* 1A*, strong agreement).*
- Due to the large reserve capacity of the pancreas, 'mild' to 'moderate' exocrine insufficiency can be compensated, and overt steatorrhoea is not expected unless the secretion of pancreatic lipase is reduced to <10% of normal ('severe'/ 'decompensated' insufficiency). However, patients with 'compensated' PEI also have an increased risk of nutritional deficiencies (in particular, of lipid-soluble vitamins with respective clinical consequences). *(GRADE* 1B*, strong agreement).*
- In CP, PEI results from a progressive loss of pancreatic parenchyma, and exocrine pancreatic function gradually decreases during the course of the disease. Thus, morphological signs of CP and functional impairment usually develop in parallel, but this is not always the case. *(GRADE* 1B*, strong agreement).*

s-MRCP for the diagnosis of PEI

- The s-MRCP technique reveals ductal morphological alterations and simultaneously gives semi-quantitative information on functional changes. Therefore, s-MRCP is probably the most appropriate morphological test for the assessment of pancreatic exocrine function. *(GRADE* 1C*, agreement).*

Pancreatic function tests for the diagnosis of PEI

- In a clinical setting, a non-invasive pancreatic function test should be performed for the diagnosis of PEI. The coefficient of fat absorption (CFA) is generally accepted as the gold standard, but it is neither specific nor easily applicable to clinical practice. The fecal elastase-1 (FE-1) test is feasible and widely available and is therefore most frequently used in this setting. Very low FE-1 values are most probably associated with PEI, whereas high values allow to exclude it. The ^{13}C mixed triglyceride breath test (^{13}C-MTG-BT) offers an alternative to CFA, but availability is limited. *(Grade* 1B*, agreement).*
- A function test is also required for the diagnosis of CP, particularly in patients with inconclusive morphological changes of the disease. *(Grade* 2B*, strong agreement).*
- Every patient with a new diagnosis of CP should be screened for PEI with a pancreatic function test, since morphological findings and symptoms are not reliable in this setting. *(Grade* 1A*, strong agreement).*
- In order to detect maldigestion prior to the occurrence of overt clinical symptoms, the presence of PEI should be evaluated annually in patients with CP. Apart from this, function tests should be repeated if previously normal when symptoms occur or deteriorate and can be attributable to PEI. *(Grade* 1B*, strong agreement).*

Nutritional markers and assessment of efficacy of enzyme replacement therapy

- To evaluate the efficacy of enzyme replacement therapy, it is sufficient in most cases to verify the normalisation of nutritional parameters and symptomatic improvement. When symptoms of exocrine insufficiency persist in spite of adequate pancreatic enzyme replacement therapy (PERT), function tests (^{13}C-MTG-breath test and quantitative faecal fat) are recommended to evaluate treatment efficacy. *(Grade* 2B*, strong agreement).*
- Established blood nutritional parameters such as prealbumin, retinol-binding protein, transferrin, fat soluble vitamins, and minerals/trace elements (including serum iron, zinc and magnesium) should be quantified to measure malnutrition in patients with CP. *(GRADE* 2C*, strong agreement).*

Surgical treatment of CP

Surgical treatment has no role in asymptomatic and uncomplicated CP. This section deals with the technical aspects of surgical treatment; the treatment for pain is detailed in section 8.

- Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP. *(GRADE* 2B*, agreement).*
- Early surgery is favoured over surgery at a more advanced stage of the disease in terms of optimal long-term pain relief, long-term improved QoL, and risk of postoperative PEI *(GRADE 2B-2C, weak agreement).* In addition, pancreatic resection techniques have a higher risk of PEI than drainage techniques. *(GRADE* 2C*, weak agreement).* No recommendation can be drawn from the evidence regarding the effect of early surgery on developing endocrine pancreatic function. *(GRADE* 2C*, strong agreement).*

Surgical treatment in patients with enlarged pancreatic head

- In patients with CP and an enlarged pancreatic head (>4 cm in diameter on CT or MRI imaging), duodenum-preserving pancreatic head resection (DPPHR) and conventional pancreaticoduodenectomy (PD) are equally effective for short-term and long-term pain relieve. Endocrine and exocrine insufficiency are comparable after both strategies at the short-term and long-term assessment, and neither DPPHR nor PD succeed in interrupting the progression of CP toward endocrine and exocrine failure. *(GRADE* 1B*, strong agreement).* QoL is significantly improved after DPPHR compared to PD. *(GRADE* 1B*, agreement),* and occupational rehabilitation remains significantly better with DPPHR compared to PD. *(GRADE* 2B*, strong agreement).* There is a non-significant trend towards improved long-term mortality with DPPHR. *(GRADE* 2B*, strong agreement).*
- Modifications of DPPHR – the Beger and Berne procedures – are equal in terms of pain relief, postoperative morbidity and mortality. The operating time and length of hospital stay is significantly shorter for the Berne procedure than for the Beger procedure. *(GRADE* 1B*, strong agreement).* There are no differences in long-term outcomes between the Beger, Berne and Frey procedures. *(GRADE* 1B*, strong agreement).*

Surgical treatment in patients without duct system dilatation

- A total pancreatectomy should be considered in patients without duct system dilatation (main duct diameter <5 mm), who have severe pain resistant to conventional medical,

endoscopic and previous surgical treatment. *(GRADE* 1C, *agreement).*

Surgical treatment in patients with a dilated pancreatic duct

- For patients with painful CP, a dilated main pancreatic duct (≥5 mm) and a normal-sized pancreatic head (<4 cm in diameter), a lateral pancreaticojejunostomy with a Roux-en-Y loop and Frey's procedure provide comparable pain control (low quality of evidence). No recommendation can be made for the preferred surgical technique in these patients. *(GRADE* 2B, *strong agreement).*
- An experienced high volume pancreatic centre is recommended for the surgical treatment of CP. The decision for surgery in CP should be made by an interdisciplinary expert panel that includes at least surgeons, endoscopists and gastroenterologists. *(GRADE* 2C, *strong agreement).*

Surgical treatment in patients with groove pancreatitis

- In patients with groove (paraduodenal) pancreatitis, the initial therapy should involve medical treatment; endoscopic drainage procedures may occasionally be helpful. If these approaches fail, the patient should be referred for surgery. *(GRADE* 2C, *strong agreement).*
- Surgery should be aimed at pain relief and/or complete pain resolution, and should solve the patient's malnutrition status (body weight gain), on condition that the patient stops alcohol and drug abuse. *(GRADE* 2C, *strong agreement).*
- In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis. *(GRADE* 2C, *strong agreement).*

Medical therapy for exocrine pancreatic insufficiency

- PERT is indicated for patients with CP and PEI in the presence of clinical symptoms or laboratory signs of malabsorption (nutritional deficiencies). An appropriate nutritional evaluation is recommended to detect signs of malabsorption. *(GRADE* 1A, *strong agreement).*
- Enteric-coated microspheres or mini-microspheres of <2 mm in size are the preparations of choice for PEI. Micro- or mini-tablets of 2.2–2.5 mm in size may be also effective, although scientific evidence in the context of CP is more limited. Comparative clinical trials of different enzyme preparations are lacking. *(GRADE* 1B, *strong agreement).*
- Oral pancreatic enzymes should be distributed along with meals and snacks. *(GRADE* 1A, *strong agreement).*
- A minimum lipase dose of 40,000–50,000 Ph.U. (Eur.Ph.U. or USP) is recommended with main meals, and half that dose with snacks. *(GRADE* 1A, *strong agreement).*
- The efficacy of PERT can be evaluated adequately by the relief of maldigestion-related symptoms (e.g. steatorrhoea, weight loss, flatulence) and the normalisation of the nutritional status of the patients. In non-responder patients, the use of pancreatic function tests (CFA or ^{13}C-MTG-BT) with oral enzymes may be of help. *(GRADE* 1B, *strong agreement).*
- In cases of unsatisfactory clinical response, the enzyme dose should be increased (doubled or tripled) or a proton pump inhibitor (PPI) should be used. *(GRADE* 1B, *strong agreement).* If these strategies fail, another cause for maldigestion should be sought. *(GRADE* 2B, *strong agreement).*

Endoscopic therapy (ET)

- ET has no role in asymptomatic and uncomplicated CP. *(GRADE* 2B, *agreement).* This section deals with the technical aspects of ET and the treatment for pain is detailed in section 8.

Patients with painful CP and dilated main pancreatic duct (MPD)

- In patients with uncomplicated painful CP and a dilated MPD, ET is recommended as the first-line treatment after failed medical therapy following discussions by a multidisciplinary team. The clinical response should be evaluated at 6–8 weeks; if it appears unsatisfactory, the patient's case should be discussed again by a multidisciplinary team of endoscopists, surgeons and radiologists, and surgical options should be considered. *(GRADE* 2B, *agreement).*
- The efficacy of ET has been found to be lower compared with surgery in a single randomised trial, but this included a small number of highly selected patients at the later stage of the disease. *(GRADE* 2B, *agreement).*
- The best responders to ET are patients with obstructing stones located in the head of the pancreas, complete stone clearance and absence of MPD stricture, with a short disease duration and a low frequency of pain attacks before ET, together with the discontinuation of alcohol and tobacco. *(GRADE* 2B, *agreement).*

Role of extracorporeal shock wave lithotripsy (ESWL) in patients with calcifying CP

- ESWL can be considered as first-step treatment for larger, radiopaque stones (≥5 mm) obstructing the MPD, and is usually followed by the endoscopic extraction of stone fragments (*Grade* 1B). In centres with expertise, ESWL alone may be a more cost-effective option. *(GRADE* 2C, *agreement).* We suggest performing non-contrast enhanced computed tomography before ESWL to determine the location, size, number and density of stones (weak recommendation, low quality evidence). *(GRADE* 2C, *agreement).*
- ESWL should target stones with a minimal diameter of 2–5 mm, starting in the head of the pancreas and progressing to the tail to permit elimination of stone fragments. *(GRADE* 2C, *agreement).*
- Pancreatitis is the most frequent complication of ESWL. Other complications include haematuria, gastrointestinal bleeding, hepatic subcapsular haematoma and perforation. *(GRADE* 2C, *agreement).*
- At long-term after ESWL alone or combined with endoscopic stone extraction, pain relapses requiring analgesics or more invasive treatment has been reported in 5–45% of patients. *(GRADE* 2B, *agreement).*

ET of dominant main pancreatic duct strictures

- Dominant MPD strictures in the head of the pancreas are defined as strictures with an upstream MPD dilation ≥6 mm in diameter or strictures that prevent the outflow of contrast medium. Stricture dilation alone has yielded disappointing results while satisfactory long-term results have been reported in more than two-thirds of patients with temporary plastic stenting. *(GRADE* 1C, *agreement).*
- The use of straight polyethylene pancreatic stents (8.5–10 Fr) with the shortest possible length, tailored to the location of the MPD stricture is recommended. Thinner MPD stents (≤8.5 Fr)

are associated with more frequent hospitalisations for abdominal pain than 10 Fr stents. *(GRADE* 1C, *agreement).*
- Stent exchange may be performed either at regular intervals (for example, three months) or 'on-demand' in patients with a recurrence of pain and MPD dilatation. However, an "on demand" stent exchange is the preferred strategy, as the duration of the clinical effect is unpredictable and is not correlated with stent clogging. *(GRADE* 1B, *agreement).*
- It is recommended to treat dominant MPD strictures located in the head of the pancreas and associated with pain by single plastic stenting for at least 12 months with at least one planned stent exchange within one year to prevent complications related to longstanding pancreatic stent occlusion. Criteria used for not replacing a temporary plastic stent after removal are adequate contrast medium outflow in the duodenum and easy passage of a 6 Fr catheter through the residual dilated stricture. *(GRADE* 1B, *agreement).*
- For refractory MPD strictures (defined as persistent symptomatic dominant strictures after one year of single stent placement) multiple pancreatic duct stenting, a trial of 3–6 months with a fully covered self-expandable metallic stent (FC-SEMS) or surgical pancreaticojejunostomy is recommended. *(GRADE* 2C, *agreement).*
- Simultaneous placement of multiple, side-by-side, pancreatic stents could be applied more extensively, particularly in patients with MPD strictures persisting after 12 months of single plastic stenting. *(GRADE* 1C, *agreement).*
- Adverse events of pancreatic duct stenting include stent occlusion and stent migration. (GRADE 1B, agreement).

ET for common bile duct (CBD) stricture secondary to CP

- CBD strictures should be treated if responsible for symptomatic (recurrent acute cholangitis, obstructive jaundice) or persistent (>1 month) cholestasis. Temporary biliary stenting, usually for one year with regular stent exchange in the case of plastic stents, is the mainstay of treatment. We suggest electing ET for patients deemed to comply with repeat ERCPs and who are at high surgical risk, present with portal hypertension or have local abdominal conditions contraindicating surgery. Multiple side-by-side plastic stents or FC-SEMS, no single plastic stents, should be used. *(GRADE* 2C, *agreement).*
- Resective surgery should be considered in other patients as well as those with an inflammatory mass of the head of the pancreas or suspected neoplasia. *(GRADE* 2A, *strong agreement).*

Treatment of pancreatic pseudocysts (PPC)

- Chronic PPC should be treated in the presence of symptoms, complications (infection, bleeding, or rupture), or compression of surrounding organs (gastric, duodenal or biliary obstruction). *(Grade* 2A, *strong agreement).*
- Treating asymptomatic PPCs, which have reached a size of >5 cm in diameter and which do not resolve within 3–6 months, should also be considered due to the risk of PPC complications. *(GRADE* 2C, *strong agreement).*
- In the presence of a recent episode of acute pancreatitis or if the PPC was not detected on prior examinations, the PPC should be observed for at least six weeks to allow for either spontaneous resolution or maturation of the cyst wall. *(GRADE* 1B, *strong agreement).*
- ET is recommended for chronic PPCs whenever possible. Transpapillary drainage is preferred over transmural drainage for small (<6 cm) PPCs communicating with the main pancreatic duct in the head or body of the pancreas. If transmural pseudocyst drainage is elected: (a) it should be performed under echoendoscopic guidance and (b) several double-pigtail plastic stents should be inserted to drain the PPC into the digestive lumen until cyst resolution, with a minimum of two months of stenting. *(Grade* 2A, *strong agreement).*
- In the presence of pancreatic duct stones and/or pancreatic duct stenosis, a pseudocyst should be treated as part of an overall therapeutic concept. *(GRADE* 1B, *moderate agreement).*
- Diagnostic EUS-guided fine needle aspiration of a cyst may be performed for suspected infected cystic contents or for suspected cystic neoplasm. *(GRADE* 2C, *strong agreement).*
- If a malignant cystic lesion is suspected, a surgical therapeutic approach should be chosen. *(GRADE* 1C, *strong agreement).*

Treatment of vascular pseudoaneurysms

- Vascular pseudoaneurysms that develop secondary to CP should be treated. *(GRADE* 1C, *strong agreement).*
- Angiographic embolisation is the method of choice for the treatment of haemorrhagic pseudoaneurysms. Surgery remains reserved mainly for patients in whom an operation is also indicated for other CP complications. *(GRADE* 1C, *strong agreement).*

Treatment of pain in CP

- Pain is the first presentation of CP in the majority of patients. *(GRADE* 1B, *strong agreement).* There is no evidence that pain symptoms 'burn out' in all patients with ongoing CP. *(GRADE* 2C, *moderate agreement).* There is no convincing evidence that endocrine and exocrine pancreatic insufficiencies are associated with pain relief. *(GRADE* 2C, *moderate agreement).*
- Pain intensity and the pain pattern over time (constant vs intermittent pain) have been shown to reduce QoL in patients with CP. *(GRADE* 1A, *strong agreement).*
- Pancreatic (stones, strictures, inflammatory masses, PPC) and extra-pancreatic complications (e.g. peptic ulcer, gastrointestinal cancer) may contribute to pain in the individual patient and should be thoroughly investigated at the time of diagnosis and if pain symptoms are worsening. *(GRADE* 1B, *strong agreement).*
- Pain in CP should be assessed using a multidimensional approach, including evaluation of pain intensity (e.g. VAS), pain pattern (constant vs intermittent) and its impact on daily function and QoL (e.g. QLQ-C30). *(GRADE* 1B, *strong agreement).*

Medical therapeutic strategies for pain in CP

- Cessation of alcohol, and possibly smoking, improves pain in CP and is highly recommended. *(GRADE* 1B, *moderate agreement).*
- PERT is not recommended for pain treatment in CP, although it may have beneficial effects on abdominal discomfort related to PEI. *(GRADE* 1B, *moderate agreement).*
- Antioxidants are not generally recommended for pain treatment in CP. *(GRADE* 1B, *moderate agreement).* The efficacy of antioxidant therapy may be related to the aetiology of CP and associated malnutrition. Although antioxidants can reduce pain slightly in patients with CP, the evidence is not sufficient to recommend that therapy be used routinely for the typical Western CP patient.
- The standard guideline for medical analgesic therapy in CP follows the principles of the 'pain relief ladder' provided by the

World Health Organization (WHO). *(GRADE* 1B, *strong agreement).* Paracetamol is preferred over NSAIDs as level I analgesic due to its limited side effects. Tramadol is the preferred level II analgesic due to its efficacy and safety profile. Strong oral opioids, at the lowest possible dose, are indicated as level III analgesia; dose escalation and addiction should be avoided.
- Adjuvant analgesics that can be used for pain in CP include low-dose antidepressants, gabapentinoids (pregabalin) and anxiolytics.

Endoscopic therapy for pain in CP

- As described above (point 6), ET is effective in patients with an obstructive type of pancreatic pain and in patients with pancreatic duct dilatation. *(GRADE* 2C, *moderate agreement).* ET could be useful as a bridge to surgery. *(GRADE* 1B, *moderate agreement).* ET is less effective for pain in CP and has a shorter-term effect compared with surgery. *(GRADE* 1B, *moderate agreement).*
- ESWL therapy is effective for disintegrating stones in the main pancreatic duct and provides pain relief in patients with CP. (GRADE 2B-2C, weak agreement).

Other nonsurgical treatments for pain in CP

- Treatments such as EUS-guided plexus block, splanchnic nerve block, spinal cord stimulation, transcranial magnetic stimulation and acupuncture may be effective in selected cases of painful CP. *(GRADE* 1C, *moderate agreement).*

Surgery for pain in CP

- As described above (point 4), different surgical techniques (resection, decompression or mixed surgical techniques) are effective for long-term pain relief in patients with CP. *(GRADE* 1B, *strong agreement).* Correct patient selection in a multidisciplinary approach and appropriate timing for referral to surgery are key to a successful outcome.

Nutrition

Nutritional evaluation

- Malnutrition is common among patients with CP. *(GRADE* 2B, *strong agreement).* PEI, anorexia secondary to abdominal pain, nausea and vomiting, alcohol and other substance abuse and diabetes mellitus may all contribute to malnutrition in patients with CP. *(GRADE* 2C, *strong agreement).*
- Patients with CP should undergo initial screening for malnutrition either with the community malnutrition universal screening tool (MUST) or hospital nutritional risk screening (NRS-2002) [15]. More specifically, dietary intake should be documented as well as symptoms consistent with malnutrition and those symptoms that have an increased risk of secondary anorexia (pain, nausea and vomiting). *(GRADE* 1B, *moderate agreement).* A physical examination should be performed and should include anthropometric measurements of mid-arm circumference, triceps skin-fold and hand-grip strength. *(GRADE* 2B, *moderate agreement).* Screening for a deficiency of proteins, fat-soluble vitamins (A, D, E and K), zinc and magnesium should be also considered. *(GRADE* 2A, *moderate agreement).*

Prevention and treatment of malnutrition

- Patients who are well nourished should be encouraged to follow normal healthy eating advice. PEI should be corrected in those patients who are nutritionally compromised. Improved nutritional status can be achieved with nutritional assessment and individualised dietary counselling by an experienced dietician. *(GRADE* 1B, *strong agreement).*
- Dietary fat restriction and very high fibre diets should be avoided. *(GRADE* 1C *strong agreement).* Small, frequent, high-energy meals should be recommended for patients with malnutrition. *(GRADE* 2C *strong agreement).* Nutritional intervention should be carried out alongside pancreatic enzyme replacement therapy (PERT). *(GRADE* 2C, *strong agreement).*
- For most patients with CP, oral nutritional supplements are not required. For those who are undernourished and cannot meet their nutritional requirements orally despite dietary intervention, oral nutritional supplements may be useful. MCT supplements are not recommended. *(GRADE* 2C, *strong agreement).*
- Specific recommendations on the supplementation of vitamins A, E and K are not possible, nor it is possible to provide specific guidelines on dosage and administration methods, as there are few studies. Clinical evaluation is advised, along with adequate PERT and dietary intervention. *(GRADE* 1B, *strong agreement).* Vitamin D deficiency may be treated with oral supplementation or by a single intramuscular injection. *(GRADE* 2C, *strong agreement).*
- Parenteral nutrition is indicated in patients with gastric outlet obstruction secondary to duodenal stenosis, in patients with complex fistulising disease and in patients with apparent severe malnutrition prior to pancreatic surgery if enteral feeding is not possible. *(GRADE* 1C, *strong agreement).*
- Enteral nutrition is indicated in patients with malnutrition who are not responding to oral nutritional support. *(GRADE* 2C, *strong agreement).* It is recommended that enteral nutrition be administered via the naso-jejunal route in patients with pain, delayed gastric emptying, persistent nausea or vomiting. *(GRADE* 2C, *strong agreement).* Jejunostomy feeding tube insertion should be considered in those requiring enteral nutrition for longer than 30 days. Peptide, medium chain triglyceride-based enteral feeds may be used in patients with PEI. *(GRADE* 2C, *strong agreement).* Enteral nutrition is indicated with PERT administered alongside where necessary. *(GRADE* 2C, *strong agreement).*

Evaluation and treatment of osteoporosis in patients with CP

- Patients with CP are at high risk of developing osteoporosis and osteopaenia *(Grade* 1A*)*, and are at high risk of suffering a low trauma fracture *(Grade* 1B*). (GRADE* 1B, *strong agreement).* To identify those at risk, regular assessment of bone density by dual-energy X-ray absorptiometry (DXA), along with regular measurement of serum 25(OH)-vitamin D should be undertaken. *(GRADE* 1C, *strong agreement).*
- Basic preventative measures (adequate diet, particularly calcium and vitamin D intake, regular weight-bearing exercise, and smoking/alcohol avoidance) should be encouraged for all CP patients. For those with osteopenia, basic preventative measures should be implemented and DXA should be repeated every two years. Patients with osteoporosis (or vertebral fractures) should receive appropriate medication, screening for other causes, and/or referral to a bone specialist, along with basic preventative measures. *(GRADE* 1C, *strong agreement).*

Evaluation and treatment of diabetes mellitus in CP

Definition and risk factors

- Diabetes mellitus secondary to CP (as well as to other pancreatic diseases) is classified as pancreatogenic diabetes or, previously, type 3c diabetes. The American Diabetes Association has recently classified it as CP-related diabetes (CPRD) [16].
- Diabetes is a common complication of CP, although its occurrence varies widely from 5% to >80%, depending largely on aetiology, geographical location and duration of follow-up. It appears to be a common complication of both idiopathic/tropical CP and alcoholic CP. *(GRADE* 1B, *strong agreement).*
- The risk of developing diabetes increases with surgical intervention (especially distal pancreatectomy), increasing age *(GRADE* 1B, *strong agreement)*, (heavy) smoking, the presence of pancreatic calcifications *(GRADE* 1C, *strong agreement)*, and with the duration of CP *(GRADE* 1B, *strong agreement).* There is some evidence of an association with gender and family history. *(GRADE* 2A, *strong agreement).* There is insufficient evidence of a relationship between diabetes and BMI or zinc status. *(GRADE* 2C, *strong agreement).* There is no evidence that a higher dietary fat intake influences the development of diabetes in CP. *(GRADE* 2C, *strong agreement).* The development of diabetes does not appear to be influenced by the presence of various genetic mutations associated with CP. *(GRADE* 1B, *strong agreement).*

Evaluation and diagnosis of pancreatogenic diabetes

- The initial evaluation of a patient with CP should include fasting plasma glucose (FPG) and HbA1c. Criteria for a diagnosis of CPRD are FPG$\geq$126 mg/dL (7.0 mmoL/L) or HbA1c $\geq$ 6.5% (48 mmoL/mol). *(GRADE* 1A, *strong agreement).* An HbA1c<6.5% does not rule out CPRD due to the limitations of this test in this patient population. Therefore, normal HbA1c (<6.5%) should always be confirmed by FPG. *(GRADE* 1B, *strong agreement).* In the absence of unequivocal hyperglycaemia (random plasma glucose $\geq$200 mg/dL [11.1 mmoL/L]) or in cases of doubt, results should be confirmed by repeat testing or by the evaluation by a standard 75 g oral glucose tolerance test (2 h fasting glucose $\geq$200 mg/dL [11.1 mmoL/L]). *(GRADE* 1A, *strong agreement).* These tests should be performed annually, even in the absence of typical clinical symptoms of diabetes mellitus. *(GRADE* 1C, *strong agreement).*
- An absent pancreatic polypeptide response to mixed-nutrient ingestion seems to be a specific indicator of CPRD as compared to the other types of diabetes. *(GRADE* 1C, *strong agreement).* Due to feasibility, this test is only recommended in cases of doubt. In patients with an established diagnosis of CP, diagnosis of CPRD can be based on the absence of type 1 DM-associated autoantibodies together with the presence of at least two of the following four criteria: impaired beta-cell function as evaluated by HOMA-B or C-peptide/glucose ratio, no excessive insulin resistance, impaired incretin (GIP or GLP-1) secretion, and fat-soluble vitamins and/or micronutrient deficiency.
- Laboratory tests to classify the patient as accurately as possible should be performed at least once. They should include diabetes-associated antibodies, C-peptide/glucose ratio, and assessment of exocrine pancreatic function, as well as pancreatic imaging. *(GRADE* 1C, *strong agreement).*
- Patients with CPRD are generally considered difficult to manage, with potential life-threatening acute complications (hypoglycaemia and ketoacidosis). Up to 25% of the patients with T3cDM have 'brittle diabetes' with rapid swings in glucose levels. *(GRADE* 1C, *strong agreement).*
- Chronic microangiopathic complications are as frequent in CPRD patients as in other diabetic patients. The incidence of retinopathy is reportedly similar to that observed in type 1 diabetes and its prevalence increases with diabetes duration. *(GRADE* 1B, *strong agreement).* Early signs of renal dysfunction, such as microalbuminuria or glomerular hyperfiltration, are similar to that reported in type 1 diabetes mellitus, while macroalbuminuria and overt renal disease are unusual. *(GRADE* 1B, *strong agreement).* Neuropathy is also described as a common complication of CPRD. *(GRADE* 1B, *strong agreement).* There is a general acceptance that CPRD is not associated with macrovascular complications. *(GRADE* 2B, *strong agreement).*

Treatment of CPRD diabetes mellitus

- Treatment of CPRD should include efforts to promote lifestyle changes, which may improve glycaemic control and minimise the risk of hypoglycaemia. In patients with severe malnutrition, insulin therapy is commonly used as a first choice due to the desired anabolic effects of insulin in this special subset of patients. *(GRADE* 1C, *strong agreement).* If hyperglycaemia is mild and concomitant insulin resistance is additionally diagnosed or suspected, therapy with metformin may be a choice in the absence of contraindications. *(GRADE* 1C, *strong agreement).* Sulfonylureas, glinides, thiazolidines, alpha-glycosidase inhibitors, incretin-based therapies and sodium glucose co-transporter-2 (SGLT-2) should not be used for CPRD due to risk of hypoglycaemia and prominent side effects.
- Ensuring adequate and appropriate PERT is essential for diabetes therapy in patients with CP. *(GRADE* 1C, *strong agreement).*

Toxic habits and QoL

Evaluation and treatment of smoking

- There is no specific, widely accepted questionnaire for assessing smoking status. Several studies have reported positive findings regarding the relationship between smoking and CP using different questionnaires. *(GRADE* 2C, *strong agreement).*
- The key components for the treatment of smoking dependence are combinations of therapeutic education, behavioural support and medication. *(GRADE* 1A, *strong agreement).* Nicotine replacement therapy, bupropion and varenicline are efficiently proven first-line pharmacologic therapies for smoking cessation.
- There is some evidence to suggest that cessation of smoking and/or drinking may improve the course of CP; however, the global benefits of stopping smoking and/or abusive alcohol consumption are unquestionable. *(GRADE* 1C, *strong agreement).*
- Smoking seems to be an independent aetiologic factor for the development of CP. *(GRADE* 1C, *strong agreement).* Early smoking cessation after the diagnosis of the disease may reduce the risk of developing pancreatic calcifications. Alcohol abstinence seems to slow the progression of the illness.

Evaluation of quality of life (QoL) in patients with CP

- Validated questionnaires should be applied for the assessment of QoL in patients with CP. *(GRADE* 1A, *strong agreement).* SF-36, its shorter version SF-12, EORTC QLQ-C30 with, and without the

supplementary QLQ-PAD26 questionnaire [17], and GIQLI [18] can be used for assessing QoL in patients with CP. *(GRADE* 1C, *strong agreement).*

- Health-related QoL should be assessed in both in- and out-patients and during their follow-up. *(GRADE* 2C, *strong agreement).* Assessment of QoL should be included as an endpoint in clinical treatment studies of CP. *(GRADE* 2B, *strong agreement).*

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