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United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)

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Abstract

Background: There have been substantial improvements in the management of chronic pancreatitis, leading to the publication of several national guidelines during recent years. In collaboration with United European Gastroenterology, the working group on 'Harmonizing diagnosis and treatment of chronic pancreatitis across Europe' (HaPanEU) developed these European guidelines using an evidence-based approach.

Methods: Twelve multidisciplinary review groups performed systematic literature reviews to answer 101 predefined clinical questions. Recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation system and the answers were assessed by the entire group in a Delphi process online. The review groups presented their recommendations during the 2015 annual meeting of United European Gastroenterology. At this one-day, interactive conference, relevant remarks were voiced and overall agreement on each recommendation was quantified using plenary voting (Test and Evaluation Directorate). After a final round of adjustments based on these comments, a draft version was sent out to external reviewers.

Results: The 101 recommendations covered 12 topics related to the clinical management of chronic pancreatitis: aetiology (working party (WP)1), diagnosis of chronic pancreatitis with imaging (WP2 and WP3), diagnosis of pancreatic exocrine

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insufficiency (WP4), surgery in chronic pancreatitis (WP5), medical therapy (WP6), endoscopic therapy (WP7), treatment of pancreatic pseudocysts (WP8), pancreatic pain (WP9), nutrition and malnutrition (WP10), diabetes mellitus (WP11) and the natural course of the disease and quality of life (WP12). Using the Grading of Recommendations Assessment, Development and Evaluation system, 70 of the 101 (70%) recommendations were rated as 'strong' and plenary voting revealed 'strong agreement' for 99 (98%) recommendations.

Conclusions: The 2016 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.

Keywords

Chronic pancreatitis, Grading of Recommendations Assessment, Development and Evaluation, evidence-based, guidelines, pancreatic exocrine insufficiency, diabetes mellitus, endoscopic therapy

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Introduction

Chronic pancreatitis (CP) is a serious disorder which can have a severe impact on the quality of life in addition to life-threatening long-term sequelae. As well as pain, pancreatic exocrine insufficiency (PEI) can result in malnutrition – in a population apt to neglect their nutrition. Long-term complications include diabetes mellitus and pancreatic cancer. The incidence in European countries ranges from 5 to 10 per 100,000 inhabitants. With a median survival of 20 years, the calculated prevalence is around 120/100,000 inhabitants.[1]

While understanding of this illness is improving, establishing the formal diagnosis is far from being a well-known routine. While many patients with CP enter the healthcare system via a gastroenterologist or surgeon due to an acute manifestation of acute pancreatitis or pain, much of their long-term care is conducted in the community by general practitioners or diabetologists.

As a consequence, 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 these patients.

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, and a Cochrane report[10] as well as pertinent new literature, which have been included in the study. A list of abbreviations which are defined on first use in the text is also included in the Supplementary Material.

Methods

Scope and purpose

The overall objective of these guidelines is to provide evidence-based recommendations for the diagnosis and medical, endoscopic and surgical management of CP, with particular emphasis on the diagnosis and treatment of PEI as the major symptom. One particular aim is to revisit the following diagnostic tests for pancreatic function: the faecal elastase-1 (FE-1) test, the mixed-triglyceride breath test (MTG-BT), and the secretin-stimulated magnetic resonance cholangiopancreatography (s-MRCP) test. Finally, malnutrition as a consequence of PEI and the resulting pancreatic enzyme replacement therapy (PERT) has been another focus of these guidelines.

Stakeholder involvement

Individuals from all relevant professional groups involved with CP and PEI have been included. Target users of the guidelines are clinicians involved in the care of patients with CP.

General outline of the process

First phase: drafting the work plan. The HaPanEU consortium was formed as a consequence of an open call from the UEG National Societies Committee. The consortium received endorsements and funding from the UEG via a LINK award to the Swedish and German societies of Gastroenterology.[11]

Second phase: systematic literature reviews. The work was ordered into 12 working parties (WPs), which are listed at the end of the document. At the beginning of the

process, each WP identified the most important clinical questions in their field and then the entire group decided on the final set of questions for each of the areas under discussion.

Systematic review guidelines

A systematic search for relevant articles was performed using the PubMed, Embase, and Cochrane databases. Inclusion criteria were: (a) randomised or observational cohort studies, including systematic reviews, on patients with CP, that focused on the specific study questions; (b) studies published in the English language; and (c) studies available in full text. If review groups were capable of translating non-English publications they were encouraged to do so.

Exclusion criteria were: (a) non-randomised studies with less than 20 patients because of the likelihood of selection bias; (b) studies on patients with 'acute-on-chronic pancreatitis'; and (c) non-randomised studies prior to 2004. Randomised controlled trials (RCTs) prior to 2004 could only be excluded if the reviewers felt that they were not relevant to current practice.

Grading of the evidence

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. In the present document the statements are followed by qualifying comments, written by each working party and reviewed by the entire scientific board (executive committee). Relevant comments and suggestions made by the global consensus group (expert readers) have also been taken into account. Statements and their comments should be read together. In certain areas, the evidence level is low, reflecting paucity of randomised trials and of good quality diagnostic studies. For some topics, expert opinion represented the highest level of evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[12,13] (Supplementary Material, Table S1) was applied in line with the International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines on acute pancreatitis.[14] All reviewers were advised to take a GRADE system tutorial (link on UpToDate: http://www.uptodate.com/home/grading-tutorial).

Outcome reporting

The final outcomes of the systematic reviews were discussed amongst the members of the review group (WP). The review groups provided the following for each clinical question:

1. Recommendation: the GRADE strength of recommendation (1 = strong, 2 = weak) and the quality of evidence (A = high, B = moderate, C = low), together with the strength of agreement (strong/weak)[12,13] during plenary voting (see Supplementary Material, Table S1). Initially, the GRADE recommendation also included a quality of evidence level D; however, this was combined with level C (see Supplementary Material, Appendix). In the absence of studies specifically addressing a particular question, this had to be stated and the recommendation was then based on related studies or expert opinion.
2. Comments: these remarks could discuss any relevant aspect regarding the recommendation, such as important exceptions/contra-indications, availability, lack of evidence, risks and costs.

Third phase: UEG/European Pancreas Club (EPC) joint meeting, Delphi process. After a meeting during the 47th EPC (2015) in Toledo, Spain, the questions were answered and distributed amongst the entire expert group. The questions and answers that had been agreed upon, including related comments, were then uploaded to the Delphi platform and voted upon. Voting participation was 100% of the expert group. All questions with less than 80% agreement were discussed at a meeting during the UEG week (2015) in Barcelona, Spain, with Test and Evaluation Directorate (TED) voting. The comments to all questions, and particularly those with less than 80% agreement during the TED voting, were returned to the working parties for a final round of discussion.

Fourth phase: drafting the manuscript. Following the consensus reached after the UEG week (2015) and a final round of adjustments, a first draft of the manuscript was issued and agreed upon by the expert group. This was then sent out to external readers and finalised according to the comments received. In addition to this written version, an interactive smartphone app, Guideline on Chronic Pancreatitis, has been developed that can be downloaded for free (HaPanEU).

Future aspects

These guidelines reflect current, state-of-the-art procedures and will be updated by the UEG association when they believe there is a need to do so, but no longer than

10 years after their publication.[15] As sometimes occurs during literature reviews, when looking for evidence, the group identified several areas where studies are lacking and this has been stated.

Results

The 12 main topics are presented consecutively, incorporating a total of 101 questions and their respective answers. The GRADE strength of recommendation (1/2) and quality of evidence (A, B, or C) is provided[12,13] along with the strength of agreement during plenary voting. For each recommendation the comments from the reviewers and attendees at the meeting are listed.

Definition

Q0: What is the definition of CP (regardless of the aetiology)?

Statement. 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.[4] Diagnosis is established via high quality imaging modalities, which allow identification of the following signs: increased density of the parenchyma, atrophy of the gland, calcification, pseudocysts and irregularities of the main pancreatic duct and its side branches. Diagnosis should be based on imaging performed in symptomatic patients presenting with indicators suggestive of pancreatic disease. The diagnostic criteria have been reviewed elsewhere.[4] Complications of CP encompass strictures of the pancreatic duct and/or the biliary ducts, pseudocysts, pancreaticolithiasis, duodenal stenosis, malnutrition, vascular complications and recurrent or persisting pain. **(Strong agreement)**

Comments. As pathognomonic symptoms do not exist for this disease, the diagnosis has to be based on objective criteria such as cross-sectional imaging. Minimal suggested imaging requirements are detailed for both computed tomography (CT) and magnetic resonance imaging (MRI) in the Italian guidelines[6] and are specified below. There is a disease continuum from acute to chronic pancreatitis[16] and a significant percentage do progress to CP.[17]

Aetiology of CP (WP1)

Q1-1: What needs to be done to define the aetiology of CP in adult patients?

Statement 1-1. It is recommended that a comprehensive medical history, laboratory evaluation and imaging studies are performed in patients with CP. **(GRADE 2C, strong agreement)**

Comments. CP is a continuing inflammatory disorder of the pancreas, which leads to replacement of pancreatic tissue by fibrotic tissue. As a consequence, endocrine and/or exocrine insufficiency can develop.[18] In CP patients the risk of developing pancreatic carcinoma is elevated.[19] CP incidence ranges from between 1.6–23 per 100,000 and an increase in prevalence has been noted.[20]

The most common risk factor for CP is alcohol abuse, with a logarithmic risk increase, although the type of alcohol consumed is irrelevant.[21–27] The amount and duration of alcohol consumption required to develop CP has not been unequivocally defined. Some authors suggest at least 80 g/day for a period of at least six years. Smoking is most probably an independent risk factor. Since smoking leads to the progression of CP, all patients should be advised to stop smoking.[28]

Genetic factors also contribute to CP development. The most important genetic risk factors are variants in cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal-type 1 (*SPINK1*) and carboxypeptidase A1 (*CPA1*). Further genetic susceptibility genes are cystic fibrosis transmembrane conductance regulator (*CFTR*), chymotrypsinogen C (*CTRC*) and carboxyesterlipase (*CEL*).[29–34] Additionally, autoimmune processes can lead to the development of CP.

To diagnose CP, a complete medical history and clinical investigations, including imaging technologies and function tests, need to be applied. The aetiology of CP is defined after a thorough patient investigation considering all known risk factors, including alcohol consumption (for example using the AUDIT questionnaire) and smoking, as well as laboratory values (triglyceride-levels; Ca^{2+}-levels for ruling out elevated primary hyperparathyroidism (PHPT); carbohydrate deficient transferrin (CDT)/phosphatidylethanol levels), and family medical history.

Autoimmune pancreatitis (AIP) should be ruled out following current consensus guidelines and when no other aetiology can be found in patients. AIP signs include elevated immunoglobulin (Ig)G4 serum levels, the presence of lactoferrin and carbonic anhydrase auto-antibodies, and imaging showing a typical 'sausage-like' configuration of the pancreas.[35]

Cholecystolithiasis and/or choledocholithiasis alone are not considered risk factors for the development of CP. Protective environmental factors have not been described. Whether anatomic anomalies such as pancreas divisum increase the CP risk is still a matter of debate; however, with additional risk factors, pancreas divisum might lead to CP development. If no

aetiological factor can be identified, genetic screening for predisposing variants can be offered.

In recent guidelines, CP has been classified into different forms (calcifying, obstructive, autoimmune and groove). These classifications are based on clinical features, morphological characteristics and response to treatment. In calcifying CP, for example, perilobular fibrosis and acinar destruction with infiltration of acute and chronic inflammatory cells are present. Obstructive CP develops as a secondary complication due to an area of obstruction with dilatation of the pancreatic duct proximal to the stenosis, atrophy of acinar cells and fibrosis. Characteristics of AIP are discussed in detail in Q1-4. Finally, groove pancreatitis affects the groove between the pancreatic head, duodenum and the bile duct (see Q4-1.9–Q4-1.11).

Q1-2: What aetiological factors should be investigated in paediatric patients with recurrent acute pancreatitis or CP?

Statement 1-2. Cystic fibrosis needs to be ruled out by chloride iontophoresis, while genetic causes seem to be much more important in children than in adults. Laboratory evaluation needs to include Ca^{2+} and triglyceride levels. Recommended imaging modalities are abdominal ultrasound or magnetic resonance cholangiopancreatography (MRCP). **(GRADE 2C, strong agreement)**

Comments. The incidence of CP in children has been reported at 4–13 in 100,000.[36–38] As such it is of great importance that pediatricians are aware of the differential diagnosis of CP in children with abdominal pain and they should attempt to define the aetiology following a diagnosis of CP.

Until the first genetic associations were identified, the aetiology of CP in children was idiopathic in up to 70% of patients. Inherited CP is characterised by early onset of the disease (in most cases before 20 years of age) and some patients show a positive family history. In patients with a positive family history, dominant *PRSS1* mutations (p.N29I and p.R122H) are frequently found.[29] Genetic variants in *SPINK1*, *CPA1*, *CTRC*, *CEL, CFTR* and *PRSS1* (mainly p.A16V) can be found both in patients with a positive and negative family history of CP.[29–34] In contrast, a protective variant, p.G191R, has been identified in the anionic trypsinogen (*PRSS2*) gene.[39]

Patients with inherited CP can develop their first symptoms as early as their first year. In paediatric patients, genetic variants can be tested after informed consent and genetic counselling according to country-specific national guidelines. Genetic testing should be offered to patients with a positive family history as well as to paediatric patients without an identified aetiological factor.

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 IVS3 + 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*.

In every paediatric patient, cystic fibrosis has to be ruled out, since 10–15% of cystic fibrosis patients with pancreatic sufficiency (comprising 1–2% of all patients with cystic fibrosis) present clinically with recurrent attacks of acute pancreatitis.[40–42] Other aetiologies including parasites, hypertriglyceridaemia, hypercalcaemia, and anatomic anomalies are rare, but should be investigated.

Q1-3: In which CP patients should we rule out cystic fibrosis?

Statement 1-3. A diagnosis of cystic fibrosis needs to be ruled out in 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)**

Comments. The recommended investigations for ruling out a diagnosis of cystic fibrosis should follow national and international guidelines.[43] Note, this does not imply a complete sequencing of the *CFTR* gene but only of known hotspot variants. Moreover, if no further clinical signs of cystic fibrosis are present (for example, no pulmonary symptoms, no male infertility) the diagnostic workup should be restricted to sweat chloride iontophoresis.

The first description of an association between *CFTR* variants and CP was published in 1998.[31] Several association studies investigated the role of *CFTR* variants in CP and concluded that the association is not as strong as previously suspected with odds ratios of around 3–5.[44,45]

CFTR variants range from severe to mild and include polymorphisms. CP patients carrying *CFTR* variants harbour at least one mild variant allele giving them residual *CFTR* function. In many patients, CP is a complex genetic disease and these patients simultaneously carry variants in several different genes (for example, *SPINK1*, *CTRC*, *CFTR*). The interpretation of these complex genotypes is difficult and should be performed in specialised centres in the appropriate European county. Testing for rare *CFTR* variants with, in most cases, unknown functional consequences should only be performed in a research setting. Certain complex genotypes with variants in genes such as *SPINK1* and *CFTR* are associated with CP development, while others represent the expected finding of concomitant variants.

Q1-4: Should the diagnosis of AIP be ruled out in all pancreatitis patients?

Statement 1-4. If no other aetiology of CP can be identified in a patient then a diagnosis of AIP should be ruled out. **(GRADE 2C, strong agreement)**

Comments. AIP is a rare but important differential diagnosis in patients with acute and chronic pancreatitis. As such, the screening for aetiological factors should include the information needed to diagnose AIP. AIP was described for the first time in 1961 by Henri Sarles[346] and studies have demonstrated that males suffer more often from AIP (ratio 2:1). Approximately 5% of patients with CP also have AIP. Note, up to 5% of patients with suspected pancreatic adenocarcinoma are finally diagnosed as having AIP.

Symptoms include recurrent attacks of abdominal pain and jaundice in up to 50% of patients. Morphological characteristics in up to 40% of cases comprise a 'sausage'-like configuration of the pancreas, and an irregular stenosis of the pancreatic duct without prestenotic dilatation. In contrast, calcifications are rare.[46–51] AIP can be divided into type 1 and type 2 categories. In type 1 AIP, IgG4 serum levels are elevated in most cases and histological findings are in accordance with lymphoplasmocytic sclerosing pancreatitis (LPSP). Obliterative phlebitis and periductular fibrosis are also common features of type 1 AIP. In type 2 AIP, IgG4 levels are within the reference level. A typical histological change is idiopathic duct centric pancreatitis (IDCP) and granulocytic epithelial lesions (GELs). While type 1 AIP is associated with the IgG4-related disease spectrum, type 2 AIP can be accompanied by ulcerative colitis.

Type 1 AIP represents a systemic disease that may affect various organs.[46,49,52,53] The disease is unique since both pancreatic morphological changes and pancreatic insufficiency respond very well to immunosuppressive therapy.[46–51] Several reports have demonstrated the normalisation of exocrine and endocrine insufficiency under immunosuppressive medication.[46,51,54] However, the diagnosis of AIP remains challenging since patients with this disease may have atypical presentations.[35,52,55] Thus, AIP may underlie any inflammation of the pancreas and a complex workup needs to be performed. Therefore, clinical and radiological (first choice – MRCP, second – endoscopic ultrasonography (EUS)) as well as serological and immunohistochemical investigations (only in patients with other signs of AIP or with focal segmental lesions) are necessary. Some diagnostic autoantibodies have been described,[56,57] however, they are not commercially available.

Q1-5: Is there a recommended classification system that should be used when defining the aetiology?

Statement 1-5. There is no preferred classification system for defining the aetiology of CP since the available classification systems need to be evaluated in randomised prospective trials with endpoints of morbidity and mortality. Only in this way can a recommendation be made on which system to use in the future. **(GRADE 2C, strong agreement)**

Comments. Distinct classification systems have been developed for CP patients, but only the Toxic/metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute pancreatitis, and Obstructive (TIGAR-O) and the M-ANNHEIM classification systems take the aetiology of CP into account.

Classification systems are of great importance for guiding management strategies, since treatment strategies cannot rely solely on the type and degree of morphological changes in the pancreas, but need to include clinical, functional and imaging findings. So far no globally accepted classification system has been established. Classification systems currently in use are:

1. Manchester classification
2. ABC classification
3. M-ANNHEIM
4. TIGAR-O
5. Rosemont classification

The Manchester classification system uses imaging modalities and clinical signs of CP.[58] The degree of severity is mostly influenced by the presence of exocrine and/or endocrine insufficiency or the presence of complications, while imaging findings are of minor importance. The ABC classification recommends similar findings to the Manchester classification system.[59,60] The Rosemont classification was developed to diagnose CP using EUS and is described in the comments for Q2-9.[61] In the M-ANNHEIM system, the stage, severity and clinical findings of CP are integrated.[62] The M-ANNHEIM system is the only one offering a severity index and is used accordingly.[63–65] Finally, after a complex procedure, a score of between 0–25, representing the severity of CP, is calculated.[66] Different guidelines recommend using the TIGAR-O classification. This system comprises six aetiologic groups: toxic/metabolic, idiopathic, genetic, autoimmune, recurrent acute pancreatitis, and obstructive groups.[67]

Q1-6: Are there different courses of the disease?

Statement 1-6. Depending on the aetiology, CP has different disease courses and long-term complications**.** **(GRADE 1B, strong agreement)**

Comments. Categorising patients according to the underlying aetiology is clinically important. The course of the disease and the risk of developing pancreatic cancer vary considerably between different aetiologies.[68,69] For example, epidemiological studies have shown that calcifications, and exocrine and endocrine insufficiency, develop after a shorter time period in alcoholic CP patients compared to other aetiologies. Although causal treatment options for alcoholic CP are currently not available, cessation of alcohol consumption may reduce the rate of progression, decrease pancreatic pain, and partly restore pancreatic exocrine function (see WP12).[70] Smoking has been recognised as an independent risk factor for the development of CP and pancreatic calcifications.[28,71]

In patients with early onset CP, especially hereditary (<20 years), the risk of pancreatic cancer is increased considerably, and cessation of smoking may reduce the risk in this group.[72] In addition, patients with different genetic mutations demonstrate a different clinical presentation (for example later development of diabetes mellitus, and calcifications) than patients with other aetiologies.[68,69] In patients with genetic predispositions, the age of onset is generally earlier, and exocrine and endocrine insufficiency are more prevalent compared to other aetiologies.[68] Patients with inherited CP seem to have a higher risk of developing pancreatic adenocarcinoma: a meta-analysis calculated a 69-fold risk increase for these patients while other aetiologies had a 13-fold risk increase.[73] This assumption has been challenged by recent studies that demonstrated that the risk of developing a pancreatic adenocarcinoma is unrelated to the genotype.[68] Most likely, the early onset of the disease in these patients and the longer disease course are the main reasons for an increased risk of developing pancreatic cancer. According to a recent epidemiological study, the risk of cancer development in CP is actually lower than stated in previous reports.[74] Unfortunately, early screening of these patients for cancer or premalignant lesions is difficult. To date, no convincing strategy has been recommended and hopefully further studies will address these issues. The clinician should strongly advise his patients to stop smoking and to reduce, or eliminate entirely, the amount of alcohol consumed.

Finally, recent studies have demonstrated that the interaction of different genetic risk factors with each other or the interaction of other risk factors, such as pancreas divisum, with genetic variations[75] might increase the risk of developing CP. Thus it is essential for clinicians to determine the aetiology of the disease correctly.

Q1-7: In which CP patients should genetic screening be performed and which genes should be investigated?

Statement 1-7. All patients with a family history or early onset disease (<20 years) should be offered genetic testing for associated variants. **(GRADE 2C, strong agreement)**

Comments. Genetic screening for every CP patient cannot be recommended since alcohol abuse is the predominant cause of the disease in up to 60% of adult cases. In patients with early onset CP, genetic screening can be offered after informed consent (see Statement 1-2). Note, the genetic test results will neither change the medical treatment offered to the patient nor alter the disease course. However, it might enable some patients to understand their disease better and might even impact family planning. In patients with alcoholic CP, routine genetic testing cannot be recommended. Variants in *SPINK1* and *CTRC,* and to a lesser extent, common single-nucleotide polymorphisms (SNPs) in the *PRSS1* and *CLDN2-MORC4* loci, are associated with alcoholic CP.

Diagnosing CP (WP2 and WP3)

Evaluation of the various cross-imaging modalities such as MRI and computed tomography (CT) as well as EUS, contrast-enhanced ultrasound (CEUS) and even endoscopic retrograde cholangiopancreatography (ERCP) for diagnosing CP relies heavily on a recent review and meta-analysis performed by several members of the consortium, applying both the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) and GRADE criteria.[76] The results are summarised in Supplementary Material, Table S2.

Q2-1: What is the best overall imaging modality for establishing a diagnosis of CP?

Statement 2-1. EUS, MRI, and CT are the best imaging methods for establishing a diagnosis of CP. **(GRADE 1C, strong agreement)**

Comments. Imaging modalities are indispensable for the management of CP. The most frequently used imaging modalities are ERCP, abdominal ultrasonography (US), EUS, MRI and CT; however, summary estimates of their accuracy are lacking. The aim of a meta-analysis[76] was to obtain summary estimates of the sensitivity and specificity of the various imaging modalities employed for CP assessment. In addition to GRADE, the QUADAS-2 tool was used to assess the quality of the methods used in the studies. A bivariate random-effects model was used to obtain summary estimates of sensitivity and specificity. Full text was retrieved from 268 studies of which 42 studies evaluating 3392 patients fulfilled the inclusion criteria. The risk of bias was low

in only 29% of studies according to QUADAS-2 and the quality of evidence was very low according to GRADE. Estimates of sensitivity and specificity are presented in Supplementary Material, Table S2. A summary of results from 14 studies with head-to-head comparisons of various modalities confirmed the overall summary estimates (Supplementary Material, Table S3). EUS, ERCP, MRI and CT all have comparable high diagnostic accuracy in the initial diagnosis of CP. EUS and ERCP outperform the other imaging techniques and US is the least accurate. ERCP is no longer considered to be a diagnostic test for CP. The choice of imaging modality can therefore be made based on invasiveness, local availability, experience and costs.[76] Although less complete, the German S3 guidelines came to a similar conclusion.[4]

Q2-2: Which method is most appropriate for the identification of pancreatic calcifications?

Statement 2-2. 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)**

Comments. Pancreatic calcifications are common in patients with CP. It is estimated that up to 90% of patients will develop calcifications during long-term follow-up, particularly in those patients with alcohol-induced CP.[77] In the appropriate clinical context, the presence of pancreatic ductal calcifications is pathognomonic for CP and their visualisation using portal phase contrast-enhanced CT was reported to have moderate sensitivity and very high specificity (close to 100%).[78] However, very small calcifications may be obscured by pancreatic parenchymal contrast enhancement; therefore, a non-contrast-enhanced phase CT may be a necessary add-on to portal phase contrast-enhanced CT in order to depict previously undetected calcifications in the latter phase.

Q2-3: Is the use of MRI/MRCP examination for the assessment of irregularities in the main pancreatic duct, abnormal side branches, strictures and dilatations sufficient to diagnose CP?

Statement 2-3. 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)**

Comments. MRCP is based on heavily T2-weighted images and has been used in clinical imaging for more than 18 years in order to evaluate biliary and pancreatic duct abnormalities. MRCP depicts the pancreatic ductal system in CP and demonstrates narrowing, dilatation and filling defects with moderate to high accuracy.[79] One of the early studies[80] demonstrated very good correlation between ERCP and MRCP findings in patients with pancreatitis and concluded that MRCP may obviate the need for ERCP. One of the challenges of MRCP in the diagnostic evaluation of CP is its relatively low sensitivity in mild CP, since subtle changes in the main pancreatic duct and the side-branches cannot be identified as easily with MRCP as with ERCP.

Q2-4: What advantage does intravenous (IV) secretin administration provide during the MRCP examination for the evaluation of CP?

Statement 2-4. The use of IV secretin increases the diagnostic potential of MRCP in the evaluation of patients with known/suspected CP. **(GRADE 1C, strong agreement)**

Comments. The use of IV secretin stimulates pancreatic exocrine function and increases fluid excretion via the main pancreatic duct. It is useful in the evaluation of CP with MRCP as:

1. It enhances visualisation of the main pancreatic duct and abnormal side-branches compared to non-s-MRCP. In a study reviewing a cohort of 95 patients (both normal individuals and patients with CP), the overall sensitivity for the detection of CP increased from 77% to 89% after the use of secretin.[81]
2. It reveals strictures or abnormal dilatations. In a study performed in a paediatric population with a diagnosis of idiopathic CP, the use of secretin improved the overall sensitivity.[82]
3. It may quantify exocrine function.[83–86] Quantification of exocrine function has been reviewed in many studies and the results correlate well with the severity of pancreatitis.[83,84]

Theoretically, s-MRCP could be helpful in the differential diagnosis of intraductal papillary mucinous neoplasm (IPMN) of the pancreas; however, the only small study performed was inconclusive.[87]

Q2-5: Does duodenal filling (DF) during s-MRCP have a diagnostic value in grading the severity of CP?

Statement 2-5. DF during s-MRCP does not help to evaluate the grade of severity of CP. **(GRADE 2C, moderate agreement)**

Comments. It is expected that with increasing severity of CP there will be a decrease in the amount of acinar cells and fluid output, which can be detected

with s-MRCP. However, limited data exist in the literature on this specific subject. Two studies have evaluated the potential use of DF score during s-MRCP described by Matos et al.[88] in grading the severity of CP.'' As it stands in the text now, it appears that it is Matos et al. who state that there are two studies that have evaluated the potential use of DF etc, which is not true. It was actually Matos et al. that described the DF score during s-MRCP. The standard of reference in the first study[89] was the Cambridge classification of ERCP,[90] while in the second study[85] it was MRCP. Both studies agreed that the grade of CP severity cannot be evaluated on the basis of DF. This is due to the fact that a substantial number of patients with severe CP may still have normal DF (grade 3) and patients with mild changes may show reduced DF (grade 1 or 2). However, DF has been shown to correlate well with other methods for assessing the exocrine pancreatic reserve (see WP4 for the evaluation of pancreatic function).

Q2-6: What is the role of abdominal ultrasound in suspected CP?

Statement 2-6. Abdominal US can only be used to diagnose CP at an advanced stage. **(GRADE 1A, strong agreement)**

Comments. Abdominal US is frequently the first line imaging modality used in patients with abdominal pain and the suspicion of CP.[91,92] US is readily available in most facilities and can easily be repeated without the inherent risks of radiation and contrast media of other techniques. US technology has improved substantially in the last decade but studies that aim to compare US with other imaging modalities are still limited. A recent meta-analysis analysed the diagnostic performance of different imaging modalities with the inclusion of 10 US studies. Sensitivity and specificity rates for US (67%/98%) were lower when compared to CT (75%/91%) and EUS (82%/91%), respectively. The limitations of US include operator-dependency and obscured visualisation of the pancreas, for example, due to obesity or intestinal gas.[93]

The presence of pancreatic and/or intraductal calcifications is pathognomonic for CP.[94–96] Calcifications are found in roughly 40% of patients with advanced CP.[94] In US imaging, calcifications exceeding a diameter of 2 mm are visualised as hyperechoic foci with posterior shadowing. The use of colour Doppler can facilitate the detection of small pancreatic calcifications, which can be identified by the presence of twinkling artifacts.[97,98] Other typical sonographic signs of CP are duct calibre abnormalities, i.e. a dilated and irregular pancreatic duct.[91] Alterations in the size of the pancreas are nonspecific since a small atrophic gland with focal alterations can also be found in healthy elderly subjects and localised tumour-like lesions can be present in malignancy or AIP.[99,100] In moderate to severe CP, the pancreatic echotexture is frequently heterogeneous during the course of the disease.[91,101] In early CP, there are no (or only subtle) morphological changes that cannot be detected by conventional US.

Q2-7: What is the role of abdominal US in recognised CP?

Statement 2-7. US can be applied in patients with suspected CP complications. **(GRADE 2C, strong agreement)**

Comments. US can be used to visualise CP complications such as fluid collections, pseudocysts, acute CP flare-ups and pseudoaneurysms.[91,94,102] Unfortunately, prospective randomised studies that compare US with other imaging techniques are lacking. Pseudocysts and fluid collections are typically anechoic, while pseudoaneurysms can be visualised with colour Doppler.[98]

Apart from the diagnostic evaluation, US can be used for US-guided diagnostic and therapeutic pancreatic interventions such as biopsies and drainages.[103]

Q2-8: What are the indications for CEUS?

Statement 2-8. CEUS can increase diagnostic accuracy in CP patients with cystic and solid pancreatic lesions. **(GRADE 1C, strong agreement)**

Comments. CEUS improves accuracy when characterising pancreatic focal lesions. Note, prospective controlled studies in patients that define the role of CEUS in CP are lacking. US contrast agents are injected intravenously, are confined to the blood pool and allow real-time characterisation of pancreatic perfusion. Repeated administration can be performed in the same session if needed. CEUS has been used extensively in the characterisation of focal liver lesions, whereas CEUS of the pancreas is less widely used.[104–108] Sonovue, approved for echocardiography and for the differentiation of liver tumours, is the most widely used contrast agent.

Conventional B-mode US is limited in its ability to differentiate mass-forming pancreatitis from pancreatic cancer. When applying CEUS, a ductal adenocarcinoma is typically hypoechoic in the arterial phase due to its low vascularisation, whereas focal CP usually shows contrast enhancement similar to the surrounding pancreatic parenchyma.[109–111] In advanced CP, heterogeneous hypovascularisation due to fibrosis may be present, making the differential diagnosis of pancreatic cancer very difficult.[107,112]

CEUS can also be used to differentiate between neuroendocrine tumours that are highly vascularised and demonstrate a hyperenhancing pattern.[105] New algorithms are used to characterise the perfusion pattern in order to discriminate between normal pancreatic

perfusion and patterns of tumour perfusion.[113] Finally, CEUS is also useful in differentiating between avascular debris and vascularised nodules in cystic lesions.

Q2-9: What is the role of EUS in patients with suspected CP?

Statement 2-9. 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 criteria. **(GRADE 1B, strong agreement)**

Comments. EUS is considered to be the most sensitive method for diagnosing CP.[114,115] Certain criteria characterising the disease have been defined and are divided into parenchymal and ductal criteria[116,117] To date, there is no EUS optimal cut-off for establishing a diagnosis of CP. However, a cut-off of 3–4 criteria is often used. With the assumption that not all criteria are equally important, the Rosemont classification defines the EUS criteria for CP and their specific validity.[61] However, this classification does not improve the diagnostic value of the standard criteria.[118] Another problem for the validation of EUS has been the gold standard: when comparing EUS with ERCP and the secretin test, the agreement is 100% for severe forms of CP (>5 criteria), 50% for moderate forms (3–5 criteria) and 13% for mild forms of the disease (0–2 criteria). In fact, close to 25% of patients with normal secretin-cerulein tests show EUS abnormalities suggestive of CP. When the applied gold standard includes the sum of the ERCP findings, the secretin test and the clinical characteristics of the patient, EUS shows a diagnostic sensitivity >84% and a specificity approaching 100%.[119] When compared with histology as the gold standard, the sensitivity of EUS for the diagnosis of CP exceeds 80%, with a specificity of 100%.[120] Moreover, there is an excellent correlation between the number of EUS criteria present and CP severity with respect to the histology.[121]

Q2-10: What is the role of EUS in the follow-up of patients with known CP, for the (early) detection of malignancy?

Statement 2-10. 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)**

Comments. There is a lack of data regarding the role of EUS in the follow-up of patients with known CP. However, due to the accuracy of EUS in evaluating both the pancreatic parenchyma and the ductal system, this method is very useful for the detection of complications related to CP,[122] such as pancreatic cancer. EUS was recommended as a screening program for patients in the high risk group, i.e. those with hereditary CP.[123,124] Although there is no clear consensus on whether and how to conduct pancreatic cancer screening, many centres recommend the use of EUS, based on its ability to identify pancreatic masses smaller than 1 cm,[125] although this ability is reduced in the presence of CP. In fact, the differential diagnosis between inflammatory and malignant masses and the early detection of malignancy in patients with known CP remains a difficult task for all diagnostic imaging techniques.[122,126]

Q2-11: What is the role of EUS (plus elastography, contrast enhancement, and fine needle biopsy) in the differential diagnosis of solid pancreatic masses (mass-forming CP vs pancreatic cancer)?

Statement 2-11. 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. 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)**

Comments. Differentiation between mass-forming CP and other pancreatic lesions remains a challenge.[122,127] Although EUS produces high-resolution images, this procedure cannot reliably differentiate between malignant and inflammatory lesions due to the similar EUS appearance of adenocarcinoma and focal pancreatitis. In case of doubt, EUS-guided tissue acquisition can be helpful. In a general setting, the diagnostic yield of EUS-guided tissue acquisition for the diagnosis of solid pancreatic masses ranges from 80–95%.[128–133] However, in case of an underlying CP, the sensitivity of this method can decrease to between 50–75%.[134–138] An especially challenging task is to differentiate AIP from cancer.[139,140] Histological criteria have been proposed to establish the diagnosis from EUS-guided biopsies.[141] The probability of false negatives is reported to be between 5–10%, so that given operable findings on images and a suspected tumour, surgery is recommended even without prior cytological confirmation.

Based on imaging techniques, a sensitivity of 84% and a specificity of 97% have been reported for MRI combined with MRCP. A sensitivity of 93% and a specificity of 75% have been calculated for differentiating between CP and pancreatic carcinoma.[76,142] However, this does not apply when a carcinoma develops in the presence of CP. In this case, even after exhausting all diagnostic techniques, the sensitivity for detecting a

tumour is 67%, with a specificity of 45% – inferior to that documented for EUS-guided tissue acquisition.

New EUS imaging techniques, such as elastography and contrast-enhanced harmonic EUS (CEH-EUS) have been proposed to increase the diagnostic yield for this condition.[127] Several studies aiming to determine the role of these techniques in the differential diagnosis of solid pancreatic masses have been published. EUS-guided elastography has shown high levels of accuracy in establishing malignancy in solid pancreatic lesions, and has been demonstrated as being specifically useful for distinguishing between mass-forming CP including AIP and pancreatic cancer, with sensitivities ranging from 80–95% and specificity from 40–90%.[143–152] In fact, the technique may add information to EUS-guided tissue acquisition.[153] Recent meta-analyses have demonstrated the ability of EUS elastography in the characterisation of solid pancreatic masses, and the detection of malignancy.[154–157]

CEH-EUS has also demonstrated its usefulness in differentiating between the vascularisation patterns of pancreatic lesions, as hypovascular lesions are strong indicators of malignancy,[127,158–160] and this has been proved in recent studies.[159,160] A new development has been the ability to measure the contrast agent, and by quantifying the peak of enhancement, the sensitivity and specificity in differentiating between mass-forming CP and pancreatic cancer reaches 85–95%.[161,162] Another advantage of CEH-EUS, as previously documented for elastography, is its role in directing EUS-guided tissue acquisition, thus increasing diagnostic yield.[163,164] Although EUS-guided elastography and contrast enhancement may deliver accurate information, their role in this setting needs to be assessed further in future clinical trials.

In general, it must be clearly stated that all of the US-based techniques require a great deal of experience and are very much investigator-related in their diagnostic accuracy; variability is only low in the hands of experienced investigators.[165]

Diagnosing PEI (WP4)

Q3-1: How is PEI defined?

Statement 3-1. PEI refers to an insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function). **(GRADE 1A, strong agreement)**

Q3-2: What are the clinical consequences of the different grades of insufficiency?

Statement 3-2. 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)**

Comments 3-1 and 3-2. Mild PEI is defined as the reduced secretion of one or more enzymes with normal bicarbonate concentration in duodenal juice and normal faecal fat excretion; moderate PEI is defined as having a reduced enzyme output and bicarbonate concentration but normal faecal fat excretion; while severe PEI has a reduced enzyme output and bicarbonate concentration plus steatorrhoea.[166]

Steatorrhoea and azotorrhoea in severe PEI result when exocrine (mainly lipase and trypsin) pancreatic function is reduced by >90%.[167,168] Patients with steatorrhoea typically report weight loss and an increase in daily bowel movements, with fatty, bulky stools that are difficult to flush away; this occurs mainly after high-fat-containing meals. As steatorrhoea occurs after meals, it is typically observed 2–3 times a day in individuals with a normal lipid-content diet.[6,169] Clinical symptoms and signs of micronutrient deficiencies due to impaired absorption of lipid soluble vitamins include: vitamin K deficiency – ecchymoses due to clotting; vitamin E deficiency – ataxia, peripheral neuropathy; vitamin A deficiency – impaired night vision, xerophthalmia; vitamin D deficiency – contraction or muscle spasms, osteomalacia and osteoporosis. Further clinical consequences of PEI can include hyperoxaluria, urinary oxalate stones, renal insufficiency, impairment of cognitive functioning and thus working ability (with resulting financial strain) and reduced overall quality of life (QoL).[3,4,6,9,169]

Although it is commonly held that steatorrhoea is the most important clinical manifestation of PEI, some studies have shown reduced absorption of fat-soluble vitamins even in patients with mild to moderate exocrine insufficiency.[170–173] Importantly, after excluding patients with steatorrhoea (i.e. severe PEI), it was found that significantly reduced faecal elastase levels correlate well with low vitamin D3 levels in patients with an osteoporotic fracture.[174] Accordingly, mild to moderate exocrine insufficiency also appears to be of clinical relevance.

Q3-3: What are the main causes of PEI?

Statement 3-3. The main causes of PEI are loss of the pancreatic parenchyma, obstruction of the main pancreatic duct, decreased stimulation of the exocrine

pancreas and inactivation of pancreatic enzymes. **(GRADE 1B, strong agreement)**

Comments. PEI results from a loss of functioning pancreatic tissue and is seen in patients with CP and other diseases including severe acute pancreatitis, pancreatic carcinoma, cystic fibrosis and partial or total surgical resection of the pancreas (primary PEI).[175] Further potential causes of PEI are obstruction of the main pancreatic duct, decreased stimulation of the pancreas or inhibition of exocrine function by endocrine tumours or pharmacological treatment (secondary PEI).[175] In CP, PEI results from a progressive loss of functioning pancreatic tissue, which leads to insufficient secretion of digestive enzymes into the duodenum.[176] CP is the most frequent cause of PEI and, in an unselected group of patients with CP, pancreatic exocrine function was reduced by about 50–80% compared with healthy volunteers.[177] Other relatively common conditions in which PEI occurs due to a loss of functioning parenchyma include pancreatic carcinoma and previous pancreatic resection in adults[178] or cystic fibrosis in children.[179] Nearly 90% of patients recovering from necrotising acute pancreatitis also had PEI, the development of exocrine insufficiency strongly correlating with the extent of pancreatic necrosis.[180] However, PEI has also been reported during the early recovery phase of acute pancreatitis; in particular, pathological values for FE-1 were found in 12% of patients with either mild or severe acute pancreatitis and were significantly related to the aetiology of the disease.[181]

Even in patients with normal secretory capacity of the pancreas, PEI can be caused by obstruction of the main pancreatic duct due to benign or malignant diseases.[6,169] Reduced endogenous stimulation can cause or contribute to PEI in coeliac disease, diabetes mellitus, inflammatory bowel disease and after gastrointestinal surgery.[169,182] PEI has been demonstrated in approximately 50% of patients with insulin-dependent diabetes mellitus (IDDM), and in 30–50% of patients with non-insulin-dependent diabetes (NIDDM),[183–188] based on exocrine atrophy.[189] Studies using unselected patients from registries and less sensitive techniques for pancreatic function testing suggest lower frequencies of PEI, that is 26% in IDDM and 12% in NIDDM.[190–192]

Impaired pancreatic function is frequently observed after partial or total gastrectomy[193–196] and results from various causes, such as a deficient grinding of nutrients, altered gastric emptying, alteration of pancreatic innervation and post-cibal asynchrony.[197,198] PEI is also present in patients with marked protein deficiency. Rare causes of PEI include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome and congenital enzyme deficiency, such as trypsinogen or enteropeptidase (enterokinase), as well as isolated amylase, lipase or other protease deficiencies.[178] While patients with HIV may have PEI,[199] association with other conditions such as irritable bowel syndrome (IBS) is less clear.[200] Somatostatinoma[201] and somatostatin administration[202–204] may inhibit exocrine secretion and thereby cause secondary PEI.[175] Furthermore, insufficient amounts of active enzymes in the intestinal lumen can be due to their inactivation despite normal secretory activity of the pancreas, as in hyperchlorhydria.

Q3-4: When does PEI develop during the course of CP?

Statement 3-4. CP is a progressive disease and exocrine function gradually decreases during the course of the disease. **(GRADE 1B, strong agreement)**

Comments. The development and timing of the clinical manifestation of PEI in CP depends on the cause of the disease, among other factors. In patients with alcoholic CP, severe PEI with steatorrhoea usually appears about 10–15 years after diagnosis. In patients with early onset idiopathic CP or an hereditary form of the disease, exocrine insufficiency often does not manifest until even later,[4,205] despite the destruction of pancreatic tissue in the early stages of the disease. This late onset is due to the large functional reserve capacity of the pancreas.[167,206] However, as shown in a large retrospective cohort study, about 10% of patients present with steatorrhoea at the time of diagnosis.[205]

Q3-5: Can PEI be diagnosed or excluded using imaging techniques (morphological tests)?

Statement 3-5.1. Signs of CP (morphological alterations) and functional impairment usually develop in parallel, but this is not always the case. **(GRADE 1B, strong agreement)**

Comments. It is well substantiated that in the majority of patients with CP, a correlation exists between the extent of the morphological and functional changes. However, discordant findings with varying degrees of morphological and functional changes are found in about 25% of patients.[206–208] Even when EUS is used as the most sensitive technique for the detection of morphological alterations, normal morphological findings are not always equivalent to normal pancreatic function.[207,209] For example, despite normal morphology, PEI is often found in patients with the 'small duct disease' type of CP.[207] In an important study, in which EUS and secretin test results were compared with histological findings as a reference, the sensitivity of EUS for a diagnosis of 'CP' was 84%, and that of the secretin test was 86%, while a combination of the two methods

produced a sensitivity level of 100%.[210] This implies that either morphological or functional impairment can be the only sign of CP.

Statement 3-5.2. The s-MRCP technique reveals ductal morphological alterations and simultaneously gives semi-quantitative information on functional changes.[211] **(GRADE 1C, agreement)**

Comments. Given the statement above, s-MRCP is probably the most appropriate morphological test for the assessment of pancreatic exocrine function.[211] The extent of pancreatic fluid secretion can be classified using the DF score described by Matos et al.[88] (grade 0: no fluid signal in the duodenum; grade 1: fluid limited to the duodenal bulb; grade 2: fluid filling up to the genu inferius; grade 3: DF beyond the genu inferius). Pancreatic exocrine function is considered reduced when the DF score is less than grade 3. The examination requires about 45 min. The assessment of exocrine pancreatic function using the s-MRCP test correlates with the results of FE-1 measurements, the pancreolauryl test and the Lundh test,[212–215] which can be utilised in patients with CP as well as in those with other benign or malignant pancreatic diseases,[216] including cystic fibrosis.[217] However, minor degrees of DF are equivocal and require further diagnostic evaluation.

Q3-6: Which test is clinically indicated for diagnosing exocrine pancreatic insufficiency?

Statement 3-6. In a clinical setting, a non-invasive pancreatic function test (PFT) should be performed. The FE-1 test is feasible and widely available and is therefore most frequently used in this setting, while the ^{13}C mixed triglyceride breath test (^{13}C-MTG-BT) offers an alternative. The s-MRCP test may also be used as an indicator of PEI but provides only semi-quantitative data. **(Grade 1B, agreement)**

Comments. FE-1 is a very simple test for the indirect and non-invasive evaluation of pancreatic secretion.[166,218,219] This test is widely available and only requires a small stool sample for analysis. It is widely accepted that the lower the FE-1 concentration, the higher the probability of PEI. However, guidelines agree that the FE-1 test is not capable of excluding mild to moderate PEI,[175] and there is no consensus regarding the cut-off for PEI in patients with CP: figures of <15, 50, 100 and 200 μg/g have been proposed,[168,169,220] and a threshold of 200 μg/g has been used most frequently in accordance with the intended use label of the test.[175] Very low FE-1 values are most probably associated with PEI, whereas high values (>500 μg/g) allow the clinician to exclude that complication. The probability of false positive results due to stool dilution should be considered in patients with diarrhoea.[221] Finally, the more specific monoclonal FE-1 test (rather than the polyclonal FE-1 test) is most appropriate for use in clinical practice.[222]

The coefficient of fat absorption (CFA) is generally accepted as the gold standard for the diagnosis of steatorrhoea, which is characteristic of severe PEI. Currently, it is the only test accepted by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the indication and monitoring of PERT in clinical trials. The CFA requires patients to maintain a strict diet containing 100 g of fat per day over five days, and to collect the total amount of faeces excreted over the last three days of this five-day period. A CFA < 93% is considered pathological.[167] Apart from detecting only severe PEI, the test has limitations in terms of specificity (false positive results in non-pancreatic fat malabsorption), availability, patients' compliance and handling of faecal samples in the laboratory. Therefore, it is no longer used in some European countries.

The ^{13}C-MTG-BT is an appropriate alternative to the CFA, both for the diagnosis of PEI and for evaluating the efficacy of PERT in clinical practice.[223–225] Modifications of the test may allow the detection of mild to moderate PEI.[226,227] However, the test also has limitations in terms of specificity (false positive results in non-pancreatic fat malabsorption),[227] and it is not yet widely available and is only commercialised in some European countries.

Pancreatic secretion volume can be evaluated semi-quantitatively by s-MRCP. Pancreatic secretion evaluated by this technique correlates with FE-1 test results; however, its sensitivity for PEI is as low as 69%.[228,229] In addition, there is very limited evidence supporting this technique for the diagnosis of PEI in clinical practice.

Only direct tests that require the collection of duodenal juice in response to a hormonal stimulus, such as secretin and/or a cholecystokinin (CCK) analogue (or a meal), allow the quantification of pancreatic exocrine secretion and the reliable detection of mild to moderate exocrine insufficiency.[230] Therefore, they have been accepted as the reference standard.[4,175,230] Conventionally, these tests have been performed via the insertion of a naso-duodenal tube, but endoscopic variations have also been developed, are currently favoured in the USA,[210] and are increasingly used in some European countries. However, independent of the precise method of duodenal juice collection, the examination is invasive, labour-intensive and expensive. Therefore, such tests are confined to specialist centres. On the other hand, SPT and CFA are still required for

the evaluation of new tests if those are meant to detect not only severe exocrine insufficiency with overt malabsorption but also more gradual changes in pancreatic function.

Q3-7: Is a pancreatic function test required for the diagnosis of CP?

Statement 3-7. A function test is required for the diagnosis of CP. **(Grade 2B, strong agreement)**

Comments. The morphological grading systems have pitfalls regarding both sensitivity and specificity,[61,208,210,231–233] and it has been shown that either morphological or functional impairment can be the only sign of histologically proven CP.[210] Thus, a diagnosis of CP depends on a combination of clinical, histological, imaging and functional criteria. Proof of impaired exocrine function using function testing is particularly required for diagnosis in CP patients with inconclusive morphological findings. Moreover, several diagnostic and classification systems take exocrine function into account.[58–60,62,205,234] However, these are more important for clinical studies.

Q3-8: Should a pancreatic function test be performed at the time of diagnosis?

Statement 3-8. Every patient with a new diagnosis of CP should be screened for PEI. **(Grade 1A, strong agreement)**

Comments. The recommendation is based on the following aspects: as explained above, the initial pancreatic function test may provide a basis for the diagnosis of CP in a subset of patients. Moreover, the detection and treatment of exocrine failure has implications for patient outcome and follow-up.[4,9,10,235] However, exocrine failure may be present even when morphological findings are absent or minimal[206,207,209,210,236,237] so that morphological investigations alone do not allow for the assessment of exocrine function. In addition, even with unequivocal morphological findings of CP, clinical symptoms of exocrine failure are not always evident at the time of diagnosis and a lack of symptoms does not allow for the reliable exclusion of exocrine insufficiency, even if it is severe and associated with steatorrhoea.[167,205,238,239] By contrast, all available function tests detect these severe forms of the disease.

Q3-9: Should a pancreatic function test be performed during follow-up, if symptoms of malabsorption occur/deteriorate?

Statement 3-9. 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)**

Comments. It is well substantiated that the state of exocrine function will deteriorate over time in the majority of patients due to disease progression.[205,238] FE-1, as the most frequently used test, has only 54–75% sensitivity in mild to moderate PEI[218,219,230,240,241] and may therefore have to be repeated to diagnose progressive PEI. The absence of severe PEI with steatorrhoea[170,171,174,242] or its normalisation following PERT[223] does not exclude the possibility that PEI complications, such as loss of bone density and malabsorption of fat-soluble vitamins, may develop; thus more sensitive tests may be required.

Q3-10: Should a pancreatic function test be performed to monitor enzyme treatment?

Statement 3-10. 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 PERT, function tests (^{13}C-MTG-BT, acid steatocrit, and quantitative faecal fat) are recommended in order to evaluate treatment efficacy. **(Grade 2B, strong agreement)**

Comments. In general, a rapid improvement of clinical symptoms and increase in weight and BMI can be noted once patients with PEI are put on PERT. The response can be verified by measuring the said nutritional parameters in the serum.[243] The latter is important as a lack of symptoms does not exclude residual PEI.[223]

Q3-11: Are there special recommendations for specific patient groups?

Statement 3-11. Specific attention is required when screening for PEI in patients with CP and diabetes mellitus, pancreatic carcinoma, or following pancreatic resections or gastric resections. **(Grade 1B, strong agreement)**

Comments. Diabetes mellitus, pancreatic carcinoma and pancreatic resections are potential complications of CP.[3,4,9,169,182] On the other hand, even in the absence of CP, these diseases and conditions can be associated with PEI. Therefore, the likelihood of PEI is further increased in patients with both CP and one of these conditions. Following gastric resections, postcibal

asynchrony may cause further deterioration of nutrient digestion and absorption without directly affecting pancreatic secretory capacity.[177]

Q3-12: What are the blood parameters for measuring malnutrition?

Statement 3-12. Established blood parameters of malnutrition such as prealbumin, retinol-binding protein, 25-OH cholecalciferol (vitamin D), and minerals/trace elements (including serum iron, zinc and magnesium) should be measured.[173,244,245] **(GRADE 2C, strong agreement)**

Comments. The malnutrition resulting from PEI is no different from malnutrition due to other aetiologies. Accordingly, the same parameters can be measured.

Treatment for CP

Surgery in CP (WP 5)

Q4-1.1: In patients with symptoms of CP, should endoscopy or surgery be performed?

Statement 4-1.1. Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP. **(GRADE 2B, agreement)**

Comments. Physicians face a choice between endoscopy and surgery in the treatment of patients with CP and a dilated pancreatic duct (obstructive CP), without a clear consensus of opinion for this group of patients. Therefore, we assessed and compared the effects and complications of surgical and endoscopic interventions in the management of pain for obstructive CP and included relevant trials irrespective of blinding, the number of participants randomised, and the language of the article.[246–250]

We identified three eligible trials.[246–248] Two trials compared endoscopic intervention with surgical intervention and included a total of 111 participants: 55 in the endoscopic group and 56 in the surgical group. Compared with the endoscopic group, the surgical group had a higher proportion of participants with pain relief, both at mid/long-term follow-up (2–5 years: risk ratio (RR) 1.62, 95% confidence interval (CI) 1.22–2.15) and long-term follow-up (≥5 years, RR 1.56, 95% CI 1.18–2.05). Surgical intervention resulted in improved QoL and improved preservation of exocrine pancreatic function at mid/long-term follow-up, but not thereafter. However, there were no sham-controlled studies and without this one must be careful with the conclusions. There is certainly an effect of invasive procedures, but in RCTs the placebo effect may be up to 25% and the surgical and endoscopical studies were not blinded. No differences were found in terms of major post-interventional complications or mortality, although the number of participants did not allow for this to be evaluated reliably.

The third trial, with 32 participants, compared surgical intervention (17 patients) with conservative treatment (15 patients). Surgical intervention resulted in a higher percentage of participants with pain relief and better preservation of pancreatic function; however, the trial had methodological limitations, and the number of participants was relatively small.

For patients with obstructive CP and a dilated pancreatic duct, we find that surgery is superior to endoscopy in terms of pain relief. Morbidity and mortality seem not to differ between the two intervention modalities, but the trials identified do not provide sufficient power to detect the small differences expected in this outcome.

Q4-1.2: What is the optimal timing for surgical therapy in CP?

Statement 4-1.2a. To achieve optimal long-term pain relief in patients suffering from CP, early surgery is favoured over surgery at a more advanced stage of the disease.[251] **(GRADE 2B, weak agreement)**

Statement 4-1.2b. The risk of developing PEI is lower after early surgery for CP than after surgery performed at an advanced disease stage. Pancreatic resection techniques have a higher risk of PEI than drainage techniques. **(GRADE 2C, weak agreement)**

Statement 4-1.2c. No recommendation can be drawn from the evidence regarding the effect of early surgery on developing endocrine pancreatic function during follow-up since few studies exist and those that do are contradictory. **(GRADE 2C, strong agreement)**

Statement 4-1.2d. Long-term QoL is improved after early surgery (<3 years from onset) compared to surgery at a more advanced stage of disease. **(GRADE 2C, agreement)**

Comments. Information was extracted from several studies.[246–250,252,253] Multivariable analysis identified preoperative opioid use as an independent risk factor for a lower physical composed score (coefficient −4.81 (−7.36 to −2.28), $p < 0.001$). For the mental component score (MCS), preoperative opioid use was also independently associated with diminished QoL (coefficient −5.34 (−8.01 to −2.70), $p < 0.001$).[251]

Since QoL data, including assessment of pain relief, are scarce in the long-term setting, a multicentre trial evaluated these patient-oriented outcomes by

comparing early surgery to a step-up approach, including endoscopy. Accrual has been completed but results, including follow-up, will only be available in late 2017 (ESCAPE trial, ISRCTN 45877994; http://www.pancreatitis.nl).

Q4-1.3: What operative technique should be used for patients with CP and an enlarged pancreatic head?

Statement 4-1.3a. Duodenum-preserving pancreatic head resection (DPPHR) was compared to conventional pancreaticoduodenectomy (PD). The available data show that the DPPHR and PD procedures are equally effective in relieving postoperative pain. Endocrine and exocrine insufficiency are comparable after both strategies at the short-term assessment. QoL is significantly improved after DPPHR compared to PD. **(GRADE 1B, agreement)**

Statement 4-1.3b. Modifications of DPPHR – the Beger and Berne procedures – are equal in terms of pain relief, postoperative morbidity and mortality; however, the operating time and length of hospital stay is significantly shorter for the Berne procedure than for the Beger. **(GRADE 1B, strong agreement)**

Statement 4-1.3c. DPPHR was compared to conventional PD for long-term follow-up (up to 15 years). The available long-term data show continued pain relief in the majority of patients, with no differences between surgical procedures for pain and QoL outcomes. Occupational rehabilitation remains significantly better with DPPHR compared to PD. Endocrine and exocrine insufficiency were comparable after both strategies on long-term assessment. **(GRADE 2B, strong agreement)**

Statement 4-1.3d. There is a non-significant trend towards improved long-term mortality with DPPHR. **(GRADE 2B, strong agreement)**

Statement 4-1.3e. Long-term follow-up of DPPHR modifications. There are no differences in long-term outcomes between the Beger, Berne and Frey procedures. **(GRADE 1B, strong agreement)**

Comments. Pancreatic head resection represents the surgical treatment of choice for CP with pancreatic enlargement. PD and all available DPPHR modifications are potential surgical alternatives, all aiming at the relief of intractable pain and the decompression of adjacent organs.[254]

In order to evaluate short- and long-term outcomes of DPPHR versus PD in the surgical treatment of CP with pancreatic head enlargement, a systematic literature search was performed to identify available systematic reviews (SRs) and RCTs. A total of 2192 citations were retrieved, one SR[254] and 12 publications relating to seven RCTs were included.[255–266] The critical appraisal revealed trials with heterogeneous methodological qualities. The summarised results comparing PD versus DPPHR for the surgical treatment of CP were extracted from the RCT publications and the SR with meta-analysis. Two RCTs comparing DPPHR modifications with each other (Beger vs Bern, Beger vs Frey) were included without meta-analysis (which was not feasible due to a low sample size). For the remarks section, surgical aspects were also backed with non-randomised evidence as necessary.

Statement 4-1.3f. Neither DPPHR nor PD succeed in interrupting the progression of CP toward endocrine and exocrine failure. **(GRADE 1B, strong agreement)**

Comments. Since QoL data, including the assessment of pain relief, are scarce in the long-term setting, a multicentre trial evaluated these patient-oriented outcomes comparing PD versus all modifications of DPPHR. Results will be available later in 2017 (ChroPac trial, ISRCTN 38973832; http://www.chropac-trial.eu/).

Q4-1.4: What is the definition of an enlarged pancreatic head?

Statement 4-1.4. A normal pancreatic head varies considerably in size, although a diameter of >4 cm on CT or MRI imaging is usually considered as enlarged. **(GRADE 1C, agreement)**

Comments. The definition of an enlarged pancreatic head is relatively homogeneous in the literature. A diameter >35 mm[267–269] or 40 mm[247,270] is widely adopted. This diameter should be measured in the anteroposterior direction on cross-sectional imaging.[267] However, some authors do not give data regarding pancreatic head size in their series and thus do not modify the surgical treatment according to this criterion.[264,271–273] With a dilated main pancreatic duct (MPD) and a normal sized pancreatic head the differential diagnosis of a main-duct IPMN must be entertained.

Q4-1.5: What is the definition of a dilated main duct?

Statement 4-1.5. In adult patients, a main duct diameter of ≥5 mm in the pancreatic body seems amenable to ductal drainage for the majority of pancreatic surgeons. This threshold of 5 mm is therefore proposed as the definition of a 'dilated main duct'. **(GRADE: 1C, agreement)**

Comments. The definition of a dilated main duct is less consensual than that for an enlarged pancreatic head, since ducts >3–8 mm in diameter are considered as dilated. Regarding dilated pancreatic ducts, all authors consider only the maximum diameter and never provide the length and the location (cephalic vs distal) of dilated segments or the parenchymal thickness. In children with CP, a 5 mm diameter is considered sufficient to indicate surgery.[274]

Q4-1.6: When should a total pancreatectomy be considered in CP?

Statement 4-1.6. A total pancreatectomy should be considered in patients without duct system dilatation, who are resistant to conventional medical, endoscopic and previous surgical treatment and who have severe pain. **(GRADE 1C, agreement)**

Comments. The group of patients with the features described above, although small, has a very high level of suffering and a total pancreatectomy can be considered in these patients. If available, an effort should be made to combine the total pancreatectomy with islet autotransplantation (TPIAT); however, experience of this procedure is rather limited. This alternative is of particular importance in patients with an increased risk of developing pancreatic cancer (smokers; patients with hereditary pancreatitis).[275]

Q4-1.7: How to operate on a patient with painful CP, a dilated main pancreatic duct and a normal-sized pancreatic head?

Statement 4-1.7a. For these patients, a lateral pancreaticojejunostomy with a Roux-en-Y loop and Frey's procedure provide comparable pain control (low quality of evidence). However, no recommendation can be made for the preferred surgical technique in these patients. **(GRADE 2B, strong agreement)**

Statement 4-1.7b. Both a lateral pancreaticojejunostomy with a Roux-en-Y loop and Frey's procedure seem to provide equivalent pain control in patients with main duct dilatation and a normal size pancreatic head. **(GRADE 2B, strong agreement)**

Comments. In the literature, patients with a documented normal-size pancreatic head and dilated MPD were historically treated by Roux-en-Y pancreaticojejunostomy according to Partington and Rochelle. Beger's procedure was evaluated in this setting in only one retrospective study.[276] Findings were evaluated according to head size: a good result (opiates withdrawn) was observed in three out of 11 (27%) patients without head enlargement and 13 out of 16 patients (81%) with head enlargement ($p = 0.018$).[276] In some recent series, patients received a pancreaticojejunostomy and/or Frey's procedure according to the surgeon's preference or the study period. Study characteristics and the results of Roux-en-Y pancreaticojejunostomy and Frey's procedure are given in Supplementary Material, Table S4 (those series that included patients with a so-called 'cephalic inflammatory mass' were excluded).[277]

There is great heterogeneity in patients included in these series due to the variable prevalence of other potentially painful conditions (pseudocysts, biliary obstruction) and persisting alcohol consumption, which makes the comparison of results difficult. In one series,[277] wide opening of ductal system (MPD) including in the head was adopted. In another series,[278] extension of drainage by a ductal opening in the pancreatic head, with or without parenchymal resection was associated with significantly better pain control.

Q4-1.8: Is there a volume-outcome relationship in CP surgery? If so, what should be the minimal annual volume (potentially based on cancer surgery?

Statement 4-1.8. An experienced high volume pancreatic centre is recommended for the surgical treatment of CP. **(GRADE 2C, strong agreement)**

Comments. A systematic search in PubMed, Embase, and Cochrane revealed no publications on the impact of hospital or surgical volume in CP surgery. Therefore an experienced high volume centre is recommended for the surgical treatment of CP. For pancreatic resection (for pancreatic cancer) several publications were identified that indicated an advantage (concerning mortality) for high volume centres.[279–283]

The cut off (low vs high volume centre) was defined as between 10–20 cases per year per hospital. The surgical treatment of CP is commonly located in experienced pancreatic centres, as the number of CP patients is much lower than the number of pancreatic cancer patients. As resection for CP is technically similar to that for pancreatic cancer, the total number of pancreatic resections is more important than the frequency of surgery for CP. As in resectable pancreatic cancer, the decision for surgery in CP should be made by an interdisciplinary expert panel that includes an endoscopist and gastroenterologist.[284] This allows for an individual therapeutic concept so that each patient may consider non-surgical therapeutic options. In CP, improving QoL/pain is the dominant outcome parameter, while mortality is a secondary outcome parameter.

Q4-1.9: What is the role and outcome of surgery in groove (paraduodenal) pancreatitis?

Statement 4-1.9. Surgery should be performed when medical and endoscopic options have failed. 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)**

Comments. Groove pancreatitis is a rare yet well-defined form of CP that may constitute a painful condition in affected patients.[285] It presents a diagnostic challenge.[286]

Q4-1.10: What is the best timing for surgery in patients suffering from groove pancreatitis?

Statement 4-1.10. The initial treatment of groove pancreatitis should involve medical treatment and occasionally, endoscopic drainage procedures may be helpful. If these approaches fail, the patient should be referred for surgery. **(GRADE 2C, strong agreement)**

Q4-1.11: Which is the most appropriate surgical procedure for groove pancreatitis?

Statement 4-1.11. In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis (Supplementary Material, Table S5). **(GRADE 2C, strong agreement)**

Comments. There were no RCTs on this topic hence all of the studies considered are observational cohort studies or retrospective analyses. The quality of the evidence is predictably low and influenced by selection bias and we found no study comparing the results of medical, endoscopic and surgical treatments. Notably, there are no studies comparing pancreas-preserving vs pancreas-sparing procedures. Pancreas-sparing procedures have been described as surgical options when only the duodenum is involved and pancreatic involvement can be definitely ruled out. An additional argument in favour of pancreaticoduodenectomy is that there is a small, but unquantifiable, risk of pancreatic cancer in patients with presumed groove pancreatitis.[287]

Medical therapy for exocrine pancreatic insufficiency (WP6)

Q4-2.1: What are the indications for pancreatic enzyme replacement therapy (PERT) in CP?

Statement 4-2.1. PERT is indicated for patients with CP and PEI in the presence of clinical symptoms or laboratory signs of malabsorption. An appropriate nutritional evaluation is recommended to detect signs of malabsorption. **(GRADE 1A, strong agreement)**

Comments. PEI in CP is consistently associated with biochemical signs of malnutrition.[288] The indication for pancreatic enzyme replacement is classically established for steatorrhoea with faecal fat excretion of >15 g/day. Since the quantitative measurement of faecal fats is often omitted, the indication for enzyme replacement is also present with a pathological pancreatic function test in combination with clinical signs of malabsorption, or anthropometric and/or biochemical signs of malnutrition.[244,289–292] Symptoms include weight loss, diarrhoea, severe meteorism and flatulence, and abdominal pain with dyspepsia. Abnormally low nutritional markers associated with PEI and indicating PERT include fat-soluble vitamins, prealbumin, retinol-binding protein and magnesium, amongst others.[244] Therapy with oral pancreatic enzymes purely as a trial for 4–6 weeks may also be beneficial if symptoms are unclear.

Q4-2.2: What are the enzyme preparations of choice?

Statement 4-2.2. 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)**

Comments. The efficacy of pancreatic enzyme preparations depends on a number of factors: (a) mixture with meal; (b) gastric emptying with meal; (c) mixing with the duodenal chyme and bile acids; (d) rapid release of enzymes in duodenum.

Pancreatic enzyme preparations are formulated as pH-sensitive, enteric-coated, mini-microspheres that protect the enzymes from gastric acidity and allow them to disintegrate rapidly at pH 5.5 in the duodenum to release the enzymes.[293,294] The efficacy of pH-sensitive, enteric-coated, mini-microspheres in patients with CP has been demonstrated in several recent studies.[295–298] Enteric-coated preparations have been demonstrated to be more effective than conventional uncoated preparations.[299] A recent Cochrane review on the efficacy of pancreatic enzyme preparations in patients with pancreatic insufficiency secondary to cystic fibrosis demonstrated a higher efficacy for enteric-coated microspheres compared to enteric coated tablets.[300] It has been shown that mini-microspheres of 1.0–1.2 mm in diameter are emptied simultaneously with the meal and are associated with

higher therapeutic efficacy compared to 1.8−2.0 mm microspheres that still work satisfactory.[301]

Q4-2.3: How should pancreatic enzymes be administered?

Statement 4-2.3. Oral pancreatic enzymes should be distributed along with meals and snacks. **(GRADE 1A, strong agreement)**

Comments. The effectiveness of pancreatic enzyme supplements presupposes the mixing of enzymes and chyme. Thus, enzyme preparations should be taken with meals. If more than one capsule/tablet per meal must be taken, it may be beneficial to take one part of the dose at the beginning with the rest being distributed during the meal.[302,303]

Q4-2.4: What is the optimal dose of pancreatic enzymes for exocrine pancreatic insufficiency in CP?

Statement 4-2.4. A minimum lipase dose of 40,000–50,000 PhU is recommended with main meals, and half that dose with snacks. **(GRADE 1A, strong agreement)**

Comments. Although enzyme preparations include a large variety of pancreatic enzymes for digestion, the PERT dosage is based on lipase activity. The recommended initial dose is about 10% of the physiologically secreted dose of lipase into the duodenum after a normal meal.[177] That means that a minimum activity of 30,000 IU of lipase is required for the digestion of a normal meal. Since 1 IU of lipase equals 3 PhU, the minimum amount of lipase needed for digestion of a normal meal is 90,000 PhU (endogenous enzyme secretion and the orally administered enzymes taken together).

Clinical trials have evaluated different enzyme preparations given at different doses. Enzyme activity is shown in different commercially available products in accordance with procedures specified by the Fédération Internationale Pharmaceutique (FIP), the European Pharmacopoeia (PhEur) or the United States Pharmacopeia (USP). The equivalence among different units is as follows: for lipase, 1 FIP/PhEur unit = 1 USP unit; for amylase, 1 FIP/PhEur unit = 4.15 USP units; and for protease, 1 FIP/PhEur unit = 62.5 USP units.[304] Thus, since FIP, PhEur and USP are equivalent for lipase, clinical trials evaluating the efficacy of different preparations and doses on fat digestion can be compared directly.

The most recent and well-designed RCTs have shown the efficacy of PERT with enteric-coated mini-microspheres at a dose ranging from 40,000–80,000 PhU of lipase per main meal, and half that dose per snack.[297,298,303,305–307] Studies evaluating enteric-coated microspheres have shown a similar efficacy for doses ranging from 10,000–40,000 PhU of lipase per meal, indicating the lack of a dose-response relationship with these preparations.[308–310]

Q4-2.5: How should be the efficacy of PERT be evaluated?

Statement 4-2.5. 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)**

Comments. Although the disappearance of the clinical signs of malabsorption is classically considered as the most important criterion for the success of PERT, which is associated with an improvement of the QoL,[311] more recent studies have demonstrated that symptom relief is not consistently associated with normalisation of the nutritional status.[223] A recent review of reported data supports the concept of normalisation of nutritional parameters (both anthropometric as well as biochemical) as the optimal way to evaluate the efficacy of PERT.[243]

If the symptoms do not respond, or respond only partially, this may be due to other mechanisms. Several studies have shown that breath tests with ^{13}C-labelled lipids provide a good measure of fat digestion and faecal fat excretion and are therefore suitable for monitoring the effectiveness of enzyme replacement therapy.[223,288,312] The success of replacement therapy cannot be assessed by measuring the faecal concentration of elastase, because only the natural human enzyme, and not the therapeutically administered enzyme contained in pancreatin, is measured. Faecal chymotrypsin excretion provides no information about the effect of enzyme replacement therapy on nutrient digestion and nutrient absorption; however, it can be used to test for compliance (low values correspond to inconsistent intake).[4]

Q4-2.6: What should be done in cases of unsatisfactory clinical response?

Statement 4-2.6. In cases of unsatisfactory clinical response, the enzyme dose should be increased (doubled or tripled) or a proton pump inhibitor (PPI) should be used. If these strategies fail, another cause for maldigestion should be sought. **(GRADE 2B, strong agreement)**

Comments. The recommended initial dose of 10% of the cumulatively secreted lipase activity into the duodenum after a normal meal (see above) should suffice to prevent malabsorption and steatorrhoea in more than half of patients treated. Although solid scientific evidence is lacking, clinical experience shows that a doubling or tripling of this dose is necessary and helpful in some patients. The inhibition of gastric acid secretion either by H2-blockers or PPIs is of help in patients with an insufficient response to the initial enzyme dose.[290,313,314] Whether increasing the oral enzyme dose is more effective than the addition of a PPI in these patients is unknown, and both strategies should be considered as appropriate. If the secretion of gastric acid is suppressed, then uncoated pancrelipase could be used in cases of insufficient clinical response.

Patients with CP frequently have abnormal bacterial gut colonisation.[315] This may be considered as a possible cause of persistent symptoms and other disturbances if the above-mentioned measures are unsuccessful.

Q4-2.7: Should PPIs be added to pancreatic enzyme supplementation in the treatment of PEI in CP?

Statement 4-2.7. The addition of a PPI to oral pancreatic enzymes is of help in patients with an unsatisfactory response to PERT. **(GRADE 1B, strong agreement)**

Comments. Several RCTs have shown that additional acid suppression can improve the effect of PERT compared with pancreatin alone.[290,316–318] However, only very few patients with varying PEI aetiologies were included in these studies. Moreover, variable pancreatin preparations and variable drugs for acid suppression (different H2-antagonists and/or PPIs) have been investigated. Therefore, the recommendation to add a PPI to oral pancreatic enzymes in patients with an unsatisfactory response to PERT is based on data of only moderate quality. Subgroup analyses suggest that the addition of a PPI leads to a significant improvement and even normalisation of fat digestion in patients with PEI and an incomplete response to enzyme substitution therapy.[313] By contrast, patients with an adequate response to enzyme substitution therapy did not profit from an additional PPI[313,319] (Supplementary Material, Table S6). This probably explains why a recent retrospective analysis of a large patient database did not show superior effects of PERT on fat absorption in patients who received acid-suppressing therapy for other indications throughout the study.[319]

Endoscopic therapy (ET) (WP7)

Q4-3.1a: To which patients should ET be proposed?

Statement 4-3.1a. In patients with uncomplicated painful CP and a dilated MPD, we recommend ET as the first-line treatment after failed medical therapy following discussions by a multidisciplinary team (MDT). 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, in particular for patients with a predicted poor outcome following ET. The management of CP-related complications is discussed below. **(GRADE 2B, agreement)**

Q4-3.1b: Is there a role for ET in asymptomatic CP?

Statement 4-3.1b. ET has no role in asymptomatic and uncomplicated CP. **(GRADE 2B, agreement)**

Comments. In patients with uncomplicated painless CP, no study has demonstrated any benefit for ET, including for the treatment of exocrine or endocrine pancreatic insufficiency.[320–322] Nevertheless, certain CP complications may indicate treatment even if they are asymptomatic; for example, some biliary strictures and pancreatic pseudocysts (PPCs), as discussed below.

Q4-3.1c: How does ET compare with surgery with respect to timing, efficacy and cost?

Statement 4-3.1c. ET is performed first in most cases, with surgery reserved to the minority of patients whose painful symptoms do not respond well to ET. 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 stages of the disease. **(GRADE 2B, agreement)**

Comments. In an RCT that compared endoscopic EUS-guided drainage vs surgery for uncomplicated PPC in 40 patients, endoscopic drainage was significantly better than surgery in terms of cost, length of hospital stay and QoL up to three months post-procedure.[323] At a median follow-up of 18 months, clinical outcomes and QoL were similar for both groups. The total mean cost was lower for patients managed by endoscopy compared to surgery ($7011 vs $15,052). Moreover, a large review of a non-comparative historical series of endoscopic and surgical treatments that included 787 patients showed similar morbidity (13.3% vs 16.0%, respectively) and long-term PPC recurrence (10.7% vs 9.8 %, respectively) but lower mortality with the endoscopic method (0.2% vs 2.5%, respectively).[324] Finally, ET does not

significantly affect subsequent surgical therapy if it becomes necessary.

Q4-3.1d: Which patients respond best to ET?

Statement 4-3.1d. Pre-treatment factors useful to identify the best responders to ET are the location of obstructing stones in the head of the pancreas, the absence of MPD stricture, a short disease duration and a low frequency of pain attacks before ET. **(GRADE 2B, agreement)**

Comments. Factors independently associated with long-term (≥2 years) pain relief following ET for CP include the location of obstructive calcifications in the head of the pancreas (the most robust predictor of good outcome, identified in an RCT),[325] a short disease duration and a low frequency of pain attacks before ET, complete MPD stone clearance and an absence of MPD stricture at initial ET, as well as the discontinuation of alcohol and tobacco during follow-up.[321,326–328] Disease duration before ET was assessed using the dates of the first pain attack and most studies reported better clinical results in patients with a shorter disease duration.

Q4-3.2a: What are the indications for extracorporeal shock wave lithotripsy (ESWL)?

Statement 4-3.2a. 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; although, in centres with expertise, ESWL alone may be a more cost-effective option (strong recommendation, moderate quality evidence). We suggest performing non-contrast enhanced computed tomography (NCCT) before ESWL to determine the location, size, number and density of stones (weak recommendation, low quality evidence). **(GRADE 2C, agreement)**

Comments. ESWL is the gold standard for non-surgical MPD stone removal. A meta-analysis of 17 studies (a total of 491 patients) showed that ESWL is useful for clearing MPD stones and for decreasing CP-related pain.[329] ESWL is highly effective at fragmenting radiopaque pancreatic stones: a systematic review of 11 series found that ESWL successfully fragmented stones in 89% of 1149 patients.[330] However, in an RCT with long-term follow-up, comparing surgery with endoscopy plus ESWL, surgery was more effective than the combination of endoscopy and ESWL for larger stones.[247,248]

In general, stone extraction using a Dormia basket without prior lithotripsy should not be attempted as this technique fails in a majority of patients (83% and 91% in two series of 46 and 125 patients, respectively);[327,331] moreover, it carries a relatively high morbidity.[332]

Q4-3.2b: Should some stones be preferentially selected for treatment (stone size and location)?

Statement 4-3.2b. ESWL should target stones with a minimal diameter of 2–5 mm, starting in the head of the pancreas and progressing to the head to permit elimination of stone fragments. **(GRADE 2C, agreement)**

Comments. In the majority of series, stones targeted by ESWL were mostly radiopaque stones obstructing the MPD with a minimal diameter of 2–5 mm.[320,325–328,333–337] Endoscopic clearance of MPD stones targeted by ESWL is more frequently obtained in the case of single stones and stones confined to the head of the pancreas.[321,325,326,333,338] Other factors associated with complete stone clearance from the MPD that require confirmation include: (a) a stone density <820 Hounsfield units (prospective study, 128 patients),[338] (b) intravenous injection of secretin during ESWL (retrospective study, 233 patients),[339] and (c) ERCP performed >2 days as compared with ≤2 days following ESWL (retrospective study, 30 patients).[340]

Q4-3.2c: What are the potential indications for treatment by ESWL alone?

Statement 4-3.2c. ESWL alone may be the most cost-effective option but it should be reserved to centres with expertise in this technique. **(GRADE 2C, agreement)**

Comments. ESWL without subsequent ERCP may also be used to treat painful uncomplicated CP: two uncontrolled series reported spontaneous MPD stone clearance in 70–88% of 350 patients and pain relief was achieved at 44 months in 78% of the patients.[335,341] In an RCT that compared ESWL alone vs ESWL followed by ERCP in 55 patients,[325] the only significant differences between groups were a longer hospital stay and a higher treatment cost in the ESWL plus ERCP group.

Q4-3.2d: What are the post-ESWL complications?

Statement 4-3.2d. Pancreatitis is the most frequent complication of ESWL. **(GRADE 2C, agreement)**

Comments. In a prospective series of 634 patients with a treatment protocol that helped to distinguish between ESWL-related and ERCP-related complications (ERCP was performed after the last ESWL

session), 99 complications were attributed to ESWL (15.6% of patients, 6.7% of ESWL sessions), 16 of these being classified as moderate to severe (2.5% of patients). Post-ESWL pancreatitis accounted for two-thirds of the complications.[342] Other adverse events attributed to ESWL in large series include pancreatitis, skin erythema, haematuria, gastrointestinal bleeding, 'steinstrasse' (acute stone incarceration in the papilla responsible for MPD dilatation), hepatic subcapsular haematoma and perforation.[320,321,335,337,342]

Q4-3.2e: What is the frequency of long-term pain recurrence after ESWL alone or when combined with endoscopic stone extraction?

Statement 4-3.2e. At long-term, pain relapses requiring analgesics or more invasive treatment has been reported in 5–45% of patients. **(GRADE 2B, agreement)**

Comments. Long-term, complete or partial pain relief following ESWL associated with ERCP has been reported in 70–96% of the patients included in five retrospective studies (Supplementary Material, Table S7).[320–322,343] In the above-mentioned RCT that compared ESWL alone vs ESWL followed by ERCP in 55 patients,[325] at the end of follow-up (51 months) 31 patients (56%) had no pain relapse with no difference between the two treatment groups.

Q4-3.3a: How is a dominant pancreatic stricture defined? What are the long-term results of stricture dilation, temporary single plastic stenting, temporary multiple plastic stenting?

Statement 4-3.3a. Dominant MPD strictures in the head of the pancreas are defined as strictures with an upstream MPD dilation $\geq$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)**

Comments. The abovementioned definition is usually accepted.[344,345] Stricture dilation alone is not a standard treatment option for MPD strictures.[347] The same is true for single plastic stenting for a short period (six months) even if associated with repeated balloon dilation of the stricture.[348]

In five retrospective case series with long-term ($\geq$24 months) follow-up and a total of 348 patients,[349–352] pain improvement was reported in 62–83% of patients with a mean follow-up of 24–69 months after single plastic stent removal. In the largest study,[350] after a median stenting duration of 23 months, 62% of patients maintained satisfactory pain control without pancreatic stent replacement during a median time of 27 months. The majority of pain recurrence, requiring a new period of pancreatic stenting, occurred during the first year following stent removal (79%), with almost all (97%) having relapsed by 24 months.[350] Consequently, if a patient remains stable during the first year after stent removal, subsequent relapse and need for re-stenting are less likely.

Results of multiple plastic stenting were reported in a single study that included 19 patients.[353] A median number of three simultaneous stents (8.5–11.5 Fr) were left in place for seven months. At a mean follow-up of 38 months following stent removal, 84% (16/19) of the patients remained pain-free (Supplementary Material, Table S8).

Q4-3.3b: With temporary plastic stenting, which is the most appropriate stent design, length and diameter?

Statement 4-3.3b. We recommend using a straight polyethylene (8.5–10 Fr) pancreatic stent with the shortest possible length, tailored to the location of the MPD stricture. **(GRADE 1C, agreement)**

Comments. The choice of stents is influenced by the stricture severity (limiting the maximal stent diameter that might cross the stricture), its location (affecting the stent's length) and the shape of the MPD (i.e. difficult anatomy such as ansa pancreatica).

Although a bench study suggested that stent occlusion is associated with a stent diameter >8.5 Fr,[354] a larger clinical study found that patients with stents $\leq$8.5 Fr ($n = 129$, 79%) were three times more likely to be hospitalised for abdominal pain than those with 10 Fr stents ($n = 34$, 21%).[355] In 2006, a new S-type 10 Fr stent was proposed to prevent stent migration,[356] but despite good results in a small study it is not currently used.

Q4-3.3c: What is the most appropriate stent exchange schedule?

Statement 4-3.3c. 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. **(GRADE 1B, agreement)**

Comments. 'On-demand' stent exchange is the preferred strategy, as the duration of the stent's clinical effect is unpredictable and is not correlated with stent clogging.[357] With an 'on-demand' strategy, stent replacement was reported to be required after a mean period of 8–12 months.[350] Criteria used during ERCP for terminating MPD stenting include: adequate

outflow of contrast medium 1–2 min after ductal filling upstream from the stricture location after stent removal, easy passage of a 6 Fr catheter through the stricture location, and decreased focal narrowing.[349–351] Note, complete stricture resolution is not needed for pain relief.[351,358]

Q4-3.3d: What are the indications of stenting for MPD strictures? What are the criteria for not replacing a temporary stent after removal?

Statement 4-3.3d. We recommend treating 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. 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)**

Comments. Satisfactory results reported in Table 4.3-2 were obtained using the abovementioned treatment modality. Multiple plastic stenting is another option but it is technically more complex and it has not been compared with single plastic stenting.[359] Criteria used during ERCP for terminating MPD stenting include: adequate outflow of contrast medium 1–2 min after ductal filling upstream from the stricture location after stent removal, easy passage of a 6 Fr catheter through the stricture location, and decreased focal narrowing.[360–362] Note, complete stricture resolution is not needed for pain relief.[348,362]

Q4-3.3e: How are refractory MPD strictures defined and how to treat them?

Statement 4-3.3e. Refractory MPD strictures are defined as persistent symptomatic dominant strictures after one year of single stent placement. We recommend multiple pancreatic duct stenting for treating a refractory MPD stricture or a trial of 3–6 months with a fully covered self-expandable metallic stent (FC-SEMS) or surgical pancreaticojejunostomy. **(GRADE 2C, agreement)**

Comments. The above-mentioned definition is usually accepted.[345,363] For refractory MPD strictures, besides the insertion of multiple plastic stents, the temporary insertion of a FC-SEMS is an option, although uncovered and partially covered self-expandable metallic stents (SEMSs) have provided disappointing results.[364] Five recent studies have reported encouraging results with a FC-SEMS in a total of 61 patients; however, the follow-up after stent removal for this group was short (Table 4.3-2).[363,365,366] Pain improvement was reported in 40/48 patients (83%). The optimal duration of treatment with FC-SEMS should probably be around 3–6 months.[363,365,366] Furthermore, a recent systematic review suggested that both FC-SEMS and multiple plastic stents produce similarly good results.[367]

Q4-3.3f: How do temporary single plastic stenting, temporary multiple plastic stenting, temporary SEMS placement and balloon dilatation compare in terms of indications, long-term results and complications?

Statement 4-3.3f. Polyethylene 10 Fr pancreatic stents tailored to the shape of the MPD and length of the stricture are most commonly used. Occlusion of MPD stents usually occurs within 2–3 months while symptoms of CP usually recur between 6–12 months. Thinner MPD stents ($\leq$8.5 Fr) are associated with more frequent hospitalisations for abdominal pain than 10 Fr stents. Placement of a single pancreatic plastic stent achieves MPD stricture resolution in nearly 60% of cases while simultaneous placement of multiple pancreatic stents was reported to be of additional benefit in a single study. Complications related to MPD stenting are usually mild and managed conservatively. The European Society of Gastrointestinal Endoscopy (ESGE) recommends treating dominant MPD stricture by inserting a single 10 Fr plastic stent, with stent exchange planned within one year even in asymptomatic patients to prevent complications related to long-standing pancreatic stent occlusion. 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)**

Comments. Stricture dilatation alone is not a standard treatment option for MPD strictures.[330,345] The same is true for single plastic stenting for a short period (six months) even if associated with repeated balloon dilatation of the stricture.[358]

Q4-3.3 g: What are the adverse events related to pancreatic stenting in CP?

Statement 4-3.3 g. Adverse events include stent occlusion and stent migration. **(GRADE 1B, agreement)**

Comments. Pancreatic duct stenting is associated with complications such as stent occlusion (may induce the formation of pseudocysts in rare cases), stent migration, including distal migration to the

duodenum with the risk of impaction on the opposite duodenal wall and risk of duodenal perforation, and proximal migration into the pancreatic duct, with technical challenges for stent removal. Distal and proximal migration of the pancreatic stent were reported in 1.5–7.5% and 0.8–5.2% of patients in two studies.[368,369]

Spontaneous stent migration has been reported in 8% of patients with FC-SEMS, but with large differences between studies, from 0% in one study[363] to 39% in another study.[370] Moreover, adverse events such as cholestatic liver dysfunction developed in four patients (without a history of previous endoscopic biliary sphincterotomy) and may be associated with compression of the bile duct orifice due to expansion of the FC-SEMS.[363,370]

Q4-3.4a: How does ET with temporary single plastic stenting, temporary multiple plastic stenting, and temporary SEMS placement compare with surgery for biliary stricture (BS) treatment in terms of long-term efficacy, cost and complications? How to select patients for ET?

Statement 4-3.4a. Temporary stenting of common bile duct (CBD) strictures with multiple simultaneous plastic stents or covered SEMS provide long-term success in 90% of cases. This compares with stricture resolution in a minority of patients only following temporary stenting with a single plastic stent. No valid study comparing ET vs surgery was found. We recommend treating CBD strictures responsible for symptomatic (recurrent acute cholangitis, obstructive jaundice) or persistent (>1 month) cholestasis. 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, not single plastic stents, should be used. **(GRADE 2C, agreement)**

Comments. We recommend treating CBD strictures responsible for symptomatic (recurrent acute cholangitis, obstructive jaundice) or persistent (>1 month) cholestasis (strong recommendation, low quality evidence). 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. An effectual recall system should be established in order to avoid septic complications (weak recommendation, low quality evidence). 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.

Q4-3.4b: What is the indication for biliary stenting in biliary strictures in CP?

Statement 4-3.4b. CBD strictures responsible for symptomatic (recurrent acute cholangitis, obstructive jaundice) or persistent (>1 month) cholestasis are indication for stenting. We suggest electing ET in patients deemed to comply with repeat ERCPs and who are at high surgical risk, present portal hypertension or local abdominal conditions contraindicating surgery. An effectual recall system should be established in order to avoid septic complications. 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)**

Comments. The indications for the treatment stated above are generally accepted, with persistent cholestasis defined as alkaline phosphatase (ALP) levels >2–3 times the upper limit of normal values lasting for more than one month.[371–373]

Temporary biliary stenting, usually for one year with regular stent exchange in the case of plastic stents, is the mainstay of treatment. In the long-term following stent removal, stricture resolution persists in 10–38% and 44–92% of patients following single vs multiple plastic stenting, respectively.[330] Treatment with single plastic stents has been abandoned for this indication[345] and removable covered SEMSs have been proposed as an alternative to multiple plastic stents, with the advantage of requiring theoretically only two ERCP procedures.[374–378] The use of uncovered SEMSs for this indication should be banned because of the unavoidable hyperplastic tissue reaction, which usually impedes their removal.[379,380]

An RCT that compared six-month stenting using multiple plastic biliary stents vs covered SEMSs for treating CP-related biliary strictures in 60 patients found similar results with both stent models, including stent-related morbidity (23% vs 29%, respectively) and success rates two years after stent removal (90% vs 92%, respectively).[381] A meta-analysis of non-comparative studies in patients with CP-related biliary strictures found higher success rates at one-year follow-up with FC-SEMSs vs plastic stents (77% vs 33%, $p = 0.06$) but these results should not be taken into account as patients with single and multiple plastic stenting were grouped, although treatment with single plastic stents is no longer current practice.[382] Economic evaluations comparing the different treatment options are unavailable in this setting. With the FC-SEMS, a multicentre prospective study (127 patients with CP-related biliary strictures) found that the stricture had resolved in 90.5% of patients who underwent

scheduled FC-SEMS removal, with stricture recurrence observed in 10.5% of patients at 18-months follow-up.[383] Unfortunately, no 'intention-to-treat' analysis was provided.

In patients with CP and alcohol abuse, compliance with stent exchange may be problematic: in two series involving 43 patients, 70% of patients had stent-related complications (fatal in 5% of cases) because they did not present for scheduled stent exchanges.[384,385]

A single comparative, retrospective study of endoscopic vs surgical treatment for CP-related biliary strictures was identified:[386] 33 patients had primary ET (35% covered SEMS and 65% multiple plastic stents, for a mean stenting duration of 11 months) while six patients underwent surgery. The success rate at two years was 12% vs 65% for endoscopic and surgical treatment, respectively. The success rate reported after ET is highly discordant from those reported in an RCT (12% vs 90%)[381] and the authors suggested that these extremely poor results might be related to their definition of failure that included asymptomatic ALP elevation about the upper limit of normal values.

Q4-3.5: For children, in which conditions is ET recommended?

Statement 4-3.5. In children with uncomplicated painful CP and an obstructed MPD, we recommend ET as the first-line treatment after failed medical therapy. **(GRADE 1C, agreement)**

Comments. In children, CP usually presents as episodes of moderate abdominal pain.[387] Compared with adults, paediatric patients have a lower prevalence of complications including PPC and CBD strictures.[388]

Three large retrospective series reported that ET (whether or not combined with ESWL) decreases CP-related pain in children (Supplementary Material, Table S9).[389–391] In a retrospective study that included 37 children with CP, the recurrence of a flare-up of CP was more frequent in patients who had ERCP vs surgery; however one-third of patients in the ERCP group had diagnostic ERCP only.[392] Therefore, a therapeutic step-up strategy similar to that proposed in adults (conservative measures/ET/surgery) seems appropriate. The outcome of this strategy was reported in a prospective study that included 12 children and 32 months after treatment (ERCP, $n=8$; surgery, $n=2$), all children were free from a recurrence of pancreatitis without impairment of everyday activities.[393]

With respect to procedure-related morbidity, highly different rates have been reported in paediatric series (the reader is referred to Oracz et al.[391] for a review of morbidity rates); however, importantly, two large studies have suggested that morbidity rates are similar in children compared with adults.[388,394]

In a common guideline issued by the ESGE and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, therapeutic ERCP is strongly recommended in paediatric patients (>1 year old) for diseases amenable to endotherapy, including CP.

Treatment of PPCs (WP8)

The decision in whom, when, and by which procedure PPCs should be treated has been very controversial in the past. PPCs develop as a frequent complication of acute or CP. The prevalence of PPCs in CP lies between 20–40%.[395] PPCs occur most often in patients with alcoholic CP (70–78%),[396] while the second most common cause is idiopathic CP (6–16%). Within the first six weeks after an acute bout of pancreatitis, 40% of pseudocysts resolve spontaneously, whilst complications occur in 20% of cases indicating the need for intervention. The spontaneous remission of pseudocysts after 12 weeks is very rare, and complications are observed in up to two-thirds of cases. An increase in pseudocyst size to >5 cm is associated with the development of complications. If pseudocyst formation becomes symptomatic, then surgery, percutaneous or endoscopic drainage can be performed. All of these procedures demonstrate comparable results regarding technical success and recurrence rate.[396]

Q4-4.1: Should pseudocysts be treated?

Statement 4-4.1. We recommend ET for those patients with uncomplicated chronic PPCs for which treatment is indicated and that are within endoscopic reach. Transpapillary (TP) drainage is preferred over transmural (TM) drainage for small (<6 cm) PPCs communicating with the MPD in the head or body of the pancreas, or if TM drainage is contraindicated or not feasible. If TM pseudocyst drainage is elected: (a) it should be performed under echoendoscopic guidance if there is no luminal bulging and (b) several double-pigtail plastic stents (not self-expandable metal 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)**

Comments. Universally accepted indications for PPC treatment include the presence of symptoms, complications (infection, bleeding, or rupture), or compression of surrounding organs (gastric, duodenal or biliary obstruction).[397] Treatment of asymptomatic and uncomplicated PPCs is not indicated, regardless of size.[398] Note, the duration and size of PPCs do not accurately predict the probability of spontaneous

resolution (less than 10% in a CP setting) or the development of complications.[399,400]

Chronic PPCs may be drained by endoscopic, percutaneous or surgical means. Percutaneous drainage should not be performed in chronic PPCs, except in patients who are not candidates for other procedures.[401]

Q4-4.2: Which treatment modality is recommended for a chronic pseudocyst?

Statement 4-4.2. ET is recommended for chronic PPCs whenever possible. If TM pseudocyst drainage is elected: (a) it should be performed under echoendoscopic guidance and (b) several double-pigtail plastic stents, or self-expandable metal stents if solid debris (walled-off pancreatic necrosis (WOPN)) is found in the cavity, should be inserted to drain the PPC into the digestive lumen until cyst resolution, with a minimum of two months of stenting. **(Grade 2C, strong agreement)**

Comments. Surgical procedures for treating pseudocysts tend to have higher success rates, but also have a somewhat higher mortality than endoscopic pseudocyst drainage into the duodenum or stomach and an interdisciplinary therapeutic concept is recommended.[396,402] Percutaneous drainage should not be performed in chronic PPCs, except in patients who are not candidates for other procedures.[401]

Two endoscopic approaches have been described for draining PPCs into the gastrointestinal lumen: TP and TM drainage. TP drainage is feasible only in the case of direct communication between the PPC and the MPD, which occurs in 40–66% of all PPCs.[402–404] TP and TM drainage of PPC were compared in three non-randomised studies that included 173 patients (CP was diagnosed in 40–92% of patients).[402,405,406] Compared with TM drainage, TP drainage was used for smaller PPCs, was associated with lower morbidity (1.8% vs 15.4%), and had similar long-term success.[345]

With respect to TM drainage, two RCTs compared X-ray guidance alone vs X-ray guidance combined with EUS[407,408] and found a higher rate of technical success when EUS guidance was used because it can be performed even in the absence of intraluminal PPC bulging, which is observed in approximately half of cases.[406] Following TM drainage, early stent removal is associated with more PPC recurrences compared with stent maintenance, according to an RCT (28 patients) and a retrospective study (92 patients) that identified a stenting duration >6 weeks and the insertion of multiple double-pigtail stents as independent predictors of a favourable outcome.[401,409] SEMS should not be used to drain PPCs as it is more expensive and has no advantage over plastic stents, according to a systematic review that included 17 non-comparative studies.[410]

Some associated lesions may affect the strategy of PPC treatment: If extrahepatic portal hypertension is present, EUS-guided PPC drainage has been recommended to decrease the risk of bleeding.[411] This strategy has not been compared with conventional TM drainage but it has been reported to be safe in a small series of patients.[412]

The success rate in a published study of 1126 patients with TM drainage of a PPC was reported as 79.2%, with more recent studies reporting success rates significantly over 85%, which corresponds to surgical results. The mortality rate in a series involving over 30 patients was 0.2%, the recurrence rate was reported as 7.6% and the complication rate was 12.8%.[396]

Q4-4.3: Is EUS guidance needed for TM drainage of a pseudocyst?

Statement 4-4.3. TM drainage should preferably be done under EUS guidance. **(GRADE 1B, strong agreement)**

Comment. EUS is a procedure that can best assess the appearance of the pseudocyst wall, its content, location and relationship to adjacent blood vessels. Therefore, endoscopic TM drainage should be performed under EUS guidance to reduce the rate of failed puncture attempts and complications.[408] A direct comparison of the complication rate for TM needle drainage without ultrasound guidance is not available. With respect to TM drainage, when two RCTs compared X-ray guidance alone vs X-ray guidance combined with EUS,[407] they found a higher rate of technical success when EUS guidance was used because this can be performed even in the absence of intraluminal PPC bulging, which is observed in approximately half of the cases.[408] If extrahepatic portal hypertension is present, EUS-guided PPC drainage has been recommended to decrease the risk of bleeding;[411] this strategy has not been compared with conventional TM drainage but it has been reported to be safe in a small series of patients.[412]

Q4-4.4: When is TP drainage preferred over TM drainage in PPCs?

Statement 4-4.4. We recommend ET for those patients with uncomplicated chronic PPCs for which treatment is indicated and that are within endoscopic reach. TP drainage is preferred over TM drainage for small (<6 cm) PPCs communicating with the MPD in the head or body of the pancreas, or if TM drainage is contraindicated or not feasible. If TM pseudocyst

drainage is elected: (a) it should be performed under echoendoscopic guidance if there is no luminal bulging and (b) several double-pigtail plastic stents (not self-expandable metal stents) should be inserted to drain the PPC into the digestive lumen until cyst resolution with a minimum of two months of stenting. **(GRADE 2B, strong agreement)**

Comments. Universally accepted indications for PPC treatment include the presence of symptoms, complications (infection, bleeding or rupture), or compression of surrounding organs (gastric, duodenal or biliary obstruction).[397] Treatment of asymptomatic and uncomplicated PPC is not indicated, regardless of size.[398] Note, the duration and size of PPCs do not accurately predict the probability of spontaneous resolution (less than 10% in a CP setting) or the development of complications.[399,400]

Chronic PPCs may be drained by endoscopic, percutaneous or surgical means. Percutaneous drainage should not be performed in chronic PPC, except in patients who are not candidates for other procedures.[401]

Q4-4.5: When should asymptomatic pseudocysts be treated?

Statement 4-4.5. Asymptomatic PPCs, which have reached a size of >5 cm in diameter and which do not resolve within 3–6 months, should be treated. **(GRADE 2C, strong agreement)**

Comments. PPCs which are shown to be enclosed by a fibrous wall of >5 mm on imaging, are particularly suited for endoscopic or surgical drainage. Gouyon et al. were able to show, in a multivariate analysis, that a pseudocyst size <4 cm is the only prognostically favourable factor for spontaneous resolution,[413] while untreated cysts >5 cm result in complications (rupture, infection, jaundice or haemorrhage) in 41% of cases.[414] This was confirmed in a prospective case series in which up to 67% of patients with a PPC still present six months after the diagnosis of PPC suffered from nausea, vomiting and intense pain.[415]

With respect to the timing of PPC drainage, no comparative study is available and we suggest the following: if no recent episode of acute pancreatitis has been identified, PPC that are thought to be the main cause of pain or complications should be drained promptly as the spontaneous resolution of PPC is uncommon and is observed mostly for small (<3 cm) intrapancreatic collections with a long follow-up;[413] if a recent episode of acute pancreatitis has been identified, or if the PPC was not detected on prior examination, the PPC should be observed for up to six weeks to allow for either spontaneous resolution or maturation of the cyst wall;[416] MRI and/or EUS should be performed to distinguish between an acute effusion or collection (with or without necrosis) and a previously undiagnosed chronic collection.

Q4-4.6: What is the role of fine needle aspiration of cystic lesions?

Statement 4-4.6. Diagnostic needle aspiration of a cyst may be performed for suspected infected cystic contents or for suspected neoplasm. **(GRADE 2C, strong agreement)**

Comments. If diagnostic needle aspiration of the cyst confirms an infection of the contents, then drainage of the pseudocyst is indicated. Surgical resection should be carried out if malignancy is detected. In summary: If EUS-guided needle aspiration of a cyst reveals a carcinoembryonic antigen (CEA) level >400 ng/ml, a variably increased or low amylase (lipase) level, high viscosity, mucin or epithelial cells in the cyst contents, then the presence of a mucinous neoplasm must be assumed. It is then usually a mucinous cystic neoplasm (MCN), which is more prevalent in women aged between 30–50 years of age, is located usually in the pancreatic tail and demonstrates mural nodules on imaging. In this situation, the so-called eggshell pattern of calcification is typical. Prognosis after surgery is good in the presence of non-invasive growth. If, however, invasive growth is confirmed, then the average survival is 45 months.[417]

Aspiration biopsy of an MCN differs very little from an IPMN; which is regarded as a precancerous lesion. Its malignant potential depends on its location (main duct or side branch duct) and the size of the lesion as well as its solid parts. An IPMN originating from the main pancreatic duct should always be resected because in 52–92% of cases a carcinoma will develop from this lesion within a period of eight years. For lesions of the side branch duct this amounts to 6–46%.[417] Those lesions <1 cm on MRI or EUS and originating from a side branch duct may be followed-up by imaging after one year. Side-branch lesions, which are between 1–3 cm in size and exhibit no solid components, should be followed up after six months. On the other hand, lesions that are >3 cm or exhibit mural nodules or cytology with higher-grade dysplasia must be resected. Serous cystadenoma is diagnosed as pancreatitis in 30% of cystic lesions and virtually never turns malignant. In this case, aspiration of the cyst is negative for mucin, CEA and amylase and the cytology reveals glycogen-rich epithelium. Direct SpyGlass pancreatoscopy with related techniques (biopsy, confocal laser microscopy) may increase diagnostic accuracy in selected cases to determine small or focal dysplasias.[418,419]

Q4-4.7: What is the indication for surgery of cystic lesions?

Statement 4-4.7. A surgical approach should be chosen for a suspected malignant cystic lesion. **(GRADE 1C, strong agreement)**

Comments. In 2–3% of all CT scans of the abdomen, a cystic lesion of the pancreas is discovered as an incidental finding,[420] while with MRI, it can be up to 10%. More than two-thirds of these lesions are dysontogenetic cysts or PPCs. The prevalence of PPCs in CP lies between 20–40%, and of the cystic lesions which are not PPCs but genuine cystic neoplasms, 30% are benign serous cystadenomas, 45% of the resected lesions are MCNs and 25% are IPMNs. Solid pseudopapillary tumours or cystic acinic cell carcinoma are less frequently encountered. For a classification of the differential diagnosis of cystic tumours in asymptomatic patients, the question of connection to the pancreatic duct (IPMN and PPC) and the size of the cystic lesion (indication for resection in the case of IPMN or therapeutic indication for pseudocysts) is essential.[421] A short MR protocol may be used.[422] Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between premalignant cystic neoplasms, cystic malignancies and pseudocysts. There is an urgent indication for surgery if malignancy is suspected, given that healing can be achieved in this situation with a five-year survival rate of 63% after resection of a malignant tumour.[396,423,424]

Q4-4.8: What is the role of non-invasive duct visualisation for PPC?

Statement 4-4.8. Visualisation of the pancreatic duct can be performed before endoscopic or surgical drainage of the pseudocyst. **(GRADE 2B, strong agreement)**

Comments. Whether an attempt to drain the pseudocyst via the papilla should be performed using ERCP before transgastric or transduodenal pseudocyst drainage is still a matter of controversy. On the one hand, drainage of the pseudocyst via a stent in the pancreatic duct is the 'most physiological' form of drainage. Depending on the study, 22–57% of PPC have a connection with the pancreatic ductal system.[425] Based on current data, endoscopic retrograde pancreatography (ERP) can precede endoscopic TM drainage in order to detect a connection with the duct or to exclude rupture of the pancreatic duct (8% after acute necrotising pancreatitis). If a complete MPD rupture is present, TP stent placement upstream from the rupture should be attempted.[426,427] This has been shown to improve the success of TM PPC drainage in a retrospective series.[428] If the MPD rupture cannot be bridged, TM stents should be left in place for as long as the disconnected pancreatic tail secretes pancreatic juice (typically, for years).[426] In a retrospective series of 29 patients, removal of TM stents after PPC resolution led to PPC recurrence in half the cases.[429] TM drainage in the presence of an undetected rupture of the pancreatic duct or a connection of the PPC with an obstructed pancreatic duct is less promising with regard to a successful long-term therapeutic outcome. The success rate of attempted TP drainage reaches a maximum of 60%.[402] Peri-interventional antibiotic prophylaxis before ERCP is indispensable if PPC are suspected or if they are the indication for ERCP or ERP. Without antibiotic prophylaxis, the examination-related incidence of infected pseudocysts and pancreatic abscesses after ERCP increases.[430]

Q4-4.9: What are the roles of duct changes and pancreatic duct stones in the presence of a PPC?

Statement 4-4.9. In the presence of pancreatic duct stones, a pseudocyst should be treated as part of an overall therapeutic concept. **(GRADE 1B, moderate agreement)**

Comments. A relative indication for treating pancreatic cysts is the presence of CP with pancreatic duct anomalies or pancreatic ductal stones, because in this situation the rate of spontaneous resolution, even for small cysts, is a maximum of 10–26% due to the constant inflammatory stimulus.[402]

Q4-4.10: When should pancreatic stenting be performed?

Statement 4-4.10. ET of pancreatic duct obstruction can be undertaken in patients with a PPC, prestenotic duct dilatation or fistula formation. **(GRADE 2C, strong agreement)**

Comments. PPCs are maintained by pancreatic duct obstruction in the presence of prestenotic duct dilatations or fistulae if these stenoses represent a blockage to drainage. In such cases, treatment of the pancreatic duct obstruction is recommended.

Q4-4.11a: Do vascular pseudoaneurysms warrant treatment?

Statement 4-4.11a. Vascular pseudoaneurysms that develop secondary to CP should be treated. **(GRADE 1C, strong agreement)**

Comments. There are no comparative studies available that compare the active treatment of vascular pseudoaneurysms with mere observation. Nor are there studies examining the best moment for the

treatment of vascular pseudoaneurysms at different time points.

Q4-4.11b: What is the method of choice for the treatment of vascular pseudoaneurysms?

Statement 4-4.11b. Angiographic embolisation is the method of choice for haemorrhagic pseudoaneurysms. **(GRADE 1C, strong agreement)**

Comments. If a pseudoaneurysm is detected in the vicinity of the PPC, selective angiographic embolisation prior to any attempt at PPC drainage should be considered because haemorrhages associated with a PPC carry a high mortality.[431,432] Surgery should be reserved as a second-line treatment when embolisation does not resolve the bleeding.[433–435]

There is a systematic review of case series and case reports available on this issue.[433] In this assessment, the success rate of angiographic treatment was 66%. The complication rate is less than that for surgical treatment and was associated with a shorter hospital stay. Surgery should remain reserved for patients not bleeding acutely and in a good general condition, in whom an operation is also indicated for other CP complications.

Q4-4.12: What is the minimal follow-up time before endoscopic intervention in PPC after an acute episode of CP?

Statement 4-4.12. 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.[416] **(GRADE 1B, strong agreement)**

Comments. MRI and/or EUS should be performed to distinguish an acute effusion or fluid collection, with or without necrosis, from a previously undiagnosed chronic fluid collection. Timing in the case of necrosis due to acute-on-CP should be similar to what is advised in acute pancreatitis: for patients with proven or suspected infected necrotising pancreatitis, invasive intervention should be delayed where possible until at least four weeks after the initial presentation to allow the collection to become 'walled-off'.[436] EUS and MRI are the most useful techniques for assessing the presence of debris within walled-off pancreatic necrosis.[437,438]

Pancreatic pain (WP9)

Q5-1: What is the natural history of pain in CP?

Statement 5-1.1. Pain is the first presentation of CP in the majority of patients. **(GRADE 1B, strong agreement)**

Comments. Pain is the most disabling and dominant symptom in patients with CP. Even though some studies have found that a substantial proportion (5–50%) of patients do not report pain, most recent studies reveal that intermittent or constant pain of varying severity is present in most patients.[439–442] In a recent study exploring the pain pattern in 106 patients with CP, only 6% were pain-free.[443] The origin of the pain is not fully understood but is likely to be multifactorial and therefore the first appearance of pain can vary considerably.[444] Pain was previously believed to be a result of structural changes in the gland such as duct strictures and stones with local tissue hypertension.[445,446] Although this may be true in selected patients and in the early phase of the disease, the pain quickly becomes more 'neurogenic' where there is evidence of massive changes in the pancreatic nerves.[447] As a consequence of these peripheral changes, the central nervous system becomes sensitised and a range of persistent neuroplastic changes takes place. Hence, it has been suggested that pain probably has a neuropathic origin in CP.[443,448,449] Thus there may be an evolution of the pain pattern over time from the initial stages, which are dominated by 'true visceral pain' to a neuropathic-like pain with irreversible central sensitisation. However, this hypothesis requires confirmation from observational studies.

Statement 5-1.2. There is no evidence that pain symptoms 'burn out' in all patients with ongoing CP. **(GRADE 2C, moderate agreement)**

Comments. It has been hypothesised that, due to ongoing inflammation, pancreatic parenchymal destruction will eventually lead to a decrease in pain symptoms ('burn-out'), especially in patients with alcoholic CP.[439] While some studies have reported a decrease in pain symptoms after follow-up, others have shown the opposite. For example, in patients with alcoholic CP, a pain-free period of at least two years was seen in 50% of CP patients within six years, and in 80% of patients within 10 years after the first documented episode of pancreatitis. In non-alcoholic CP the pain-free period occurred in around 30% of patients within six years of the first documented episode of pancreatitis.[439,450] While in another study, relief or improvement of pain in up to 73% of the patients was seen in a follow-up of >5 years.[440]

In patients with idiopathic and alcoholic CP, pain decreased or disappeared in 64–77% of patients over a median follow-up period of 12–25 years.[205] There is little difference in subgroups of patients with (67–74%) and without (56–79%) pancreatic surgery.[205] However, other studies have reported an incidence of relapsing pain attacks in 50% of alcoholic CP patients

and 38% of non-alcoholic CP patients after a follow-up of >10 years, with little difference in the course of pain between the two groups.[451] However, more recent studies have not reproduced these findings and have found that pain does not resolve over time in most patients.[442]

Statement 5-1.3. There is no convincing evidence that endocrine and exocrine pancreatic insufficiencies are associated with pain relief. **(GRADE 2C, moderate agreement)**

Comments. Endocrine and exocrine pancreatic insufficiencies have been associated with pain relief. Studies have reported that patients who became pain-free had greater pancreatic insufficiency than patients with pain. One study reported that the incidence of endocrine and exocrine insufficiency was approximately 20% and 55% at six years and 50% and 80% at 10 years from onset, respectively.[450] Others have found differences in pancreatic insufficiency in patients with CP, for example, 31% painless vs 3% painful CP.[452] However, other studies have reported that the development of pancreatic insufficiency did not significantly influence the course of pain, in which 54% (alcoholic CP) and 73% (non-alcoholic CP) of patients still had pain attacks, despite PEI.[205,451]

There are only a few studies relating to this topic, often with different patient selection criteria, different measurements of pancreatic function, and different definitions of pain and painlessness as well as mixed groups of patients with, and without, intervention (surgery and endoscopy).

Q5-2: Does pain influence quality of life in patients with CP?

Statement 5-2. 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)**

Comment. Both a high pain intensity and constant pain, as compared to intermittent pain, have been shown to reduce QoL in patients with CP and are associated with greater rates of disability and health resource utilisation.[10,442,453]

Q5-3: Which type(s) and causes of pain should be investigated in CP?

Statement 5-3. Pancreatic and extra-pancreatic complications 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)**

Comments. The mechanisms underlying pain in CP are complex and highly variable between patients. A number of pancreatic and extra-pancreatic causes of pain should be thoroughly investigated and treated. Peptic ulcers, gastrointestinal cancers and other comorbidities are reported to have an increased prevalence in CP.[74] In addition, pseudocysts and obstruction of the duodenum or CBD are important sources of pain and should be investigated with an appropriate radiological work-up and then treated accordingly.[444]

The presence of pancreatic pathologies, such as pancreatic duct stones and strictures as well as inflammatory masses of the pancreatic head are considered by most clinicians as important sources of pain and comprise the basis for invasive treatments. These include endoscopic stone removal, pancreatic duct dilatation and stenting, as well as surgical resections and drainage procedures.[454] There is, however, no direct relationship between pancreatic morphology and pain symptoms.[455] In a large group of patients no clear source of pain is identifiable and many of these patients, commonly labelled as 'minimal change CP', may suffer from neurogenic pain.[446] Finally, adverse effects in response to medical treatment such as opioid-induced bowel syndrome as well as endoscopic and surgical complications may contribute to pain in a subset of patients.[456]

Q5-4: How should pain in CP be assessed?

Statement 5-4. Pain in CP should be assessed using a multidimensional approach, including evaluation of pain intensity, pain pattern and its impact on daily function and QoL. **(GRADE 1B, strong agreement)**

Comments. Pain is complex, thus a multidimensional approach is recommended for pain assessment and to document treatment effects. In addition to pain intensity, which is the only outcome reported in most previous studies, pain pattern over time, functional impairment and QoL should also be documented to capture the different aspects of pain.[457]

Pain intensity should be documented using a numerical scale, such as the visual analogue scale (VAS). Additionally, the pain pattern over time (constant vs intermittent pain),) and the frequency of pain exacerbations should be characterised.[442,453] Various questionnaires have been used to evaluate the impact of pain on patients' QoL, but only the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire has been formally validated for CP.[458] The Izbicki pain score has been developed to capture some of the aforementioned dimensions of pain and provides a surrogate score based on the pain attack frequency, pain intensity score (VAS), analgesic use, and duration of

disease-related inability to work.[261] However, it has, never been strictly validated in patients with CP.

Q5-5: Does cessation of smoking and alcohol influence pain in CP?

Statement 5-5. Cessation of alcohol, and possibly smoking, improves pain in CP. **(GRADE 1B, moderate agreement)**

Comments. Cessation of alcohol has beneficial effects on disease progression and pain in patients with alcoholic CP.[459,460] In addition, increasing evidence suggests that tobacco use is an important and independent risk factor for CP and that cigarette smoking accelerates disease progression.[28,461] Hence, tobacco cessation is highly recommended, although an association between smoking and CP pain has yet to be determined.

Q5-6: Does pancreatic enzyme supplementation influence pain in CP?

Statement 5-6. Pancreatic enzyme supplementation is not recommended for pain treatment in CP. **(GRADE 1B, moderate agreement)**

Comments. Pancreatic enzyme therapy for pain control in CP has been the subject of several randomised trials. Only non-enteric coated enzyme formulations have documented improvement in pain, while enteric-coated preparations have not shown any effects.[462] A meta-analysis combining all studies found no effect of enzymes on pain relief in CP.[463] Nevertheless, combining the two types of enzyme formulations in a meta-analysis is probably not appropriate given their diverse mechanisms of action.[464] At present, pancreatic enzyme supplementation is not recommended for pain relief in CP, although it may have beneficial effects on abdominal discomfort related to PEI (e.g. gas and bloating).

Q5-7: Does treatment with antioxidants influence pain in CP?

Statement 5-7. Antioxidants are not recommended for pain treatment in CP. **(GRADE 1B, moderate agreement)**

Comments. Antioxidant therapy was associated with significant and prolonged pain relief in a randomised placebo-controlled trial from India,[465] but the findings were not reproduced in a subsequent study from North America.[466] A possible explanation for this dichotomy may relate to differences in study populations; while the Indian study mostly included patients with trophic calcifying pancreatitis and malnutrition (and hence deficiency in antioxidants), the American study included a more elderly population who had alcohol as the leading aetiology of CP and a normal nutritional condition. Hence, the efficacy of antioxidant therapy may be related to the aetiology of CP and its associated malnutrition.[467] A recent Cochrane analysis concluded that: 'the current evidence shows that antioxidants can reduce pain slightly in patients with CP. The clinical relevance of this small reduction is uncertain, and more evidence is needed'.[468] Taken together, the evidence is not sufficient to recommend that antioxidant therapy be used routinely for the typical Western CP patient with alcoholic pancreatitis.

Q5-8: Which analgesics are recommended for pain in CP?

Statement 5-8. 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)**

Comments. The WHO 'pain relief ladder' was introduced for the treatment of cancer-related pain (not chronic pain). The principle is based on the sequential introduction of drugs with increasing analgesic potency, titrated until pain relief is obtained.[469] Paracetamol is the preferred level I analgesic due to its limited side effects, while non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to their gastrointestinal toxicity.[470] If necessary, PPIs should be used in patients with CP who are at high risk of developing peptic ulcers.

Tramadol is the preferred level II analgesic and was shown to be superior to morphine in patients with CP, with fewer gastrointestinal side effects for the same level of analgesia.[471] Although speculative, this may relate to the many peripheral and central actions of this drug as compared to traditional opioids.

Level III analgesia comprises the group of strong opioids, such as morphine, which are widely used for pain relief in CP. The potential for dependency and side effects is high, but unfortunately no other strong analgesics are available. Opioid treatment can be challenging in this patient group, as the tendency to addiction may be strong in the subset of patients with alcohol-induced pancreatitis. Furthermore, the metabolism of many opioids is dependent on a preserved liver and gut function, which may not be the case in many patients.[472] Although not especially documented in this patient group, there are major differences in the positive and negative effects of opioids. However, animal and human studies suggest that some drugs, such as oxycodone, may be more efficacious for the attenuation of visceral pain, including pain in CP.[473–475] This should also be taken into consideration,

as some patients who may not tolerate one opioid find effective pain relief with another. This rational for opioid rotation may be advantageous in difficult patients.[472]

The indication for opioid therapy follows the usual guidelines and varies somewhat between countries; for a comprehensive review the reader is referred to the following website: http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf. In general the lowest possible dose should be used and the drug should always be taken orally to avoid dose escalation and addiction. Note, in many patients (up to 50% of chronic pain patients in general) opioids do not alleviate pain and treatment should be stopped. Transdermal administration of opioids is not recommended as first-line opioid therapy, and should be reserved for patients having trouble with tablet ingestion and where malabsorption is suspected.[476] The clinician should also be aware that opioid-induced bowel dysfunction may lead not only to constipation, but to a variety of symptoms such as reflux, gas and abdominal distension, which can themselves be painful.[477] Hence, the tapering of opioids or opioid antagonists with local effects on the gut may improve pain and associated symptoms.[444] Finally, it has been estimated that up to 5% of patients undergoing opioid therapy may develop 'narcotic bowel syndrome,' which is a paradoxical increase in abdominal pain when the opioid dose is increased.[478] This corresponds to opioid-induced hyperalgesia of the somatic tissues and the only treatment is tapering of the opioids.

Adjuvant analgesics are a heterogeneous group of drugs initially developed for indications other than pain and include antidepressants, anticonvulsants (including gabapentinoids) and anxiolytics. Although adjuvant analgesics have been widely used in the clinic to treat pain in CP, only the gabapentinoid, pregabalin, has been investigated in a placebo-controlled randomised trial and was found to induce moderate pain relief with relatively limited side effects.[443] However, in selected patients anti-depressive drugs in low doses may be recommended, and in particular, drugs with serotonin–noradrenaline reuptake inhibition may be preferred due to the reduced adverse effect profile. In patients with a severe and debilitating pain pattern, a more aggressive top-down approach, using opioids combined with adjuvant analgesics as first line therapy, is recommended to control pain.[462]

Q5-9: Is endoscopic treatment effective for pain in CP?.

Statement 5-9.1. ET is effective in patients with an obstructive type of pancreatic pain and in patients with a pancreatic duct dilatation. **(GRADE 2C, moderate agreement)**

Statement 5-9.2. ET could be useful as a bridge to surgery. **(GRADE 1B, moderate agreement)**

Statement 5-9.3. Endoscopic drainage treatment is less effective and has a shorter-term effect compared with surgery. **(GRADE 1B, moderate agreement)**

Comments. Overall, surgical procedures may be more effective in ameliorating pain in CP[247–249] (Supplementary Material, Table S10). According to the ESGE guidelines,[345] the German S3 guidelines,[4] Spanish Pancreatic Club recommendations,[8,9] the Belgian consensus on CP,[3] Italian consensus guidelines for CP[6] and other publications, ET for painful CP is indicated in patients with an obstructive form of CP due to strictures and intraductal stones.[325,353,479] The aim of this therapy is decompression of an obstructed main pancreatic duct. However, as in surgery, all studies have used historic controls, have compared different active treatments, or have some other methodological drawbacks.[247,248] Hence, neither the natural history of the disease nor the strong placebo effects associated with invasive procedures are taken into consideration,[480,481] which limits the generalisation of the studies.

With these limitations in mind, ET proved to be effective after short-term follow-up in patients with obstructive types of painful disease as it decreased the numbers of hospitalisations for pancreatic pain and reduced the intake of analgesics.[249] Therefore, ET could be recommended as a first choice therapy in patients with obstructive CP and could serve as a bridge in situations, when surgical therapy is indicated and will follow eventually.

Q5-10: Is ESWL an effective approach for pain treatment in CP?

Statement 5-10.1. ESWL therapy is effective for disintegrating stones in the main pancreatic duct. **(GRADE 2C, weak agreement)**

Statement 5-10.2. ESWL provides pain relief in patients with CP. **(GRADE 2B, no agreement)**

Comments. ESWL therapy in painful CP is indicated when the stone obstructs the main pancreatic duct, when endoscopic extraction of the stone is limited by the size and location of the stone and by the presence of an MPD stricture.[345] ESWL stone fragmentation has the potential to clear the pancreatic duct and restore pancreatic duct flow.[344]

ESWL therapy and its effects have been documented in several studies.[329] In one randomised study

comparing ESWL alone versus ESWL combined with endoscopy, no significant differences were found.[325] In other studies, ESWL + endoscopy was found to be better than ESWL alone for the prevention of pain[482] (Supplementary Material, Table S10). However, the long-term effects of ESWL therapy depend on the correct indications for stone dissolution: ESWL therapy alone can be effective if the stone size is >5 mm, the stone is located in the head or pancreatic body, and there are no strictures of the main pancreatic duct.[343] However, for large stones with pancreatic duct stricture, ESWL should be combined with endoscopic therapy.

Q5-11: Are other treatments effective in selected cases of painful CP?

Statement 5-11. 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)**

Comments. A percutaneous coeliac plexus block has been successfully used for the treatment of pancreatic cancer pain in patients with a short life expectancy, but it has been disputed for CP. Compared to the posterior blind approach used previously, EUS-guided, transgastric coeliac plexus blocks are considered safer with respect to serious complications like paraplegia and pneumothorax.[483] Local anaesthetics are used, as neurodestructive methods with alcohol or phenol are contraindicated due to the high risk of severe deafferentation syndromes. Studies have shown improvements in pain and decreased opioid consumption for a limited period of time. However, the use of EUS-guided coeliac plexus blocks cannot be recommended as routine therapy for pain in CP since only one-half of the patients experience pain reduction. Furthermore, the beneficial effect tends to be short-lived, as <10% experience pain relief for >24 weeks.[484] Typical adverse effects to EUS-guided therapy are the transient worsening of pain, as well as diarrhoea and hypotension due to the unopposed parasympathetic activity reported in about 40% of the patients.[485]

Other methods for blocking pain transmission are radiofrequency and transthoracic splanchnic block. After a diagnostic block with a local anaesthetic, radiofrequency lesions at the Th11 and Th12 level may result in pain relief.[486] Transthoracic splanchnicectomy is also reported to decrease pain frequency and intensity as well as opioid consumption. A recent review including 16 studies and 484 patients concluded that 62% of all patients were responding (regarded as successful), and opioid use dropped from 85% to 49% of patients at follow-up after a mean of 21 months.[487] However, most patients were still suffering from pain, and no studies included a sham group. With an expected placebo response of 30%,[488] the data do not support the general use of splanchnicectomy in CP, but it may be indicated in selected patients where conventional pain therapy is not effective.

Intrathecal morphine therapy via continuous infusion pumps has been described in case series with good analgesic results.[489] Radiation therapy to the pancreas has also been studied as a treatment for CP pain.[490] In the most recent study, a single dose of 8 Gy resulted in a complete absence of symptoms in 13 out of 15 patients.[491] However, the studies need to be replicated in a controlled situation before the methods can be recommended in clinical practice.

Spinal cord stimulation via epidural lead placement at the T6–T7 level has been shown to alleviate various kinds of visceral pain including pain in CP.[492] However, the effect in CP still needs to be documented in controlled studies. Transcranial magnetic stimulation is a non-invasive technique that has also been used to treat chronic pain of various origins. In a sham-controlled study it was shown to relieve pain associated with CP.[493] Although considered a phase II study, the findings are interesting as there were almost no adverse effects. Therefore, both spinal cord stimulation and transcranial magnetic stimulation may be used in selected centres with sufficient expertise, but data are still preliminary and call for further studies.

There are only a few studies available where 'real' acupuncture has been compared to 'placebo acupuncture'. An older study showed no effect of electro-acupuncture and transcutaneous electrical nerve stimulation in CP, although pain relief, as measured on a VAS, was significantly better in the active acupuncture arm.[494] However, the study was flawed, as the placebo arm was not sufficiently blinded. Recent studies where an improved sham methodology was used showed that electro-acupuncture was superior in the treatment of postsurgical pain and therefore an effect on painful CP should also be expected.[495] As acupuncture is virtually harmless and without side effects it may be an interesting topic for further research and could be useful in selected patients.

Q5-12: What is the optimal surgical approach for alleviating pain in CP?

Statement 5-12. Resection, decompression or mixed surgical techniques achieve pain relief that is maintained over time in approximately 80% of patients. However, as studies are not sham-controlled the effect

of surgery is still debatable. **(GRADE 1B, strong agreement)**

Comments. Surgery in patients with CP may be indicated for relieving pain. The rationale being that pain may be caused by increased intraductal and/or parenchymal pressure caused by decreased drainage of pancreatic juice into the duodenum, or by the release of inflammatory mediators from masses usually located in the head of the pancreas. However, recent literature (Supplementary Material, Table S10) does not support the contention that the micro/macrostructural changes of the pancreas are exclusively related to the pain, and in many patients other mechanisms, such as nerve damage, seem to play a role.[446,455,496,497]

Furthermore, as for endoscopy, all surgical studies have compared different procedures and have not been sham-controlled. Hence, the natural course of the disease and any placebo effects have not been taken into consideration. On the other hand, the very high efficacy for pain relief in many series (up to 90%) points towards an effect in selected patients. In many countries invasive treatment is recommended in patients where pain cannot be controlled without the use of strong opioids, which carry a risk of adverse effects and addiction. Although opioid treatment may result in bowel dysfunction that may be painful per se, the rationale for this surgical indication is not clear as the so-called weak opioids and adjuvant therapies may also be addictive and in some patients cause similar or even worse adverse effects.[498] Different studies have compared surgical procedures vs ET for pain in CP and most have documented substantial pain relief in patients undergoing both derivative and resective operations.[247,249,255,257,258,264,499] Moreover, two of these studies showed a significant benefit of surgery over ET for pain control in patients with pancreatic duct obstruction.[247,249] Along these lines, an observational study documented that invasive-based treatments (endotherapy and/or surgery) were superior to a conservative (medical) treatment approach.[479] Taken together, surgery may be an option for treatment of painful CP, but the evidence for its indication and timing is limited.

Surgical options for pain are classified into three categories: (a) decompression (focusing on ductal hypertension), (b) resection (focusing on inflammatory masses in the pancreatic head), and (c) mixed techniques (see section 4.1.7).

a. *Decompression techniques* have been recommended in patients with a dilated MPD (>7–8 mm)[500] and no inflammatory mass. This constitutes a rather simple procedure with a low risk of postoperative complications and of exocrine and endocrine insufficiency. It provides pain relief in 66%–91% of patients with a low morbidity (20%) and mortality (2%).[247] However, the long-term results show that up to 50% of patients experience a recurrence of pain.[501]
b. *Resection* is indicated in patients with an inflammatory mass or post-obstructive CP affecting the pancreatic body or tail[502,503] and is partly based on the belief that the pancreatic head is a 'pacemaker' for the pain. Pancreaticoduodenectomy has demonstrated long-term pain relief in about 75% of patients,[504] although long-term postoperative morbidity is significant, involving up to 20% of cases,[262] and most authors favour the more conservative mixed techniques with resection and drainage procedures.
c. *Mixed techniques* are based on the removal of the inflammatory mass in the pancreatic head and drainage of the obstructed pancreatic region (body and tail). The most widely used techniques are the duodenal preservation (Beger) technique or the Frey method, which involves the coring out of the pancreatic head associated with a longitudinal pancreaticojejunostomy.[505] Here, the duodenum and intrapancreatic bile duct remain preserved, with advantages for post-operative nutritional status, pancreatic exocrine function, delayed gastric emptying and QoL. In RCTs, mixed interventions have shown short-term pain relief in 70–100% of patients and long-term pain relief in 82–100%.[264,268]

Other surgical procedures that may be useful in small duct disease without an inflammatory mass include a longitudinal V-shaped excision of the ventral aspect of the pancreas combined with a longitudinal pancreaticojejunostomy.[256] Total pancreatectomy with islet transplantation is the most aggressive surgical approach, but has poor evidence and obvious selection bias, and there is no prospective randomised study comparing total pancreatectomy with other surgical treatments. Insulin independence rates are substantial (around 50%) at five years, but case series have shown a reduction in morphine requirements and improved QoL.[506] However, total pancreatectomy is seldom performed in Europe mainly due to the long-term complications and a recurrence of pain in many cases. Other, less common indications for surgery are complications that unequivocally require a surgical approach, such as pseudocysts and the involvement of the biliary tree and duodenum.

In conclusion, resection, decompression or mixed techniques achieve pain relief that is maintained over time in approximately 80% of patients, but drainage surgery in combination with limited duodenum-preserving pancreatic head resection appears to be

the best surgical strategy. Surgery is in most cases superior to endoscopy but correct patient selection in a multidisciplinary approach and appropriate timing for referral to surgery are key to a successful outcome.[507]

Nutrition and malnutrition (WP10)

Q6-1: What is the risk of developing malnutrition in CP and what are the causes of malnutrition?

Statement 6-1.1. Malnutrition is common among patients with CP. **(GRADE 2B, strong agreement)**

Statement 6-1.2. 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)**

Comments. Malnutrition can be defined as 'a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease'.[508,509] The European Society of Clinical Nutrition and Metabolism (ESPEN) has recently suggested that diagnostic criteria for malnutrition should be a body mass index (BMI) $< 18.5\,kg/m^2$ or unintentional weight loss (>10% regardless of time or >5% over three months), combined with either a low BMI ($<20\,kg/m^2$ if <70 years of age or $<22\,kg/m^2$ if >70 years of age) or a free-fat mass index (FFMI) $<15\,kg/m^2$ in women and $<17\,kg/m^2$ in men.[508] However, malnutrition exists in many forms and sarcopaenia and deficiencies of specific nutrients frequently occur despite the absence of weight loss or an abnormally low BMI.

Nutritional status based on anthropometric measurements and biochemical analysis of different micro- and macronutrients has been investigated in patients with CP in several studies but definitions have been inconsistent. Therefore, it is impossible to give a compound estimate of the prevalence of malnutrition in CP. It has been repeatedly demonstrated that patients with CP have lower BMI than controls. The prevalence of being underweight in CP patient series differs from 8–39%[510–515] with a higher prevalence rate reported in studies from India. Weight loss among patients with CP appears to be common and has been observed in 20%[512] and 49%[516] of cases. However, the number of studies of the prevalence of low BMI and/or weight loss in CP is low.

Studies investigating deficiencies of different lipid-soluble vitamins have reported prevalence rates of 1–16% for vitamin A deficiency,[517–521] 33–87% for vitamin D deficiency,[518–521] 2–27% for vitamin E deficiency[519–522] and 13–63% for vitamin K deficiency. There is significant heterogeneity between studies, which are of variable quality, as well as differences in measurement techniques and ranges. Whilst biochemical deficiency of the fat-soluble vitamins appears to be reasonably common, clinical manifestations of deficiency in CP are rare, take years to develop, and occur when there is an additional co-morbidity such as diabetes, celiac disease or after surgery.

Deficiencies of water-soluble vitamins in CP are less frequent but studies are scarce;[243] however, the risk of thiamine deficiency secondary to concomitant alcoholism has to be considered. Serum concentrations below normal values of different plasma proteins is another finding that has been used as a marker for malnutrition and PEI in patients with CP. Low levels of plasma proteins are an infrequent finding in patients on PERT treatment included in RCTs,[296,511] but higher prevalence rates have been reported from observational studies with low levels of albumin, prealbumin/transthyretin and retinol-binding protein in the ranges of 6–30%,[244,523,524] 12–37%[244,288,523] and 12–68%,[244,288] respectively. Minerals and trace elements have also been investigated in CP in case-control studies with partially conflicting results.[243] Lower levels of zinc, selenium[525] and magnesium[244] have been observed in some,[244,525] but not all, studies comparing CP patients with controls. However, despite differences demonstrated at group level, most patients with CP still present within normal range values of these parameters and the prevalence of clinically overt deficiencies is low.[243,244]

In general, studies on the nutritional status of CP patients are hampered by patient selection, small patient numbers, varying rates of concomitant PEI and the use of PERT, thus the generalisability of reported rates of deficiencies can be questioned.

No studies have specifically addressed the relative importance of the different causes of malnutrition in patients with CP. PEI is the most important cause of malnutrition in CP and should always be considered when malnutrition is suspected in these patients.[8]

Q6-2: How is malnutrition detected in patients with CP?

Statement 6-2.1. Patients with CP should undergo initial screening for BMI either with the community malnutrition universal screening tool (MUST) or hospital nutritional risk screening (NRS-2002). 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)**

Statement 6-2.2. A physical examination should be performed, if ascites or oedema are present and should include anthropometric measurements of mid-arm circumference, triceps skin-fold and hand-grip strength. **(GRADE 2B, moderate agreement)**

Statement 6-2.3. Screening for a deficiency of fat-soluble vitamins (A, D, E and K), zinc, magnesium and glycated haemoglobin (HbA_{1c}) should be considered. **(GRADE 2A, moderate agreement)**

Comments. Nutritional screening should be a simple and rapid process using the community MUST, which can be extended to the NRS-2002 tool in hospitals, and is recommended by ESPEN.[526] Although not specifically designed or tested in CP, both tools have a high degree of inter-rated reliability ($\kappa = 0.88–1.00$) for identifying patients that will benefit from nutritional intervention. These tools have been retrospectively validated and subsequently prospectively validated in an RCT of 212 patients.[527–529] A previous RCT showed that dietary counselling for a balanced diet is as good as commercial food supplements and that dietary intake should be addressed early.[530]

Two prospective studies of 58 and 62 patients with CP have shown a significant decrease in the lean muscle mass and body fat compared to controls.[170,510] Deficiency of fat-soluble vitamins, magnesium, haemoglobin, albumin, prealbumin, retinol-binding protein and HbA_{1c} levels above the upper limit of normal have been associated with pancreatic insufficiency.[173,244,520,522]

Q6.3: What recommendations regarding diet and intake of proteins, fat and carbohydrates can be given to patients with CP?

Statement 6-3.1. 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)**

Statement 6-3.2. Dietary fat restriction and very high fibre diets should be avoided. **(GRADE 1C strong agreement)**

Statement 6-3.3. Small, frequent, high-energy meals should be recommended for those with malnutrition. **(GRADE 2C strong agreement)**

Statement 6-3.4. Nutritional intervention should be carried out alongside PERT. **(GRADE 2C, strong agreement)**

Comments. Professional dieticians or nutritionists should be involved.[2,175] Sixty CP patients, defined as malnourished (>10% weight loss within six months and/or a BMI $< 18.5\,kg/m^2$), were randomised to receive individualised dietary counselling by an experienced dietician or a polymeric medium chain triglyceride (MCT) oral nutritional supplement. There was a significant improvement in anthropometric measurements ($p = 0.001$), a reduction in pain ($p = 0.001$) and fat malabsorption ($p < 0.007$) in both groups. However, there was no significant difference between the two arms of the study, leading to the conclusion that dietary intervention by a specialist dietician was as effective as oral nutritional supplements in patients with CP.[530]

An observational study of 40 male patients with CP identified higher energy intakes than healthy male controls ($p < 0.01$). Despite this, nutritional markers were lower in the CP group ($p < 0.001$), even though PERT had been used in 32/40 patients.[531] Nutritional requirements are estimated at 25–35 kcal/kg and 1.2–1.5 g nitrogen/kg[532,533] and this study serves as a useful reminder that malabsorption will render these estimates inaccurate for oral and enteral nutrition in the presence of malabsorption.

Whilst low fat diets remain commonplace, studies show that 30–33% of energy from dietary fat is well tolerated by patients with PEI.[530] Carbohydrate and protein malabsorption is significant, and can account for between 10–30% of dietary carbohydrate malabsorption,[534] and >7 g nitrogen malabsorption[535] per day. In energy terms, 7 g nitrogen equates to 44 g protein, resulting in a 175 kcal loss from nitrogen malabsorption. Assuming a 50% carbohydrate, 2000 kcal/day diet, carbohydrate malabsorption may account for up to 300 kcal per day. Consequently, dietary fat restriction is only recommended as a last resort for controlling symptomatic steatorrhoea in patients where dose adjustments in pancreatic replacement therapy and the addition of PPIs have not resulted in satisfactory symptom relief.[175,536,537] The inappropriate use of low fat diets can mask clinical symptoms of malabsorption; however, some patients avoid fat unconsciously.

Dietary fibre has been associated with a reduction in enzyme availability in a trial with 12 CP patients comparing a normal diet and a diet supplemented with 75–80 g dietary fibre. Fat intake was controlled at 100 g fat per day.[538] Significant increases in faecal fat ($p < 0.005$) were observed in the fibre-supplemented group; therefore, very high fibre diets are not recommended.[532]

Q6-4: Are oral nutritional supplements, with or without MCTs, indicated in CP?

Statement 6-4.1. 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.

Statement 6-4.2. MCT supplements are not recommended. **(GRADE 2C, strong agreement)**

Comments. For most patients with CP, oral nutritional supplements are not required to maintain nutritional status. In CP patients, 10–15% are estimated to require oral nutritional supplements, whilst >80% can be managed by diet and PERT when necessary.[289] The theoretical advantage of MCTs is that they are less dependent on lipase activity for their absorption.[535] However, initial studies have not shown any clear benefit of MCTs over standard long-chain triglycerides when used in combination with PERT.[535,539] Therefore, the use of MCTs has either not been recommended at all[3,4,6] or only as a last resort[289,540] in recently published guidelines.

One RCT investigated the efficacy of oral nutritional supplements in patients with CP and severe malnutrition (with a BMI < 18.5, or >10% weight loss over six months).[530] Dietary counselling achieved equal gains in BMI, mid-upper-arm circumference and triceps skinfold thickness compared to the use of a commercial supplement enriched with MCTs. However, both groups also received PERT and it is not possible to conclude from this study what the additional gain from dietary intervention was over PERT treatment. Furthermore, the study was performed in India on very malnourished subjects who consumed a mainly vegetarian diet, limiting the generalisability to CP patients in the western world.

To date, no other study has investigated the effectiveness of oral nutritional supplements in CP, which constitutes an important gap in research. For undernourished patients with CP, as with all undernourished patients, it is more desirable to implement dietary strategies to improve oral intake (rather than using supplements or nutritional support), not least for economic reasons. For those who are unable to meet their requirements with dietary intervention alone, oral nutritional supplements are a simple way to improve oral intake, and might delay or reduce the need for enteral tube feeding.

Q6-5.1: When is micronutrient supplementation indicated in CP?

Statement 6-5.1. Specific recommendations on the supplementation of vitamins A, E and K are not possible, as there are few studies. Clinical evaluation is advised, along with adequate PERT and dietary intervention. **(GRADE 1B, strong agreement)**

Q6-5.2: How should it be administered?

Statement 6-5.2. Vitamin D deficiency may be treated with oral supplementation or by a single intramuscular (IM) injection. **(GRADE 2C, strong agreement)**

Comments. There is a dearth of studies on the management of nutrient deficiency in CP, with the exception of vitamin D. One study[541] found that oral vitamin D (1520 IU/day) was significantly more effective at increasing serum 25 hydroxyvitamin D (25[OH]D) than UVB radiation in patients with CP. This level of oral supplementation achieved an increase of 32.3 nmol/l (95% CI 15–50) over the 10-week trial. Another study[542] supplemented 40 patients with tropical CP with either 600,000 IU or 300,000 IU (single IM injection) or IM saline. All three groups received daily calcium and oral vitamin D3 (500 IU). After nine months, the higher dose was more effective at increasing serum vitamin D levels. There were no reports of hypervitaminosis or hypercalcaemia, despite the high doses.

It seems practical to replace fat-soluble vitamins in those patients with low serum levels along with documented malabsorption and poor dietary intakes; however, few, if any studies have examined the efficacy or safety of supplementing vitamin E, vitamin A or vitamin K in patients with biochemical deficiencies. This constitutes a significant research gap. In addition, at least one study[518] has reported excess levels of vitamin A in patients with CP. Therefore, blanket supplementation for all CP patients is not advised, nor is it possible to provide specific guidelines on dosage, administration methods or specific patient types that will benefit from supplementation. Therefore, for these nutrients, a case-by-case clinical judgment approach is advised. Where possible, fat-soluble vitamin levels should be measured as part of the overall nutritional work-up. In all cases, appropriate and adequate PERT should be established, and priority should be given to optimising nutrient intake, including detailed dietary assessment and monitoring.[532,543]

Q6-6. When is parenteral nutrition indicated in CP and by what means should it be provided?

Statement 6-6. Parenteral nutrition is indicated in patients with gastric outlet obstruction secondary to duodenal stenosis, in patients with complex fistulating disease and in patients with apparent severe malnutrition prior to pancreatic surgery if enteral feeding is not possible. **(Level 1C, strong agreement)**

Comments. More than 80% of patients suffering from CP can be treated adequately with normal food

supplemented by pancreatic enzymes and only about 10–15% of all patients will require oral nutritional supplements.[526] Enteral nutrition preserves immune function and mucosal architecture and decreases the possibility of hyperglycaemia while parenteral nutrition increases the risk of catheter infections and sepsis complications.[289] Tube feeding is indicated in approximately 5% of patients with CP.[526] Therefore, parenteral nutrition is only indicated if the patients do not reach their requirements because gastric emptying is blocked, the patient needs gastric decompression, it is impossible to introduce a tube into the jejunum, or a complicated fistula is present.[8,289,526,533] Parenteral nutrition is mainly performed over a short-term period and long-term studies are lacking.

Q6-7. When is enteral nutrition indicated in CP and by what means should it be provided?

Statement 6-7.1. Enteral nutrition is indicated in patients with malnutrition who are not responding to oral nutritional support. **(GRADE 2C, strong agreement)**

Statement 6-7.2. 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)**

Statement 6-7.3. Enteral nutrition is indicated with PERT administered alongside where necessary. **(GRADE 2C, strong agreement)**

Comments 6-7.1-3. Oral nutritional support is adequate for improving nutritional status in the majority of patients with CP.[530] RCTs that specifically investigate indications for, as well as optimal administration of, enteral nutrition in CP are generally lacking and current guidelines are based on observational studies, expert opinion and clinical experience. ESPEN states that enteral nutrition is indicated if the patients cannot ingest sufficient calories or prior to surgery.[544]

A retrospective review of 58 patients[545] and a case series of three patients[544] demonstrated the benefits of naso-jejunal feeding, which was associated with an improvement in nutritional status, and a reduction in pain, pseudocysts and inflammation.[544,545]

Enteral nutrition should be used alongside an oral diet in those with poor oral intake, and parenteral nutrition should be used when enteral nutrition is not tolerated.[289,526] Enteral nutrition by the naso-jejunal route may be beneficial in those patients with postprandial pain, persistent nausea, vomiting, obstructed pancreatic ducts, or are unable to tolerate gastric feeding. Surgical jejunostomy should be considered in those requiring enteral nutrition for longer than 30 days.[289,533] The successful use of naso-jejunal feeding alongside naso-gastric drainage has been reported in CP patients with gastric outflow obstruction.[546]

There is limited high quality evidence for the composition of enteral feeds in CP. However, most clinicians support the use of small peptide/MCT feeds,[547] and improvements in nutritional status have been reported in over 70 CP patients receiving this composition of feed.[544–546] Pancreatic enzymes can be administered alongside the feed[539,548] in those patients whose nutritional status does not improve with peptide/MCT-based feeds.

Q6-8.1: What is the risk of developing osteoporosis/osteopaenia in CP?

Statement 6-8.1. 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)**

Q6-8.2: How can those at risk of developing osteoporosis/osteopaenia be identified?

Statement 6-8.2. 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)D should be undertaken. **(GRADE 1C, strong agreement)**

Q6-8.3: What is the recommended management for the prevention and treatment of these conditions?

Statement 6-8.3. 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 (Grade 1C). For those with osteopaenia, basic preventative measures should be implemented and DXA should be repeated every two years (Grade 1C). 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)**

Comments 6-8.1-3. A systematic review and meta-analysis[510] found that, in a pooled sample of 513 patients from 10 studies, almost a quarter (23.4%) of

patients with CP had osteoporosis and 39.8% had osteopaenia, with a combined osteoporosis/osteopaenia rate of 65% (95% CI 54.7–74). The corresponding osteoporosis rate for controls was 8.6–10.2%, based on only two studies with usable data.[549] In general the studies were heterogeneous and not amenable to subgroup analysis, however five studies[172,511,520,550,551] found an association between bone mineral density (BMD) and fat malabsorption, while there was no clear relationship overall between serum 25(OH)D and BMD. A study of bone histomorphometry in CP found that patients exhibited loss of cortical thickness and trabecular bone volume with micro-architectural deterioration compared to controls.[552]

The high prevalence of osteoporosis and osteopaenia appears to correlate with clinically relevant outcomes. A higher-than-average fracture rate was noted among CP patients compared to population-based controls in a study from Denmark (adjusted hazard ratio (HR) 1.7, 95% CI 1.6–1.8).[553] Likewise, in a US American study,[554] the rate of low-trauma fracture was similar, or higher, in patients with CP compared to other 'high-risk' gastrointestinal diseases. In the latter study, the risk of fracture for CP was 4.8%, compared to coeliac disease (5%), Crohn's disease (3%), gastrectomy (5.4%), cirrhosis (4.8%) and controls (1.1%). Several factors contribute to low BMD in CP, serum 25(OH)D insufficiency, poor diet, smoking, malabsorption and poor physical activity levels. More recently, an association between chronic systemic inflammation and elevated bone turnover in CP was reported. While DXA remains the primary diagnostic tool, bone turnover markers[173,522] could act as useful complementary markers where the mechanisms of bone turnover are unclear, or to evaluate the use of therapeutic agents, thereby reducing the necessity for repeated BMD assessments.

Interventional studies on bone health in CP are lacking. One study of 30 patients found that enteral vitamin D supplementation at a relatively modest dose (1520 IU daily) was effective in increasing serum 25(OH)D in CP patients with confirmed fat malabsorption (change in 25(OH)D levels: 32.3 nmol/l, 95% CI 15–50).[541] Unfortunately, there is a dearth of studies investigating the efficacy of therapeutic agents for osteoporosis in patients with CP, which constitutes a significant research gap. Direction may be sought from existing bone management guidelines for other malabsorptive/gastrointestinal diseases.

The American Gastroenterological Association (AGA) recommends that patients with inflammatory bowel disease, coeliac disease and post-gastrectomy should undergo DXA if they have at least one other additional osteoporosis risk factor.[555] Similar selective testing in CP would mandate DXA for post-menopausal women, those with previous low-trauma fractures, men >50 years, and those with malabsorption. However, given the high risk for osteoporosis and fracture (and associated morbidity and cost), it may be prudent to extend a baseline bone density assessment to all patients with CP, as well as ensuring that basic preventative measures are implemented in standard clinical practice.[543] For those with osteopaenia, basic preventative measures should be implemented in line with the AGA recommendations for other gastrointestinal conditions, and DXA should be repeated every two years.

Diabetes mellitus (WP11)

Introduction. Diabetes mellitus is defined as a regulatory dysfunction of the metabolism mainly characterised by chronic hyperglycaemia. The underlying causes may be impaired insulin secretion or insulin resistance or a combination of both. Due to this causal heterogeneity, diabetes mellitus is currently classified as four different types, comprising types I–IV.[556,557]

Diabetes mellitus secondary to pancreatic diseases (such as CP) is classified as pancreatogenic diabetes or Type IIIc diabetes mellitus (T3cDM) according to the current classification of diabetes mellitus.[556,557] Exocrine pancreatic diseases underlying T3cDM include both benign and malign conditions such as acute, relapsing and CP of any aetiology, haemochromatosis, cystic fibrosis, fibrocalculous pancreatopathy, pancreatic trauma, pancreatectomy, pancreatic agenesis and pancreatic cancer. Even within this T3cDM group, there may be different diabetes subtypes relating to different pathophysiologies of the underlying pancreatic diseases.[558] Therefore, it is important to stress that the following suggestions focus solely on T3cDM due to CP. A summary diagram is provided (Supplementary Material, Figure S1).

Q7-1: What is the risk of developing T3cDM diabetes in CP?

Statement 7-1. 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)**

Comments. *Type of diabetes:* T3cDM may be misclassified (usually as type 2 diabetes); however, most studies on the risk of diabetes in CP do not specify the type of diabetes.[559] Factors that influence the risk of developing type 2 diabetes (such as family history and BMI) are certain to impact the occurrence of T3cDM in CP, as both type 2 and T3cDM can co-exist.[560]

Aetiology and geography: Several studies noted that an alcohol aetiology increased the risk of developing diabetes compared to other aetiologies.[561–564] However, diabetes was diagnosed in as few as 5% (Australia) and 7% (South Korea) of CP patients,[565] where alcohol-induced pancreatitis patients were in the majority. Meanwhile, the occurrence of diabetes in Malaysia and Southern India was reportedly 50% and 55% respectively[565] with a majority of tropical or idiopathic pancreatitis diagnoses. There is regional variation even within India, with patients in Northern India[566] having a lower occurrence of diabetes (31%) than in the South (65%),[565] along with a lower percentage of tropical pancreatitis aetiology. In Indian idiopathic CP, those with late-onset disease tend to develop diabetes more frequently.[562,566] In Japan, three studies identified that 30%,[565] 39.7%[564] and 46.3%[563] of CP patients had a diagnosis of diabetes, with the latter identifying the diabetes as a 'true' T3cDM, that is, being diagnosed following a CP diagnosis. For autoimmune CP, the pre-steroid therapy occurrence was 24%, doubling post-steroid therapy to 48% in one small study of 21 patients.[305] Over a quarter (26%) of subjects developed diabetes in a French study of 200 hereditary CP patients.[567]

Q7-2: What factors affect the risk of developing diabetes in CP?

Statement 7-2.1. The risk of developing diabetes increases with surgical intervention (especially distal pancreatectomy) and with increasing age. **(GRADE 1B, strong agreement)**

Statement 7-2.2. The evidence appears to support an association between (heavy) smoking and the development of diabetes. Most studies support a link between the presence of calcifications and the risk of developing diabetes. **(GRADE 1C, strong agreement)**

Statement 7-2.3. Most studies show that the risk of diabetes increases with the duration of disease. **(GRADE 1B, strong agreement)**

Statement 7-2.4. There is some evidence of an association with gender and family history. **(GRADE 2A, strong agreement)**

Statement 7-2.5. There is insufficient evidence of a relationship between diabetes and BMI or zinc status. **(GRADE 2C, strong agreement)**

Statement 7-2.6. There is no evidence that a higher dietary fat intake influences the development of diabetes in CP. **(GRADE 2C, strong agreement)**

Statement 7-2.7. The development of diabetes does not appear to be influenced by the presence of various genetic mutations. **(GRADE 1B, strong agreement)**

Comments. *Surgery*: Those who undergo pancreatic resection have an increased risk of diabetes, with 37% of previously non-diabetic patients developing de novo diabetes following surgery.[253] The type of surgery may impact the likelihood of developing diabetes; those undergoing distal pancreatectomy had a risk ratio of 2.4 for the development of diabetes (57% of distal pancreatectomy patients had diabetes after five years, compared to 36% of pancreaticoduodenectomy patients, and in fact there was no increased risk for diabetes associated with pancreaticoduodenectomy compared to the natural history of CP).[568] A study of Chinese patients also identified distal pancreatectomy as being an independent risk factor for developing diabetes (HR of 5.4).[569] Other risk factors for developing diabetes following surgery for CP include an increased BMI, and higher pre-operative fasting glucose/glycosylated haemoglobin (HbA_{1c}) levels (570) (Supplementary Material, Figure S1).

Smoking: In a five-country study of smoking in alcoholic CP, smoking was shown to increase the risk of developing diabetes after the diagnosis of CP by an HR of 2.3.[28] In an Italian cohort of idiopathic CP patients, heavy smoking was associated with the development of diabetes (HR 3.9).[571] A second study on early-onset idiopathic CP found that smoking was a strong independent risk factor (odds ration (OR) 4.252) for developing diabetes (and that alcohol was of lesser importance).[562] In a study of 445 patients from China, smoking was an independent risk factor for developing diabetes both before and after invasive therapy (endoscopy and surgery).[569] In patients with AIP, high tobacco usage was associated with the occurrence of diabetes, with those with a >10-pack year history of smoking developing diabetes more frequently than 'low' smokers (including never- and ex-smokers), 50% vs 27% respectively.[572] Conversely, a study of 241 patients with CP found that smoking was not associated with the development of diabetes,[573] and Malka and colleagues[568] found that smoking was not a risk factor for the development of diabetes in a multivariate analysis of 500 patients. However, the latter study compared the percentage of smokers between diabetes and non-diabetes groups, without examining the degree of smoking.

Calcifications: Diabetes tends to develop more frequently in those with calcific CP[566] with the relative risk varying from 3.2 (in surgical patients)[568] to 7.7 (in idiopathic CP).[562] The presence of calcifications was an independent risk factor for developing diabetes (prior to invasive therapy) in a study of Chinese patients

with CP.[569] Conversely, no association was found between the presence of calcifications and the risk of developing diabetes in a surgical group.[253]

Duration of disease: The diabetes risk was 50% after 10 years, increasing to 83% after 25 years.[568] Insulin requirement increased from 26% to 53% during the same time-frame. Ito and colleagues[563] also reported that the prevalence of diabetes increases with time. In a cohort of 418 patients with hereditary pancreatitis in 14 countries, there was a clear, linear, cumulative risk of endocrine failure from 1.3% at age 10 years, to 79.1% at age 80 years.[68] However, in a surgical group, there was no association between the development of diabetes and the length of post-operative follow-up, pre-operative duration of CP, or the total duration of CP (median follow-up, 56 months).[253]

Age: In hereditary CP, the mean age of diabetes occurrence in France was 38 years, according to a study published in 2009.[567] The risk of diabetes increases considerably with age, and patients over the age of 40 years carried an OR of 9.2 for the development of diabetes.[562]

BMI/lean body mass: Aside from pre-operative BMI, there are few studies examining the effect of lean body mass, fat mass, or obesity on the risk of developing diabetes in patients with CP. One study (idiopathic patients from India) found that BMI was not an independent risk factor for diabetes on univariate analysis.[562] However, as type 2 diabetes may be superimposed onto T3cDM in CP, it must be supposed that increasing BMI also increases the risk of diabetes in CP.

Gender: A strong gender variation was noted in one study[564] in which 42.4% of males developed diabetes versus 27.8% of females. However in an all-India study,[561] the reverse was noted, with non-alcoholic females (44%) being more likely to develop diabetes than non-alcoholic males (31%).

Family history: In idiopathic CP, a positive family history resulted in an OR of 3.5 for developing diabetes.[562] As with BMI, since type 2 diabetes and T3cDM may co-exist, a family history of type 2 diabetes is likely to impact the development of diabetes in patients with CP.

Genetic mutations: In a small study of 79 patients, there was no significant difference in the risk of developing diabetes for those with both the secretory trypsin inhibitor (*SPINK 1*) and *PiZ* mutations vs no mutations.[574] In a cohort of 200 patients with hereditary CP, the presence, or absence, of a *PRSS1* gene mutation did not influence the diabetes risk.[567] In another cohort study of hereditary pancreatitis, specific gene mutations had no influence on the age of onset of diabetes.[68]

Diet and nutrition: In a study from Spain[575] on the effect of a high-fat diet (defined as >30% of total daily calorie intake from fat) on complications in CP, there was no evidence that a high-fat diet resulted in a higher risk of developing diabetes. One study of 101 CP patients (34 alcoholic and 67 tropical aetiologies) showed that erythrocyte zinc levels were lower in those with diabetes than in non-diabetics.[524]

Q7-3: How should T3cDM be diagnosed in CP?

Statement 7-3.1. The initial evaluation of a patient with CP should include fasting plasma glucose (FPG) and HbA_{1c}. Criteria for a diagnosis of T3cDM are FPG $\geq$ 126 mg/dl (7.0 mmol/l) or $HbA_{1c} \geq 6.5\%$ (48 mmol/mol). **(GRADE 1A, strong agreement)**

Statement 7-3.2. An $HbA_{1c} < 6.5\%$ does not rule out T3cDM due to the limitations of this test in this patient population. Therefore, normal HbA_{1c} (<6.5%) should always be confirmed by FPG. **(GRADE 1B, strong agreement)**

Statement 7-3.3. 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 (OGTT, 2 h fasting glucose $\geq$200 mg/dl (11.1 mmol/l)). **(GRADE 1A, strong agreement)**

Statement 7-3.4. These tests should be performed annually, even in the absence of typical clinical symptoms of diabetes mellitus. **(GRADE 1C, strong agreement)**

Comments 7-3.1-4. Current clinical criteria issued by the WHO, many national European diabetes associations and the American Diabetes Association (ADA) are based on FPG and 2 h plasma glucose (2hPG) following an OGTT (Supplementary Material, Figure S1). FPG $\geq$ 126 mg/dl and/or $HbA_{1c} \geq 6{,}5\%$ and/or plasma glucose $\geq$200 mg/dl confirmed by a 2 h glucose measurement after ingestion of 75 g oral glucose (OGTT) are cut-off points for diagnosing diabetes mellitus.[557,576] Although there are several other methods of assessing the insulin reserve in CP (serum/urinary insulin, serum/urinary C-peptide, beta-cell stimulation with arginine, glucagon or tolbutamide), there is little evidence that these have any effect on clinical decision-making.[577–579] The argument for FPG and/or HbA_{1c} over 2hPG is primarily related to feasibility. HbA_{1c} is known to have limitations in CP patients suffering from multiple conditions;[580] therefore, a negative HbA_{1c} (<6.5%) does not rule out diabetes in this population.

In summary, since there is a high prevalence of diabetes mellitus in CP as described above and the

deterioration of glucose metabolism is well known to be associated with multiple serious health risks, an early diagnosis of diabetes mellitus is crucial and annual screening is suggested.

Q7-4: How to distinguish T3cDM from type 1 and type 2 diabetes mellitus?

Statement 7-4.1. An absent pancreatic polypeptide response to mixed-nutrient ingestion seems to be a specific indicator of T3cDM as compared to the other types of diabetes. **(GRADE 1C, strong agreement)**

Comments. Due to feasibility, this test is only recommended in cases of doubt. As differentiating between the two types of diabetes is not easy, the criteria below might be helpful (Supplementary Material, Figure S1):

Major criteria (must be present):

- Established diagnosis of CP
- Absence of type 1 diabetes mellitus-associated autoimmune markers

Minor criteria (two of four must be present):

- Impaired beta cell function (e.g. homeostatic model assessment for beta-cell dysfunction (HOMA-B), C-peptide/glucose ratio)
- No excessive insulin resistance
- Impaired incretin secretion (e.g. glucagon-like peptide-1 (GLP-1), pancreatic polypeptide)
- Deficiencies of fat-soluble vitamins and/or presence of micronutrient deficiency/insufficiency (in the absence of enzyme therapy and/or nutrient supplementation)

Statement 7-4.2. 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)**

Comments. One of the most problematic issues with T3cDM is defining it precisely and differentiating it from the other types of diabetes as different types might precede each other or might be superimposed on each other. To date, certain diagnostic criteria, which have been proposed by two research groups, appear helpful.[560,581] However, probably due to the potential overlap of the different diabetes types, they all fall short to a certain degree. An absent pancreatic polypeptide response to mixed-nutrient ingestion seems to be a specific indicator of pancreatogenic diabetes.[560]

Q7-5.1: What is the prevalence of acute diabetes complications for patients with T3cDM?

Statement 7-5.1. Patients with T3cDM 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)**

Comments 7-5.1. Patients with T3cDM can develop potential life-threatening acute complications[578,582–586] may develop 'brittle diabetes'[587–593] with rapid swings of glucose levels from hyperglycaemia (due to unsuppressed hepatic glucose production) to severe hypoglycaemia after administration of exogenous insulin (due to the lack of a contra-regulatory hormone response).[594–600] Repeated hypoglycaemic events may result in hypoglycaemia unawareness because of the progressive decrease in the glucose threshold for triggering symptoms.[601]

Total or partial pancreatectomy is often associated with the resection of the duodenum, gallbladder, distal common bile duct and, often, distal stomach. The consequences of such extensive ablative surgery result, not only in pancreatic hormone deficiency, but also in the deterioration of gut hormones.[257,602] However, several authors have recently reported that the glycaemic control of patients with T3cDM has improved compared to that reported in earlier studies.[603–608] Several factors may explain these changes: nowadays insulin-dependent diabetes and malabsorption can be controlled more effectively than in the past with new drugs, including insulin analogues. Moreover, the rate and severity of hypoglycaemia are affected by the underlying pancreatic disease. For example, in patients undergoing total pancreatectomy for alcoholic CP, hypoglycaemic events are more frequent and severe if alcohol abuse persists.

Finally, improving patient awareness and compliance irrespective of socio-economic class, increasing referrals to a diabetes centre, and the widespread use of glucose meters may have contributed to the improvement of glycaemic control and stability over time. However, although there are no large, prospective controlled clinical trials estimating the true incidence of brittle diabetes after total pancreatectomy, in clinical practice the diabetes management of these patients is often problematic, especially in relatively young individuals where the risk of developing chronic

complications later in life has to be carefully balanced against the risks of repeated life-threatening severe hypoglycaemia.

Q7-5.2: What is the prevalence of chronic diabetic complications for a patient with T3cDM?

Statement 7-5.2a. Chronic microangiopathic complications are as frequent in T3cDM 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)**

Statement 7-5.2b. 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)**

Statement 7-5.2c. Neuropathy is also described as a common complication of T3cDM. **(GRADE 1B, strong agreement)**

Statement 7-5.2d. There is a general acceptance that T3cDM is not associated with macrovascular complications. **(GRADE 2B, strong agreement)**

Comments 7-5.2a-d. *Chronic* diabetic complications *(microangiopathy and macroangiopathy):* The underlying pancreatic disease and the relatively short duration of follow-up make it difficult to estimate the incidence and prevalence of diabetes complications in these patients.[609–619] The incidence of retinopathy is similar to that in type 1 diabetes mellitus and its prevalence increases with diabetes duration.[611,613,620–624]

Early signs of renal dysfunction, such as microalbuminuria or glomerular hyperfiltration, are similar to that reported in type 1 diabetes mellitus,[613,625,626] while macroalbuminuria and overt renal disease are unusual.[627–630] Neuropathy is also described as a common complication of T3cDM.[563,630] It is generally accepted that T3cDM is not associated with macrovascular complications since concomitant PEI, lower cholesterol levels and lower caloric intake may all reduce cardiovascular risk. However, with increasing life expectancy, cases of diabetic macrovascular complications have been reported in patients after pancreatic surgery.[609,612,631] These data support the need to treat patients with diabetes after pancreatic surgery with the goal of preventing long-term complications while minimising the risk of life-threatening severe hypoglycaemia.[632–639]

Q7-6: What is the optimal pharmacological treatment for T3cDM

Statement 7-6.1. No evidence-based study relating to treatment practice in T3cDM has been reported to date. Treatment 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)**

Statement 7-6.2. 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)**

Statement 7-6.3. Ensuring adequate and appropriate PERT is essential. **(GRADE 1C, strong agreement)**

Comments 7-6.1-3. No evidence-based study relating to treatment practice in T3cDM has been reported to date and all the large clinical diabetes trials have specifically excluded patients with T3cDM. The commonly prescribed agents are the same as for type 2 diabetes (Supplementary Material, Figure S1). The maldigestion of carbohydrates due to coexisting PEI, concomitant alcohol consumption and hepatic disease, a lack of compliance with the prescribed diet and/or medical therapy, and enhanced intestinal transit hamper the appropriate glycaemic treatment of these patients.

Treatment should include efforts to promote lifestyle changes (minimise high glycaemic-index foods, healthy diet, physical activity, abstinence from alcohol and smoking cessation, etc.), which may improve glycaemic control and minimise the risk of hypoglycaemia. Some authors suggest a trial of oral antidiabetic agents followed by insulin therapy when the need arises.[640,641] In patients with severe malnutrition, insulin therapy is commonly used as a first choice therapy due to the desired anabolic effects of insulin in this distinctive subset of patients. 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. However, metformin treatment might not be tolerated by a majority of patients since its main side effects include nausea, abdominal complaints, diarrhoea and weight reduction.[642] Metformin should be avoided in patients with ongoing alcohol abuse because of the risk of lactic acidosis.

Regarding the prescription of other oral agents for the treatment of diabetes:

Sulfonylureas are associated with an increased risk of severe and prolonged hypoglycaemia, are often contraindicated due to the accompanying liver disease[643] and should not be prescribed.
Glinides are also associated with an increased risk of hypoglycaemia; however, their half-life is much shorter than that of sulfonylureas and glinides at low doses may be considered before switching the patient to insulin therapy.
Thiazolidines should be avoided due to prominent side effects (bone fractures, fluid retention, congestive heart disease).
Alpha-glycosidase inhibitors can aggravate existing exocrine insufficiency and should not be prescribed.
Incretin-based therapies are reported to have a high frequency of prominent gastrointestinal side effects. Additionally, they are currently under discussion because of a potential association with an increased risk of pancreatitis.[644–647]
Sodium glucose co-transporter-2 (SGLT-2) inhibitors have been described as being able to induce euglycaemic diabetic ketoacidosis in insulin-deficient patients (both type 1 diabetes and T3cDM)[648,649] and should not be prescribed until they are proven safe in these patients.

Most patients do not respond satisfactorily to oral agents and should be switched to insulin treatment, for example, twice-daily pre-mixed insulin or multiple daily injections.[650] Patients should be treated using general insulin dosage guidelines as established for type 1 diabetes mellitus. Insulin pump therapy may also be considered for patients who experience a brittle form of diabetes mellitus despite being sufficiently motivated. A helpful algorithm for diabetes therapy in T3cDM was suggested.[640]

Establishing adequate oral PERT is very important in T3cDM[651] since patients are likely to develop malnutrition-related problems due to the lack of exocrine pancreatic enzymes. Thus ensuring adequate and appropriate PERT should be instituted early on to prevent qualitative malnutrition and metabolic complications.[520,521,652] Malnutrition may also affect glucose management, increasing the susceptibility of patients to swings in glucose levels.[653,654]

Assessments and quality of life (WP12)

Life-style factors influencing the natural course of CP as well as the outcome in terms of QoL have been brought more into focus during recent years.[453,655]

Q8-1: How should smoking be assessed in patients with newly diagnosed or suspected CP?

Statement 8-1. 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)**

Comments. The studies addressing the role of smoking on the aetiology and clinical course of CP have categorised the patients in different ways.[27,28,461,573,656–662]

The NAPS2[460,659,663] classified smoking status as 'never smoked' (<100 cigarettes in lifetime), or 'ever smoked' (>100 cigarettes). 'Ever smokers' were then categorised as 'past' or 'current' smokers. The amount of smoking was classified as <1 or 1 or more packs per day (ppd). The number of pack-years of smoking was calculated from the self-reported amount of smoking (average number of cigarettes smoked per day and the duration of smoking) and stratified as <12, 12–35, and >35 pack-years.

A Danish group[461] calculated grams of tobacco consumed, assuming one cigarette to be equivalent to 1 g of tobacco, one cheroot or one pipe to 3 g of tobacco, and one cigar to 5 g of tobacco, and separated the patients into five groups ('never-smokers', 'ex-smokers', and smokers of 1–14, 15–24, and >24 g/d of tobacco). Pack-years of smoking were calculated as (years of smoking × daily grams of tobacco)/20.

The European Smoking Cessation Guidelines,[664] issued in 2012, recommend that smoking status be defined using the following questionnaire:

1. Have you ever smoked?
2. How many cigarettes have you smoked in your life? Is it more or less than 100? (80 cigarettes = 100 g of tobacco as one cigarette contains 0.8 g of tobacco).
3. Do you smoke every day/on certain days/in specific situations? Which situations?
4. How many years have you been smoking?
5. How many cigarettes (or other tobacco products, e.g. pipes, cigars etc.) do you usually smoke per day?
6. For how many years/months have you quit smoking?

Definitions: a 'daily smoker' is a person who has smoked on a daily basis for at least three months; an 'occasional smoker' is a person who has smoked, but not on a daily basis; a 'non-smoker' is a person who has not smoked more than 100 cigarettes in his/her life-time (or <100 g of tobacco, in the case of pipes, cigars or other tobacco products); an 'ex-smoker' is a person who has quit smoking for at least six months.

Q8-2: What are the most efficacious methods for treating nicotine dependence in patients with CP?

Statement 8-2. The key components for the treatment of smoking dependence are combinations of therapeutic education, behavioural support and medication. **(GRADE 1A, strong agreement)**

Comments. Smoking is the leading preventable cause of death worldwide. There are no specific studies comparing different methods for treating nicotine dependence/smoking cessation in CP. Furthermore, the treatment of smoking dependence should not depend on a single method: according to the European Smoking Cessation Guidelines, issued by the European Network for Smoking and Tobacco Prevention (ENSP), the key components of successful cessation (remission) are combinations of therapeutic education, behavioural support and medication; however, the preparation and motivation to quit, age, comorbidity and numerous personal factors affect the chances of success.[665] About 90–95% of unaided attempts to quit smoking end in failure. A detailed protocol for smoking cessation is beyond the scope of this document. Trained personnel should manage the treatment of smoking dependence.

In the setting of primary care, the classic steps known as the '5 As' are helpful for planning the treatment:[666]

Ask: Systematically identify all tobacco users at every visit.
Advise: Strongly urge all tobacco users to quit.
Assess: Determine willingness to make a quit attempt.
Assist: Aid the patient in quitting (provide counselling-style support and medication).
Arrange: Ensure follow-up contact.

Systematic reviews have shown that a combination of counselling and pharmacotherapy for treating nicotine dependence is more effective for smoking cessation than each of the two methods taken separately.[667,668] Nicotine replacement therapy, bupropion and varenicline are efficiently proven first-line pharmacologic therapies for smoking cessation according to the ENSP guidelines.[665] Second-line medications include clonidine and nortriptyline.[665] In addition to pharmacological therapy, patients benefit from individual cognitive-behavioural counselling, telephone support, group counselling and educational materials.[665]

Q8-3.1: What are the effects of smoking on the progression of CP?

Statement 8-3.1. 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)**

Comments. Smoking seems to be an independent aetiologic factor for the development of CP; with evidence from case-control studies,[27,656,657] cross-sectional studies[658] and cohort studies.[460,461,659] Smoking is associated with progression from acute to CP,[669] to a more frequent and earlier development of calcifications[28,573,660–662] and also to increased mortality[670] although there are conflicting reports.[671] In some studies, an association between smoking and the development of diabetes mellitus[28,662] and PEI[573] has been described, but there are conflicting reports regarding both diabetes[573,661] and PEI.[661]

It has been reported that patients in constant pain are more likely to be 'current' (rather than 'past' or 'never') smokers compared to patients with an intermittent pattern of pain.[442] An absence of smoking at the last follow-up evaluation has been associated with long-term clinical success of ET for pain.[328] Smoking is an established risk factor for pancreatic adenocarcinoma in the general population, and it is reported to increase the risk of this serious complication in patients with hereditary pancreatitis.[672]

Q8-3.2: Once the disease has been diagnosed, what impact does stopping drinking and/or smoking have on the course of the disease?

Statement 8-3.2. Smoking seems to be an independent aetiologic factor for the development of CP. **(GRADE 1C, strong agreement)**

Comments. There are few studies that focus specifically on the effects of smoking and/or alcohol cessation in the natural course of established CP. However, there is evidence from observational studies that early smoking cessation after the diagnosis of the disease reduces the risk of developing pancreatic calcifications.[673] In addition, alcohol abstinence seems to slow the progression of the illness[674] and may result in better pain control.[675]

Q8-4: How do we assess quality of life in patients with CP?

Statement 8-4. Validated questionnaires should be applied for the assessment of QoL in patients with CP. **(GRADE 1A, strong agreement)**

Comment. Different validated questionnaires have been applied to assess QoL in CP patients. The use of questionnaires enables a standardised multidimensional evaluation of QoL. The following questionnaires are

most frequently used in CP patients: Short-Form Health Survey 36 (SF-36) and its shorter version, SF-12; EORTC QLQ-C30 with, and without, the supplementary QLQ-PAN26 questionnaire; the Gastrointestinal Quality of Life Index (GIQLI) was specifically developed for patients with gastrointestinal diseases.[676] The pain dimension can be assessed either using a VAS[677] or the Izbicki pain score[261] (see Q5-4: 'How should pain in CP be assessed?'). GIQLI was first introduced in 1995, comprises 36 questions and is intended for use in patients with a range of different gastrointestinal diseases, including CP.[676,678] No questionnaire has been designed specifically for patients with CP.

The EORTC QLQ-C30 was originally designed to assess QoL in patients with all types of cancer and consists of 30 questions.[458] It has been used frequently in CP patients and most items of the QLQ-C30 questionnaire are highly relevant for CP patients (for example, questions relating to pain and diarrhoea). This tool comprises one global item (global health), five functional domains evaluating physical, cognitive, emotional and social domains, three symptom scales (fatigue, pain, and nausea/vomiting), five single items for symptoms (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea), and one item for the financial impact of the disease. Changes in the mean QoL score of 5–10%, 10–20% and >20% represent small, moderate and large changes in QoL, respectively.[679]

As a supplement to the QLQ-C30 form, a questionnaire was developed that specifically addresses patients with pancreatic cancer (QLQ-PAN26) and includes 26 questions.[458] The module was intended particularly for patients with pancreatic cancer undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy. Both QLQ-C30 and QLQ-PAN26 have also been validated in patients with CP.[680] The QLQ-PAN26 modification includes two extra questions having significance for patients with alcoholic CP (guilt about alcohol consumption and the burden of abstinence).

The SF-36 was initially designed for non-disease-specific population studies but proved to be a reliable and valid tool for assessing QoL in patients with CP.[681] The test includes eight different domains (including physical, emotional, mental, social and general health sections) with 36 questions for measuring physical, emotional and social role functioning and symptoms such as bodily pain.

A study using a shorter version of the survey with only 12 items (SF-12) demonstrated that the loss of information in applying the SF-12 rather than the longer survey was very low and that the SF-12 was a viable alternative to the SF-36.[515] The scores for each version range from 0–100.[515]

Q8-5: When do we assess quality of life in patients with CP?

Statement 8-5.1. Health-related QoL should be assessed in both in- and out-patients and during their follow-up. **(GRADE 2C, strong agreement)**

Statement 8-5.2. Assessment of QoL should be included as an endpoint in clinical treatment studies of CP. **(GRADE 2B, strong agreement)**

Comments. Assessing QoL in both in- and out-patients with CP is rarely done nowadays in routine clinical practice and is mostly limited to clinical studies.

In a modern, patient-centred healthcare system patients should be assessed with regard to their health-related QoL, which is the perceived QoL of a patient represented by social, mental and physical well-being in relation to health and disease. This is particularly important in patients with chronic diseases such as CP, which is a chronic and still incurable disease that frequently affects all dimensions of a patient's well-being. Multidimensional QoL questionnaires facilitate a multidimensional approach to the patient and problematic issues can be met by a multidisciplinary team of general practitioners, gastroenterologists, surgeons, psychologists, pain specialists, dieticians, social workers and others.

QoL questionnaires have shown that the following factors (amongst others) contribute to lower QoL in CP: pain, a low BMI, early retirement, unemployment, depression, fatigue, fear of the future. These questionnaires can be used in the follow-up of patients with CP for investigating changes in QoL over time,[682] and the results can be used in the modification and adjustment of treatment decisions.

QoL questionnaires have been used extensively as an endpoint in evaluating treatment outcomes in patients with CP. Accordingly, QoL is assessed prior to and after endoscopic and surgical procedures, EUS-guided coeliac plexus blockade,[683] thoracosopic splanchnicectomy,[684] ESWL,[343,685] ERCP[322] enzyme replacement therapy and medical management of pain.

Q8-6: Which questionnaire should be used to assess QOL in patients with CP?

Statement 8-6. SF-36, its shorter version SF-12, EORTC QLQ-C30 with, and without the supplementary QLQ-PAD26 questionnaire, and GIQLI can be used for assessing QOL in patients with CP. It takes 12 min to complete the SF-36 form but only 2 min to fill out the SF-12 questionnaire – making this test suitable as a screening tool even for the daily busy clinical practice. **(GRADE 1C, strong agreement)**

Comments. In the setting of clinical studies, the QLQ-C30 and SF-36 are the most widely used questionnaires studying QOL in patients with CP. No studies have been performed to compare the validity and reliability of both tests in patients with CP in order to determine whether one test is superior to the other.

Even in a busy outpatient clinic, CP patients can use the waiting time before consultation to fill out the SF-12 questionnaire. The less time-consuming questionnaire may even increase the motivation and participation of patients in clinical studies to complete QoL questionnaires. The SF-12 showed excellent correlation with the longer SF-36 questionnaire ($r = 0.960$, $p < 0.001$).[515] In one study, SF-12 was compared to QLQ-C30 in 163 patients with CP and the SF-12 was found to be more reliable and easier to use in routine clinical practice.[686]

Conclusions

The HaPanEU/UEG guidelines on the management of CP are the result of an international, multidisciplinary, evidence-based approach. These guidelines provide recommendations for key aspects of the medical and surgical management of CP combined with comments based on the available literature and the opinions of leading pancreatologists from Europe.

The focus should now shift towards the optimal dissemination and implementation of these guidelines, which is not a given likelihood.[687] Several studies have indicated that guideline implementation is frequently suboptimal, at least in acute pancreatitis,[688,689] and hence a structured, ongoing effort is required, especially since guidelines in gastroenterology tend to fall short of other disciplines.[690] To overcome these shortcomings, guideline dissemination will be facilitated by free online access. There will also be a Smartphone application (HaPanEU) available to allow easy access and facilitate guideline use in daily practice as such apps are becoming increasingly popular.[691–693]

Although there is no optimal strategy for ensuring good implementation of any set of guidelines,[694] there is clearly a role for pancreatologists in this process. By informing specialist and non-specialist colleagues and encouraging them to use these guidelines, by presenting the guidelines at local or national meetings, and by writing about and referring to these guidelines in national and international journals, pancreatologists can optimise their implementation. Some evidence also suggests that instituting a process of audit feedback could increase awareness and improve guideline implementation,[695] These guidelines will also be useful when designing future studies as they reflect the current 'benchmark' for diagnosing and treating CP. This holds particularly true for imaging techniques. The existence of evidence-based guidelines obviously does not relieve clinicians from their professional obligation to keep up-to-date with new developments in CP. In particular, the results of ongoing RCTs (www.clinicaltrials.gov) should be taking into account. How then to decide when to update these guidelines? Some have argued that clinical guidelines should be updated continuously. Although appealing, this is clearly impractical and the HaPanEU working group will use a published framework on how to decide when to initiate an update.[15]

The HaPanEU/UEG evidence-based guidelines on the management of CP should result in reduced variation in practice and an improvement in patient outcome across Europe. The challenge now is to ensure high compliance in clinical practice and future trial design.[453]

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