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REVIEW

Swedish national guidelines for chronic pancreatitis

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ABSTRACT

Chronic pancreatitis (CP) should be suspected in the case of recurrent upper abdominal pain of unknown origin and/or clinical signs of exocrine pancreatic insufficiency (EPI). Alcohol is the most common etiological factor associated with CP, others being smoking, male gender, and hereditary forms. CP is often associated with recurrent episodes of acute exacerbations.

As of today, there is no accepted clinical definition of CP. However, irreversible morphological changes within the pancreas often occur, including dilatation of the main and branch pancreatic ducts, calcifications in ducts and parenchyma, parenchymal atrophy, and development of pseudocysts, though less so in the early phase of CP.

ABBREVIATIONS: AP: acute pancreatitis; BW: body weight; CF: cystic fibrosis; CP: chronic pancreatitis; CT: computed tomography; DM: diabetes mellitus; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; EUS-FNA/FNB: fine-needle aspiration/fine needle biopsy; EPI: exocrine pancreatic insufficiency; MDC: multidisciplinary conference; MRCP: magnetic resonance cholangio-pancreatography; MRI: magnetic resonance tomography imaging; PC: pancreatic cancer; PD: pancreaticoduodenectomy; PERT: pancreatic enzyme replacement therapy; PPI: proton pump inhibitors; PPPD: pylorus-preserving pancreatoduodenectomy; SGA: Subjective Global Assessment; US: abdominal ultrasound; VAS: visual analog scale

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Summary

Swedish guidelines for chronic pancreatitis.

Chronic pancreatitis (CP) should be suspected in case of recurrent upper abdominal pain of unknown origin and/or clinical signs of exocrine pancreatic insufficiency (EPI). Alcohol is the most common toxic agent associated with CP, other factors being smoking, male gender, and hereditary forms. CP is often associated with recurrent episodes of acute exacerbations.

As of today, there is no accepted clinical definition of CP. However, irreversible morphological changes within the pancreas often occur, including dilatation of the main and branch pancreatic ducts, calcifications in ducts and parenchyma, parenchymal atrophy, and development of pseudocysts, though less so in the early phase of CP.

Diagnosis and classification

Endoscopic ultrasound (EUS), computed tomography (CT), and magnetic resonance tomography imaging (MRI)/magnetic resonance cholangio-pancreatography (MRCP) are recommended for initial diagnosis of CP, among which EUS is considered the most sensitive method. Simple and reliable methods are lacking for diagnosing EPI. Fecal elastase, nutritional markers in blood, secretin-enhanced MRI, and advanced morphological changes as seen on imaging are supportive, though usually occur late during the course of disease. A standardized characterization of morphological pancreatic changes is recommended. Etiology can be classified e.g., with the TIGAR-0 or M-ANNHEIM classifications, staging with M-ANNHEIM or Manchester classifications, and morphology with the Cambridge or Rosemont classifications.

In case of hereditary CP and in children/youths with idiopathic recurrent pancreatitis, genetic testing (for hereditary pancreatitis) is recommended.

Management of children with pancreatitis should be performed on the basis of a multi-disciplinary conference (MDC) that includes pediatric gastroenterologists, surgeons, endoscopists (with a knowledge of ERCP in children), dieticians, and members of the pain team.

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Treatment and follow-up

CP is associated with a substantial risk for co-morbidity and a 3.5–5 times increase in mortality. There is a high risk of malnutrition, diabetes mellitus, pain, and the development of dependence of morphine analogs. Furthermore, an increased risk of developing pancreatic cancer has been noted. Local complications include pseudocysts, fistulas, pseudoaneurysms, and biliary, pancreatic or duodenal stenosis. Relieve of alcohol use and smoking is part of the treatment and pain management often includes early contact with a specialist.

Nutritional treatment and pancreatic enzyme substitution

There is a substantial risk of developing malnutrition and repeated small meals are preferred to reach an adequate energy intake. Nutritional treatment may require the involvement of a dietician. Enzyme replacement is recommended when diarrhea, weight loss, or clinical/laboratory findings of malnutrition are noted. Standard recommendation of enteric-coated microspheres is 40,000–50,000 lipase units with every main meal and half that with every snack. Evaluation of the effect is based on the normalization of gastrointestinal symptoms and improvement of nutritional parameters. In case of insufficient effect, the dose may be doubled, with or without addition of a protone-pump inhibitor.

Endocrine treatment

Treatment of diabetes mellitus secondary to CP does not differ from the general established management of type 1 and 2 diabetes mellitus.

Pain treatment

Principles in CP follow recommendations from the World Health Organization (WHO) for chronic or malignant pain conditions. Paracetamol is usually the first treatment of choice, while NSAIDs should be avoided due to the risk of gastrointestinal complications. When opioid analogs are used, the indication should be re-evaluated after 3 months. Pancreatic enzyme replacement therapy (PERT) has no effect on pain in CP.

Surgical and endoscopic treatment

Endoscopic treatment is performed first in most patients after failed medical treatment in uncomplicated painful CP and a dilated main pancreatic duct. This does not affect a potential concomitant surgical intervention. Indications for pancreatic surgery should be discussed at a multidisciplinary conference (MDC), including the attendance of an experienced (pancreatic) surgeon and a gastroenterologist. Surgery can relieve pain in CP with a success rate of up to 80%. Best effects are observed when surgery is performed in comparably early stages of CP (within 3 years from onset of symptoms) and if performed prior to the development of opioid dependency.

Complications in CP

Contrast-enhanced CT can confirm the suspicion of local complications or development of pancreatic cancer. Focal pancreatic lesions should be discussed at the MDC. Treatment of pseudocysts is only performed in the presence of symptoms or complications. EUS-guided internal drainage is the preferred strategy. In biliary stenosis, endoscopic or surgical treatment is recommended when episodes of cholangitis, progression of biliary stricture, and/or jaundice are seen.

Introduction

The Swedish national guidelines for chronic pancreatitis (CP) with updates have taken previously published guidelines by a number of professional organizations [1–6], Cochrane reviews [7,8], and European guidelines [9] into consideration. The GRADE system was used for quality of evidence and strength of recommendations [10,11], where strength of recommendations was 1 = strong, 2 = weak, and quality of evidence A = high, B = moderate, C = low. Recommendations are followed by remarks/comments.

The Swedish Society of Gastroenterology (Svensk Gastroenterologisk Förening) ordered an expert committee to provide an update on management of CP, replacing the previous Swedish guidelines published in 2003 [12]. The format was 51 predesigned questions with recommendations according to the GRADE system and remarks on each. These guidelines were published on the homepage of the Swedish Society of Gastroenterology, revised June 2019 [13], and a comprehensive summary was published in Läkartidningen (the Journal of the Swedish Medical Association) [14], both in Swedish.

Definitions, etiology, and classification

Definitions

1. What is CP?

Statement: CP is a progressive, inflammatory process in the pancreas replacing pancreatic parenchyma by fibrous connective tissue, leading to progressive exocrine and endocrine pancreatic insufficiency. The course may be associated with repeated episodes of acute pancreatitis (AP). Radiological changes are not apparent in the early stage. *GRADE1B, strong agreement.*

Remarks: No accepted clinical definition of CP exists. Morphological changes include irregular dilatation of the main pancreatic duct and side branches, calcifications in ducts and parenchyma, parenchymal atrophy, and pseudocysts [15].

2. Is CP associated with a decrease in survival?

Statement: CP is associated with an increased risk of comorbidity and mortality. *Grade IB, strong agreement.*

Remarks: CP is associated with a 3.5–5 times increased risk of mortality [16–18].

3. When should CP by suspected?

Statement: CP is suspected in long-term or recurrent abdominal pain, with or without exocrine (diarrhea) or endocrine pancreatic insufficiency. *GRADE 2C*, agreement.

Remarks: Abdominal pain is a dominating symptom, with malabsorption and diabetes mellitus (DM) occurring comparably late during the course of the disease. Risk factors like male gender, high alcohol intake, smoking and family history strengthens the suspicion.

4. Pain characteristics in CP?

Statement: Pain is a frequent early symptom in CP, though quality and intensity may vary during the course and between patients. *GRADE 1B, strong agreement.*

Remarks: Pain is often a dominating symptom in CP, though 10–20% report minor or no pain. The location is often in the upper part of the abdomen, frequently radiating toward the back, and with increased intensity following intake of meals. Pain type A is characterized by short episodes of pain and long painless intervals, while type B pain is represented by chronic pain with high intensity and shorter pain-free intervals [13,19,20].

5. How can pain be measured in CP?

Statement: Pain can be measured by intensity, pattern, and influence on daily activities. The usual measurement for pain intensity is the visual analog scale (VAS). *GRADE 1B, strong agreement.*

Remarks: VAS has been used in clinical studies and allows documentation of the pain course [21,22].

6. Which risk factor is the most important in CP?

Statement: Alcohol is the most important independent risk factor for CP. *GRADE 1A, strong agreement.*

Remarks: High alcohol intake (> 50–80 g alcohol daily) during several years (males predominate), may lead to AP, recurrent pancreatitis episodes and finally CP [18,23].

7. What is the role of nicotin as a risk factor for CP and its course?

Statement: Nicotin is an independent risk factor for CP and smoking increase progression and pain development. *Grade 1B, strong agreement.*

Remarks: The association between nicotin and CP is well characterized with nicotin representing an independent risk factor, that increases the risk for disease progression and abdominal pain [24,25].

8. Is primary hyperparathyroidism (pHPT) a risk factor for CP?

Statement: pHPT with hypercalcemia is a very unusual cause of AP. Case reports indicate that CP may develop. *GRADE 2C, agreement.*

Remarks: Very few patients with AP or CP have pHPT (1%) and around 10% of pHPT patients develop some kind of pancreatitis [26,27].

9. Is pancreas divisum a cause of CP?

Statement: Pancreas divisum may, in combination with other risk factors, probably represent a cause of CP. *GRADE 2C, strong agreement.*

Remarks: The clinical relevance of pancreas divisum and the association with the development of AP or CP has been debated. The prevalence of pancreas divisum in CP patients is higher than in controls, suggesting that the risk for pancreatitis is increased in combination with other risk factors like alcohol or SPINK1 mutations [28].

10. What is the role of genetic factors in the development of CP?

Statement: Less than 5% of CP have known genetic risk factors. Variants in some genes e.g., CFTR, SPINK1, Chymotrypsin C and Carboxypeptidase A1 increase the risk of CP, especially when combined with other risk factors (e.g., alcohol). Mutations in the cationic trypsinogen-gene (PRSS1) is a rare cause of CP, representing autosomal hereditary disease. These patients have an increased risk of developing pancreatitis already in childhood with subsequent development of CP. Hereditary pancreatitis is associated with an increased risk of pancreatic cancer (PC). *GRADE 1A, strong agreement.*

Remarks: SPINK1 is a trypsin inhibitor and mutations result in loss of function. Variants of the SPINK1 gene are more frequent in CP than in controls [29,30].

Cystic fibrosis (CF) is an autosomal recessive hereditary disease due to genetic variants in the CFTR gene. Eighty-five percent develop EPI already in early childhood due to protein plugs by the highly viscous pancreatic secretion, causing pancreatic atrophy. A combination of SPINK1 and CFTR mutations has also been reported in CP [31].

Hereditary pancreatitis is an autosomal dominant disease due to PRSS1 variants. The prevalence is low and recurrent pancreatitis episodes during childhood result in CP, and a significant increase in developing PC. The cumulative risk of PC is about 10% by the age of 50 and above 50% by the age of 75 years [32].

11. How should CP be classified?

Statement: Classification systems exist according to etiology and stage, using clinical parameters, and histological and morphological (imaging) changes. The M-ANNHEIM classification allows grouping to etiology, stage, and severity of disease. All CP patients should be classified according to etiology. A standardized characterization of morphological

pancreatic changes is recommended (e.g., Cambridge or Rosemont classification). *GRADE 2C, strong agreement.*

Remarks: Several classification systems have appeared, though infrequently used in the daily management of CP patients. The TIGAR-O and the M-ANNHEIM classifications group patients according to underlying etiology: toxic-metabolic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent acute pancreatitis (R), and obstructive (O) [33].

The M-ANNHEIM classification identifies seven sub-categories: alcohol (A), nicotin (N), nutrition (N), hereditary (H), efferent pancreatic duct factors (E), immunological factors (I), and metabolic/miscellaneous (M) factors [34], and also allows definition of CP severity (stages I–IV) and determines activity grade of CP (pain, pancreatic insufficiency, type of analgetics, complications) and results in five groups (M-ANNHEIM severity index A-E).

The Manchester classification allows three stages of CP (mild, moderate, advanced/end-stage) depending on five different parts (imaging, abdominal pain, analgetics, endocrine/exocrine function, peripancreatic complications) [35]. An alternative classification (Büchler et al.) is based upon three stages (A, B, C) classifying clinical and morphological changes [36].

The Cambridge classification (Grades 0–4) depend on the extent of pancreatic changes (Grade 4 is advanced changes like cysts, ductal stones, strictures) [37,38] and has been used for ERCP (endoscopic retrograde cholangiopancreatography) and imaging (CT, MRCP, US, EUS). Standardization of morphological changes is recommended.

According to the Rosemont classification, major and minor morphological changes were strictly defined by endoscopic ultrasound (EUS). The presence of these minor/major criteria enable the diagnosis 'consistent of CP', 'suggestive of CP', 'indeterminate of CP', or 'normal' [39].

12. When should hereditary pancreatitis be suspected and how to investigate?

Statement: Children and adolescents with idiopathic recurrent pancreatitis episodes should at least be tested for mutations in the PRSS1, SPINK1, and CFTR genes. Patients with a family history of CP should be tested for hereditary pancreatitis. *GRADE 2B, strong agreement.*

Remarks: Hereditary pancreatitis is an autosomal dominant hereditary disease resulting in recurrent pancreatitis, CP and a high risk of developing PC [40]. The average age at the first pancreatitis episode is 10 years and 70% have mutations in the PRSS1 gene. Some 80% develop CP and more than 45% of these will develop PC [41]. These patients should be included in a surveillance program and other risk factors like nicotin and alcohol should be discontinued.

13. Is CP a risk factor for pancreatic cancer?

Statement: The risk of developing PC is increased in patients with CP. *GRADE 2B, agreement.*

Remarks: CP is associated with an increased risk of PC [42] with 5% of CP patients developing PC [43]. This risk is increased if smoking [44].

Hereditary pancreatitis has a 50 times increased risk of developing PC with 50% of these patients developing PC during their lifetime [45], the risk increasing by a factor 8 when combined with smoking [40].

Clinical presentation and diagnosis

14. Which imaging techniques can be used for the diagnosis of advanced CP?

Statement: Advanced CP can be diagnosed using transabdominal US, CT, MRI, MRCP, and EUS. EUS, DT and MRI/MRCP have a higher accuracy for initial diagnosis of CP. *GRADE 1C, strong agreement.*

Remarks: Advanced CP is characterized by morphological changes like calcifications, irregular dilatation of the main pancreatic duct, multiple dilatations of branch ducts, parenchymal atrophy or focal enlargement e.g., of the pancreatic head. Transabdominal ultrasound is considered to have less diagnostic value, particularly in the early stage of CP [46,47], though the easy access of US allows its use for screening on the suspicion of pancreatitis or in CP with intensified abdominal pain. Due to the 5% risk of post-ERCP pancreatitis, ERCP is only used if a therapeutic intervention is planned.

DT and MRCP have replaced ERCP for the diagnosis of CP, identifying morphological changes of the pancreas with high accuracy [48,49]. The combination of MRI/MRCP allows the delineation of both the pancreatic parenchyma and the pancreatic duct with high precision [50,51]. CT can easily diagnose CP at an advanced stage, e.g., demonstrating calcifications with a significantly higher sensitivity than MRI [52].

EUS is the most sensitive method for diagnosing CP in its early stage [53,54], with a sensitivity exceeding 80% if compared with histological diagnosis [55]. EUS also allows for fine needle biopsy rendering histological diagnosis.

In autoimmune pancreatitis, CT and MRI can demonstrate the focal or diffuse ('sausage'-like) inflammation of the parenchyma and EUS-FNB further increase diagnostic accuracy [56,57].

15. Which imaging diagnostic methods are suitable to investigate progression and complications in known CP?

Statement: CT is used to investigate progression and suspicion of complications. *GRADE 2C, strong agreement.*

Remarks: Contrast-enhanced CT identifies the severity of CP and enables the detection of complications (mainly fluid accumulations, pseudocysts, thromboses) [58,59]. MRI/MRCP demonstrates ductal rupture, development of fistulas, and may allow characterization of the content in pancreatic/peripancreatic fluid collections [59,60]. EUS can be used if diagnostic uncertainty remains and can be combined with therapeutic interventions like EUS-guided drainage of pseudocysts or infected walled-off necrosis (WON) [59,61]. Abdominal US can be used for selection of patients with suspicion of complications for further investigations.

16. How can CP be differentiated from pancreatic cancer?

Statement: Differentiating focal pancreatitis from PC can be challenging and should be discussed at an MDC. Contrast-enhanced CT, MRI, and EUS on demand are used on suspicion of PC. CA 19-9, especially with marginal increase, is unspecific. *GRADE 2C, strong agreement.*

Remarks: Both patients with CP and PC can present with a similar past medical history, similar signs and symptoms, and even similar imaging findings. This differentiation is especially difficult in segmental and focal forms of CP. Up to 10% of patients subjected to pancreatic resection due to suspicion of PC will not have an underlying malignancy on histopathological examination of the resected specimen. MRI may better delineate a malignancy from a focal pancreatitis [62] and CT and MRI are considered equal for the differentiation of pancreatic tumors [63]. PET-CT presently has no primary role in confirming a suspected pancreatic cancer. EUS can be combined with elastography where PC has a harder consistency and low elasticity as compared to CP [58,64]. EUS-guided fine needle biopsy has also comparably high accuracy, though being falsely negative in about 10% of patients with PC [65], and even together with elastography the detection of cancer in a chronic inflamed pancreas may be difficult [66].

Characteristic hypovascularization of pancreatic cancer can be demonstrated by contrast-enhanced EUS [67].

Needle puncture for cytology should be decided at MDC and preferably be performed through EUS.

17. What is exocrine pancreatic insufficiency?

Statement: Exocrine pancreatic insufficiency (EPI) can be defined as a marked reduction of pancreatic enzyme activity in the gut lumen resulting in maldigestion. *GRADE 1A, strong agreement.*

Remarks: EPI has been defined in a comparably uniform fashion in recent guidelines [2,4,9,47]. The present definition stems from a functional perspective where exocrine function is extensively reduced to a level where a normal digestion is no longer possible [68]. Steatorrhea occurs at a late stage when exocrine pancreatic function has decreased by more than 90% [69]. Even though CP is the most common cause of EPI, other conditions, such as obstruction of the pancreatic duct, should be considered [70].

18. Which are the symptoms of exocrine insufficiency?

Statement: Typical symptoms of exocrine pancreatic insufficiency (EPI) are steatorrhea, weight loss, and a decrease in muscle mass; although, EPI can though occur without obvious symptoms. *GRADE 1B, strong agreement.*

Remarks: In EPI, the reduced digestion of fat is the main factor that contributes to signs and symptoms. Lipase is the most important enzyme for digestion of fat. Reduced lipase production together with a low pH level due to decreased bicarbonate secretion of the pancreas, contribute to a low lipase activity in the GI tract [71]. Symptoms of steatorrhea (excretion of >7 g of fat in 24 h) can encompass oily, foul-smelling diarrhea with undigested food. Maldigestion of fat results in weight loss and the decreased absorption of fat soluble vitamins (vitamins A, D, E, and K) and minerals with an increased risk for osteoporosis [72].

19. How to diagnose EPI?

Statement: Simple and reliable methods for the diagnosis of EPI are lacking, though typical symptoms and imaging demonstrating CP allow the diagnosis EPI. *GRADE 1B, strong agreement.*

Fecal elastase, nutritional markers in blood, secretin-enhanced MRI, and signs of advanced morphological changes of the pancreas may support the diagnosis EPI. *GRADE 2C, agreement.*

Remarks: There is today no simple and reliable method for the diagnosis EPI. It is reasonable to use this diagnosis and initiate treatment with enzyme substitution in patients with CP and symptoms indicating EPI (steatorrhea, weight loss, osteopenia) without further investigation of pancreatic function [4,9,47]. There is an association between the magnitude of morphological changes in CP and the probability of EPI [73].

Elastase is an enzyme in pancreatic juice that is stable during the gastrointestinal passage. The concentration can be measured in stool and correlates with the exocrine pancreatic secretory capacity [74]. The exact cut-off level of fecal elastase for the diagnosis of EPI is still a matter of debate. Controlling markers of malnutrition in blood can be of great value when diagnosing EPI [72,75] and comprise e.g., (pre-)albumin, retinol-binding protein (RBP), and minerals like zinc, magnesium, and iron [76].

Quantification of exocrine pancreatic secretion is expensive, not easily available and primarily used for research purposes. These measures include determination of the amount of fecal fat [77] and the performance of a breath test based on the oral intake of ^{13}C-labeled fatty acids [78]. The secretin test determines bicarbonate and/or pancreatic enzyme levels in pancreatic juice sampled by a catheter after placement into the duodenum and after stimulation of the pancreas with either intravenous secretin and/or cholecystokinin [79] or a standardized test meal (Lundh's test) [80].

Clinical management

20. Which patients should be referred to a specialist?

Statement: Suspicion of CP should result in referral to a gastroenterologist for further investigation and diagnosis. The majority of patients can subsequently be managed in a primary care setting. In case of complications, patients should be referred to a specialist. *GRADE 1C, strong agreement.*

Remarks: Long-term treatment of CP includes modification of lifestyle factors (such as cessation of alcohol intake and smoking), symptom control, as well as treatment of pain. Consultation of a specialist for pain management and alcohol/nicotine dependencies are recommended. In case of failure of conventional conservative treatment, patients should be referred to a gastroenterologist.

Further endoscopic and possible surgical interventions should be discussed at a multidisciplinary conference attended by experienced endoscopists (ERCP) and pancreatic surgeon [81].

21. What needs to be controlled during follow-up of patients with CP?

Statement: At follow-up, smoking, alcohol consumption, use of analgetics, and weight should be checked. Symptoms of maldigestion indicate the need of pancreatic enzyme replacement therapy (PERT) or adjustment of ongoing therapy. *GRADE 1B, strong agreement.*

During follow-up, basal blood tests as well as amylase, liver function, HbA1c and nutrition parameters, are recommended for surveillance of complications and malnutrition. *GRADE 1C, strong agreement.*

Remarks: Common complications are exocrine insufficiency [19] and in the later stage diabetes mellitus [25]. The risk of these complications is strongly associated with the duration of CP. Malnutrition and associated complications (e.g., osteoporosis) [70,73] are commonly caused by a combination of decreased oral food intake due to pain, ongoing alcohol abuse, and EPI. Less common complications are pseudocysts, compression of the biliary tract and duodenum, and portal and splenic vein thrombosis.

Total alcohol abstinence is recommended, and follow-up of alcohol use has been shown to prevent recurrence in alcohol-related AP [82]. Follow-up by a multidisciplinary team was shown to decrease alcohol consumption in CP patients [83]. Cessation of smoking in CP patients is important [84], as continuation of smoking increases the progression of CP and the risk of complications [85]. Abdominal pain in CP patients can be caused by several pancreatic and extra pancreatic conditions and requires a thorough patient history and potential additional investigations.

In spite of ongoing PERT, persistent diarrhea and weight loss can occur, frequently attributed due to a too low pancreatin dosage [86].

22. What differentiates pancreatitis in children as compared to adults?

Statement: There are several etiological factors for pancreatitis in children and genetic factors have a higher relevance than in adults. AP in children is often mild and recovers rapidly. Recurrent AP may result in CP.

Remarks: The etiology of pancreatitis in children differs from in adults [87]. Genetic changes play an important role in CP and is often part of multifactorial etiology [88].

CF is due to mutations in the CFTR gene and results in a highly viscous pancreatic secretion resulting in progressive pancreatic atrophy [89], though usually not associated with inflammation or pain. Approximately 85% of CF children older than 5 years of age have EPI [90]. The development of AP or CP in CF is fairly uncommon, but pancreatitis can be the first symptom of an underlying CF [91].

23. How is CP diagnosed in children?

Statement: Morphological pancreatic changes indicating CP in combination with abdominal pain, exocrine, and/or endocrine pancreatic insufficiency defines CP. The diagnosis can also be made by histopathology. *GRADE 2C, strong agreement.*

Remarks: Morphological (imaging) changes of the pancreas indicating CP can also be applied in children [19]. More novel classification systems allow the characterization of etiology, clinical stage, and severity (M-ANNHEIM classification) [34,81].

Definition of CP in children requires at least one of the following three criteria

1. Abdominal pain suggestive of 'pancreatic pain' and imaging indicating chronic pancreatic injury
2. Findings implying EPI and imaging findings of chronic pancreatic injury
3. Findings indicating endocrine pancreatic insufficiency and imaging findings of chronic pancreatic injury

or

Histopathological findings at surgery or pancreatic biopsy suggestive of CP.

The International Study Group of Pediatric Pancreatitis: InSearch for a Cure -INSPPIRE has described definitions of CP in children (see Table below).

Definitions according to the INSPPIRE group:

1. **Imaging changes indicating chronic pancreatic injury**: ductal injury (irregularity of the main pancreatic duct or side branches, intraductal filling defects, stones, strictures, or dilatation), and parenchymal changes (general or focal atrophy, irregular contour/accenuated lobular architecture, cavities, calcifications, irregular echogenecity). Imaging modalities may include: CT, MRI/MRCP/MRI with secretin stimulation, ERCP, abdominal US, endoscopic US (EUS: 5 criteria according to the Rosemont classification must be fulfilled).
2. **Exocrine pancreatic insufficiency**: Fecal elastase (< 100 µg/g feces – two separate samples at least one month inbetween), or coefficient of fat absorption < 90% at 72h fecal fat sampling, **and** imaging findings as above.
3. **Endocrine pancreatic insufficiency** according to the WHO classification 2006 for diagnosis of DM (f-glucose $\geq$ 7.0 mmol/l or plasma glucose $\geq$ 11.1 mmol/l 2 hrs after glucose tolerance test 1.75 g/kg (maximum 75 g in children) **and** imaging findings as above.

24. Which imaging modalities should be used in children?

Statement: Transabdominal US, EUS, and MRI/MRCP are used when investigating the pancreas in children. *GRADE 2C, strong agreement*. CT should be used with caution in children due exposure to radiation.

Remarks: Transabdominal US is a simple initial screening method, being non-invasive, easily accessible, and without radiation risks. MRI can be performed even in very young children when sedated, and the image quality of MRCP can be improved by intravenous secretin (s-MRCP) [92]. ERCP is only indicated if therapeutic interventions are planned and requires deep sedation. In children above the age of 5, the pancreas can be evaluated by EUS. Due to the risk of radiation, CT is only used when strictly indicated (e.g., complications of AP/CP).

25. Management of CP in children?

Statement: Management of children with pancreatitis should be performed by a multidisciplinary team including pediatric gastroenterologists, surgeons, endoscopists (with experience of ERCP in children), dieticians, and pain experts. Endoscopic treatment is usually effective and safe. *GRADE 1C, strong agreement.*

Remarks: Management of children with AP or CP does not essentially differ from that in adults (enzyme substitution, endoscopy, surgery). Endoscopic treatment of CP in a pediatric population seems both effective and safe [93]. EPI should be diagnosed and treated as soon as possible to prevent malnutrition in growing children and adolescents. A breath test based on ^{13}C-Mixed Triglycerides (MTG) represents a potential for diagnosis, monitoring and optimization of PERT in children with CF and EPI [94]. Total pancreatectomy with islet cell transplantation (TPIAT) is a treatment option in children with pain refractory to medical and endoscopic treatment [95].

Nutrition and malnutrition in CP

26. Is there a risk of malnutrition in CP patients?

Statement: Patients with CP are at increased risk of developing malnutrition. *GRADE 2B, strong agreement.*

Remarks: Malnutrition in CP is common [3] and is the result of a complex interplay of the underlying disease, metabolic changes, and decreased calorie intake (due to pain after food intake). Cachexia emphasizes the disease-caused inflammatory state contributing to malnutrition and the challenging nutritional treatment [96].

27. How should screening for malnutrition be performed in patients with CP?

Statement: Patients with CP should be screened for malnutrition. This includes thorough history taking, including assessment of current weight, possible weight loss, and evaluation of malnutrition markers in blood. *GRADE 1B, strong agreement.*

Remarks: A limited number of screening instruments are validated and translated into Swedish, though the Subjective Global Assessment (SGA)is considered as the gold standard for investigating malnutrition, though not taking the underlying etiology into consideration. Guidelines from ESPEN (European Society for Clinical Nutrition and Metabolism) [97] recommend Nutrition Risk Screening (NRS) from 2002 and Malnutrition Universal Screening Tool (MUST) for nutritional screening. Low levels of calcium, magnesium, zinc, S-folate, and thiamine may occur as a consequence of CP but are not included as variables in instruments for screening [76]. CRP and albumin levels may indicate an inflammatory condition contributing to cachexia, malnutrition, and nutritional energy use [97].

28. Are changes in frequency and amount of nutritional intake (carbohydrates, fat, protein) recommended in CP?

Statement: Small and repeated meal intakes (limitation of fat intake) are often preferable in order to reach adequate energy intake. *GRADE 2B, strong agreement.*

Remarks: Repeated small meals with normal fat content are recommended in CP [2]. A reduced intake of fat should be avoided, but can result in symptom control in severe steatorrhea, though may result in less energy intake and less uptake of fat soluble vitamins. Sufficient amounts of pancreatic enzyme replacement therapy (PERT) is a key factor to enable proper digestion and absorption of nutrients in patients with EPI [98].

Recommended nutritional intake:
Energy intake: 25-35 kcal/day/kgbw
Protein intake: 1.0-1.5 g/kg
Fat: 30 energy per cent, especially vegetable fat
Fiber: low intake recommended?

29. When is nutritional supplementation in patients with CP required (or 'indicated')?

Statement: Normal oral food intake is in most CP patients sufficient, although when the energy intake is insufficient, nutritional supplementation in combination with enzymes (PERT) can be required. If these are not sufficient, peptide-based nutritional drinks, the so-called elementary diet, can be tested. *GRADE 2C, strong agreement.*

Remarks: Elementary diet is a nutritional complete drink based on essential and non-essential amino acids, carbohydrates, fat (long- and medium-chain triglycerides (LCT and MCT)), vitamins, minerals, and trace elements. This diet is probably effective but difficult to tolerate and thereby associated with a low compliance [98].

30. When is enteral or parenteral nutrition in patients with CP required?

Statement: Ordinary oral food intake is the preferred route of nutrition in most patients with mild to moderate severe pancreatitis. If oral intake is not possible or should be avoided, enteral nutrition is preferred to parenteral nutrition. *GRADE 2C, strong agreement.*

Parenteral nutrition might occasionally be necessary in case of complications like complex fistulations, severe pain in combination with malnutrition, or (sub)ileus. *GRADE 1C, strong agreement.*

Remarks: Enteral nutrition can be delivered continuously through a nasogastric or nasojejunal tube. Parenteral nutrition should only be administered in those cases where oral and enteral nutrition is not possible or insufficient to meet the nutritional requirements of the patient [96,98,99].

31. Can medium chain triglycerides (MCT) decrease symptoms in CP?

Statement: Formulas including MCT play no general role in nutritional support but are instead costly and difficult to tolerate. *GRADE 2C, strong agreement.*

Remarks: In enteral nutrition, a formula including MCT could be preferred due to difficulty of administering enzymes together with normal enteral nutritional feeding [96].

32. Should a dietician be involved in CP?

Statement: Nutritional treatment after consultation of a dietician is recommended. *GRADE 2C, strong agreement.*

Remarks: The purpose is to secure adequate nutritional intake, prevent weight loss in adults and secure growth in children. All children with CP should have nutritional treatment involving consultation of a dietician [2,100].

Therapy

Surgical and endoscopic therapy

33. Can surgical treatment be recommended for pain management in CP?

Statement: Surgery relieves pain with a sustainable effect in up to 80% of selected patients. *GRADE 2B, agreement.*

Surgical treatment due to pain is most effective in the early stages of CP (< 3 years from onset of symptoms). *GRADE 2C, weak agreement.*

In uncomplicated painful CP with a dilated main pancreatic duct, endoscopic treatment is performed first in most patients after failed medical therapy. *Grade 2B, agreement.*

Pancreatic surgery should be considered before opioid dependency is present. This is valid for patients in whom strong opioids are required for more than 3 months despite optimal conservative treatment. Indication for pancreatic surgery should be assessed at an MDC including an experienced surgeon and gastroenterologist. *GRADE 1C, strong agreement.*

Remarks: Endoscopic treatment is usually performed first after failed medical therapy, but does not affect subsequent potential surgical therapy. Best responders can be identified by location of obstructing stones in the head of the pancreas, no main duct stricture and a comparably short duration of disease [9,101]. In case of obstructive main pancreatic duct stones, extracorporeal shock wave lithotripsy (ESWL) is recommended for stones exceeding 5 mm (located in the head/body of the pancreas), followed by endoscopic clearance of fragments [101]. No randomized controlled clinical studies exist comparing surgery with conservative management. In some patients with advanced pancreatitis, the natural course of pain can include spontaneous pain relief after a long period of time (10–15 years) after onset of symptoms, whereas in others the chronic pain will not subside [102]. The remission is though unpredictable and a strategy to await spontaneous pain relief is unethical and has not been considered appropriate by the American Gastroenterological Association (AGA) [103]. Compared to endoscopy, surgery has demonstrated better outcomes with a high percentage of pain relief (up to about 80%) in both a short- and long-term perspective [104–106]. The success rate of surgery is considerably lower when performed in the later course (up to 3–6 years after onset of symptoms) and in the presence of opioid dependency prior to surgery [107]. There are no studies indicating at which pain level surgery should be performed [104], but late treatment may further affect the quality of life negatively, with increased costs, and a further risk of opioid dependency [83,108].

34. Which surgical techniques are recommended for pain management in CP?

Statement: Pancreatoduodenectomy or 'mixed techniques', like Beger's or Frey's operation, have similar results and can be recommended for patients with an inflammatory mass in the head of the pancreas. *GRADE 1B, agreement.*

Pancreatoduodenectomy is recommended in CP where a cancer in the pancreatic head cannot be ruled out. *GRADE 2C, agreement.*

Decompression/drainage surgical procedures can be considered when the main pancreatic duct is dilated (> 7 mm) and no malignancy is suspected. *GRADE 2C, agreement.*

Distal pancreatectomy is indicated in patients with CP in the tail of the pancreas and/or the suspicion of malignancy in the tail. *GRADE 2B, agreement.*

Remarks: Surgical options for pain in CP include surgical decompression/drainage [109], resection [83], and 'mixed techniques' [110]. Decompression/drainage surgery can be considered in case of a dilated main pancreatic duct (> 7 mm) [110] and no focal inflammatory mass. The hypothesis is that an increased pressure in the ductal system and surrounding pancreatic parenchyma cause dilatation of the pancreatic duct, triggering chronic abdominal pain [111].

Resectional techniques are used when there is a focal inflammatory mass in the pancreas and especially if a pancreatic cancer cannot be ruled out. The inflammatory mass in the head of the pancreas has been considered the origin of pancreatic pain in CP [110,112] and for this reason resectional surgery, such as pancreaticoduodenectomy (PD) or pylorus-preserving pancreatoduodenectomy (PPPD), is recommended.

'Mixed techniques' include a combination of resection and surgical decompression/drainage procedures with removal of the inflammatory mass in the head of the pancreas and drainage of the blocked pancreatic region (body and tail). Two techniques are mainly used, i.e., partial resection of the pancreatic head with preservation of the duodenum (the Beger technique; [110]) and the Frey's operation (and variants thereof), where tissue in the head of the pancreas is removed together with a longitudinal pancreatojejunostomy [113].

Long-term pain relief is somewhat lower (about 50%) following decompression/drainage surgery [114] as compared to PD (70–89%) [115], and 'mixed techniques' result in pain relief in 82–100% [109,116].

Distal pancreatectomy is indicated if there is an inflammatory mass in the body or tail of the pancreas or an obstructive CP affecting the body or tail of the pancreas [117], though distal pancreatectomy in CP is rarely performed [118]. However, when distal pancreatectomy is performed (strict indications) in predominantly left-sided disease, obstructive CP or large pseudocysts, pain relief in up to 90% of patients has been reported [119].

Interventional therapy

35. Which other interventional treatment options exist for pain management in CP?

Statement: Procedures of plexus nerve blockage cannot be recommended in CP and has only a short-term effect. *GRADE 2B, agreement.*

Remarks: There are lacking evidence for the overall effects of nerve blockage. Plexus blockades are only performed by EUS nowadays and there are lacking evidence of long-term effects [120,121]. For this reason, there is a need of proper randomized studies for the evaluation of the effect of nerve blockage procedures in CP.

36. How should pancreatic pseudocysts be treated in CP?

Statement: Treatment should be reserved for symptomatic pseudocysts and in the presence of associated complications. *GRADE 2C, strong agreement.*

Endoscopic internal drainage guided by endoscopic ultrasound is to be preferred prior to surgical drainage. *GRADE 2A, strong agreement.*

Ruptured pseudoaneurysm as a complication to pseudocysts is recommended angiographic endovascular treatment with embolization and surgery reserved for situations where endovascular treatment is ineffective. *GRADE 1C, strong agreement.*

Remarks: A pancreatic pseudocyst is a fluid accumulation with high concentration of amylase, surrounded by a fibrous capsule. Most pseudocysts are small and asymptomatic and less than 10% result in complications [122]. Thus, treatment is recommended only when symptoms/complications are present (e.g., pain, vascular compression, compression of stomach, or duodenum, biliary stenosis, infection, bleeding, or a pancreaticopleural fistula).

A communication between the pseudocyst and the pancreatic duct allows endoscopic drainage through the papilla via a stent inserted in the main pancreatic duct. Transmural (transduodenal or transgastric) drainage *via* EUS is recommended in the absence of communication with the main pancreatic duct [123], a procedure which is highly effective and associated with low morbidity [124].

Surgery is preserved for large or multiple symptomatic pseudocysts or when complications – like stenoses or stones – are not accessible by endoscopy.

There are no major differences when comparing surgery and EUS-guided drainage in terms of rates of success, complications, and recurrence [125]. Though, the EUS approach is associated with a shorter hospital stay and lower costs [126]. In case of recurrence, a step-up-approach from endoscopic therapy to surgery is recommended [127]. There is in practice a large variation in the clinical management of pseudocysts as shown by a Swedish survey [128].

Rupture of a pseudoaneurysm is the most dangerous complication of pseudocysts where angiography with endovascular embolization is the treatment of choice. Surgery is restricted to those cases where embolization is unsuccessful [129].

37. What is the preferred treatment of a CP-related biliary stenosis–endoscopy or surgery?

Statement: Treatment of biliary stenosis is recommended in case of episodes of cholangitis, progressive increase of biliary stricture with bile duct dilatation, choledocholithiasis, jaundice or increased liver enzymes. Surgery should be considered for treatment of symptomatic biliary stenosis. *GRADE 2C, agreement.*

Endoscopic stent treatment could be used for temporary stabilizing the patient condition prior to surgery, in patients not being candidates for surgery, or not willing to undergo surgical treatment. *GRADE 2C, agreement.*

Endoscopic therapy with duct decompression can be used as the only treatment but is less effective and with shorter patency as compared to surgery. *GRADE 1B, agreement.*

Remarks: The incidence of biliary stenosis in CP varies and in up to half of cases spontaneous regression of jaundice is seen. Indications for biliary drainage are episodes of cholangitis, a progressive increase of biliary stenosis with bile duct dilatation, and recurrence of common bile duct stones [130]. Endoscopic or surgical treatment can be offered, where stent treatment is associated with a higher frequency of recurrence in cholangitis, why surgical by-pass can be recommended in operable patients [131].

38. How should CP-related duodenal stenosis be managed?

Statement: Duodenal obstruction should be treated surgically in complete or partial obstruction without improvement after up to 3 weeks conservative treatment. *GRADE 2C, strong agreement.*

Remarks: Duodenal obstruction occurs in 1% of CP due to an inflammatory mass in the head of the pancreas or paraduodenal pancreatitis [132]. With a partial obstruction, conservative treatment is initiated and if this fails (in about 12%) surgical intervention may be indicated.

39. How should asymptomatic patients with CP and a dilatation of the main pancreatic duct be treated?

Statement: Treatment of asymptomatic patients without complications is not recommended. *GRADE 2B, agreement.*

40. How should fistulas and ascites related to CP be diagnosed and treated?

Statement: Fistulas and ascites related to CP are diagnosed when high levels of amylase are observed in the pathological fluid (ascitic fluid, pleural effusion). Initial conservative management with enteral or parenteral nutrition is recommended, and the addition of somatostatin analogs is considered. Endoscopic treatment or surgery is recommended in case of lack of improvement. *GRADE 1C, agreement.*

Remarks: Communication between the pancreatic ductal system and the abdominal cavity cause ascites and communication with the pleural cavity results in pleural effusion, in both cases amylase levels in the fluid are highly elevated. MRCP can be used to localize the site of leakage and

fistulation [133]. For management, there are no proper randomized studies available, but a step-up-strategy is recommended [133,134]: (A) medical treatment with enteral or parenteral nutrition. Jejunal enteral feeding and the addition of somatostatin analogs to decrease the volume of pancreatic secretion [135]; (B) endoscopic treatment of the ductal system [136]; (C) surgical treatment [134,135].

41. How should varicose veins following splenic vein thrombosis in CP be diagnosed and managed?

Statement: Bleeding from varicose veins due to splenic vein thrombosis should be treated with splenectomy. *GRADE 1C, strong agreement.*

Prophylactic splenectomy can be considered in asymptomatic gastric varicose veins due to splenic thrombosis when the patient is subjected to surgery for other complications from CP. *GRADE 2C, agreement.*

Pharmacological therapy

42. Which is the optimal pharmacological treatment of pain in CP?

Statement: Primarily, causes of CP should be eliminated, such as abstinence of smoking and alcohol. *GRADE 1B, strong agreement.*

Pain treatment in CP should be in accordance with principles of the World Health Organization (WHO) for chronic non-malignant pain conditions. *GRADE 1B, strong agreement.*

Remarks: Causes of CP should be eliminated when initiating pain treatment, frequently including cessation of smoking and the use of alcohol [5]. Paracetamol is often the first treatment of choice, while NSAIDs should be avoided (due to gastrointestinal side effects). If stronger analgetics are used, tramadol should be considered prior to the use of opioids. Administration of opioids by long-lasting formulations (depot tablets) was reported to be associated with less side effects compared to pain patches [137]. Increased levels of analgetics may require adjuvant e.g., tricyclic antidepressants, gabapentin and pregabalin. PERT has no effect on pain in CP.

43. Which treatment is recommended in diabetes mellitus secondary to CP?

Statement: Treatment of diabetes mellitus (DM) secondary to CP does not differ from other types of DM type 1 and 2 treatment. Treatment strategies that predispose to hypoglycemia should be avoided. *GRADE 1C, strong agreement.*

Remarks: DM associated with CP (DM-CP, type 3c according to the American Diabetes Association (ADA)) differs from DM types 1 and 2 by an increased risk of hypoglycemia due to altered secretion of glucagone, and treatment strategies that predispose to hypoglycemia should be avoided [138]. The risk of hypoglycemia is especially problematic in patients with inadequate follow-up, alcohol abuse or autonomous neuropathy [139]. For insulin treatment, basal insulin analogs (detemir, glargin) as monotherapy or in combination with pre-prandial insulin analogs (aspart, lispro, glulisin) is recommended as they decrease the risk of hypoglycemia.

44. Is pancreatic enzyme supplementation recommended in CP?

Statement: PERT is recommended in CP when diarrhea, weight loss or other clinical or laboratory signs of malnutrition exist. *GRADE 1A, strong agreement.*

Remarks: The most important clinical consequence of CP is malnutrition with steatorrhea due to maldigestion of triglycerides [67]. Pancreatic ES improves absorption of fat in CP and EPI [140], also normalizing uptake of fat soluble vitamins and levels of prealbumin and ferritin also in patients without evident steatorrhea [77]. Steatorrhea is a late event in CP (occurring in about 50% after a median of 10–12 years after onset of disease) and ES is recommended in all CP patients with diarrhea, weight loss or other symptoms of malnutrition [1]. Osteoporosis is also comparably frequent in CP [141], most probably due to malabsorption of vitamin D [74].

45. Which pancreatic enzyme preparation should be used and how should it be administered?

Statement: Standard treatment is enzyme preparations in enteric-coated mini microspheres. Recommended dose is 40,000–50,000 lipase units per meal (×3) and half that dose on demand at meals in between. *GRADE 1A, strong agreement.*

Remarks: The effect of pancreatic enzyme preparation is depending on enzymatic activity released in the duodenum. The pancreatic enzymes are administered in pH-sensible enteric-coated microspheres, protecting against gastric acid when blended with the meals and broken down in the duodenum due to the changed pH value and release of the microspheres [142]. Smaller microspheres (1.0–1.2 mm) released together with the meal [143] was associated with a 25% higher therapeutic effect as compared to microspheres with a diameter of 1.0–2.0 mm [144]. The recommended dose is 40,000–50,000 units of lipase at every meal (breakfast, lunch, dinner) and half that dose on demand in between meals, increasing uptake of fat and normalizing gastrointestinal function [1,78,145]. The effect of PERT seems to be higher when enzymes are administered during or immediately after intake of a meal [146].

46. How can the effect of pancreatic enzyme replacement therapy (PERT) be determined?

Statement: Clinical improvement of nutritional parameters and normalization of gastrointestinal symptoms are sufficient criteria to evaluate the effect of PERT. *GRADE 1B, strong agreement.*

In patients not responding to treatment, laboratory methods for determining uptake of fat (fat absorption coefficient, ^{13}C breath test) can be used.

Remarks: Nutritional parameters and clinical variables (body weight, consistency and frequency of stool) can be

sufficient to evaluate the effect of PERT. Breath test (^{13}C) can be used to further evaluate the effect in CP [78,147].

47. What to do with incomplete response to treatment with pancreatic enzyme replacement therapy (PERT)?

Statement: In case of insufficient effect of PERT, the dose can be increased (doubled or tripled), alternatively a proton pump inhibitor (PPI) can be added. Other causes of poor response like poor compliance and bacterial overgrowth should be excluded. *GRADE 1B, strong agreement.*

Remarks: Despite PERT in adequate preparations and dosages, digestion may still not be normalized [78]. Poor patient compliance, low intestinal pH and the existence of intestinal bacteria overgrowth are most common explanations for poor treatment response. The use of PPI may increase PERT efficiency [148].

48. Does pancreatic enzyme supplementation (oral PERT) improve quality of life in patients with CP?

Statement: PERT improves quality of life in CP. *GRADE 1B, agreement.*

Remarks: Quality of life is improved by PERT in CP [8,149].

49. Is pancreatic enzyme supplementation (PERT) recommended to decrease frequency and severity of pain in CP?

Statement: PERT is not recommended to decrease frequency and severity of pain in CP. *GRADE 1B, agreement.*

Remarks: Meta-analyses demonstrate that PERT does not affect pain or recurrence in patients with CP [1,150,151].

50. When should PPI be used in exocrine insufficiency due to CP?

Statement: PPI should be added if the effect of adequate dosage of PERT is insufficient. *GRADE 1B, strong agreement.*

Remarks: Adequate response to PERT does not require the addition of PPI. A severely reduced bicarbonate secretion from the pancreas may though be insufficient to neutralize the pH in the duodenum [148], decreasing the effect of PERT even in adequate or high dosage, in which case PPI is recommended.

51. Is oral pancreatic enzyme replacement therapy (PERT) recommended in patients with CP after pancreatic surgery?

Statement: PERT is recommended following pancreatic surgery, and pancreatic exocrine insufficiency or malnutrition. *GRADE 1B, strong agreement.*

Remarks: Surgery may impair pancreatic function. Exocrine insufficiency occurs in most patients with CP and different types of pancreatic resections [152–154], and PERT is recommended [3,68].

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Author contributions

The members of the expert committee contributing to the guidelines are listed in alphabetical order and are considered to having contributed equally. The final preparation of the English version has been done by RA and ML.

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