English language version of the S3-consensus guidelines on chronic pancreatitis: Definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis[1]

Englischsprachige Version der S3-Leitlinie Chronische Pankreatitis

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Schlüsselwörter
- Pankreas
- Chronische Pankreatitis
- Leitlinie

Key words
- pancreas
- chronic pancreatitis
- guideline

Abstract

Chronic pancreatitis is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganisation of the pancreas leads to a progressive exocrine and endocrine pancreatic insufficiency. In addition, characteristic complications arise, such as pseudocysts, pancreatic duct obstructions, duodenal obstruction, vascular complications, obstruction of the bile ducts, malnutrition and pain syndrome. Pain presents as the main symptom of patients with chronic pancreatitis. Chronic pancreatitis is a risk factor for pancreatic carcinoma. Chronic pancreatitis significantly reduces the quality of life and the life expectancy of affected patients. These guidelines were researched and compiled by 74 representatives from 11 learned societies and their intention is to serve evidence-based professional training as well as continuing education. On this basis they shall improve the medical care of affected patients in both the inpatient and outpatient sector. Chronic pancreatitis requires an adequate diagnostic workup and systematic management, given its severity, frequency, chronicity, and negative impact on the quality of life and life expectancy.

Zusammenfassung

Die chronische Pankreatitis ist eine Erkrankung der Bauchspeicheldrüse, bei der rezidivierende Entzündungsschübe zu einem Ersatz des Pankreasparenchyms durch narbiges Bindegewebe führen. Diese Narbenbildung des Pankreas führt zu einem fortschreitenden Verlust der exokrinen und endokrinen Pankreasfunktion. Darüber hinaus treten typische Komplikationen auf zu denen die Bildung von Pseudozysten, Stenosen im Pankreasgang, Obstruktionen des Zwölffingerdarms, Gefäßkomplikationen, einer Obstruktion des Gallengangs, eine Mangel- und Fehlernährung sowie ein Schmerzsyndrom gehören. Das wichtigste Symptom der chronischen Pankreatitis sind abdominelle Schmerzen. Die chronische Pankreatitis stellt einen Risikofaktor für die Entstehung des Pankreaskarzinoms dar. Die chronische Pankreatitis reduziert sowohl die Lebensqualität als auch die Lebenserwartung betroffener Patienten deutlich. Die hier vorgelegte Leitlinie wurde von 74 Vertretern aus 11 Fachgesellschaften als Basis für eine evidenzbasierte Fort- und Weiterbildung zusammengestellt. Ihr Ziel ist es, die medizinische Versorgung betroffener Patienten sowohl im ambulanten als auch im stationären Bereich zu verbessern. Wegen ihrer Krankheitsschwere, ihrer Häufigkeit, ihres chronischen Verlaufs und ihres deutlich negativen Einflusses auf die Lebensqualität und die Lebenserwartung, bedürfen Patienten mit chronischer Pankreatitis einer angemessenen Diagnostik und systematischen Therapie.

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Contents

The present guidelines were compiled by the German Society of Gastroengerology, Digestive and Metabolic Diseases (Guideline coordinators: Prof. Dr. M. M. Lerch MD, Department of Medicine A, University Medicine Greifswald; Prof. Dr. J. Mössner MD, Department of Gastroenterology and Rheumatology, University Hospital Leipzig).

The following Professional Associations/Organisations participated in compiling these guidelines:

- German Society for General and Visceral Surgery (DGAV)
- German Society for Internal Medicine (DGIM)
- German Society of Pathology (DGP)
- German Society for Paediatric Gastroenterology (DPGE)
- Austrian Society for Gastroenterology and Hepatology (ÖGGH)
- Swiss Society of Gastroenterology (SGG)
- Swiss Society of Visceral Surgery (SGVC)
- Working Group of Pancreatectomy Patients
- German Pancreas Aid
- German Radiology Society (DRG)
- bng German Association of Private-practice Gastroenterologists

Scope and validity of the guidelines

The recommendations of these guidelines are intended primarily for specialists involved in the diagnostics and treatment of pancreatitis patients in hospital and outpatient settings. The guidelines are intended to impart knowledge in the context of continuing education and shall serve to achieve optimal medical care of patients. Further, the guidelines provide those suffering from chronic pancreatitis with information about their disease. The guidelines are intended to facilitate decision making regarding diagnostic and therapeutic measures. Nevertheless, disease severity and manifestation must always be assessed individually for each patient, and the patients' general health status shall be considered in any further steps taken. Deviations from the recommendations of the guidelines are possible and may be required in individual cases. The guidelines are valid for five years and were originally published in German (Z Gastroenterol. 2012;50:1176 – 224, reference 486).

Working group members

The compilation of the different topics was undertaken in various working groups. The individual working groups and their members are listed in **Table 1**. The heads of the working groups are highlighted in bold letters.

Table 1 Members of the Working Groups.

working group 1 "Function Tests"
head: Jutta Keller, Hamburg
head: Matthias Löhr, Stockholm/Sweden
Philip Hardt, Gießen
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head: Jürgen Riemann, Ludwigshafen
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Alexander Schneider, Mannheim
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Table 1 (Continuation)

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Jutta Keller, Hamburg
Remy Meier, Liestal, Switzerland
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working group 10 "Paediatrics"
head: Philip Bufler, Munich
Dirk Grothues, Regensburg
Jobst Henker, Dresden
Klaus-Michael Keller, Wiesbaden
Dietrich von Schweinitz, Munich
Heiko Witt, Munich

Methodology

In these guidelines, the level-of-evidence grades are presented according to the Oxford Classification (**Table 2**). The recommendations are expressed to reflect the strength of the recommendations (**Fig. 1**). Exceptions are recommendations which represent a "clinical consensus point" (CCP) and describe good clinical practice for treatment where a higher degree of published evidence is lacking.

The definition of consensus strength was reached by the percentage approval of the consensus conference participants: Strong consensus > 95 %, consensus 75 – 95 %, majority approval 50 – 75 %, no consensus < 50 %.

Further, extensive details regarding the organisational process and the methodological principles of the S3-consensus guideline development process (literature research, classification of evidence and recommendation grades, consensus process, etc.) are referred to in the methodological guideline report.

Table 2 Classification of evidence according to the Oxford grading system.[1]

level of evidence grade	description
Ia	"evidence" from a systematic review of randomised controlled trials (RCT)
Ib	"evidence" from suitably planned RCTs
Ic	all-or-none principle studies
IIa	"evidence" from a systematic review of well-planned cohort studies
IIb	"evidence" from a well-planned cohort study/low-quality RCT (e. g., < 80 % follow-up)
IIc	"evidence" from outcome research studies
IIIa	"evidence" from a systematic review of well-planned case-control studies
IIIb	"evidence" from an individual case-control study
IV	"evidence" from case series / poor quality cohort and moderate case-control studies
V	expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

[1] According to the "Oxford Centre of Evidence Based Medicine", www.cebm.net.

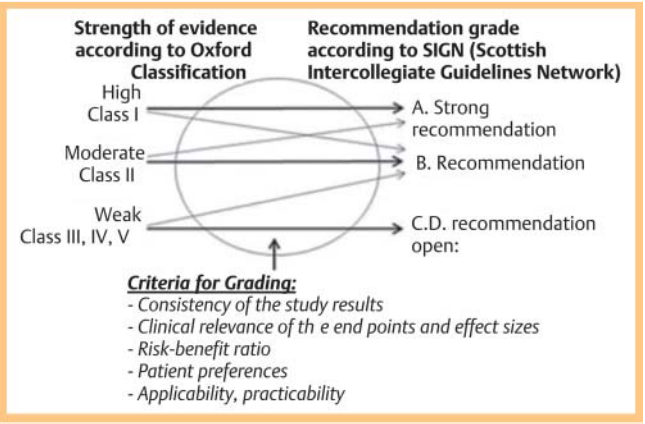

Fig. 1 Conversion of level of evidence into recommendation grades (modified illustration from "Lehrbuch Evidenzbasierte Medizin in Klinik und Praxis" (Text book of evidence-based medicine in clinic and practice), Ed. Kunz et al., Deutscher Ärzte-Verlag 2008, page 367).

Basic principles

Chapter 1 – Definition and Epidemiology

1 – 1: Definition (WG1-WG10)

Statement 1 – 1 - 1 Definition

Chronic pancreatitis is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue.

This fibrotic reorganisation of the pancreas leads to a progressive exocrine and endocrine pancreatic insufficiency. In addition, characteristic complications arise, such as pseudocysts, pancreatic duct obstructions, duodenal obstruction, vascular complications, obstruction of the bile ducts, malnutrition and pain syndrome. Pain presents as the main symptom of patients with chronic pancreatitis. Chronic pancreatitis is a risk factor for pancreatic carcinoma.

Chronic pancreatitis significantly reduces the quality of life and the life expectancy of affected patients.

[Strong consensus]

Explanatory note

For centuries the pancreas was a "terra incognita", hidden behind the stomach, and therefore the pathophysiological role of this organ remained unknown. As recently as 1761, Jean-Baptista Morgagni reported the first autopsy case of chronic pancreatitis and it took another 60 years until Kuntzmann made the connection between fatty stools (steatorrhoea) and a disease of the pancreas. Even in the 21st century, the time period between onset of symptoms and establishing the diagnosis of chronic pancreatitis is disproportionately long. The reason for this is the absence of specific laboratory parameters and the unspecific clinical symptoms which characterise its clinical presentation. The first modern method of establishing the diagnosis of pancreatic disorders in general originated in 1929, when Elman introduced measuring amylase (diastase) levels in serum into routine clinical practise. Following this discovery, Comfort and co-workers succeeded in describing the natural course of chronic pancreatitis from clinical observations, knowledge gained from surgical procedures, and autopsy studies. They reported for the first time an association

with long-term alcohol consumption, the frequent occurrence of the disease in the third and fourth decades of life, and typical complications such as loss of the endocrine or exocrine function of the pancreas.

The incidence of chronic pancreatitis increases proportionally with the amount of alcohol consumed in the general population. The incidence worldwide is reported to be between 1.6 to 23 per 100 000 with an increasing prevalence [1]. Although most patients with chronic pancreatitis are treated as outpatients, in 2008 there were 10 267 (ICD-10: K86) hospital admissions for chronic pancreatitis in Germany alone (Federal Statistics Office). This does not include those patients who were coded as having acute pancreatitis including those due to an acute episode of chronic pancreatitis (50 673 cases). This substantiates the high socio-economic significance of the disease. Mortality from chronic pancreatitis is reported to be 12.8 – 19.8 %, with a mean observation period of 6.3 – 9.8 years [2 – 4]. Total mortality in the same studies was reported to be 28.8 – 35 %. Continued alcohol consumption results in a significantly reduced survival rate. Thirty-three percent of patients suffering from chronic pancreatitis are no longer able to pursue their profession [5]. The number of patients who leave the workforce and gainful employment due to prolonged illness or continued alcohol consumption, or become who disabled and are forced to retire prematurely during the course of the disease amounts to 40 % [3]. Mortality is increased 3.6 fold in comparison with the normal population. The ten-year survival rate is 70 % and the 20-year survival rate is 45 % in comparison with 93 % and 65 %, respectively, for an age-adjusted cohort. Continued alcohol abuse has a negative effect on the prognosis of the disease with a hazard ratio (HR) of 1.6, continued smoking with an HR of 1.4, and liver cirrhosis with an HR of 2.5 [6].

Many aspects of the pathogenesis of chronic pancreatitis are still unclear. Alcohol is the most important risk factor and the most common cause during adulthood. When children are affected by chronic pancreatitis, a genetic component is often involved. Smoking in itself appears to be an important factor in the onset and progression of chronic pancreatitis [7, 8].

Since the formulation of the first German consensus recommendations [9], understanding of chronic pancreatitis has improved considerably, from its basic principles to its management. This can be attributed to significant advances in the clarification of the pathomechanisms of the disease and a larger number of valid epidemiological observations as well as prospective, in some cases randomised, therapy trials.

The aim of these guidelines is to summarise and evaluate the current level of knowledge with respect to definition, aetiology, diagnostics and management of all types of chronic pancreatitis in adults and children, and to provide this information in a practice-relevant form. The intention of the guidelines is to serve evidence-based professional training and continuing education and on this basis to improve the medical care of affected patients in both the inpatient and outpatient sector.

To do this, a fundamental prerequisite was to confine the guidelines to the clinical presentation of chronic pancreatitis only (acute pancreatitis was excluded). Chronic pancreatitis requires an adequate diagnostic workup and systematic management, given its severity, frequency, chronicity, and negative impact on the quality of life and life expectancy.

Chapter 2 – Aetiology (WG3)

2 – 1: Causes of chronic pancreatitis

Statement 2 – 1-1

Alcohol can be regarded as a confirmed cause of chronic pancreatitis.
[Level of evidence grade 3b, strong consensus]
Case-control studies have excluded a linear relationship between the level and duration of alcohol abuse and the occurrence of chronic pancreatitis, suggesting a logarithmic relationship instead.
[Level of evidence grade 4, strong consensus]

Comments

Retrospective case-control studies with sufficient case numbers are available which suggest a causal relationship between alcohol abuse and chronic pancreatitis [10 – 16]. In a study from Marseille in 1995, Levy et al. substantiated a logarithmic relationship between the relative risk of developing pancreatitis and the quantity of consumed alcohol and protein. A minimum of 80 g alcohol per day over a period of 6 – 12 years is assumed to be a risk for the development of chronic pancreatitis. It is currently not possible to specify a threshold value. The type of consumed alcohol has no influence on the increased risk. Patients with chronic pancreatitis or cirrhosis of the liver do not differ significantly with regard to the amount of consumed alcohol. An average of 18 ± 11 years elapses between the start of excessive alcohol consumption and the development of pancreatitis. The prevalence of chronic pancreatitis correlates with the amount of alcohol consumed in the general population [12, 17, 18].

Chronic pancreatitis is not caused by cholecystolithiasis or choledocholithiasis. Neither clinical studies nor data from animal studies substantiate a causal relationship for a biliary origin of chronic pancreatitis (however, evidence does exist for acute pancreatitis or, when gallstone disease remains untreated, also for recurrent acute pancreatitis) *[level of evidence grade 4]*. According to national and international guidelines, there is an indication for cholecystectomy in patients with cholecystolithiasis after an episode of acute pancreatitis [19, 20]. For pathophysiological reasons, it is possible that the disease chronifies after recurrent acute episodes, but this should not occur if the bile duct is cleared of gallstones in a timely fashion. Untreated, microlithiasis/sludge in the common bile duct (CBD) can result in recurrent episodes of pancreatitis. Signs of chronic pancreatitis, such as calcifications or higher-grade ductal changes, have not been reported to date in this context [21, 22].

Primary hyperparathyroidism can lead to chronic pancreatitis, with or without calcifications *[level of evidence grade 4]*. Case series are available of patients with primary hyperparathyroidism (pHTP) which substantiate an increased rate of pancreatitis (acute and chronic). A causal connection is assumed to exist with elevated serum calcium levels [23]. About 1 % of patients with pancreatitis also have pHTP, and 12 % of patients with pHTP also have pancreatitis [24]. Consequently, patients with pHPT have a 28-fold increased risk of developing pancreatitis. No controlled studies are presently available [23, 24].

Diabetes mellitus type 1 or 2 is not an independent risk factor for chronic pancreatitis. Diabetes mellitus type 3c (pancreoprivic) can be a consequence of chronic pancreatitis *[level of evidence grade 4]*. Individual case series are available which exclude an as-

sociation between diabetes mellitus and chronic pancreatitis. The association between chronic pancreatitis and diabetes mellitus type 3c is undisputed. Destruction of the islets of Langerhans by the progressive inflammatory reaction results in the loss of expression and secretion of insulin, glucagon and somatostatin. Thus, diabetes in this case is the result of chronic pancreatitis, not its cause [25].

The discussion about whether pancreas divisum is a risk factor for the development of chronic pancreatitis continues to be contentious. During the consensus conference, a statement was agreed upon with the following wording: The presence of pancreas divisum without any further risk factors tends not to lead to chronic pancreatitis *[level of evidence grade 3b]*. Pancreas divisum develops from an incomplete fusion of the dorsal (duct of Santorini) with the ventral (duct of Wirsung) excretory duct of the pancreas during embryonic development. As a result, both ducts drain into the duodenum via separate papillae (major and minor duodenal papillae). Pancreas divisum is the most common congenital malformation of the pancreas.

Autopsy studies report the frequency of pancreas divisum to be between 5 and 10 %; it is found in 6 – 26 % of patients with idiopathic chronic pancreatitis [26 – 35]. If a further risk factor is present (e. g., alcohol, SPINK-1 mutations) chronic pancreatitis can develop. Cohorts reported in support of an increased risk for chronic pancreatitis in the presence of pancreas divisum were often not examined for other risk factors (e. g., genetic factors). Endoscopic intervention may be appropriate in individual cases. The occurrence of acute idiopathic pancreatitis during childhood should prompt an aetiological search for anomalies of the hepatopancreaticobiliary system [30].

There is no good evidence that a papillary tumour can result in chronic pancreatitis *[level of evidence grade 4]*. Individual case reports show an association between a papillary tumour and recurrent episodes of pancreatitis; chronification, however, has not been reported. Resection of papillary tumours which trigger pancreatitis episodes normally prevents chronification [36].

Statement 2 – 1-2

Patients with chronic pancreatitis who smoke should be strongly recommended to participate in a smoking cessation programme, as cigarette smoking accelerates progression of the disease.
[Level of evidence grade 3b, recommendation level A, strong consensus]

Comments

Smoking accelerates the progression of chronic pancreatitis and maybe regarded as a cause of the pathogenesis. Larger, in part prospective, cohort studies involving up to 695 patients show that smoking leads to exacerbation of the pancreatic pain and to calcifications [2, 6, 7, 16, 37 – 42]. Even with alcohol abstinence, continued smoking results in a more rapid progression of chronic pancreatitis [39, 40]. The study by Yadav et al. [38] shows that patients without a history of alcohol but with 21 – 35 pack years have an increased risk of chronic pancreatitis ($p < 0.05$, odds ratio, OR, 3.26) [38]. It is highly probable that future studies will establish smoking as an independent risk factor.

Statement 2 – 1-3

Mutations in the cationic trypsinogen gene lead to chronic pancreatitis with a penetrance of up to 80 % and an autosomal dominant inheritance pattern.
[*Level of evidence grade 1c, strong consensus*].

Comments

The three linkage analyses published in 1996 demonstrated a linkage with a locus on chromosome 7q35 for hereditary pancreatitis [43, 44]. Further genetic analyses revealed an association of the disease with mutations in the trypsinogen gene (PRSS1) (initially p.N29I and p.R112H) [43]. Clinical data from the EUROPAC collaborative register substantiate an association between trypsinogen mutations and the occurrence of the disease in patients [45]. Trypsinogen is a key molecule in the pathogenesis of pancreatitis. As many as 66 % of patients with hereditary pancreatitis have a mutation of the PRSS1 gene. The prevalence of hereditary pancreatitis is 0.3 per 100.000 (selection: [43 – 52]).

Statement 2 – 1-4

Mutations of the SPINK1 gene predispose to idiopathic (sporadic) chronic pancreatitis.
[*Level of evidence grade 1a, strong consensus*].

Comments

The meta-analysis of 2431 patients and 4857 controls published in 2008 substantiated with an odds ratio (OR) of 11.0 that the N34S mutation in the gene encoding the serine protease inhibitor Kazal type 1 (SPINK1) is associated with chronic pancreatitis. The OR for idiopathic pancreatitis is reported as 14.97. Further, rarer mutations in the SPINK1 gene are also associated with the development of chronic pancreatitis. An OR of 4.98 for the N34S mutation is calculated for the group of alcohol-induced pancreatitis. Altogether, mutations of the SPINK1 gene occur in as many as 30 % of patients with idiopathic chronic pancreatitis [53, 54], but only in 1 – 2 % of the general population.

Statement 2 – 1-5

Twenty-five to 30 % of patients with idiopathic pancreatitis carry molecular changes in the CFTR gene, in comparison with approx. 15 % of the healthy population. Thus, CFTR mutations represent a risk factor for chronic idiopathic pancreatitis.
[Level of evidence grade 3b, strong consensus]

Comments

In all case series published to date, there is evidence of an increased risk for idiopathic pancreatitis if a mutation exists in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, yet without clinical signs of cystic fibrosis. Cystic fibrosis (mucoviscidosis), a disease with an autosomal recessive inheritance pattern and an estimated incidence of 1:2500, is characterised (amongst other things) by pancreatic insufficiency and chronic lung disease. Pancreas involvement varies from a complete loss of exocrine and endocrine function to almost normal pancreatic function. Recurrent episodes of pancreatitis are observed in 1 – 2 % patients with unimpaired exocrine pancreatic function but extremely rarely in patients with exocrine insufficiency [55]. In comparison with the normal population, patients

with idiopathic pancreatitis have about twice as many molecular changes in their CFTR gene [56 – 60].

Statement 2 – 1-6

Patients with a chymotrypsin C mutation have an increased risk of developing chronic pancreatitis.
[Level of evidence grade 3b, strong consensus]

Comments

Since the first report of mutations of the chymotrypsin C (CTRC) gene in the year 2008 [61], the association of this mutation with idiopathic chronic pancreatitis, alcoholic chronic pancreatitis and hereditary pancreatitis has been reproduced in at least three independent cohorts [62, 63]. Mutations of the CTRC gene occur in 3.3 % of patients with idiopathic pancreatitis. Under experimental conditions, CTRC gene mutations lead to endoplasmatic reticulum stress (ER stress) in acinar cells, which is considered the cause of the cell damage [61 – 64].

Summary of the aetiology of chronic pancreatitis

There are no population-based data from Europe on the aetiology of chronic pancreatitis. Alcohol abuse is the predominant predisposing cause during adulthood in 50 – 84 % of the cases, depending on where the study was carried out. The second most common group is idiopathic pancreatitis, accounting for up to 28 % of the cases. Here, genetic susceptibility factors play a role in up to 45 % of cases. Using Comfort and Steinberg's definition, hereditary pancreatitis is present in up to 1 – 4 % of patients. Anatomical variations do not lead to chronic pancreatitis with any certainty. Primary hyperparathyroidism can lead to chronic pancreatitis. The available figures on the incidence and prevalence are not reliable *[level of evidence grade 4]*.

In addition to the above-mentioned aetiologies, **autoimmune pancreatitis** was most recently characterized. This is a systemic fibroinflammatory disease in which the pancreas is one of the affected organs. Autoimmune pancreatitis was first reported by Henri Sarles in 1961 [65]; the concept of the clinical entity "autoimmune pancreatitis" was mentioned for the first time by Yoshida et al. in 1995 [66]. The largest comparative study recruited 731 cases [67]. Men are affected more commonly than women (2:1) [68]. In Asia, the prevalence of autoimmune pancreatitis is considered to be 5 – 6 % in a cohort of patients with chronic pancreatitis. About 5 % of patients who underwent surgery for suspected pancreatic carcinoma had histological confirmation of autoimmune pancreatitis [69]. Clinical symptoms include discrete abdominal pain, jaundice (50 %) and recurrent episodes of pancreatitis. Radiological findings include a diffuse or segmental stenosis of the pancreatic duct, frequently without prestenotic dilation, "sausage-shaped pancreas" and, rarely, calcifications. In the Asian patients in particular, increased serum levels of immunoglobulin (Ig) G and IgG4 were found. Lactoferrin and carboanhydrase-II antibodies were also found, albeit rarely and of questionable diagnostic relevance. Increased IgG-4 levels are found in only about 50 % of those affected with auto-immune pancreatitis in the European population. Autoimmune pancreatitis is characterised histologically by a dense periductal lymphoplasmacytic infiltration with obliterative phlebitis and periductal fibrosis (type 1 autoimmune pancreatitis) or granulocytic epithelial lesion (GELSs) in ~45 % of patients (type 2 autoimmune pancreatitis, mostly female, associated with chronic inflammatory bowel disease, no IgG4, rarely recurrent), with similar alterations in other organs.

The diagnosis of autoimmune pancreatitis is reached according to the HiSORT criteria, a combination of criteria which include histology, serology, other organ involvement and response to steroid therapy [68, 70]. The diagnosis is confirmed by a rapid response to steroids. As autoimmune pancreatitis is not part of these guidelines, please refer to the literature listed below [65, 66, 68 – 78].

2 – 2: Genetic testing in chronic pancreatitis

Statement 2 – 2-1

Patients with chronic pancreatitis and first or second degree relatives affected by pancreatitis should be offered molecular genetic testing for mutations in the PRSS1 gene, which are associated with the development of hereditary pancreatitis. This is particularly relevant if the initial manifestation age of the affected individual is in childhood or young adulthood.
[Level of evidence grade 3b, recommendation grade B, consensus].

Comments

As early as 1952, Comfort and Steinberg reported a hereditary form of pancreatitis with an autosomal dominant inheritance pattern [79]. These patients are now recruited to the patient registers EUROPAC and CAPER. An increased risk of developing pancreatic carcinoma is substantiated for patients with trypsinogen (PRSS1) mutations [80]. Work is currently being done to develop efficient tumour prevention strategies for this patient group. An increased cancer risk has so far not been substantiated for mutations in the SPINK1, CFTR and CTRC genes. Knowledge of the genetic cause has currently no clinical consequences for the treatment of the patient. Health-insurance coverage should be discussed with the patient or her/his relatives prior to performing the genetic test. Genetic testing of non-affected family members should not be conducted outside of research projects [79, 81].

Statement 2 – 2-2

PRSS1 gene mutation analysis should be undertaken in patients with a positive family history (one or two first-degree relatives with idiopathic chronic pancreatitis), two or more episodes of acute pancreatitis without identifiable cause before age 25, or idiopathic chronic pancreatitis with initial symptoms before age 25.
[Level of evidence grade 3b, recommendation grade B, consensus].

Comments

Carriers of a PRSS1 mutation have a cumulative risk of up to 49 % of developing pancreatic carcinoma by age 75 when they suffer from chronic pancreatitis. This risk is significantly higher than for all other known aetiologies of chronic pancreatitis. Despite its reduced penetrance, the autosomal dominant inheritance pattern suggests a causal relationship between PRSS1 mutations and the development of chronic pancreatitis [45, 46, 48, 49, 80 – 82]. Which procedure for tumour screening is best suited for this high-risk group is currently being examined.

Statement 2 – 2-3

A mutation analysis of changes in the SPINK1, CFTR, or CTRC genes or another associated genetic alteration may be undertaken within the scope of research projects or for in-depth clarification of underlying causes.
[Level of evidence grade 3b, recommendation grade C, consensus]

Comments

There is no provable increased risk of tumour development in patients with mutations in these susceptibility genes compared to other aetiologies of chronic pancreatitis. It may be assumed that these are susceptibility factors which predispose to the disease, but do not trigger it on their own. Even the detection of mutations in these genes does not allow a definite aetiological classification of chronic pancreatitis and does not generally provide any alternative therapeutic options [45, 46, 53, 60, 61].

Chapter 3 – Diagnostic procedures for exocrine insufficiency (WG1)

▼

3 – 1: Definition of exocrine insufficiency

Exocrine pancreatic insufficiency is defined as the functional impairment of pancreatic enzyme and bicarbonate secretion – regardless of the cause. The main causes of exocrine pancreatic insufficiency in adults are chronic pancreatitis, pancreatic carcinoma and previous pancreas resection [83]. Impaired pancreatic function is also expected after (sub-) total gastrectomy as well as in patients with marked protein deficiency or progression of cystic fibrosis (mucoviscidosis). Rare causes include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome and congenital enzyme deficiency, such as trypsinogen, enteropeptidase (enterokinase) or α1-antitrypsin deficiencies, as well as amylase, lipase or other protease deficiencies. Typical symptoms of exocrine insufficiency are abdominal symptoms, steatorrhoea and signs of malnutrition.

Development and clinical features of exocrine pancreatic insufficiency

In principle, the development of steatorrhoea and other symptoms of exocrine pancreatic insufficiency is already to be expected at the time of diagnosis of chronic pancreatitis, becoming more marked from about ten years after appearance of the symptoms of chronic pancreatitis *[level of evidence grade 1b–2b]*.

The moment when exocrine pancreatic insufficiency due to chronic pancreatitis will appear depends on the cause of the disease, among other things. In patients with alcoholic chronic pancreatitis, clinically manifest exocrine pancreatic insufficiency usually appears about 10 – 15 years after development of the first symptoms. In patients with an early onset of idiopathic chronic pancreatitis or a hereditary form of the disease, exocrine insufficiency often does not manifest until after an even longer period [84] *[level of evidence grade 2b]*. The usually late manifestation of exocrine insufficiency, despite destruction of pancreatic tissue already in the early stages of the disease, is due to the large functional reserve capacity of the pancreas. It is widely agreed that decompensation associated with steatorrhoea and creatorrhoea does not occur until secretion of the corresponding enzymes has been reduced by more than 90 – 95 % [85, 86] *[level of evidence grade 1b/2b]*. However, there are patients who primarily present with signs and symptoms of exocrine insufficiency, such as malnutrition and/or abdominal symptoms (diarrhoea/steatorrhoea, abdominal distension/meteorism, pain).

Steatorrhoea is a typical symptom of high-grade exocrine pancreatic insufficiency. This may, however, also be missing or have other causes. On the whole, there is no clinical symptom which unequivocally confirms or excludes exocrine pancreatic insufficiency *[level of evidence grade 1b-2b]*. Clinically, steatorrhoea cannot be reliably detected. Inspection of the stools is also unreliable, even when done by an experienced practitioner [87, 88] *[level of evidence grade 2b]*. Absence of clinical symptoms of steatorrhoea is even much less reliable; the negative predictive value is only 31 % [89] *[level of evidence grade 2b]*.

Moreover, the possible causes of diarrhoea and other abdominal symptoms are manifold, even in patients with chronic pancreatitis, and exocrine pancreatic insufficiency in patients with chronic pancreatitis is not the only cause of malnutrition; rather, these may for instance be due to a pain-related reduction of nutrition or continued alcohol consumption as well as an increased basal metabolic rate [90].

On the other hand, exocrine pancreatic insufficiency which is not associated with symptomatic steatorrhoea can also have a negative effect on nutritional parameters such as body weight [89] *[level of evidence grade 2b]*. Moreover, some studies substantiate reduced absorption of fat-soluble vitamins in patients with mild to moderate exocrine insufficiency ([91], 1b/2b, [92] 2b, [93]), and some recent data have documented significantly reduced faecal elastase levels in patients with osteoporotic fracture, which correlates with low vitamin D3 levels [94] *[level of evidence grade 3b]*. Patients with steatorrhoea were excluded from this study. Hence, there appears to be a clearly increased risk of osteoporosis and fracture even with subclinical, i. e., mild to moderate, exocrine insufficiency.

Relationship between exocrine insufficiency and morphological changes in patients with chronic pancreatitis

Exocrine pancreatic function and morphological signs of chronic pancreatitis usually, but not always, run parallel. Exocrine pancreatic insufficiency is also possible even in the absence of morphological evidence of chronic pancreatitis *[level of evidence grade 1b–2b]*.

Isolated older studies have shown a virtually complete correlation between normal morphology and normal exocrine function, but also severe changes with regard to both parameters [95] *[level of evidence grade 1b]*. It is also well substantiated that in the majority of patients with chronic pancreatitis, a correlation exists between the extent of morphological and functional disturbances. According to the results of several other studies, discordant findings with varying degrees of morphological and functional changes are found in about one-fourth of patients [87] *[level of evidence grade 2b]* [96, 97] *[level of evidence grade 1b–2b]*, [98] *[level of evidence grade 1b–2b]*, and the absence of morphological signs of chronic pancreatitis is not to be equated with normal pancreatic function. This is also true even after using highly sensitive examination techniques, such as endoscopic ultrasound, as several recent studies have shown [98] *[level of evidence grade 1b–2b]*, [97] *[level of evidence grade 1b–2b]*, [99] *[level of evidence grade 2b]*. Even in the presence of normal morphological findings, 28 % of patients examined had exocrine pancreatic insufficiency as verified by measuring enzymatic activity in duodenal contents [100, 101] *[level of evidence grade 2b]*. In another study, in which endoscopic ultrasound and the secretin test were compared with histological findings as a reference, the sensitivity of

endoscopic ultrasound for the diagnosis "chronic pancreatitis" was 84 %, and that of the secretin test 86 %. The specificity of endoscopic ultrasound was higher than that of the secretin test (100 % vs. 67 %), but a combination of the two examination methods produced a sensitivity level of 100 % [102] *[level of evidence grade 2b]*. Exocrine pancreatic insufficiency despite normal morphological findings appears to exist particularly in patients with the "small duct disease" type of chronic pancreatitis [97] *[level of evidence grade 1b-2b]*.

Statement 3 – 1-1

In Germany, the secretin test is currently the available reference procedure for directly measuring exocrine pancreatic function. It should be used to establish new function tests and may be useful for medical appraisals and expert opinion reports.
[*Level of evidence grade 1b, recommendation grade A (first partial statement), strong consensus*].

Statement 3 – 1-2

A non-invasive pancreatic function test should be carried out in clinical situations. The faecal elastase test (with mono specific antibodies) is suited to this purpose because it is easy to conduct. Breath tests using ^{13}C-labelled lipids are possible alternatives.
[*Level of evidence grade 5, recommendation grade B, consensus, clinical consensus point for the preference of non-invasive tests*]

Comments regarding statements 3 -1- 1 and 3 -1- 2

Measuring faecal elastase levels in a random stool sample is currently the best clinically available and most widely used pancreatic function test in Germany. The following pancreatic function tests are also clinically available: measurement of faecal fat excretion, measurement of chymotrypsin activity in stool, breath test with ^{13}C-labelled substrates (preferentially ^{13}C-labelled mixed triglycerides), secretin test.
Measuring the quantitative amount of fat secreted in the faeces is rarely performed in Germany nowadays because of the effort involved and the unpleasant procedure of collecting and processing large quantities of stool. The qualitative faecal fat test, on the other hand, is routinely performed in most large laboratories. Breath tests with ^{13}C-labelled substrates (preferentially ^{13}C-labelled mixed triglycerides) are also available but less well established. Chymotrypsin activity in stool is rarely used at present.

The Pancreolauryl® test is no longer available in Germany. As the most exact technique for quantifying exocrine pancreatic function, the secretin-pancreozymin test (or the secretin-caerulein test) is no longer practicable in this form because the only available cholecystokinin analogue Takus® has been taken off the market. The remaining option, therefore, is to perform a tube test, stimulating only secretin. This normally results in a sharp rise in pancreatic bicarbonate secretion, which is regarded as the most important parameter measured, but enzyme secretion is also somewhat stimulated. However, this examination is not only labor-intensive, requiring insertion of a nasoduodenal tube, it is also expensive. It is therefore confined to specialist centres and strictly selected indications. The endoscopic variation of the secretin test, with repeated endoscopic aspiration of duodenal juices after secretin stimulation, is increasingly favoured in the USA and can in principle be carried out in any endoscopy department with standard equipment. The technique is rarely used, however, because of the long examination time (up to 60 min).
To date, MRI-based techniques are used in an increasing number of studies measuring exocrine pancreatic function. However, an additional, semi-quantitative parameter for assessing exocrine pancreatic function can now be obtained, for example, by determining fluid secretion into the duodenum during secretin-enhanced MRCP (magnetic resonance cholangiopancreatography) to image the pancreaticobiliary ductal system [103, 104] *[level of evidence grade 2b]*, [105].
Sensitivity and specificity of the available pancreatic function tests are listed in **Table 3** [*level of evidence grade* **Table 3**] see [106].

Statement 3 – 1-3

A pancreatic function test should be performed once chronic pancreatitis has been diagnosed.
[*Level of evidence grade 1b–2b, recommendation grade B, strong consensus*].

Comments

The statement is founded on the following (see also Sections 3 – 2 and 3 – 3):

1. In a given case, the initial pancreatic function test provides a basis for a diagnosis because it is rare for patients with chronic pancreatitis to have no pathological findings in their morphological investigations.
2. Even with unequivocal morphological findings which justify the diagnosis of chronic pancreatitis, clinical symptoms (history and inspection of the stools) are unreliable for recognising

Table 3 Sensitivity and specificity of the available pancreatic function tests.[1]

test	mild exocrine insufficiency	moderate exocrine insufficiency	severe exocrine insufficiency		level of evidence grade
	sensitivity (%)	sensitivity (%)	sensitivity (%)	specificity (%)	
faecal elastase 1	54 %	75 %	95 %	85 % (96 % / 79 %)[2]	1a/b
qualitative faecal fat test	0 %	0 %	78 %[3]	70 %[3]	
chymotrypsin activity in stool	< 50 %	approx. 60 %	80 – 90 %	80 – 90 %	1a/b
^{13}C (mixed triglyceride) breath test	62 – 100 %		90 – 100 %	80 – 90 %	1b/2b

[1] The direct invasive pancreatic function tests (secretin and secretin-pancreozymin tests) were used as reference methods. Sensitivity and specificity are therefore not stated for these.
[2] Average specificity, in brackets: Specificity for various controls (healthy volunteers/patients).
[3] In relation to quantitative faecal fat test.

exocrine insufficiency, even if it is severe and associated with steatorrhoea. These severe forms, however, are reliably detected by all clinically available function tests. The initial exclusion of severe exocrine insufficiency is therefore appropriate.

3. Conversely, the possible causes of diarrhoea and other abdominal symptoms are manifold, even in patients with chronic pancreatitis, and exocrine pancreatic insufficiency in patients with chronic pancreatitis is not the only cause of malnutrition. Rather, this can be due for instance to a pain-related reduction of food intake or continued alcohol consumption as well as an increased basal metabolic rate [90].

Statement 3 – 1-4

In the case of new or increasing symptoms, which could be due to exocrine pancreatic insufficiency, measurements of pancreatic function should be repeated if previous results were unremarkable.
[*Level of evidence grade 2b, recommendation grade B, consensus*].

Comments

The development of symptoms of exocrine pancreatic insufficiency in a patient with known chronic pancreatitis is possible at any time, even if steatorrhoea usually only develops several years after the appearance of initial symptoms. Mild impairment of exocrine pancreatic function may have clinical significance; this becomes evident from the clinical context *[level of evidence grade 2b]*.

Statement 3 – 1-5

Diabetics have an increased risk of developing exocrine pancreatic insufficiency. Pancreatic function tests, therefore, should be performed for clinical symptoms of exocrine pancreatic insufficiency.
[*Level of evidence grade 2b, recommendation grade B, consensus*].

Comments

A significant proportion of patients with type 1 and type 2 diabetes mellitus suffer from exocrine pancreatic insufficiency [107 – 110]. This is explained by a deficient insulo-acinar axis [111] and significant exocrine atrophy [112], among other factors. Thus, if relevant signs and symptoms are present, a pancreatic function test is appropriate.

Chapter 4 – Diagnostic imaging (WG2)

The diagnosis of chronic pancreatitis is based on clinical, morphological and functional parameters. Due to the insufficient correlation of the three diagnostic pillars with clinical signs and symptoms, they should be used in a complementary way. Transabdominal ultrasound is regarded as the basic morphological diagnostic technique.

Statement 4 – 1-1

After anamnesis and clinical examination, an ultrasound scan of the pancreas has the first preference. If the signs of pancreatitis are equivocal (inhomogeneous gland, normal width of the pancreatic duct) and clinical suspicion persists, then endoscopic ultrasound (EUS) should be performed. Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) provides a cytological and/or histological diagnosis of focal lesions. Computer tomography (CT) and MRI as well as MRCP are supplementary diagnostic techniques for unclear pancreatic changes detected on ultrasound and during endoscopic ultrasound. In particular, an MRCP should be performed to obtain more detailed information about the pancreatic ductal system if necessary.
[*Level of evidence grade 2a, recommendation grade B, consensus*]

Comments

In the diagnostics of chronic pancreatitis, endoscopic ultrasound has the highest accuracy [113 – 116]. In comparative studies with endoscopic retrograde cholangiography (ERC), endoscopic ultrasound achieved comparable results [117, 118]. In a prospective study comparing MRCP with endoscopic retrograde cholangiopancreatography (ERCP) to diagnose malignant tumours, MRCP demonstrated a higher sensitivity (84 %) than did ERCP (70 %), with equal specificity (94 %). Purely diagnostic ERCP should no longer be used because of its higher morbidity and mortality rates. Comparative studies between MRCP and EUS showed a better discriminatory power for endoscopic ultrasound, especially with early forms of chronic pancreatitis [119]. Diagnostic ERCP should only be used in exceptional cases [120 – 123] which include unclear cases of suspected autoimmune pancreatitis.

Statement 4 – 1-2

Sensitivity and specificity of the individual imaging techniques for the diagnosis of chronic pancreatitis are listed in ◉ **Table 4**.
[*Level of evidence grade 2b*]

Comments

There are no prospective randomised studies comparing endoscopic ultrasound (EUS), ultrasound (US) and CT for diagnosing chronic pancreatitis. Prospective comparative studies are only available comparing ERCP with EUS and MRCP with EUS [120, 124] and US with ERCP [133]. It has been shown that EUS is superior to ERCP, especially for assessing early forms of pancreatitis. The only ultrasound study available demonstrated a sensitivity of 81 % for US in comparison with 53 % for ERCP. Some studies substantiate that patients with changes on EUS, but an initially unremarkable ductography in their ERP, demonstrate pathological changes in their ductal system in the form of chronic pancreatitis or demonstrate histological changes of chronic pancreatitis as the disease progresses [131, 134]. In a comparative study with secretin stimulation, EUS vs. ERP revealed similar results (sensitivity

examination	sensitivity	specificity	level of evidence	references
CT	n/a	n/a	2b	[124]
ERCP	70 – 80 %	80 – 100 %	2a	[98, 120, 124 – 127]
MRCP	88 %	98 %	2b	[121, 122]
US	60 – 81 %	70 – 97 %	2a	[124, 128, 129]
EUS	80 – 100 %	80 – 100 %	2a	[113, 120, 130 – 132]

Table 4 Sensitivity and specificity for the individual imaging techniques.

72 % vs. 68 %, specificity 76 % vs. 79 %) [125, 126]. In the first instance, ultrasound should be performed for suspected chronic pancreatitis and, if the result is normal, the higher spatial resolution of EUS will be able to detect any early parenchymal changes indicative of chronic pancreatitis. CT scanning still has an essential role in pre-operative planning [113, 128, 129, 131 – 134].

Statement 4 – 1-3

The various criteria of the different imaging techniques should be modified for adults and employed according to the Cambridge classification:
[*Level of evidence grade 2a, recommendation grade B, strong consensus*].

ERCP
Cambridge 0: no pathological alterations on good visualization of pancreatic duct system
Cambridge 1: less than 3 abnormal side branches, main duct normal
Cambridge 2: more than 3 abnormal side branches, main duct normal
Cambridge 3: 3 or more abnormal side branches plus abnormal main pancreatic duct
Cambridge 4: as in 3, plus cysts, duct calculi, duct obstruction (stricture), involvement of adjacent organs

Transabdominal ultrasound:
Cambridge 0: normal organ, duct < 2 mm, regular contour
Cambridge 1: echo-dense gland contour, gland enlarged (up to 1.5-fold), duct < 3 mm, lobular honeycomb appearance
Cambridge 2: contour irregularities, irregular hyperechoic main pancreatic duct > 3 mm, lobular texture with echo-dense septations
Cambridge 3: as in 2, plus cysts, focal calcifications
Cambridge 4: as in 3, plus duct stones, duct obstruction, tumorous enlargement of the gland > 2-fold, splenic vein thrombosis

Endoscopic ultrasound:
Cambridge 0: none
Cambridge 1: lobular honeycomb appearance – duct < 3 m
Cambridge 2: hyperechogenic duct, hyperechogenic foci, hyperechoic contour, duct < 3 mm
Cambridge 3: lobular honeycomb appearance, septated, hyperechogenic foci, duct > 3 mm, irregular duct, no duct calculi
Cambridge 4: as in 3, plus calcifications, duct calculi, cysts

CT/MRCP:
Cambridge 0: none
Cambridge 1: not possible to demarcate duct system on CT/MRCP using current methods
Cambridge 2: Two or more of the following pathological changes:
- pancreatic duct between 2 and 4 mm in the pancreatic body
- mild pancreatic enlargement
- heterogeneous parenchymal structure
- small cystic changes (< 10 mm)
- duct irregularities
- pathological side branches > 3

Cambridge 3: All changes named under 2 plus pathological main duct (> 4 mm)
Cambridge 4: One of the changes named under 2 or 3 plus one or more of the following:
- cystic structures > 10 mm
- parenchymal calcifications
- intraductal filling defects (calcifications)
- duct obstruction (strictures)
- major duct irregularities

Comments
The gold standard for assessing chronic pancreatitis was, until now, ERP using the Cambridge classification [135]. The Cambridge classification and its adaptation for cross-sectional imaging (US, EUS, CT/MRCP) should be used for diagnosing chronic pancreatitis in adults. It still corresponds to the state of the art *[level of evidence grade 3a]*.
The Cambridge criteria for assessing the pancreatic ductal system is still used for ERCP, but only for patients referred for interventional ERP. Non-invasive techniques (ultrasound, CT, MRCP, EUS) are employed for patients with suspected chronic pancreatitis. Whereas the Cambridge criteria only describe the pancreatic ductal system, it is possible to include both the ductal system and the adjacent parenchymal structures with the above-mentioned imaging techniques. These methods employ the criteria of the Cambridge classification to describe the ductal system. MRCP in particular implements the nomenclature of the Cambridge classification [113, 117, 135, 136].
Due to its higher morbidity, ERP, as an invasive diagnostic technique, should be replaced by alternative imaging techniques with identical validity [115, 117, 137, 188]. Randomised comparative studies using ERP and the imaging techniques are only available for EUS and MRCP. Based on comparisons of the individual imaging techniques, it is appropriate to adopt the Cambridge classification for ultrasound, CT and MRCP in order to achieve standardisation of nomenclature [121, 122].
Early changes of chronic pancreatitis are only detectable using EUS. Pathognomonic reporting criteria from comparative studies involving chronic pancreatitis have been compiled which correlate directly with the probability of the disease [113]. Prospective histopathological studies have shown with a specificity of 100 % that EUS is more sensitive than MRCP when more than four criteria are present [113, 114, 116 – 122].

Statement 4 – 1-4

At the moment, ultrasound elastography cannot be recommended for diagnosing chronic pancreatitis.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].
It may, however, be helpful for the differential diagnosis of focal lesions.
[*Level of evidence grade 3b, recommendation grade C, strong consensus*]

Comments
To date, monocentric studies involving elastography have examined patients with space-occupying lesions of the pancreas [138]. So far, two studies have shown that elastography can differentiate well between malignant and benign focal lesions (sensitivity 91.4 %, specificity 87.9 % [139]; sensitivity 100 %, specificity 92.9 % [140]). The study by Saftiou et al. involving 68 patients, however, included only 11 patients with chronic pancreatitis. The study by Iglesia et al. reported 27 patients with inflammatory pancreatic changes, but did not distinguish between acute and chronic pancreatitis. A study by Janssen et al. demonstrated that for chronic

pancreatitis, elastography generated images comparable with those for ductal carcinoma. EUS elastography currently has no significance for diagnosing chronic pancreatitis. Patients with chronic calcifying pancreatitis should be prospectively examined by elastography in order to verify the value of this technique in differentiating between focal chronic pancreatitis and pancreatic carcinoma in chronic pancreatitis. There are initial indications that elastography may be helpful in diagnosing autoimmune pancreatitis [141].

The morphological findings of chronic pancreatitis (CP) can be assessed using the following classification systems:

1. Manchester Classification [142]:

* Mild CP: ERP, CT, US, EUS – evidence of chronic pancreatitis, no peripancreatic complications, preserved endocrine and exocrine function; abdominal pain; no regular analgesia
* Moderate CP: ERP, MRT, CT, US, EUS – evidence of chronic pancreatitis, pain despite analgesics, defective endocrine or exocrine function
* Severe CP: as for moderate (with or without abdominal pain), plus: biliary stricture, portal hypertension, duodenal stenosis, as well as exocrine or endocrine insufficiency

2. ABC System (Ramesh, modified according to Büchler) [143, 144]:

* Stage A: Pain, positive imaging on US, ERP, MRT, EUS, no exocrine or endocrine insufficiency
* Stage B: Pain, positive imaging, no exocrine or endocrine insufficiency, plus complications (obstruction CBD, duodenum, pseudocyst, fistula, etc.), but without exocrine and endocrine insufficiency
* Stage C: Pain, positive imaging, with exocrine (C1) or endocrine dysfunction (C2), with or without complications

3. Rosemont Classification based on endoscopic ultrasound [113]:

* In addition to parenchymal changes (hyperechoic foci with and without shadowing, honeycomb-type lobularity, cysts, hyperechoic strands), ductal changes (main pancreatic duct calculi, irregular duct, dilated side branches, hyperechoic duct wall) are also described. Prospective histopathological studies demonstrated that EUS was more sensitive than MRP with a specificity of 100 % if more than four criteria were present [116, 119].

4. M-ANNHEIM Classification [145]:

* Pain, pain control, need of surgery, exocrine insufficiency, endocrine insufficiency, morphology (according to Cambridge criteria), gland complications and imaging based on CT or US or MRT or EUS.

Comments

The Manchester classification conclusively combines imaging findings of chronic pancreatitis with clinical findings and converts them into a simple classification table for chronic pancreatitis [142]. In this system, the dominating criterion for the severity of pancreatitis is evidence of exocrine or endocrine insufficiency and/or evidence of complications. The various imaging findings tend to play a subordinate role with regard to severity. The ABC system of Ramesh and Büchler represents a comparable form of classification [143, 144]. It requires positive imaging for all stages, while the presence of exocrine or endocrine insufficiency and/or complications alone determines the severity of chronic pancreatitis. The Rosemont classification describes the presence of chronic pancreatitis using EUS criteria [113]. The number of presenting parameters correlates with the severity of the chronic pancreatitis. This has been confirmed in histopathological studies. This system does not include clinical findings for evaluation. The M-ANNHEIM classification attempts to characterise patients according to aetiology, clinical stage and severity [145]. The severity of the inflammatory reaction is evaluated using clinical symptoms and therapeutic interventions. At the end of a complex classification system, there is a point system (0 – 25 points) which describes the severity of chronic pancreatitis [145].

All classification systems should be tested in prospective randomised studies for their validity. The target criterion must be the calculation of morbidity and mortality in order to measure the effects of treatment.

The choice of imaging technique depends on the expected complication [*level of evidence grades: ultrasound 3a; EUS 2a, CT 4, MRI 3a*].

Necroses

Contrast-enhanced ultrasound (CEUS) is capable of detecting necroses to the same degree as contrast-enhanced CT. This is particularly advantageous in patients with impaired kidney function. However, quantification as demanded by Balthazar und Moertele for evaluating the degree of severity is not possible [146, 147]. A US- or CT-guided fine needle biopsy can follow if infected necrosis is suspected. Contrast-enhanced MRT can also detect necrotic pancreatic tissue [148, 149].

Cysts

Larger cysts are easily detectable using transabdominal ultrasound [150, 151]; their criteria are clearly defined (echo-free, tangential artefact, dorsal acoustic enhancement). Findings which deviate from this are referred to as atypical cysts. In this context, cystic neoplasms should be considered in the differential diagnostics and other imaging techniques used.

The highest detection rates for the differentiation of cystic pancreatic lesions are achieved by EUS and MRT/MRCP. Cystic neoplasms can be well differentiated from pseudocysts or peri-intestinal fluid accumulations using EUS und MRT/MRCP. In case of doubt, a EUS-FNA with the asservation of cyst fluid (cytology, lipase and carcinoembryonic antigen [CEA] determination) may follow. There is no comparative literature available.

Pseudoaneurysms

Upon detection of cystic changes within the pancreas, ultrasound should be performed in combination with colour Doppler ultrasonography in order to reliably detect perfusions in the lesion as an indication of a pseudoaneurysm. This should be obligatory before any interventions.

CT angiography and MR angiography are very well suited for identifying pseudoaneurysms. There are no comparative imaging studies available.

Carcinoma

Once chronic pancreatitis has been diagnosed, transabdominal ultrasound and endoscopic ultrasound can only distinguish between carcinoma and inflammation only to a limited degree. In case of doubt, an EUS-FNA should follow; this can raise sensitivity to over 85 % with good specificity [152, 153]. The probability of false negative findings is reported to be between 5 and 10 %, so that given operable findings on images and a suspected tumour, surgery is recommended even without prior cytological confirmation (see Adler et al. [154]).

A sensitivity of 84 % and a specificity of 97 % have been reported for MRT combined with MRCP. A sensitivity of 93 % and a specifi-

city of 75 % have been calculated for differentiating between chronic pancreatitis and pancreatic carcinoma [155]. This does not apply when a carcinoma develops in the presence of chronic pancreatitis. In this case, even after exhausting all diagnostic techniques, sensitivity for detecting a tumour is 67 %, with a specificity of 45 %.

Explanatory note

More recent studies involving CE-US and endoscopic ultrasound show [156] that both necroses and pancreatic carcinoma appear as demarcated hypoperfused focal lesions [139, 140, 157 – 159]. In the presence of acute pancreatitis, necrosis may be assumed if positive clinical presentation and laboratory findings are taken into account. In the presence of chronic pancreatitis, imaging may suggest focal necrosis or carcinoma [160] of relevance for the decision for surgery, an EUS-FNA of the focal lesion is appropriate, although a considerable rate of false negative findings is to be expected [161].

Statement 4 – 1-5

Cytological or histological fine EUS-guided needle aspiration can be recommended to differentiate between autoimmune pancreatitis and other pancreatic diseases.
[*Level of evidence grade 2c, recommendation grade B, consensus*].

Comments

Forty percent of patients with autoimmune pancreatitis present with a focal lesion. The diagnostic accuracy of endoscopic ultrasound for diagnostic classification of a pancreatic lesion using endoscopic ultrasound-guided fine needle aspiration is reported to be 95 % for lesions < 10 mm and 100 % for lesions > 3 cm. According to HiSORt criteria, the cytological/histological diagnosis is the gold standard for establishing autoimmune pancreatitis. If autoimmune pancreatitis is suspected based on imageing or clinical findings, endoscopic ultrasound-guided FNA may be performed [68, 162, 163].

Statement 4 – 1-6

If EUS and MRI/MRCP are feasible, ERP cannot be recommended as the primary diagnostic procedure. In individual cases (e. g., insufficient diagnostic reliability of EUS and MRI/MRCP) an ERP may be indicated. If autoimmune pancreatitis is suspected, diagnostic ERP may be employed.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].

Comments

Either EUS or MRCO, or the combination of both examinations is usually sufficient for diagnosing chronic pancreatitis. ERP carries too high a risk of developing post-ERCP pancreatitis, especially in the early stages of chronic pancreatitis. The rate of post-ERCP pancreatitis is 3.5 % in an unselected patient population. In the majority of cases, post-ERCP pancreatitis assumes a mild course; however, in 10 % of cases, a severe course develops with the possibility of a fatal outcome. Therefore, as a rule, its use for purely diagnostic purposes is not justified.

Four criteria with high sensitivity and specificity were developed for diagnosing autoimmune pancreatitis and for differentiating it from pancreatic carcinoma using ERP: (1) Long stenotic segment > 1/3 of the length of the pancreatic duct, (2) without downstream dilatation of the pancreatic duct, (3) dilatation of the side branches, (4) multifocal strictures along the pancreatic duct all indicate the presence of autoimmune pancreatitis. Japanese guidelines [164] require ERCP for diagnostics; comparative examinations for MRCP are not yet available. Since serological parameters (IgG4, IgG) are of limited informative value in the Western population, diagnostic ERP for establishing autoimmune pancreatitis plays a larger role in Europe than in Japan [165] and remains one of the last indications for Diagnostic ERP in cases where the diagnosis of autoimmune pancreatitis annot be confirmed by other means.

Chapter 5 – Management of acute episodes

Introduction

Especially for the management of acute episodes of recurrent pancreatitis, the same principles are valid as for acute pancreatitis, and less so for typical chronic calcifying pancreatitis. For this reason, the clinically important aspects in the management of acute pancreatitis and its complications will be addressed in the following passage. The acute episode of chronic pancreatitis is one of the most common gastroenterological disorders. The incidence of new cases of acute pancreatitis lies between 10 and 79 per 100 000 inhabitants. There were 50 673 hospital discharges for acute pancreatitis in Germany in the year 2008. Therefore, approx. 1.2 % of the clinical patient population is affected [19]. An increasing incidence has been observed in recent years. Clinical symptoms such as band-like upper abdominal pain and vomiting, together with a rise in serum amylase or lipase levels more than 3-fold above normal, lead to the diagnosis of acute pancreatitis. With serum lipase values below the threefold normal value, the revised criteria of the Atlanta Classification of 1994 (publication pending) suggest the use of an imaging technique to establish the diagnosis (e. g., contrast-enhanced CT). The most common cause of an acute episode of chronic pancreatitis is continued alcohol abuse or dietary factors. In terms of severaty, two forms of acute episodes of chronic pancreatitis can be distinguished, the development of which is independent of the aetiology of the disease: acute interstitial oedematous pancreatitis (75 – 85 %) with a mortality rate below 1 % and acute haemorrhagic necrotising pancreatitis (15 – 25 %) with mortality between 10 and 24 %. It is essential that patients with acute pancreatitis be treated in the hospital on an in-patient basis to ensure adequate care. Frequent requirement for follow-up assessments of the clinical findings, of laboratory parameters and the imaging results make optimal out-patient care virtually impossible. At the time of admission to the hospital, it is usually difficult to differentiate between the majority of patients with a mild and uncomplicated course (about 80 %) and those patients with a severe course, which is usually burdened by multiple organ complications (about 20 %). Apart from the physical examination by an experienced physician, various parameters have been identified to allow an assessment of the prognosis: A complicated course can usually be expected in patients with three or more signs of organ complication, e. g., in the Ranson or Imrie score, or with clinical signs of a systemic complication (e. g., respiratory or renal failure), or with the identification of pancreatic necrosis on the contrast-enhanced CT scan. Currently, C-reactive protein (CRP), haematocrit and persistent (> 48 hours) organ failure are considered to be parameters of high prognostic significance for predicting the degree of severity of acute pancreatitis.

Treatment

Statement 5 – 1-1

Rapid and adequate fluid replacement is crucial for prognosis and should therefore be initiated.
[*Level of evidence grade 2b, recommendation grade A, strong consensus*]

Comments

The crucial therapeutic measure in the treatment of acute pancreatitis (and the most common treatment error if not undertaken) is adequate fluid replacement. A Japanese retrospective analysis demonstrated that mortality in a patient group with acute pancreatitis was 61.2 % if less than 3.5 litres of fluid had been infused in the first 24 hours of hospitalisation [166 – 168]. Acute prerenal kidney failure within the first 48 hours after admittance to hospital correlated with increased mortality. Every increase of serum urea levels by 5 mg/dl raises mortality by a factor of 2.2 [169, 170]. However, the excessive administration of fluid results in local complications and global respiratory failure. In order to establish adequate fluid replacement, the clinical course using two regimens of fluid replacement were examined in a prospective randomised study involving patients with severe acute pancreatitis (APACHE-II score > 14). One group received 10 s–15 ml/kg/h until the fluid deficit was corrected, measured by fulfilling two or more of the following criteria: heart rate < 120/min, mean arterial pressure 65 – 85 mmHg, urine output > 1 ml/kg/h, haematocrit < 35 %. The second group received less fluid replacement with 5 – 10 ml/kg/h. In the group receiving 10 – 15 ml/kg/h, 94.4 % of the patients had to be artificially ventilated in comparison with 65 % in the group with 5 – 10 ml/kg/h. Mortality in the group which received the greater volume was significantly increased, as were local complications such as abdominal compartment syndrome or sepsis [164]. If invasive monitoring of fluid deficit is not possible, then treatment with 5 – 10 ml/kg/h can be recommended *[level of evidence grade 1b, recommendation grade A]*. Volume administration should, if possible, be regulated by a thermodilution system. Neither haematocrit nor CVP have proven adequate for assessing volume deficit. Based on the findings of the VISEP study on sepsis management, crystalloid solutions – not colloids such as hydroxyl ethyl starch (HES) – should be used for fluid replacement [171]. There is a general consensus (international guidelines) that rapid and adequate fluid replacement is important for the prognosis [19, 166, 167, 172, 173].

Statement 5 – 1-2

The insertion of a nasogastric tube not beneficial in the absence of subileus or ileus or symptoms is associated with vomiting.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].

Comments

The insertion of a nasogastric tube is indicated as prophylaxis and therapy for a paralytic ileus. However, today the idea of 'resting the pancreas' by nasogastric suction of gastric juices is obsolete [174 – 177].

Statement 5 – 1-3

Acid suppression for stress ulcer prophylaxis can be recommended for severe forms of the disease.
[*Level of evidence grade 3a, recommendation grade C, consensus*]

Comments

Controlled studies on stress ulcer prophylaxis are not available. Prophylaxis is generally recommended.

Statement 5 – 1-4

Adequate pain management is essential.
[*Level of evidence grade 2b, recommendation grade A, strong consensus*]

Comments

Patients with an acute episode of pancreatitis often suffer from extreme visceral pain. Adequate analgesia is therefore one of the most important and often most urgent aims of treatment. The argument that morphine possibly causes contraction of the duodenal papilla, thus creating an additional obstruction for pancreas secretion, is obsolete according to the current state of knowledge *[level of evidence grade 2b]*. Today, we know that this effect either does not occur with the majority of analgesics of this group or is so insignificant that it plays no clinical role. Some morphine-analogue analgesics are successfully used for pain control in acute pancreatitis. Tramadol, which is very popular for reasons of controlled-substance legislation, often causes nausea and vomiting in patients with acute pancreatitis, so that its use in this disease is not to be recommended. Some centres have meanwhile achieved good results with the use of thoracic epidural analgesia (EPA). This often not only results in rapid analgesia in the patients, but in addition prevents or treats paralytic ileus. The prerequisite for the use of EPA is that the patient is alert and responsive and that no manifest coagulopathy is present [178 – 182].

Statement 5 – 1-5

Clinical symptoms may demand initial fasting.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

Fasting has a positive effect on the course of paralytic ileus, which can occur as a consequence of acute pancreatitis. In addition, many patients subjectively experience fasting as a relief from their nausea, vomiting and pain. According to more recent studies, fasting has no positive effect on the clinical course or prognosis of acute pancreatitis itself. Above all, the notion that the pancreas needs to be "rested" by fasting is now regarded as obsolete. Both experimental and clinical studies have convincingly substantiated that exocrine secretion is blocked during the course of pancreatitis, making the suppression of secretion as a therapeutic principle pointless [183]. Therapeutic reversal of the secretion block in pancreatitis would be, at least in terms of pathophysiology, a more promising treatment approach. Enteral tube feeding is superior to parenteral nutrition in acute pancreatitis.
Ten prospective randomised clinical studies [184 – 193] have meanwhile demonstrated that enteral nutrition is superior to parenteral nutrition in acute pancreatitis. The reasons for this not only lie in the cost of parenteral nutrition (six times more ex-

pensive than enteral tube feeding), but above all in the complications of parenteral nutrition. Apart from the risk of an additional source of infection from the central venous catheter, animal studies have shown the development of intestinal villous atrophy within a few days of exclusively parenteral nutrition, which then facilitates bacterial translocation into the adjacent parenchymatous organs. In patients with necrotising pancreatitis, the translocated bacteria preferentially colonise pancreatic necrosis and can cause one of the most feared complications of pancreatitis: infected necrosis or pancreatic abscess. Enteral nutrition administered via a nasojejunal tube oralternatively via a nasogastric tube (shown by most recent studies to be equally effective) counteracts translocation and has proven itself as an alternative to parenteral nutrition [194 – 197]. The administration of the total caloric requirement via an enteral nutrition tube is not possible in all patients with necrotising pancreatitis and additional intravenous supplementation is occasionally required to prevent catabolism. Nevertheless, enteral calories should be administered whenever possible to prevent intestinal villous atrophy. All those who question this paradigm shift in the treatment of acute pancreatitis should note that in none of the studies on enteral nutrition in patients with acute pancreatitis was a clinically relevant disadvantage associated with this treatment method as opposed to full parenteral nutrition. Imrie et al. demonstrated that the rate of pulmonary complications is significantly reduced by enteral nutrition [195].

Statement 5 – 1-6

Any required intensive care management is based on standardised principles, which apply in particular to the treatment of sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ failure.
[*Strong consensus, clinical consensus point*]

Comments

New prospective studies on the use of intensive-care procedures specific to pancreatitis do not exist. A multicentre study on the role of the PiCCO thermodilution method for monitoring volume in acute pancreatitis has already begun [198].

Statement 5 – 1-7

An early return to oral nutrition should be pursued.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*].

Comments

More recent studies indicate that eating can have a positive effect on the course of mild acute pancreatitis in comparison with fasting. Resuming eating, which should begin as early as possible in the pain-free patient, can start with easily digestible food. In a multicentre cohort study on symptom relapse in acute pancreatitis, Lévy et al. were able to show that about 20 % of patients suffer recurrence upon resuming eating, and that the probability of recurrence depends on the extent of necrosis, i. e., the severity of the pancreatitis [199]. A meta-analysis, which includes all three of the studies published on this topic (274 patients), confirms this result [200]. The value of so-called pancreas diets or bland diet for pancreas patients is not only completely unproven – they are also hardy palatable for normal taste buds. A recently published randomised trial suggests not to prescribe complete fasting for mild acute pancreatitis [201]. This produced a reduction in the length of hospital stay and a more rapid reconvalescence. The work by Teich et al. confirms this therapeutic approach [202].

Statement 5 – 1-8

Enteral feeding should preferably be done via a nasogastric or nasojejunal tube in severe forms of pancreatitis.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

Studies were unable to show that nasojejunal tube feeding is superior to nasogastric tube feeding [193, 194, 201, 203, 204]. The two methods are therefore to be regarded as equally applicable, and the choice depends on local and patient-related circumstances. The superiority of enteral over parenteral nutrition has already been elucidated above.

Statement 5 – 1-9

Parenteral administration of immune-modulating supplements should not be performed.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*].

Comments

The significance of immunonutrition is currently unclear, although its cost is clearly higher. Studies have not been able to substantiate an unequivocal or favourable effect on the disease course [205 – 208].

Statement 5 – 1-10

Antibiotics should not be generally administered in a prophylactic manner.
[*Level of evidence grade 1a, recommendation grade B, strong consensus*].

Comments

A mild course of the disease does not require antibiotic prophylaxis. The attitude toward treating acute pancreatitis with antibiotics has changed several times over the past years. More recent studies have convincingly shown that a blanket approach to antibiotic prophylaxis does not offer any advantages and only contributes to the selection of resistant organisms. On the other hand, patients with proven infected pancreatic necrosis profit considerably from antibiotic treatment. The most recent meta-analysis of prophylactic antibiotic administration, which also includes the data of the most recent "Meropenem Study" by Dellinger et al. [209] and thus incorporates seven studies with a total of 467 patients in the analysis, found no change in the rate of infected necrosis [210]. Total mortality was also not significantly reduced in the antibiotic therapy group.
In the severe forms of the disease, numerous studies and meta-analyses were unable to substantiate a significant advantage of antibiotic prophylaxis as a matter of principle with regard to extrapancreatic infection, infected pancreatic necrosis and mortality. A significant advantage with regard to infected necrosis was demonstrated for the beta-lactam antibiotic imipenem, but not, however, with regard to mortality. All studies had methodologi-

cal weaknesses, the foremost of which was inadequate study power. Given the high mortality rate of the severe necrotising form of the disease, the administration of antibiotics which penetrate infected necrotic tissue in the pancreas (e. g. beta-lactams, chinolones, amongst others) is assumed to be beneficial in this subgroup due to their ability to reduce mortality [209 – 216].

Statement 5 – 1-11

Probiotics should not be given. They tend to have an unfavourable effect on the course of pancreatitis.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*].

Comments

Probiotics are living microorganisms said to have a number of positive effects on health. Olah and colleagues conducted two randomised controlled studies on the prophylaxis of infected necrosis in patients with acute pancreatitis. Both studies substantiated that the use of probiotics lowers the incidence of infectious complications [186, 217]. All the more surprising, therefore, were the results of the PROPATRIA study of the Dutch Pancreatitis Study Group. In a double-blind placebo-controlled study involving 298 patients with severe acute pancreatitis, the authors observed that the administration of a probiotic preparation (Ecologic 641: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococccus lactis, Bifidobacterium bifidum* and *Bifidobacterium lactis*) did not result in a significant reduction of infectious complications, but rather in a significant increase in mortality, caused predominantly by intestinal necrosis in the verum group [218, 219]. The administration of probiotics for the treatment of acute pancreatitis should therefore cease until further studies have clarified the reasons behind this finding [218, 220, 221].

Statement 5 – 1-12

Necrotic infection suspected on clinical and/or imaging grounds can be confirmed by fine needle aspiration.
[*Level of evidence grade 2b, recommendation grade D, strong consensus*]

Comments

Laboratory parameters alone, such as procalcitonin, cannot confirm necrotic infection. Physical examination, laboratory parameters and contrast-enhanced CT together can usually provide sufficient evidence for assuming infected necrosis and to initiate appropriate (mostly antibiotic) treatment. Confirmation by fine needle aspiration is possible, but usually not required and not overly sensitive [19, 173, 222].

Statement 5 – 1-13

All conservative options should initially be exhausted for the treatment of infected necrosis. When drainage or necrosetomy of infected necrosis is required Endoscopic/interventional therapy should be preferred to an open surgical procedure. If endoscopic/interventional or surgical procedures are employed, it should be as late as possible in the disease course.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*].

Comments

A surgical approach for acute necrotising pancreatitis is only indicated for confirmed infected necrosis and not for sterile necrosis. Over the last two decades, the therapeutic concept has changed from an aggressive surgical approach to conservative interventional management. Originally, the indication for necrosectomy was established once multiple organ failure had occurred. This approach was associated with a mortality of 65 %, which cast doubt on the benefit of the surgical approach in this situation. Even in the year 2003, the mortality rate of open necrosectomy was 47 % [223]. Open necrosectomy should therefore be avoided whenever possible because the surgical trauma induces a SIRS, which is difficult to contain [224]. A study by Mier et al. substantiates that a surgical approach within two weeks after onset of disease is associated with significantly higher mortality [225]. A combined conservative and interventional approach is at least equal to the surgical approach, even in the presence of infected necrosis [226]. Over the past few years, a number of studies have shown that minimally invasive therapeutic approaches such as percutaneous drainage or laparoscopically assisted necrosectomy provide very promising results [227, 228]. The minimally invasive "step-up approach" results in a significantly better clinical course, as shown in the PANTER study (combined endpoint: mortality and severe complications) [229]. Transgastric or transduodenal endoscopic necrosectomy can be regarded as a new and much less invasive therapeutic approach. To date, approximately 250 treatment cases have been reported in the literature. The indication was either confirmed infected necrosis or pancreatic abscess. The technical success rate in these highly selected patients was 92.1 %, with complications such as colonic fistula, haemorrhage, prosthesis dislocation, pain after more than 24 hours, perforation or gravitation abscess being reported in 19.6 % of cases. Mortality in this patient group was 5.6 %, long-term treatment success was 81.2 % and the median number of interventions was 2.3 [230 – 233]. On the whole, this procedure is a very promising therapeutic approach given the correct indication and ideally 4 weeks after onset of disease [221, 226, 229, 234 – 241].

Chapter 6 – Indications for interventional or surgical treatment

▼

The band-like upper abdominal pain is the cardinal symptom of chronic pancreatitis, together with weight loss, steatorrhoea and diabetes mellitus. In the absence of causal therapeutic approaches, treatment is restricted to symptom control by means of enzyme replacement, pain therapy and optimal control of endocrine insufficiency. 30 % to 60 % of patients develop complications such as strictures of the common bile duct, inflammatory space-occupying lesions, pancreatic pseudocysts, or pancreatic ductal stones, which require interventional or surgical treatment. The following deals with the indications for treatment.

Statement 6 – 1-1

Interventional or surgical treatment should be undertaken for persistant severe pain requiring opiate analgesics.
[*Level of evidence grade 2b, recommendation grade B, consensus*]

Comments

The severe pain of chronic pancreatitis requiring opiate analgesics can be effectively treated by both endoscopic and surgical procedures *[level of evidence grade 2b/3b from several studies]* [242]. Surgical procedures (drainage) are superior to endoscopic procedures with regard to long-term pain reduction; they are, however, associated with higher mortality but lower morbidity. There are 25 studies with a *level of evidence grade 2b or 3a* available dealing with the treatment of pain from chronic pancreatitis by endoscopy, ESWL, thoracoscopic splanchnicectomy, surgical resection and draining procedures [242]. A direct comparison between surgery and endoscopy was carried out in only two studies with *level of evidence grade 1b* [243, 244]. Both studies demonstrated an advantage for the surgical procedure in the long term.

Statement 6 – 1-2

If a resectable pancreatic carcinoma is suspected, then surgery should be performed.
[*Level of evidence grade 2b, recommendation grade A, consensus*]

Comments

If a space-occupying lesion of the pancreas is present and suspected (resectable) pancreatic carcinoma cannot be excluded, surgical resection should then be performed. Explanatory statement: Without surgery, the life expectancy of patients with pancreatic carcinoma is less than one year; after successful resection the median five-year-survival rate is 20 – 25 % [*Level of evidence grade 1a*] [245, 246].

Statement 6 – 1-3

Exocrine pancreatic insufficiency as the only presenting symptom of chronic pancreatitis is not an indication for surgical or interventional treatment.
[*Strong consensus, clinical consensus point*]

Comments

Since exocrine pancreatic insufficiency is usually well treatable with drugs and there are no consistent studies available showing that exocrine pancreatic function is lastingly improved by endoscopic intervention or surgery, surgical or interventional procedures cannot be recommended for the treatment of exocrine pancreatic function.
Virtually no studies on endoscopy exist in this context. The final results of exocrine pancreatic function after a Beger, Kausch-Whipple or Frey procedure are very heterogeneous [247].

Statement 6 – 1-4

Endocrine pancreatic insufficiency as the only presenting symptom of chronic pancreatitis is no indication for surgical or interventional treatment of chronic pancreatitis.
[*Strong consensus, clinical consensus point*]

Comments

Occasional positive case series exist which demonstrate an improvement of the endocrine metabolic state after resection of a pancreatic carcinoma. Randomised studies showing a positive effect on the endocrine metabolic state after resection for chronic pancreatitis are not available [248]. There was strong consensus that the existing case series do not justify the recommendation for surgery solely to improve endocrine insufficiency. The recommendation was therefore ranked as a clinical consensus point despite the formal *level of evidence grade 4*.

Statement 6 – 1-5

Surgical or interventional treatment should be carried out for persistent clinical symptoms of gastric outlet obstruction or duodenal stenosis due to chronic pancreatitis.
[*Strong consensus, clinical consensus point*]

Comments

Gastric outlet obstruction or duodenal stenosis due to chronic pancreatitis should be corrected by interventional or surgical means [*strong recommendation, but only consensus of expert clinical opinion*]. Comparative studies are not available addressing whether resection surgery, bypass surgery or endoscopic insertion of self-expanding metal stents offer greater advantages [249] (see Surgical Treatment).

Statement 6 – 1-6

Symptomatic pseudocysts should be treated. The endoscopic or surgical treatment of a symptomatic pseudocyst should be carried out regardless of its size.
[*Level of evidence grade 2a, recommendation grade B, strong consensus*].

Comments

Endoscopy or surgery should be performed on pseudocysts which have resulted in complications such as gastric outlet obstruction, haemorrhage, pain, cholestasis or vascular stenosis. The surgical procedures to treat pseudocysts tend to have higher success rates, but have the disadvantage of a somewhat higher mortality rate than endoscopic pseudocyst drainage into the duodenum or stomach [*recommendation grade B*] [151].

Statement 6 – 1-7

In the presence of an inflammatory tumour of the head of pancreas, primary endoscopy and insertion of a stent into the bile duct should be performed for bile duct obstruction with duct dilatation. However, if symptoms or cholestasis persist after temporary endoscopic therapy, then surgical resection should be performed.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for bile duct obstruction due to chronic pancreatitis does not produce a long-term effect beyond one year [250].
A prospective study showed a much poorer long-term effect of insertion for distal bile duct obstruction when calcifications were present in chronic pancreatitis [251].

Chapter 7: Endoscopic and interventional management of chronic pancreatitis

The natural course of chronic pancreatitis shows that between 30 and 60 % of all patients ultimately require intervention. In at least 30 % of cases, conservative management, supplemented by endoscopic therapeutic interventions, appears to be sufficient. In 10 to 40 % of cases, stenosis of the common bile duct (CBD) developed, which required intervention. A further complication is the development of stenosis of the pancreatic duct. For the latter case, the indication for insertion of an endoprosthesis (stent) has to date not been adequately elucidated. No prospective controlled studies are available which demonstrate a positive effect of stent drainage of a dominant stenosis in the duct of Wirsung. Some studies found that the insertion of a prosthesis into the pancreatic duct can induce secondary changes due to the stent with subsequent fibrosis and stricture [252, 253]. Removal of the obstruction of the pancreatic duct is often effective for pain management in the shorter term, and success rates of between 37 and 94 % have been reported [254]. Metabolic side effects of stent therapy in the pancreatic duct have not yet been studied in the long term. Pancreatic pseudocysts develop as a frequent complication of acute or chronic pancreatitis. A further endoscopic/interventional procedure for treating chronic pancreatitis is extracorporeal shock wave lithotripsy (ESWL) for stones of the pancreatic duct. Before the introduction of ESWL in 1989, surgery was often the only option for removing pancreatic duct stones which could not be removed endoscopically. Several retrospective studies have addressed the question of the clinical benefit of ESWL for pancreatic duct stones (see Statement 7 – 2-5). Endoscopic and interventional treatment of pseudocysts is a procedure commonly used in clinical practice.

7 – 1: Treatment of pseudocysts in chronic pancreatitis

The decision on whom, when and by which procedure pancreatic pseudocysts should be treated has been very controversial in the past. Pancreatic pseudocysts develop as a frequent complication of acute or chronic pancreatitis. The prevalence of pancreatic pseudocysts in chronic pancreatitis lies between 20 and 40 % [255]. Pancreatic pseudocysts occur most often in patients with alcoholic chronic pancreatitis (70 – 78 %) [2]. The second most common cause is idiopathic chronic pancreatitis (6 – 16 %), followed by biliary pancreatitis (6 – 8 %) [256]. Within the first six weeks after an acute episode of pancreatitis, 40 % of the pseudocysts resolve spontaneously, while in 20 % of cases, complications such as infection, displacement of adjacent tissue or adjacent organs, rupture of the cyst or persistent pancreatitis render an intervention necessary. Spontaneous remission of pseudocysts after 12 weeks is very rare, and complications are observed in up to 2/3 of cases. The increase in size of pseudocysts to over 5 cm is associated with the development of complications. If pseudocyst formation becomes symptomatic, either surgery or percutaneous or endoscopic drainage can be performed. All of these procedures demonstrate comparable results regarding technical success and recurrence rate. Thus, endoscopic drainage should be performed, given its lower morbidity [151].

Statement 7 – 1-1

If a pancreatic pseudocyst causes complications, interventional or surgical treatment should be performed.
[*Level of evidence grade 2a, recommendation grade B, strong consensus*].

Comments

The literature available on interventional therapy of pancreatic pseudocysts as a form of pain management is very limited, as currently no single randomised study is available. Most of the data is based on retrospective case series [257 – 262]. Based on the poor data situation, there are three systematic reviews of the evidence at hand [151, 263, 264]. Compiled studies reported that pain relief was achieved in a large number of patients through surgical, endoscopic or percutaneous drainage techniques. Given that a high rate of pain relief was achieved in these retrospective series (about 80 %), all three systematic reviews came to the conclusion that, although conservative management of chronic pancreatitis also results in pain relief in a certain percentage of patients, percutaneous, endoscopic or surgical drainage is still a more effective form of pain management. It is not possible to derive a significant difference in the comparison of the three procedures from the published data. In summary, however, it may be assumed from what little data there is that pseudocyst drainage improves the pain of the patients. Appropriate randomised controlled studies are urgently needed. The literature currently available on the suitable therapeutic intervention for other complications caused by pancreatic pseudocysts is even more scant. If pancreatic pseudocysts result in obstruction of the bile duct or pancreatic duct, then the pseudocyst should be treated. If cholestasis does not improve after drainage of the pseudocyst alone, then stent placement into the bile duct or a resection procedure may be indicated. This is presented in the relevant sections on the treatment of obstruction of the CBD and pancreatic duct in patients with chronic pancreatitis (see Sections 7 – 2 and 7 – 3).
Further complications which make endoscopic or surgical treatment of the pseudocyst necessary include the following: compression of large abdominal vessels; clinically relevant gastric outlet obstruction or duodenal stenosis; infection of the pancreatic pseudocyst; pancreaticopleural fistula formation, abdominal distension, nausea and vomiting due to the pancreatic pseudocyst.
Endoscopic interventional therapy of a haemorrhagic pseudocyst is associated with a high risk of bleeding. It should therefore be treated surgically.

Statement 7 – 1-2

Initial therapy for symptomatic pancreatic pseudocysts can be endoscopic drainage of the pseudocyst, followed by surgery should the pseudocyst recur.
[*Level of evidence grade 3a, recommendation grade C, strong consensus*]

Statement 7 – 1-3

The choice between endoscopic and operative pseudocyst drainage should be made based on the location of the cyst and the type of additional pathomorphological changes.
[*Level of evidence grade 3b, recommendation grade A, strong consensus*]

Comments

Endoscopic procedures of draining a pancreatic pseudocyst are less prone to complications than surgical procedures. Not all pseudocysts are successfully and lastingly treatable by endoscopic pseudocyst drainage alone and therefore require surgery. Studies comparing the two procedures are not available. Efforts

should be made to establish an interdisciplinary therapeutic concept [151, 265].

Statement 7 – 1-4

Asymptomatic pancreatic pseudocysts which have reached the size of more than 5 cm in diameter and which do not resolve within six weeks can be treated.
[*Level of evidence grade 2a, recommendation grade C, majority approval*]

Comments

Pancreatic pseudocysts shown by imaging to be enclosed by a more than 5-mm wall of connective tissue are particularly suited for endoscopic or surgical drainage. In a multivariate analysis, Gouyon showed that a pseudocyst size < 4 cm is the only prognostically favourable factor for spontaneous involution [266]. Bradley et al. demonstrated that untreated cysts larger than 5 cm result in complications (rupture, infection, jaundice, or haemorrhage) in 41 % of cases [267].

Statement 7 – 1-5

Drainage of pseudocysts can be carried out by transgastric, transduodenal or transpapillary approaches. Percutaneous drainage is also possible, but is associated with the risk of external fistula formation and is more burdensome for the patient.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

The examiner should select the access route for endoscopic transmural drainage of pseudocysts which, upon endoscopic ultrasound assessment, appears to be the safest. This depends on the size, vessels in the vicinity and location of the pseudocyst. Comparative studies showing the superiority of one endoscopic access route over the other (either through the stomach or duodenal wall) are not available. Experience has shown that transcutaneous drainage carries the risk of persistent cutaneous fistula formation. Furthermore, an existing transcutaneous drain can adversely affect the patient's quality of life. Hence, if drainage of pseudocysts is indicated, endoscopic transmural drainage is preferred [151, 265].

Statement 7 – 1-6

Transmural drainage should be performed under endoscopic ultrasound guidance.
[*Level of evidence grade 3, recommendation grade B, strong consensus*].

Comments

Endoscopic ultrasound is a procedure which can best assess the nature of the pseudocyst its wall, content, location and relationship to adjacent blood vessels. Endoscopic transmural drainage should therefore be performed under endoscopic ultrasound guidance to reduce the rate of failed puncture attempts and complications [268]. A direct comparison of the complication rate for transmural needle drainage without ultrasound guidance is not available. However, a higher complication rate must be assumed. For this reason, the recommendation was upgraded to "B". The success rate for the 1126 published cases of patients with transmural drainage of a pancreatic pseudocyst is reported to be 79.2 %, with the more recent studies reporting success rates well over 85 %, which corresponds to surgical results. The mortality rate in larger series involving over 30 patients was 0.2 %. The recurrence rate is reported to be 7.6 % and the complication rate 12.8 % [151].

Statement 7 – 1-7

Diagnostic needle aspiration of the cyst may be performed for suspected infected cystic contents or for suspected neoplasm.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

If diagnostic needle aspiration of the cyst confirms an infection of the contents, then drainage of the pseudocyst is indicated. Surgical treatment should be carried out if malignancy is detected. Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between cystic malignancies and pseudocysts. In summary: If EUS-guided needle aspiration of a cyst reveals a CEA > 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 and 50 years of age, is located usually in the pancreatic tail and demonstrates mural nodules on imaging. The so-called eggshell pattern of calcification is typical. Prognosis after surgery is good, given non-invasive growth. If, however, invasive growth is confirmed, then average survival is 45 months. A malignant lesion may be assumed with a CEA value > 6000 ng/ml. Aspiration biopsy of an MCN differs only slightly from an intraductal papillary mucinous neoplasm (IPMN). IPMN is regarded as a precancerous lesion. Its malignant potential depends on 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 develops from this lesion within eight years. For lesions of the side branch duct, this occurs in 6 – 46 % [269]. Lesions less than 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 and 3 cm in size and exhibit no solid components should be followed up after six months. However, lesions which are larger than 3 cm or exhibit mural nodules or cytology with higher-grade dysplasia must be resected. IPMN can occur as multifocal lesions; in this case, they behave in a more aggressive manner [270]. Without a positive case history, a serous cystadenoma is diagnosed as pancreatitis in 30 % of cystic lesions and virtually never becomes malignant. In this case, aspiration of the cyst is negative for mucin, CEA and amylase. Cytology reveals glycogen-rich epithelium.

Statement 7 – 1-8

A surgical approach should be chosen for a suspected malignant cystic lesion.
[*Level of evidence grade 4, recommendation grade A, strong consensus*]

Comments

In 1 % of all CT scans of the abdomen, a cystic lesion of the pancreas is discovered as an incidental finding [271]. More than two-thirds of these lesions are dysontogenetic cysts or pancreatic pseudocysts. The prevalence of pancreatic pseudocysts in chronic pancreatitis lies between 20 and 40 %. Of the cystic lesions which are not pancreatic pseudocysts but genuine cystic neoplasms, 30 % are benign serous cystadenomas, 45 % of the resected lesions are mucinous-cystic neoplasms and 25 % intraductal papillary mucinous neoplasms. Solid pseudopapillary tumours or cystic acinic cell carcinoma are less frequently encountered. For classification of the differential diagnosis of cystic tumours in asymptomatic patients, the question of connection to the pancreatic duct (IPMN and pancreatic pseudocysts) and the size of the cystic lesion (indication for resection in the case of IPMN or therapeutic indication for pseudocyst) is essential. Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between premalignant cystic neoplasms, cystic malignancies and pseudocysts.

Surgery is always urgently indicated if malignancy or a precursor of a malignant lesion is suspected, given that a cure can be achieved with a five-year survival rate of 63 % after resection of a malignant cystic tumour [151, 272 – 274].

Statement 7 – 1-9

The pancreatic duct can be imaged before endoscopic or surgical drainage of the pseudocyst.
[*Level of evidence grade 3b, recommendation grade C, strong consensus*]

Comments

Whether an ERCP with the attempt of draining the pseudocyst via the papilla should be performed 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 pancreatic pseudocysts have a connection with the pancreatic ductal system [259]. Based on current information, an ERP can precede endoscopic transmural drainage in order to detect a connection with the duct or to exclude rupture of the pancreatic duct (8 % after acute necrotising pancreatitis). Transmural drainage with undetected rupture of the pancreatic duct or a connection of the pancreatic pseudocyst with an obstructed pancreatic duct is less promising with regard to long-term treatment outcome. On the other hand, the success rate of attempted transpapillary drainage lies at a maximum of 60 %. Such an attempt puts the patient at risk of an ERCP-induced pancreatitis, whereas direct transgastric or transduodenal cyst drainage is very effective and is associated with few complications [151, 265]. Peri-interventional antibiotic prophylaxis before ERCP is a requirement if pancreatic pseudocysts are suspected or if they are the indication for ERCP or ERP. Otherwise, the risk of retention of infected contrast medium rises if there is a communication with the pancreatic ductal system. Without antibiotic prophylaxis, the examination-related incidence of infected pseudocysts and pancreas abscesses after ERCP increases [275].

Statement 7 – 1-10

In patients with chronic pancreatitis associated with advanced pancreatic duct changes, especially pancreatolithiasis, any pseudocyst should be treated as part of the overall therapeutic concept.
[*Level of evidence grade 2b, recommendation grade B, consensus*]

Comments

A relative indication to treat pancreatic cysts is the presence of chronic pancreatitis with pancreatic duct anomalies or pancreatic ductal stones, because in such cases, the rate of spontaneous involutions, even for small cysts, is only a maximum of 10 – 26 % due to the constant inflammatory irritation [151, 265].

Statement 7 – 1-11

Treatment of pancreatic duct obstruction can be undertaken in patients with a pancreatic pseudocyst, prestenotic duct dilatation or fistula formation.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

Pancreatic pseudocysts are maintained by pancreatic duct obstruction in the presence of prestenotic duct dilatations or fistulae, if these stenoses block drainage. In these cases, treatment of pancreatic duct obstruction is therefore recommended.

Statement 7 – 1-12

Vascular pseudoaneurysms secondary to chronic pancreatitis should be treated.
[*Strong consensus, clinical consensus point*]

Comments

There are no comparative studies available which compare active treatment of vascular pseudoaneurysms with mere watchful waiting. Nor are there studies examining the best moment for treatment of vascular pseudoaneurysms at different points in time.

Surgical or radiological interventional treatment of pseudoaneurysms is in accordance with current clinical practice.

Statement 7 – 1-13

Angiographic embolisation is the method of first choice for haemorrhagic pseudoaneurysms.
[*Level of evidence grade 3a, recommendation grade B, strong consensus*]

Comments

A systematic review of case series and case reports exist on this topic [276]. In this study, the success rate of angiographic treatment was 66 %. The complication rate is less than that for surgical treatment and is associated with a shorter hospital stay. The operation should be restricted to patients in good general condition, in whom an operation is also indicated for other complications of chronic pancreatitis.

7 – 2: Treatment of pancreatic duct alterations and pancreatic ductal stones in patients with chronic pancreatitis

In patients with chronic pancreatitis, the pressure in the pancreatic duct is initially increased, regardless of aetiology and dilatation of the duct of Wirsung [277]. An important role in the pathogenesis of pain is ascribed to ductal and interstitial hypertension and possible relative pancreatic ischaemia. The aim of endoscopic and surgical decompression therapy in patients with chronic pancreatitis and pain and/or clinical episodes of acute pancreatitis is to remove the obstruction to the flow of exocrine pancreatic juice. Techniques such as sphincterotomy, dilatation, ESWL and stent insertion have been modified for the pancreatic duct. The endoscopic procedure can precede the surgical procedure. It is an alternative to surgery and is associated with low morbidity and low mortality. Endoscopic interventions do not impair surgery that might be necessary at a later date. Furthermore, clinical success after endoscopic reduction of the intraductal pressure does provide some indication of the later result of surgical drainage or a resection procedure.

Statement 7 – 2-1

Pancreatic ductal stones which cause pain by obstructing the flow of pancreatic juice, induce recurrent episodes of pancreatitis, maintain a pseudocyst or fistula or cause other complications can be treated by endoscopic or surgical means.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

Pancreatic ductal stones are the result and not the cause of chronic pancreatitis or pancreatic duct obstruction. They can, however, lead to a consecutive obstruction of the flow of pancreatic juicefrom the duct and thus maintain pseudocysts or fistulae. They can also cause recurrent episodes of inclammation or contribute to the pain of patients with chronic pancreatitis if the flow of pancreatic juice is obstructed. Under these conditions, treatment of pancreatic ductal stones appears appropriate. There are, however, no studies available which have compared the treatment of pancreatic ductal stones with a sham intervention.

Case series and one meta-analysis are available which show an alleviation of pain after treatment of pancreatic ductal stones; comparative studies involving the spontaneous course or randomised studies, however, do not exist.

Endoscopic treatment appears particularly suited for treating solitary stones and proximal obstructions, but surgical drainage procedures have been shown to be superior for distal obstructions.

The literature contains no comparative studies on endoscopic or surgical procedures vs untreated cohorts or in direct comparison with the natural progression of the disease. In two studies in which endoscopic treatment was compared with surgical operations (drainage), surgical treatment was significantly better with respect to long-term pain reduction [243, 244].

Statement 7 – 2-2

Pancreatic duct obstructions which cause pain by imparing the flow of pancreatic juices, induce recurrent episodes of pancreatitis, maintain a pseudocyst or fistula or cause other complications can be treated by endoscopic dilatation and stent placement.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

If there is an indication for treatment according to the conditions named under 7-2-1, endoscopic management using dilatation and placement of a stent can be performed. The literature contains no studies involving dilatation of pancreatic duct obstruction in comparison with a sham intervention. In a prospective non-randomised study, rapid improvement of symptoms was achieved by insertion of a pancreatic stent in inoperable patients, although further interventions were frequently necessary [278]. Some studies substantiate that the insertion of a prosthesis into the pancreatic duct can induce secondary alterations due to the stent with subsequent fibrosis and stricture [252, 253]. Removal of the obstruction of the pancreatic duct is effective for the treatment of pain in the short term. Success rates between 37 % and 94 % have been reported. In the largest hitherto examined cohort of 1021 patients, a long-term reduction of pancreas-related pain was achieved in 84 % of cases [279]. However, in 79 % of the patients, stent therapy for pain management had to be repeated within one year and in 97 % of the patients within two years. Metabolic side-effects have not been examined over the long term.

Statement 7 – 2-3

A stent may be endoscopically placed into the pancreatic duct if pancreatic ductal stones or stenosis of the pancreatic duct near the papilla obstruct flow. No general recommendations can be made about the necessary duration of stent therapy.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].

Comments

Benign strictures of the duct of Wirsung can develop as a complication of an impacted stone or as a result of acute inflammatory parenchymal changes with compression or stricture of the duct of Wirsung [280]. The success rate of stent insertion was examined taking the rise in pressure due to the stone into consideration as a cause of pain development and recurrent episodes of chronic pancreatitis [280 – 289]. Pancreatic stent placement was technically successful in 308 of 328 patients, and in 66 %, an improvement of symptoms after stent management of a dominant obstruction was reported at follow-up (follow-up observation period: 8 – 39 months). On the whole, those patients profited in whom stones or obstruction had maintained a pancreatic fistula or pseudocyst, or had induced an obstruction or episodes of pancreatitis. Endoscopic drainage with stone extraction and stent therapy is an effective measure to control pain in some patients with dilated duct of Wirsung [261]; it can delay the need for surgery or make it superfluous, and can also provide an indication of the potential effectiveness of a drainage operation [290]. Better pain management, however, was achieved by pancreaticojejunostomy in two randomised controlled studies [242 – 244]. Thus, endoscopic therapy reduced pain or provided complete pain relief in 32 % [244] and 65 % [243], respectively, whereas this was achieved in 75 % [244] and 86 % [243], respectively, by pancreaticojejunostomy. The different success rates of endoscopic therapy in the two studies are possibly due to the longer duration of the stent therapy adopted by Dite et al [243].

There are currently no reliable data available regarding the necessary duration of stent therapy [243, 244, 261]. Some authors recommend treatment over one year with an exchange of the stent at least every three months; however, there are no comparative data available on this.

Statement 7 – 2-4

In the prescence of contraindications against surgical treatment, a completely coated self-expanding metal stent can be inserted into the duct of Wirsung for pain control.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments
Individual case reports and small case series suggest that coated self-expanding metal stents may be inserted into the pancreatic duct to treat the pain of chronic pancreatitis. Their advantage over plastic stents lies in their longer period of patency. Long-term results of their benefit are lacking. It is advised not to use uncoated self-expanding metal stents in the pancreatic duct due to the rapid proliferation of duct epithelium as a reaction to the metal mesh [291, 292].

Statement 7 – 2-5

Individual pancreatic ductal stones, which cause pain by obstructing the flow of pancreatic juices, induce recurrent episodes of pancreatitis, maintain a pseudocyst or fistula or cause other complications, can be treated by ESWL.
There is increasing evidence that the subsequent endoscopic removal of the pancreatic ductal stones or their fragments is not decisive for the effectiveness of the procedure. The ESWL treatment of pain in patients with parenchymal calcifications has not been substantiated in any studies.
[*Level of evidence grade 2b, recommendation grade C, strong consensus*].

Comments
ESWL can be employed to remove obstructing stones. A meta-analysis demonstrated a significant effect on pain reduction, albeit with a strong heterogeneity of the results [293]. All the studies included in the meta-analysis were case series without untreated or sham-operated control groups.
In a cohort study [294], a better result was reported regarding the technical freedom from stones by using ESWL with subsequent endoscopic stone retrieval, in comparison with ESWL alone. Only one randomised controlled study has been published to date comparing ESWL of pancreatic ductal stones with and without subsequent ERP to remove fragments from the main pancreatic duct. In that study, the subsequent endoscopic stone extraction had no influence on pain relief after two years [295].
Both endoscopic treatment and ESWL alone enable good pain control in some patients [243, 244, 261, 296, 297].

7 – 3 Endoscopic treatment of bile duct obstruction in patients with chronic pancreatitis

In 10 to 44.6 % of cases, obstruction of the common bile duct (CBD) requiring intervention develops in patients with chronic pancreatitis. Indications for endoscopic intervention include significant cholestasis, episodes of cholangitis, prevention of secondary biliary cirrhosis, and differentiation of the cause of pain (obstruction of the CBD vs. chronic pancreatitis). Several studies have assessed the efficacy and cost efficiency of endoscopic drainage of the CBD. Because only 1/3 of the endoscopically treated patients profited long term, endoscopic therapy is only indicated as a transient approach until definitive surgery, as an acute intervention in septic patients, or in inoperable patients or those unwilling to undergo surgery. In principle, there is a risk of developing cholangitis after endoscopic stent placement. The administration of prophylactic long-term antibiotics together with ursodeoxycholic acid to prolong stent patency has not been proven effective in various clinical studies [298 – 302]. The commonly occurring complications include stent occlusion by cellular detritus, microcolonies of bacteria, or extracellular, fibrillar material [303].

Statement 7 – 3-1

If chronic pancreatitis produces distal bile duct obstruction together with clinical signs of cholangitis, then endoscopic drainage of the obstruction should quickly be performed.
[*Strong consensus, clinical consensus point*]

Comments
Published studies in which endoscopic therapy of cholangitis resulting from mechanical cholestasis is compared with expectant observation are lacking. Treatment of mechanical cholestasis as part of the therapy for cholangitis is important and well substantiated by clinical experience.

Statement 7 – 3-2

If chronic pancreatitis causes distal obstruction of the bile duct with cholestasis or jaundice, then surgical treatment or endoscopic stent therapy should be performed. If calcifications are present in the pancreas, then surgical treatment should be preferred.
[*Level of evidence grade 4, recommendation grade B, consensus*]

Comments
There are no published studies available comparing active treatment of mechanical cholestasis in the context of chronic pancreatitis with expectant observation. The recommendation grade was classified as “grade B” because treatment of mechanical cholestasis appears to be substantiated by clinical experience.
Cholestasis in patients with chronic pancreatitis may be remedied by endoscopic or surgical means, although endoscopic stent therapy is of lasting success for more than 12 months in only one-third of patients. A prospective study showed an even poorer long-term effect of stent management of distal bile duct obstruction in patients with calcifying pancreatitis (long-term effect 9 %) [251]. In these cases, therefore, surgical treatment is clearly preferred. A retrospective analysis of all treated patients observed for an average of 45 months demonstrated that stent therapy for obstruction of the CBD in patients with chronic pancreatitis has no additional effect beyond one year [250]. Surgical treatment should therefore be planned if CBD obstruction reoccurs after one year of stent therapy.

Statement 7 – 3-3

Treatment involving the insertion of several stents simultaneously for distal bile duct obstruction can be recommended.
[*Level of evidence grade 3b, recommendation grade C, strong consensus*]

Comments

The placement of multiple plastic stents into the bile duct to treat bile duct obstruction in patients with chronic pancreatitis is superior to both insertion of solitary plastic stents and that of uncoated metal mesh stents. In a prospective, non-randomised monocentric study, the long-term success rate after insertion of 4 to 5 stents into the CBD was higher than after one single stent [304].

Statement 7 – 3-4

Coated metallic stents can be inserted in cases of distal bile duct obstruction.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].

Comments

The insertion of coated metallic stents has demonstrated good results in case series. Randomised studies comparing coated metallic stents with single or multiple plastic stents are still lacking [305, 306].

Statement 7 – 3-5

Treatment for distal common bile duct obstruction in patients with chronic pancreatitis involving endoscopically inserted stents should not be conducted longer than 12 months. Stents should be changed every three months at the latest.
[l*Level of evidence grade 4, recommendation grade B*]

Comments

The insertion of stents into the bile duct is suitable for treating obstruction of the bile duct in patients with chronic pancreatitis and extrahepatic cholestasis. Long-term success, defined as no further need to change the stent every three months without recurrence of cholestasis, is only achieved in about one-third of patients [289, 307 – 310]. Stents should be exchanged at least every three months; otherwise, occlusion of the stent could cause cholangitis. The change interval is less critical with the insertion of multiple stents [311].

Statement 7 – 3-6

The management of chronic bile duct obstruction after an unsuccessful attempt at endoscopic treatment should be surgical.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*].

Comments

Resecting surgical procedures to treat bile duct obstruction in patients with chronic pancreatitis are effective and sustainably successful. The long-term results of the Beger, Büchler, Kausch-Whipple and Frey surgical procedures do not differ from each other with regard to quality of life, exocrine pancreatic insufficiency, endocrine pancreatic insufficiency, pain or recurrence rate [312 – 314].

Statement 7 – 3-7

If surgical treatment of cholestasis in patients with chronic pancreatitis is indicated, then preoperative endoscopic insertion of a stent into the bile duct should only be undertaken if 1. surgery cannot be done promptly or 2. cholangitis is present.
[*Level of evidence grade 2a, recommendation grade B, strong consensus*].

Comments

A multicentre prospective randomised study examined the effect of preoperative endoscopic stent insertion into the CBD for mechanical cholestasis resulting from chronic pancreatitis or carcinoma of the pancreatic head before pancreas resection. A study involving patients with a postoperative pancreatic tumour showed that preoperative drainage significantly increased the rate of complications [315]. Similar data are available from the Heidelberg working group, but have so far only been published as an abstract.

Statement 7 – 3-8

The shorter the statistical and individual life expectancy of a patient, the higher the comorbidity and the more difficult the foreseeable technical feasibility of an operation (e. g., marked collateral blood circulation with extant portal hypertension), all the more should endoscopic treatment of a bile duct obstruction due to chronic pancreatitis be preferred to pancreas resection surgery. The more important a lasting therapeutic result after one single operation is, the longer the statistical and individual life expectancy of a patient, the better her/his general condition, and the lower the expected morbidity and mortality of pancreas resection surgery, the more a surgical approach should be chosen.
[*Consensus, clinical consensus point*]

Chapter 8: Pain management

▼

Pain is the leading clinical symptom for 80 – 95 % of patients. Studies on the natural course of the disease show that the intensity of the pain often declines with duration of the disorder ("burn-out of pain") [40]. In the majority of cases, the reduction of pain intensity correlates with the development of calcifications and the loss of exocrine and endocrine function. In America, the annual cost caused by pain due to chronic pancreatitis amounts to 638 million dollars [316]. The cause of the pain is multifactorial. Pancreas-related causes of pain include inflammatory infiltrates of the parenchyma and nerve sheaths, especially of the sensory nerves. Obstructed flow of pancreatic juice by duct obstruction and stones can produce a rise in pressure. Nevertheless, drainage of the duct or reduction of secretion with the aid of drugs (somatostatin analogues) does not usually result in adequate pain reduction. Increased pancreatic parenchymal pressure causes pain due to tension in the pancreas capsule, similar to the development of pancreatic pseudocysts. Extrapancreatic causes of pain include concomitant and secondary disorders, such as gastric or duodenal ulcers and meteorism, caused by abnormal bacterial colonisation of the intestine in maldigestion.

Statement 8 – 1-1

A validated pain score, such as that published by Bloechle et al. in 1995 or the visual analogue scale (VAS), should be used as a tool for quantifying pain in patients with chronic pancreatitis.
[*Level of evidence grade 1b, recommendation grade B, strong consensus*]

Comments

There are altogether only two studies [317, 318] available which present validation of a pain scale. The older study [317] assesses a pancreatitis-specific pain score. The following are rated on a scale of 0 – 100: frequency of the pain attacks (0 never, 100 daily), the intensity of the pain on the VAS (1 – 100), the analgesic (100 morphine, 1 acetylsalicyclic acid) and the pain-related absence from work (100: permanent, 0: not in the last year).
The more recent study [318] compares the SF-12 with the SF-36 Quality of Life Questionnaire. Both studies also include aspects of pain which have an effect on the quality of life. An explicit pain score, assessed independently of the quality of life data, is not included in the evaluation. Nevertheless, both the SF-12 and the SF-36 in this study have been assessed as valid, albeit only for the assessment of the quality of life. The pain score published in 1995 is therefore the only validated score explicitly for pain in patients with chronic pancreatitis. Its wider dissemination and above all its use in therapy studies should be pursued.

Statement 8 – 1-2

Pain management in patients with chronic pancreatitis can follow the WHO three-step analgesic ladder.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments

The literature contains four randomised controlled studies involving 10 to 40 patients. Unfortunately, the WHO pain management plan was not consistently used in any of these studies. Only the effectiveness of various morphine derivatives was examined. The question regarding the effectiveness of the WHO pain management plan cannot therefore be answered using available literature. Nevertheless, analgesics are clinically indicated to treat patients with pain from chronic pancreatitis in order to achieve pain relief or reduction of pain until definitive treatment (e. g., endoscopic or surgical).

Statement 8 – 1-3

The duration of a trial therapy for pain with the aid of drugs in patients with chronic pancreatitis can be decided on a case by case basis. If this alone does not yield the desired results, however, re-evaluation should be conducted regularly in order to augment the treatment with an endoscopic or surgical procedure if necessary.
[*Level of evidence grade 5, recommendation grade B, strong consensus*]

Comments

How long pain therapy can be performed using conservative means and when endoscopic or surgical treatment is indicated cannot be answered from the literature available today.

In general, the majority of authors regard obstruction of the duct of Wirsung as an indication for endoscopic or surgical intervention. However, a retrospective cohort study demonstrated good pain control after pancreaticojejunostomy even in patients without obstruction of the duct of Wirsung [319].

Statement 8 – 1-4

Weaning off pain medication can follow the WHO three-step analgesic ladder in reverse order.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments

Conservative pain management of chronic pancreatitis on the whole follows the WHO three-step analgesic ladder, although this was not specifically designed for patients with chronic pancreatitis.
The literature lacks studies showing how this analgesic plan might be de-escalated, for example, after an endoscopic intervention or surgery. It seems logical to follow the WHO three-step analgesic ladder in reverse order, re-assessing the patient's pain relief at each step. Superiority or inferiority to another graduated plan or to simply discontinuing the pain medication has not, however, been examined.

Statement 8 – 1-5

A validated pain score, such as that published by Bloechle et al. in 1995 or the visual analogue scale (VAS), should be used as a tool for monitoring the reproducible success of pain management in patients with chronic pancreatitis.
[*Level of evidence grade 1b, recommendation grade B, strong consensus*]

Comments

Assessing the success of pain therapy is determined by the reduction of pain during therapy. For this purpose, pain quantification is necessary. This has already been addressed in Statement 8 – 1-1. The pain score according to Bloechle et al. [317] is the best validated, precisely because it is able to demonstrate pain reduction achieved by successful therapy.

Statement 8 – 1-6

Octreotide should not be used to treat pain associated with chronic pancreatitis.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments

Since the pain in patients with chronic pancreatitis is also caused by increased pancreatic parenchymal and ductal pressure, the approach of reducing the amount of pancreatic juice and thus lowering the pressure is pathophysiologically coherent. Apart from numerous single case reports and retrospective case series, a double-blind crossover study [320] and an unblinded crossover study exist comparing octreotide with octreotide long-acting release (LAR) [321]. In both studies, pain was largely measured with the VAS. The double-blind crossover study comparing octreotide with saline administration [320] was unable to detect reduction in pain or analgesic requirement while effectively

blocking pancreatic secretion. The unblinded crossover study showed no difference between octreotide and octreotide LAR with regard to pain reduction.
In summary, it may be said that the only study comparing octreotide with saline administration was unable to show a significant reduction in pain, while at the same time a further study showed no advantage of octreotide LAR over octreotide. Thus, the value of octreotide in the treatment of pain associated with chronic pancreatitis remains unproven by studies.

Statement 8 – 1-7

Pancreatic enzymes should not be used to treat pain associated with chronic pancreatitis.
[*Level of evidence grade 1a, recommendation grade A, consensus*]

Comments

The rationale behind pancreatic enzyme therapy for pain relief is based on the assumption of a negative feedback mechanism for the release of the cholecystokinin releasing peptide. This in turn leads to a reduced release of cholecystokinin and so to reduced exocrine pancreas secretion. In a Systematic Review of the Cochrane Collaboration published in 2009, ten RCTs with a total of 361 patients were identified which examined the various aspects of the effectiveness of pancreatic enzyme supplements [322]. Six of the studies compared enteric encapsulated preparations with placebo, one compared an unencapsulated preparation with placebo, two examined different preparations, and one study examined different dosage regimens. The heterogeneity of the selected dependent variables and the lack of statistical parameters do not allow the data to be pooled. Three of five studies using a pain score showed a significant reduction in pain; two on the other hand did not. One of four studies which quantified analgesic usage reported a reduction in the consumption of analgesics. Not one single study examined long-term effects of the various types of treatment. The authors reach the conclusion that the use of pancreatic enzyme supplements had no proven positive effect on the symptom of pain or, due to an absence of data, improvement in the quality of life [322]. A randomised controlled study published since then (25 patients verum, 29 placebo) showed no significant effect on pain reduction [323].
Due to the different inclusion criteria, which are in part not clearly explained in the studies, it is not possible to deduce whether the cause of the pancreatitis, the presence of exocrine pancreatic insufficiency or a certain formulation of the preparations used was responsible for the lack of therapeutic success.

Statement 8 – 1-8

At the moment, antioxidants should not be used to treat pain associated with chronic pancreatitis.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

Oxidative stress is a possible factor in the development of chronic pancreatitis. Increased levels of free oxygen radicals have been detected in the serum and pancreatic juice of patients with chronic pancreatitis. Based on this knowledge, treatment using antioxidants could help to reduce cellular damage from pancreatitis and thus prevent pain. One initial study involving patients with recurrent acute and chronic pancreatitis demonstrated a significant improvement in the number of acute episodes as well as in chronic pain, but particularly the latter was only included in the per protocol analysis. In fact, only 20 of the initial 28 patients were assessed [324]. In a further study involving 36 patients, an improvement regarding pain as well as the quality of life was also demonstrated, but here too only 19 patients completed the study [325]. Evaluation of the study leaves important questions open, since a one-sided p-value was employed and the items of the SF-36 questionnaire used were evaluated individually without correcting for multiple testing. In a double-blind placebo-controlled study from India, 71 patients were treated with antioxidants and 56 with placebo over a period of six months. Over the study period, there was a significant reduction in the number of days with pain arising from the pancreas in the verum arm [326]. The study was discontinued before the recruitment target was reached and also demonstrated further methodological flaws. Evidence that antioxidants have a role in the treatment of pain from chronic pancreatitis is therefore still lacking.
Viewed altogether, antioxidants may possibly have a role in pain therapy of CP. However, since in all of the studies mentioned, preparations were used which contain beta-carotene– the administration of which is associated with the development of bronchial carcinoma in smokers when given in combination with retinol or alpha tocopherol, and taking into consideration that the majority of all patients with chronic pancreatitis also smoke – a general recommendation for treatment with antioxidants cannot be made at present [327, 328].

Statement 8 – 1-9

Electro-acupuncture and transcutaneous electrical nerve stimulation (TENS) should not be used to treat pain associated with chronic pancreatitis.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

Information regarding complementary or other new forms of treatment is often only available as case reports. Altogether, only three studies have been identified in which a sufficient number of patients were examined in a standardised manner.
In a randomised study, electro-acupuncture and transcutaneous electrical nerve stimulation (TENS) were each compared with placebo, demonstrating no effectiveness with regard to pain reduction or use of analgesics [329].

Statement 8 – 1-10

Montelukast should not be used to treat pain associated with chronic pancreatitis.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

A three-month treatment with the leukotriene receptor antagonist montelukast also showed no significant reduction in pain [330].

Statement 8 – 1-11

Radiotherapy cannot be recommended for the treatment of pain associated with chronic pancreatitis.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments

In a pilot study, significant reduction in pain and reduction of acute episodes were achieved with one session of radiotherapy in 12 of 15 patients [331]. Given the increased risk of developing a malignant tumour with chronic pancreatitis, its use appears fraught with risk and thus cannot be recommended.

Statement 8 – 1-12

Coeliac plexus block or thoracoscopic splanchnicectomy may be considered for treating pain associated with chronic pancreatitis.
[*Level of evidence grade 4, recommendation grade C, strong consensus*]

Comments

The literature contains no randomised controlled trials comparing coeliac plexus block with placebo. On the other hand, meta-analyses exist [332, 333] which examined the efficacy of coeliac plexus block in a large patient population and showed reduction in pain in about 50 % of patients. This pain reduction, however, did not last for more than a few weeks. If pain is the only principal symptom and no significant secondary complications of chronic pancreatitis are detected by imaging, thoracoscopic splanchnicectomy may be undertaken to control the pain. The concept of pancreatic denervation was mentioned for the first time in 1943 by Mallet-Guy. The procedure was rediscovered in 1993 and modified into a minimally invasive procedure by the introduction of video-assisted thoracoscopy. A prospective long-term study was able to demonstrate that adequate pain control was achieved with a perioperative morbidity of 7 % by bilateral splanchnicectomy in patients who respond well to epidural anaesthesia [334]. This study was not randomised and therefore has only a very low level of evidence grade.
A case-control study [335] showed that the results of splanchnicectomy after previous use of opioids are worse than in treatment-naive patients, although thoracoscopic splanchnicectomy showed significantly better results vs. control patients who received purely symptomatic treatment.
In conclusion, it may be said that coeliac plexus block for pain associated with chronic pancreatitis is only effective in the short term (a few months) and is clearly inferior to surgical management. Splanchnicectomy is, to a certain extent, a modification of coeliac plexus block, which can be performed by thoracoscopy. Although there is a paucity of data, it showed good results in individual cases. The indication for coeliac plexus block can only be pursued in patients who cannot be given reliable, effective, long-term pain control. This means that in patients who are in an inoperable state for pancreatic surgery or have an unfavourable prognosis due to their general condition, coeliac plexus block may be undertaken. Nevertheless, the coeliac plexus block is only effective for a few weeks to months.

Statement 8 – 1-13

If there are no contraindications, coeliac plexus block should be performed as a bilateral injection under endoscopic ultrasound guidance.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments

Randomised controlled studies are available comparing endoscopically guided with CT-guided plexus block indicating superiority of the endoscopic ultrasound guidance [336].
Studies also exist on the question of an endoscopic ultrasound-guided plexus block with one or two injections (no significant difference) [337], as well as the comparison of a coeliac plexus block vs. pancreaticogastrostomy (superiority of the surgical procedure) [338] and endoscopic ultrasound guidance vs fluoroscopy for coeliac plexus block (superiority of the endoscopic ultrasound guidance) [339]. Endoscopic ultrasound guidance appears to be better suited for coeliac plexus block than CT-guided plexus block, with 30 % of patients still profiting from it after 24 weeks as opposed to 12 % after CT-guided injection [336]. Whether one or two injections should be given appears irrelevant in terms of pain relief [337]. As the oldest technique for coeliac plexus block, fluoroscopy on the other hand is clearly inferior to endoscopic ultrasound guidance [339].
Furthermore, a cohort study examined the central single endoscopic ultrasound-assisted plexus block in comparison with the bilateral approach [340]. This showed that pain reduction after bilateral injection was better after seven days than after the central single injection (70 vs. 46 %). With more institutional experience with CT-guided coeliac plexus block, this may be regarded as an alternative technique.

Statement 8 – 1-14

As the most effective long-term form of pain therapy for chronic pancreatitis, surgery should be performed.
[*Level of evidence grade 1a, recommendation grade A, consensus*]

Comments

Two randomised controlled studies achieved better pain management by surgical treatment involving a pancreaticojejunostomy than by endoscopic treatment [243, 244, 341]. Thus, endoscopic therapy yielded pain reduction or complete pain relief in 32 % [244] and 65 % [243], respectively, whereas this was achieved by pancreaticojejunostomy in 75 % [244] and by resection in 86 % [243].

Chapter 9 – Enzyme replacement for chronic pancreatitis

▼

The indication for pancreatic enzyme replacement therapy is clinically given by the weight loss of more than 10 % of the body , weight, steatorrhoea with faecal fat excretion of more than 15 g/d, dyspeptic symptoms with severe meteorism or diarrhoea. The majority of enzyme supplements contain pancreatin, a pulverised extract from porcine pancreas, with the main components being lipase, amylase, trypsin and chymotrypsin. Pancreatin is not absorbed from the gastrointestinal tract, but is inactivated by enteric bacteria and digestive secretions, and eliminated in the faeces.

The option of a gastric-acid-protected administration as encapsulated microsphere formulations has clearly improved efficacy of pancreatic enzyme replacement. The measure of success of treatment is improvement of the disease symptoms.

Chapter 9 – 1: Enzyme replacement for chronic pancreatitis

Statement 9 – 1-1

Pancreatin should be supplemented in patients who present unequivocal steatorrhoea or in whom it is assumed (methods of detection: faecal fats > 15 g/day, if available, otherwise: pathological faecal fat excretion or pathological pancreatic function test in combination with clinical signs of malabsorption).
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Statement 9 – 1-2

Pancreatin should also be supplemented given even less pathological faecal fat excretion (7 – 15 g/day) if there are signs of malassimilation (e. g. weight loss) or the patient presents abdominal symptoms, which can be attributed to maldigestion and malabsorption.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments 9 -1- 1 and 9 -1- 2

The indication for pancreatic enzyme replacement is established for steatorrhoea with faecal fat excretion of more than 15 g/day. Since the quantitative measurement of faecal fats is often no longer performed, the indication for replacement is also present with a pathological pancreatic function test in combination with clinical signs of malabsorption [90, 342 – 344]. This includes weight loss and abdominal pain with dyspepsia, severe meteorism or diarrhoea. Conversely, pancreatin is also to be supplemented if faecal fat excretion is pathological (> 7 g/day) without reaching the critical value of 15 g/day, yet the above-mentioned clinical signs of malabsorption are present [90]. Therapy with pancreatin purely as a trial for 4 – 6 weeks may also be beneficial if symptoms are unclear.

Statement 9 – 1-3

During replacement therapy, reducing malabsorption by sufficient oral nutrition (all main food groups and vitamins) and, if necessary, effective treatment of the abdominal symptoms should be pursued. A complete normalisation of digestion and absorption of nutrients is usually not attainable.
[*Level of evidence grade 2b, recommendation grade A, strong consensus*]

Comments

Untreated severe exocrine pancreatic insufficiency results in a severe malabsorption syndrome, which in the long term is not compatible with life. Clinically, this manifests itself mainly in the form of steatorrhoea, deficiency of fat-soluble vitamins together with its sequelae, and weight loss, even to the extent of cachexia [85, 86, 92, 93, 345]. Malabsorption can also lead to abdominal complaints such as diarrhoea/steatorrhoea, abdominal distension/meteorism and pain.
Among other things, these may be due to intestinal motility disorders caused by maldigestion and malabsorption [343].

Statement 9 – 1-4

The success of pancreatin replacement therapy should be monitored primarily using clinical parameters (weight gain, long-term normalisation of the vitamin status, cessation of abdominal symptoms).
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Statement 9 – 1-5

If there is clinical doubt whether persistence of symptoms can be explained by inefficacy of enzyme replacement, then faecal fat excretion or pancreatic function tests to measure nutrient digestion during therapy (e. g., breath tests with ^{13}C-labelled lipids) should be used.
[*Level of evidence grade 2b, recommendation grade B, consensus*]

Comments 9 -1- 4 and 9 -1- 5

The disappearance of clinical signs of malabsorption is the most important criterion for the success of pancreatic enzyme therapy and is associated with an improvement of the quality of life [346]. If the symptoms do not, or only partially, respond, this may also be due to other pathomechanisms. 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 pancreatin therapy [347 – 349]. 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 are measured. Faecal chymotrypsin excretion does not provide any information about the effect enzyme replacement therapy has on nutrient digestion and nutrient absorption; it can, however, be used to test for compliance (low values correspond to inconsistent intake).

Statement 9 – 1-6

Pancreatin should be taken with meals.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments

The effectiveness of pancreatic enzyme supplements presupposes the mixing of pancreatin and chyme. If more than one capsule/tablet per meal must be taken, it may be beneficial to take one part of the dose immediately at the beginning of and the rest distributed during the meal [86, 350].

Statement 9 – 1-7

Preparations with acid protection should be used in patients with preserved gastric acid secretion owing to the acid instability of pancreatic enzymes.
[*Level of evidence grade 2b, recommendation grade A, strong consensus*]

Comments
Lipase activity in particular is irreversibly destroyed at pH values below 4 [351]. Such low values are present in the stomach during most of the postprandial period and, in patients with exocrine insufficiency, also in the duodenum due to limited bicarbonate secretion [86]. Without concomitant acid suppression, preparations with acid protection lower faecal fat excretion more than those without [352].

Statement 9 – 1-8

Because the mixing of chyme and pancreatin is required for optimal effectiveness, preparations should be chosen which consist of acid-protected particles with a diameter of ≤ 2 mm.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments
This critical value is in principle only relevant for patients with a preserved pylorus [353]. However, small particle sizes can facilitate and/or accelerate gastric emptying and/or release of enzymes, even after distal gastric resection.

Statement 9 – 1-9

The administered pancreatin dose should contain adequate enzymatic activity for the digestion of one meal.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*].

Statement 9 – 1-10

The dosage of pancreatin preparations is based on lipase activity. 20 000 to 40 000 units (Ph. Eur.) per main meal should be administered as an initial dose; approx. 10 000 (to 20 000) lipase units for the digestion of smaller between-meal snacks.
[*Level of evidence grade 1b, recommendation grade B, strong consensus*]

Statement 9 – 1-11

The enzyme dose should be doubled, if necessary tripled, if the effect is inadequate.
[*Strong consensus, clinical consensus point*]

Statement 9 – 1-12

Pancreatin powder or granulate should be combined with an acid inhibitor if the effect is still inadequate.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Statement 9 – 1-13

If this does not result in the desired treatment outcome, another cause of the persistent symptoms should be investigated.
[*Strong consensus, clinical consensus point*]

Comments 9 – 1-9 to 9–1-13
The clinical efficacy of pancreatin preparations is determined by the administered dose, the time of intake, acid protection and size of the pancreatin particles, specific biochemical properties of the preparation (which depend on its origin), as well as past and concomitant disorders of the patient to be treated. The latter refers to, for example, postoperative conditions with alterations of the gastrointestinal anatomy (e. g., after gastric resection) as well as complementary therapy with certain medications (e. g., treatment with proton pump inhibitors in patients taking nonsteroidal antirheumatic agents) [323, 342, 348, 350, 352 – 359]. The recommended initial dose is about 5 – 10 % of the cumulatively secreted lipase activity into the duodenum after a normal meal [360] and should therefore suffice to prevent malabsorption and steatorrhoea [85]. Clinical experience shows, however, that a doubling or tripling of this dose is necessary and helpful in some patients. If secretion of gastric acid is suppressed, then unprotected pancreatin can be administered. This is often particularly beneficial because it immediately takes effect once the protective coating has dissolved.
Patients with chronic pancreatitis frequently have an abnormal bacterial colonisation [361]. This may be considered a possible cause of persistent symptoms and other disturbances, if the above-mentioned measures are not successful.

Statement 9 – 1-14

Almost all pancreatic enzyme supplements available in Germany contain porcine pancreatin. These medications may also be taken by patients who otherwise refuse porcine products (for religious or ethical reasons).
[*Strong consensus, clinical consensus point*]

Comments
Pancreatic enzyme products from cattle are a theoretical alternative, but in practice this is irrelevant due to their low lipase activity. Preparations with fungal (Rhizopus oryzae, Aspergillus oryzae) enzymes have less favourable biochemical properties (higher acid stability, but rapid deactivation in the presence of low bile acid concentrations) and are therefore of only limited clinical applicability. Bacterial enzymes and human lipase produced using gene technology are not yet relevant in the treatment of exocrine pancreatic insufficiency. Even in religions which reject the consumption of pork, the use of porcine pancreatic enzymes is permitted as a medical therapy (e. g., Koran, Sura 5, Verse 1). The patient should, however, be made aware of the origin of the preparations.

Statement 9 – 1-15

When administering pancreatic enzyme supplements, attention should be paid to abdominal symptoms (in < 10 % abdominal pain, bowel movement changes, nausea/vomiting) and allergic reactions (in < 1 % of patients) as possible adverse reactions.
[*Level of evidence grade 3b, recommendation grade B, strong consensus*]

Statement 9 – 1-16

Very high doses of enzymes (> 10 000 – 20 000 units of lipase per kg body weight per day) should be avoided if possible.
[*Strong consensus, clinical consensus point*]

Comments 9 – 1-15 and 9 – 1-16
Primarily one working group has reported the very rare (< 0.1‰) development of fibrosing colonopathy with the risk of ileus after the administration of extremely high doses of pancreatin in children with cystic fibrosis [362]. A causality has not been established and is considered improbable [363 – 366]. On the whole, such high doses are not necessary anyway in patients with exocrine pancreatic insufficiency based on chronic pancreatitis (see above). In particular, adjuvant acid suppression and/or treatment with alternative or additional means (if necessary) should be considered in the event of patients becoming refractory to the above standard doses.

Statement 9 – 1-17

In patients with diabetes mellitus and newly initiated or increased pancreatin therapy, blood glucose levels should be monitored more closely for a short time because the improved uptake of carbohydrates can result in hyperglycaemia.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments
Patients with chronic pancreatitis and associated diabetes mellitus may encounter more significant problems with controlling their blood sugar levels if pancreatin therapy is initiated or discontinued. This includes emergency situations requiring treatment: In a study by O'Keefe et al. symptomatic hypoglycaemia developed during placebo treatment and ketoacidosis after recommencing pancreatin therapy [367].

Chapter 9 – 2: Nutrition for patients with chronic pancreatitis

Statement 9 – 2-1

Malnutrition in patients with chronic pancreatitis may not only be the result of exocrine pancreatic insufficiency, but also due to or complicated by reduced food intake due to pain or continued alcohol consumption. In addition, some of the patients have an increased basal metabolic rate.
[*Level of evidence grade 3b, strong consensus*]

Statement 9 – 2-2

Patients with chronic pancreatitis and clinically manifest exocrine pancreatic insufficiency (weight loss, malnutrition) should receive pancreatic enzyme replacement therapy, together with individually tailored medical nutritional intervention in order to prevent or stop any deterioration of the nutritional state in a targeted way.
[*Strong consensus, clinical consensus point*]

Statement 9 – 2-3

Medical nutritional intervention should try to provide an adequate supply of nutrients, vitamins and trace elements as wel as an individually tailored coverage of the daily energy requirement in order to avoid a catabolic state.
[*Level of evidence grade 5, recommendation grade A, strong consensus*]

Comments on 9 - 2-1 to 9 – 2-3
Malnutrition and underweight in patients with chronic pancreatitis are associated with increased mortality [368] and are therefore to be avoided as far as possible. For this purpose, patients with exocrine insufficiency usually require a combination of enzyme replacement therapy (see above) and adequate medical nutritional treatment. It should be noted that some of the patients have an increased basal metabolic rate [369]. Given the grave sequelae from malnutrition in patients with chronic pancreatitis, a recommendation grade A was given with strong consensus.

Statement 9 – 2-4

Fundamentally, patients with chronic pancreatitis and clinically manifest exocrine pancreatic insufficiency should be treated with a normal isocaloric diet and adequate pancreatic enzyme replacement. To improve the response, the nutrition intake should be distributed over 4 – 6 (appropriately smaller) meals.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments
A normal balanced, sufficiently isocaloric diet according to the patient's preferences is recommended; there is no established specific pancreas diet [90]. Provided it is well tolerated, adequate fat intake should be ensured. Data from animal studies indicate that diets with a high fat and protein content plus adequate enzyme replacement can improve the effectiveness of fat absorption [370].

Statement 9 – 2-5

A low fat diet cannot be (generally) recommended. Only if subjectively troublesome clinical symptoms of fat maldigestion occur with further progression of exocrine pancreatic insufficiency despite adequate oral enzyme replacement may the amount of fat eaten be reduced, depending on tolerability.
[*Level of evidence grade 5, recommendation grade C, strong consensus*]

Comments
Fat is important as a central source of energy for avoiding and treating catabolism. If fat consumption must to be reduced for reasons of intolerability despite adequate enzyme replacement therapy, it is necessary to ensure that the subsequent compensatory oral intake of other sources of energy (carbohydrates, proteins) is increased to maintain isocaloric nutrition.

Statement 9 – 2-6

Medium-chain triglycerides are absorbable without the effect of lipase and thus improve fat absorption in patients with exocrine insufficiency who are not receiving enzyme replacement therapy. They should not be recommended in conjunction with enzyme administration.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments
In conjunction with enzyme administration, medium-chain triglycerides appear to result in a further increase of fat absorption.

They should therefore not be recommended under these conditions [371].

Statement 9 – 2-7

Additional nutritional methods (oral, enteral or parenteral) may be necessary for patients with advanced exocrine pancreatic insufficiency.
[*Level of evidence grade 2b, recommendation grade C, strong consensus*]

Comments
Drinking supplementary liquid meals is required by about 10 – 15 % of all patients, enteral tube feeding is necessary in approximately 5 %, and parenteral nutrition in less than 1 % of cases [90]. They are not usually intended for the treatment of exocrine pancreatic insufficiency, but rather for patients with complications of the disease, namely gastric outlet obstruction or complex fistula systems. This is usually a temporary measure, e. g., before definitive surgical management.

Statement 9 – 2-8

As a rule, alcohol consumption should be avoided in chronic pancreatitis.
[*Level of evidence grade 2b, recommendation grade A, strong consensus*]

Comments
Alcohol consumption is an important pathogenetic factor for the progression of exocrine pancreatic insufficiency in patients with chronic pancreatitis [372]. As there are currently no data on whether in the presence of chronic pancreatitis the consumption of small amounts of alcohol (e. g., < 20 g/day) is damaging, it is appropriate to recommend general abstinence from alcohol.

Statement 9 – 2-9

A deficit of vitamins and trace elements should be specifically compensated.
[*Level of evidence grade 2b, recommendation grade A, consensus*]

Comments
Patients with chronic pancreatitis and exocrine pancreatic insufficiency take in less than the recommended daily allowance of vitamins and trace elements. Thus, deficiencies of the fat-soluble vitamins A, D, E and K as well as of calcium, magnesium, zinc, thiamine and folic acid often occur. A reduced intake has also been reported for riboflavin, choline, copper, manganese and sulphur. Although the ingestion of vitamin C and selenium was within the recommended daily values, it was less than in healthy controls [92, 93, 373].

Statement 9 – 2-10

The indication to replace vitamins and trace elements in adults should be based primarily on clinical symptoms of deficiency. Additional monitoring of serum levels is only required in individual cases.
[*Strong consensus, clinical consensus point*]

Comments
A routine control of these parameters in adults cannot be recommended due a lack of data.

Statement 9 – 2-11

In children, the indication for replacement should be given generously and already before the development of clinical deficiency symptoms.
[*Strong consensus, clinical consensus point*]

Comments
In children, subclinical deficiency states can develop and cause a failure to thrive over time.

Chapter 10 – Surgical procedures and their indications ▼

Surgery of chronic pancreatitis effectively treats intractable pain and/or local complications [244, 374]. Since endoscopic techniques can, in principle, also be used for these indications, an early interdisciplinary discussion is essential to determine the therapeutic concept best suited to the individual patient.
Above all, the long-term prospects of success of endoscopic therapy should be considered. The correct moment for surgery is difficult to determine and remains a contentious issue. Evidence is mounting, however, that timely surgical intervention can at least delay progressive pancreatic insufficiency.
Apart from the success rate, complications and in particular mortality of the therapeutic procedures should be included in the decision-making process. Historically, pancreatic surgery is associated with a high morbidity rate, but has made dramatic improvements in recent decades by advances in surgical techniques, perioperative management and the foundation of pancreas centres [374 – 378].

10.1: Surgical procedures and their indications

Statement 10 – 1-1

Surgery should be undertaken when malignancy is suspected in a patient with known pancreatitis.
Surgery should be undertaken after failed endoscopic or interventional therapy for on-going pain and/or local complications such as symptomatic obstruction of the pancreatic duct, bile duct or duodenum. Surgery can be undertaken for pseudocysts with concomitant ductal alterations.
[*Recommendation grade B, level of evidence grade 3, consensus*]

Comments
There is no therapeutic, potentially curative alternative to surgical resection for suspected malignancy. Whereas the median overall survival rate in the presence of pancreatic carcinoma is only 6 months, a five-year survival rate of over 20 % and a median survival rate of approx. 24 months can be achieved by surgical resection [246, 379].
Resection of the head of pancreas is also the most effective therapeutic option for treating pain associated with pancreatitis and local complications [374, 380]. The individual risk of surgery should be weighed against the therapeutic benefit in any given case.

Statement 10 – 1-2

The standard surgical procedure for chronic pancreatitis associated with inflammatory pseudotumour of the head of pancreas is pancreatic head resection. A variation of the duodenum-preserving pancreatic head resections (Beger, Frey, Bern, Hamburg procedures) or the Kausch-Whipple procedure (in the classical or pylorus-preserving variation) should be performed.
[*Level of evidence grade 1a, recommendation grade A, strong consensus*]

Comments

Pancreatic head resection is the most effective surgical procedure for an inflammatory mass of the pancreatic head and is superior to pure drainage surgery and endoscopic interventions. Duodenum-preserving pancreatic head resections (DPPHR) are superior to the Kausch-Whipple procedure in the short and medium term over a follow-up observation period of up to two years [377, 378, 381, 382]. The treatment efficacy of the three variations of duodenum-preserving pancreatic head resection is equivalent [383]. The surgical procedure according to the Bern modification is technically the least sophisticated. The long-term outcome after the Kausch-Whipple procedure and after duodenum-preserving pancreatic head resection is comparable. A randomised multicentre study, funded by the German Research Foundation (DFG), is currently recruiting [248, 384 – 394].

Statement 10 – 1-3

An intraoperative internal drainage of the CBD/bile duct is indicated for pre-operative cholestasis (imaging, laboratory results). It should be adopted for all procedures of DPPHR. A T-drain may be inserted.
[*Level of evidence grade 1c, recommendation grade B, strong consensus*]

Comments

Whereas in the classical and pylorus-preserving Kausch-Whipple procedure a biliodigestive anastomosis is always constructed to drain the bile duct, this is not performed routinely during DPPHR. By resecting the pancreatic head, the bile duct is freed of pancreatic tissue in all DPPHR variations (Beger, Frey, Bern, Hamburg); the bile duct is usually opened within the pancreatic head only in patients with preoperative cholestasis and reinserted into the resection cavity. This internal bile duct drainage may be performed in all modifications of DPPHR. A T-tube to divert bile in the postoperative phase until the anastomosis has healed can, but does not have to, be placed.
Conditions under which a deviation from the recommendation Statement 10 – 1-1 should/can be made:

Statement 10 – 1-4

A Kausch-Whipple procedure (classical or pylorus-preserving) should be performed if malignancy of the pancreatic head is suspected and a duodenum-preserving pancreatic head resection not chosen.
[*Level of evidence grade 1c, recommendation grade A, strong consensus*]

Statement 10 – 1-5

Frey's procedure or a drainage operation can be performed if there is no inflammatory mass of the pancreatic head but the pancreatic duct is obstructed.
[*Level of evidence grade 3, recommendation grade C, strong consensus*]

If congestion of the pancreatic duct is predominant, pure drainage procedures such as the lateral pancreaticojejunostomy (Partington-Rochelle procedure) or Frey's procedure with limited pancreatic head resection [395, 396] have good primary success rates. The results are indeed better than after endoscopic therapy [244], but demonstrate a poorer long-term outcome in comparison with pancreatic head resection procedures [374, 397]. Furthermore, these procedures only promise success given a very wide ductal system (> 7 mm) without inflammatory tumour of the pancreatic head. They are therefore an option in less than 10 % of cases [398].
The majority (> 85 %) of patients, however, present an inflammed, enlarged head of pancreas and a secondary obstruction of the pancreatic duct. These patients rarely experience improvement of their clinical symptoms from a drainage procedure, and so resection procedures are preferable.

Statement 10 – 1-6

In patients with portal hypertension and formation of venous collaterals, the various modifications of duodenum-preserving pancreatic head resection which do not require transection of the pancreas may be employed.
[*Recommendation grade C, level of evidence grade 4, strong consensus*]

Comments

Beger procedure: In the duodenum-preserving pancreatic head resection procedure by Beger et al. [399], the pancreas is transected above the portal vein and the inflammatory space-occupying lesion in the pancreatic head resected, leaving behind a 5- to 8-mm-wide parenchymal collar on the wall of the duodenum. In some cases, this may result in restoration of portal venous flow, which also applies to the Kausch-Whipple procedure, although this usually does not succeed due to the chronic blood flow obstruction. However, the work by Blöchle et al. has shown that in segmental non-occlusive portal hypertension caused by chronic pancreatitis, portal venous flow can indeed be restored by a decompressing removal of the obstruction [400].
Reconstruction is achieved with a Roux-en-Y diversion using a jejunal loop and end-to-side anastomosis to the pancreatic corpus and side-to-side anastomosis to the enucleated pancreatic head. The prerequisite for the long-term success of this technique is a pancreatic duct to the left which allows probe insertion without obstruction. If the bile duct obstruction is impassable, the bile duct may be opened and connected to the head of pancreas as an internal bile duct anastomosis.
Frey's procedure: In the USA, Beger's technically more complex duodenum-preserving pancreatic head resection did not establish itself. Frey et al. subsequently developed a modification, in which a circumscribed enucleation of the pancreatic head is combined with a longitudinal pancreaticojejunostomy, corresponding to the Partington-Rochelle drainage operation [401, 402]. This procedure seems appropriate in the presence of an inflam-

matory space-occupying lesion of limited size in the pancreatic head combined with ductal obstruction of the pancreatic duct. The Hamburg and Berne variations are technical simplifications of Beger's duodenum-preserving pancreatic head resection [388, 403].
In patients with portal venous thrombosis and cavernous transformation of the portal vein, procedures which do not transect the mesenterico-portal axis are preferred (Hamburg, Bern). The indication for surgery in this difficult patient population requires extensive interdisciplinary communication because fatality and mortality are significantly increased. Nevertheless, complete pain relief and return to work can also be achieved in this patient population [244, 313, 390, 392, 401, 403 – 411].

Statement 10 – 1-7

In patients with segmental inflammatory pancreatic changes (e.g., traumatic lesions of the pancreatic head), segmental pancreatic resection or, if necessary, even a left-sided pancreatic resection may be performed.
[*Level of evidence grade 4, recommendation grade C, strong consensus*].

Comments
Indications for segmental pancreatic resection include segmental inflammatory alterations located in the transition area between pancreatic corpus and head or in the pancreatic corpus. The main argument for segmental pancreatic resection to remove inflammatory alterations in the pancreatic corpus lies in the lower postoperative morbidity in comparison with partial pancreaticoduodenectomy and left-sided pancreatic resection, as shown in numerous publications [412]. Because considerably less viable pancreatic parenchyma is removed during segmental resection, the development of postoperative diabetes mellitus or exocrine pancreatic insufficiency is less frequent [413 – 419]. Only two fatalities have been reported amongst the more than 350 segmental pancreatic resections documented in the literature [420, 421]. The postoperative surgical morbidity of approx. 20 – 30 % is acceptable. Also, satisfaction and quality of life of the patients is very good at 97.4 %. If clinically indicated, segmental resection of the pathologically and morphologically identifiable finding can be performed [420 – 422].

Statement 10 – 1-8

A case of small-duct disease involving the entire gland can be treated surgically by V-shaped excision.
[*Level of evidence grade 3, recommendation grade C, consensus*]

Comments
Very rarely, cases of chronic pancreatitis are also seen in which the pancreatic duct is discovered not to be dilated, contrary to the high-pressure theory. These cases are defined as "small-duct disease". The frequency of this disease manifestation is very controversial. In recent years, an increasing number of patients have been diagnosed with autoimmune pancreatitis, which is characterised morphologically by an inflammation of the parenchyma without dilatation of the duct. Therefore, it is important today to differentially diagnostically exclude autoimmune pancreatitis in patients with small-duct disease.
Because surgical therapy of small-duct disease by pancreatic head resection or a pure duct drainage procedure did not produce satisfactory results [423, 424], the V-shape excision technique was developed for this clinical situation [388, 403]. In a prospective study, this technique achieved long-term pain relief, together with a significant improvement in the quality of life in more than 85 % of patients [403]. The low postoperative morbidity and mortality rates also show that this procedure can be safely performed in centres specialized in pancreatic surgery.

Statement 10 – 1-9

The modifications of duodenum-preserving pancreatic head resection which do not require transection of the pancreas may be regarded as procedures of choice in cases of portal hypertension resulting from obstruction of the portal vein / superior mesenteric vein.
[*Level of evidence grade 4, recommendation grade C, strong consensus*]

Comments
For further explanation, see Comments on Statement 10 – 1-6.

Statement 10 – 1-10

A Kausch-Whipple procedure or one of the various forms of DPPHR may be performed for obstruction of the superior mesenteric vein or portal vein.
[*Level of evidence grade 4, recommendation grade C, strong consensus*]

Comments
A Kausch-Whipple procedure or a Beger DPPHR procedure can achieve improvement of portal venous flow in cases of obstruction of the portal vein and superior mesenteric vein. Among other things, the success rate depends on the degree and duration of obstruction. The technical operability depends on the formation of collaterals and inflammatory adhesions [248].

Statement 10 – 1-11

Suspected malignancy which has developed during chronic pancreatitis often cannot be preoperatively excluded with a sufficient degree of certainty. Therefore, if pancreatic cancer is suspected, surgery should be performed.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments
A thorough pre-operative medical history should be obtained and any new symptoms such as weight loss, fever, or night sweats (B symptoms) noted. Tomographic imaging (CT or MRI) and the results of previous examinations should be at hand. Laboratory parameters should include baseline CA19 – 9 for postoperative follow-up reviews. Endoscopic ultrasound should be performed for its better local resolution.
Bearing in mind that the indication for surgery for suspected pancreatic carcinoma in chronic pancreatitis is absolute and the surgical technique is predetermined, preoperative diagnostics should not be prolonged. The Kausch-Whipple procedure or a pylorus-preserving pancreatic head resection is indicated [407 – 409].

Statement 10 – 1-12

A duodenum-preserving pancreatic head resection should not be performed for suspected pancreatic carcinoma, as dissemination of the tumour would occur from incision of the tumour during duodenum-preserving pancreatic head resection, thus precluding any potential cure.
[*Strong consensus, clinical consensus point*]

10.2. Treatment of postoperative complications

Pancreas surgery has progressed from high-risk operations, which in years past were often regarded as heroic interventions, to operations with a manageable perioperative risk [425, 426]. Mortality has also been clearly reduced in recent years at highly specialised centres. This is especially the case for surgery of chronic pancreatitis, because a fibrotic, hard pancreas is less vulnerable and reconstructions tend to heal better. A standardised surgical technique and improved perioperative management of the patients have contributed significantly to this.

Statement 10 – 2-1

In the majority of cases, pancreatic fistulae can be treated conservatively or interventionally. The choice of therapy depends on the clinical state of the patient.
[*Level of evidence grade 3, recommendation grade C, strong consensus*]

Comments

The critical operative steps during a pancreaticoduodenectomy and left-sided pancreatic resection are pancreatic anastomosis and pancreatic stump closure [385, 386]. The consensus definition for POPF (postoperative pancreatic fistula) of the International Study Group for Pancreatic Fistula (ISGPF) is oriented on the amylase concentration in the drainage fluid: POPF is defined as an amylase content in the drain output greater than three times the serum amylase level on or after the third postoperative day. Three grades – A to C – reflect the clinical impact on the patient after development of a POPF (**Table 5**). An initial validation and a multicentre study made a retrospective calculation that the prevalence of POPF as defined by the ISGPF is approximately 30 %, with Grade A fistula without clinical relevance being the predominant case [427 – 429]. Unlike fistulae after left-sided pancreatic resection which do not result in activation of pancreatic juice by the intestinal enzyme enterokinase, the pancreatic fistulae which develop in rare cases after pancreatic head resection in patients with chronic pancreatitis are potentially more dangerous. Diagnostic examinations for fistulae are performed by determining amylase and lipase levels via an intra-abdominal drain, CRP measurements, as well as ultrasound and tomographic imaging [430 – 433].

10.3: Follow-up after surgical management

Statement 10 – 3-1

Interventional or surgical therapy may be indicated with renewed cholestasis after surgery.
[*Level of evidence grade 3, recommendation grade C, strong consensus*]

Comments

CBD obstruction after a Kausch-Whipple procedure is defined as renewed cholestasis and is usually the result of a bile duct leak which has healed with scar formation. Whereas initially an endoscopic or interventional dilatation and/or stent therapy might be appropriate, revision surgery is necessary if the problem persists [434].

Statement 10 – 3-2

Persistent postoperative pain should be treated according to the WHO pain treatment ladder.
[*Level of evidence grade 2a, recommendation grade B, strong consensus*]

Comments

Postoperatively, pain is significantly reduced in approx. 90 % of all patients after pancreatic head resection. Just as for pre-operative pain, postoperatively persistent pain is treated with analgesics according to WHO pain plan. Cause of persistent pain can be unrelated to the pancreas following established chronification of the pain. However, recurrence of pain after initial pain relief can also develop as a result of a recurrence of the inflammatory pancreatic tumour and renewed pancreatic duct obstruction. In these cases, revision surgery is possibly indicated, involving renewed duodenum-preserving pancreatic head resection or Whipple's procedure [435, 436].

Statement 10 – 3-3

Residual pancreatectomy in patients with chronic pancreatitis can only be recommended in exceptional cases.
[*Level of evidence grade 3, recommendation grade C, strong consensus*]

Comments

Residual pancreatectomy is not indicated for persistent pain or completely atrophic or calcified pancreas [426, 437]. Residual pancreatectomy is only indicated as a last resort for postoperative septic complications after unsuccessful interventional therapy [438].

grade	clinical status, CT result	adjustment of management, intervention	hospital stay
A	good, no fluid accumulation	no, consider CT diagnostics	not prolonged
B	often good, peripancreatic fluid	yes, no invasive intervention	usually prolonged
C	critical, peripancreatic fluid	yes, percutaneous drainage or revision laparotomy	prolonged
definition	drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity.		

Table 5 ISGPF consensus definition of postoperative pancreatic fistulae (adapted from [430]).[1]

[1] ISGPF: International Study Group for Pancreatic Fistula.

Statement 10 – 3-4

Revision surgery may be undertaken if medication or endoscopic procedures to treat recurrence following primary surgery fail.
[*Level of evidence grade 3a, recommendation grade C, consensus*]

Comments
Revision operations are among the most difficult abdominal operations. If pain persists or recurrent cholestasis cannot be successfully treated by medication, interventional or endoscopic means, however, then the most promising therapy is resection surgery, as in the primary situation. Today, revision surgery is no longer associated with increased mortality, but should nevertheless be performed in experienced centres [279, 434].

Chapter 11 – Monitoring and follow-up of chronic pancreatitis

Statement 11 – 1-1

During chronic pancreatitis, treatable complications may develop, such as endocrine and exocrine insufficiency, acute episodes, the development of pseudocysts, cholestasis and an increased risk of pancreatic carcinoma. For this reason, monitoring/follow-up should be performed after establishing the diagnosis.
[*Consensus, clinical consensus point*]

Comments
Prospective studies which substantiate the benefits of follow-up reviews do not exist. Twenty years after diagnosis, mortality in patients with chronic pancreatitis is 38.4 % higher than in an age-adjusted control cohort [439].
The risk of developing pancreatic carcinoma is increased 16-fold in patients with chronic pancreatitis and by 25-fold in those who also smoke. As calculated in a recent meta-analysis, the relative risk of developing pancreatic carcinoma for chronic pancreatitis is 13.3 % (95 % CI 6.1 – 28.9 %) and 69 % for hereditary pancreatitis (95 % CI 56.4 – 84.4 %) [440]. The lifetime risk for developing pancreatic carcinoma in patients with chronic pancreatitis is a maximum of 5 % *[level of evidence grade 2b]* [439 – 442]. Clinical experience therefore calls for a yearly follow-up (clinical findings, transabdominal ultrasound, laboratory tests including HbA_{1c}).

Statement 11 – 1-2

The long-term complications of diabetes are responsible for the development of endocrine insufficiency in patients with poorly controlled metabolism. The risk of hypoglycaemia is increased in patients with pancreoprivic diabetes. This results in increased mortality. Glucose metabolism should therefore be monitored.
[*Level of evidence grade 3b, recommendation grade A, strong consensus*]

Comments
Eight years after diagnosing chronic pancreatitis, 50 % of patients suffer from diabetes mellitus requiring therapy. Episodic hypoglycaemia occurs in up to 79 % of patients and severe hypoglycaemia in up to 41 %. Mortality in patients with diabetes mellitus is significantly increased. Median survival is 8.7 years after establishing the diagnosis of pancreoprivic diabetes. Diagnosis and follow-up monitoring of diabetes mellitus should be performed according to the guidelines of the German Diabetes Society [http://www.uni-duesseldorf.de/AWMF/ll/ll_057.html] [443 – 449].

Statement 11 – 1-3

The development of exocrine insufficiency leads to malnutrition and secondary complications such as osteoporosis. Follow-up monitoring can be recommended.
[*Level of evidence grade 4, recommendation grade D, consensus*]

Comments
Exocrine pancreatic insufficiency results in cachexia and secondary complications such as vitamin deficiency and osteoporosis. Diagnostic tests and treatment for osteoporosis should therefore be carried out in patients with chronic pancreatitis according to the guidelines of the German Umbrella Association of Osteoporosis (DVO). Individually tailored nutritional intervention should be carried out to prevent deterioration of the nutritional state. Follow-up monitoring is indicated according to the guidelines of the German Society for Nutritional Medicine [89, 450, 451].

Statement 11 – 1-4

It may be beneficial to screen high-risk groups at regular intervals for the development of pancreatic carcinoma. The length of examination intervals has not yet been clarified. Proven examination algorithms are not available at the moment.
[*Level of evidence grade 3b, recommendation grade D, strong consensus*]

Statement 11 – 1-5

High-risk groups for secondary complications include carriers of PRSS1 mutation and smokers.
[*Level of evidence grade 3b, strong consensus*]

Comments
Carriers of PRSS1 mutations have a cumulative risk up to 49 % of developing a pancreatic carcinoma by age 75 in the presence of chronic pancreatitis. This risk is significantly higher than for all other known aetiologies of chronic pancreatitis. Rapid progression of the disease in patients who smoke is well substantiated, together with an associated increased risk for developing pancreatic carcinoma [2, 6, 7, 37 – 39, 41, 42, 45, 46, 48, 49, 80, 452 – 454].

Statement 11 – 1-6

Follow-up examinations of patients with chronic pancreatitis should be undertaken at intervals of 6 – 12 months, so that treatable complications can be recognised in time.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments
The moment of diagnosis does not correspond to the duration of the disease, and already eight years after diagnosis, 50 % of patients with chronic pancreatitis develop diabetes mellitus. Since complications such as exocrine or endocrine insufficiency are associated

with a considerable degree of morbidity and an increased mortality rate if untreated, follow-up examinations appear appropriate. The aim of follow-up monitoring includes diagnosis and treatment of exocrine or endocrine insufficiency, intervention for patients with cachexia or pain, as well as the treatment of local complications (gastric outlet obstruction, pseudoaneurysms, complicated pseudocysts). Follow-up examinations should not only be performed after developing warning signs (pain, diabetic metabolic state, weight loss, jaundice, vomiting, loss of appetite, recurrent episodes), as all relevant complications of chronic pancreatitis have usually already caused irreversible damage once warning signs appear [2, 6, 7, 37 – 39, 41, 42, 45, 46, 48, 49, 80, 89, 443 – 455].

Statement 11 – 1-7

Apart from clinical and laboratory examinations, follow-up examinations involving transabdominal ultrasound as a non-invasive but widely used technique can be recommended.
[*Level of evidence grade 2b, recommendation grade C, consensus*]

Comments

The sensitivity of diagnosing pancreatic disease with transabdominal ultrasound is 94 %; however, specificity is only 35 %. The sensitivity of the case history, physical examination and transabdominal ultrasound reaches 94 %. Specificity can be increased by subsequent examination techniques such as EUS, ERCP or CT, but not sensitivity. Transabdominal ultrasound therefore appears suitable as an initial examination. An additional imaging modality might be necessary to confirm the diagnosis [456].

Statement 11 – 1-8

Where there is reasonable suspicion of a complication of chronic pancreatitis or pancreatic carcinoma, further examinations should be conducted. These can include imaging using contrast-enhanced ultrasound, endoscopic ultrasound, contrast-enhanced CT, MRI/MRCP or ERCP.
[*Strong consensus, clinical consensus point*]

Comments

This is in line with clinical practice. The gold standard for detecting complications of chronic pancreatitis is contrast-enhanced CT. However, it must be pointed out that CT is not well suited for diagnosing early pancreatic cancer. In fact, none of the above-mentioned techniques can exclude operable cancer with reasonable certainty against the background of chronic pancreatitis. A combination of imaging techniques may be necessary if there is clinical suspicion. At the moment, at least, endoscopic ultrasound appears to be superior to the other imaging techniques, not least due to the option of taking a biopsy. See topic area "Imaging techniques in patients with chronic pancreatitis" (selection: [152, 157]).

Statement 11 – 1-9

Tumour markers should not be used for follow-up monitoring (Ca19.9, CEA or others).
[*Level of evidence grade 2a, recommendation grade B, strong consensus*]

Comments

Tumour markers are unsuitable as screening tests for pancreatic carcinoma, even in patients with chronic pancreatitis. Falsely high values must be expected in patients with cholestasis. To date, no cost-benefit analyses exist which substantiate the use of tumour markers in patients with chronic pancreatitis.
The diagnostic sensitivity and, above all, specificity of tumour markers for differentiating a space-occupying lesion in the pancreas are not adequate [457].

Statement 11 – 1-10

Further diagnostics should be carried out in the event of unexplained weight loss, new-onset diabetes mellitus, change in pain character, cholestasis without acute painful episode, and recurrent episodes of pancreatitis of unknown origin.
[*Level of evidence grade 4, recommendation grade B, strong consensus*]

Comments

All known complications of chronic pancreatitis are curable, reversible or at least amenable to treatment during the asymptomatic early stage. Thus, it must be the goal of the attending physician to make a diagnosis before warning signs develop. A consensus exists that, for the above-named reasons, diagnostic examinations should be performed. Controlled studies examining the value of early diagnosis of complications of chronic pancreatitis and early intervention are urgently needed. Patients with chronic alcoholic pancreatitis die more frequently of cancer of the hypopharynx, oesophagus or stomach. This should be borne in mind during follow-up monitoring [458, 459].

Statement 11 – 1-11

According to the guidelines of the German Diabetic Society (DDG), soon after pancreatic resection, a test should be carried out to exclude a latent or manifest diabetic metabolic state and thus avoid long-term consequences.
[*Level of evidence grade 3b, recommendation grade A, consensus*]

Comments

Up to 52 % of cases develop impaired glucose tolerance after resection of the pancreas. 22 % develop insulin-dependent diabetes mellitus. A postoperative follow-up is therefore indicated. For this reason, the classification is recommendation grade A [313, 382, 389, 390, 460].

Statement 11 – 1-12

Prophylactic total pancreatectomy in patients at high risk of pancreatic carcinoma (hereditary pancreatitis) should not be performed.
[*Level of evidence grade 4, recommendation grade B, strong consensus*]

Comments

No prospective studies on total pancreatectomy are available. A general recommendation for total pancreatectomy cannot be expressed due to high morbidity and considerable mortality. Median survival following total pancreatectomy in patients with benign disease is 8.2 years. The average 5-year survival rate was 50 % in a recently published Japanese cohort. Professor Büchler's

group reports an identical mortality over a follow-up observation period of 23.5 months in comparison with patients after Whipple's procedure for chronic pancreatitis. The decision for total pancreatectomy should always be reached by an interdisciplinary team. After-care in specialist centres should be arranged to reduce morbidity [461 – 464]. The guidelines group classified this recommendation as being of high clinical relevance. For this reason, the classification is recommendation grade B.

Chapter 12 – Diagnostics and treatment of chronic pancreatitis in childhood

Acute and acute recurrent pancreatitis in childhood is far more common than previously assumed and, depending on its cause, can lead to chronic pancreatitis. The most common causes are trauma, infections, systemic disorders, medications and structural bile duct lesions; a large proportion is idiopathic. During childhood, pancreatitis usually has a mild course and the prognosis is good. In a retrospective 10-year analysis (1991 – 2000) by the University Hospital Dresden, a total of 156 children were treated as in-patients for acute pancreatitis. That corresponds to 0.29 % of the total patient population. Only one child, a four-year-old girl, had severe haemorrhagic necrotising pancreatitis with a complicated, but not fatal, course. Another child with multiple recurrences was diagnosed with hereditary pancreatitis. All the other 154 children with mild acute pancreatitis made a full recovery. An analysis of literature data involving 589 children with acute pancreatitis and an average age of 9.2 ± 2.4 years (1 week–21 years) revealed the following causes of pancreatitis: idiopathic 23 %, trauma 22 %, structural anomalies 15 %, multiple system disorders 14 %, medications 12 %, infections 10 %, hereditary and metabolic disorders 2 % each [465]. There appear to be regional differences, however, in the frequency of the individual causes, as evident from an article from Japan published in 1994 [466]. In this analysis, 204 cases which had been published in the Japanese literature were compared with 304 cases published in Western countries. Almost half of the Japanese cases were due to a congenital abnormal biliary tract, while traumatic causes dominated in the children affected in the Western countries, alongside a large number of idiopathic cases.

Statement 12 – 1-1

Diagnostics and therapy of chronic pancreatitis in children and adolescents should be carried out under the direction of a paediatric gastroenterologist in cooperation with an experienced paediatric surgeon or visceral surgeon, paediatric radiologist and possibly an interventional endoscopist.
[*Consensus, clinical consensus point*]

12.2: Imaging in children with chronic pancreatitis

Statement 12 – 2-1

Transabdominal ultrasound should be employed as the primary imaging modality for chronic pancreatitis in childhood.
[*Strong consensus, clinical consensus point*]

Comments

Transabdominal ultrasound is the primary imaging technique for investigating chronic pancreatitis in children because the examination is simple to perform and does not involve radiation exposure. However, there are no comparative studies on the validity of ultrasound imaging in children. The benefit of ultrasound contrast agents in children has not been evaluated [467].

Statement 12 – 2-2

Endoscopic ultrasound can be performed during childhood.
[*Level of evidence grade 4, recommendation grade C, strong consensus*]

Comments

Endoscopic ultrasound is technically possible in children from about age 5 and is primarily performed for fine-needle aspiration or to investigate calcifications [468 – 470]. X-ray and CT of the abdomen should only be performed in exceptional cases to diagnose chronic pancreatitis in children.

Statement 12 – 2-3

MRCP should be employed in children as cross-sectional imaging technique of first choice to demonstrate biliary ducts and the pancreatic duct.
[*Strong consensus, clinical consensus point*]

Statement 12 – 2-4

The validity of MRCP can be improved by the administration of secretin.
[*Level of evidence grade 4, recommendation grade C, strong consensus*]

Comments

MRCP is the tomographic imaging technique of choice to demonstrate the bile ducts and the pancreatic duct in children because the examination is hardly invasive and does not involve radiation exposure. One study showed that the intravenous application of secretin resulted in a better demonstration of pancreatic side branches [467, 471]. In children < 6 years, it is usually only possible to perform MRCP under general anaesthesia.

Statement 12 – 2-5

In childhood, ERCP is primarily carried out for planned interventions.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments

ERCP is technically difficult to perform in children < 5 years of age and is exclusively employed for planned interventions [472]. Endoscopic ultrasound is only used for special indications in children and has a higher sensitivity than MRCP in the diagnostics of CP.

Statement 12 – 2-6

In the first year of life, the size of the pancreas proportionally increases the most. The size of the pancreas as measured by ultrasound does not allow reliable conclusions to be drawn on the presence of chronic pancreatitis in childhood.
[*Level of evidence grade 2b, recommendation grade B, strong consensus*]

Comments

In an older study involving 300 children and adolescents between the ages of 0 and 19 years, normal standard values for pancreatic size were determined by ultrasound. The pancreatic head has a diameter of 1.0 ± 0.4 to 2.0 ± 0.5 cm in the anterior-posterior plane (infant to young adulthood), the body of the pancreas a diameter of 0.6 ± 0.2 to 1.1 ± 0.3 cm, and the pancreatic tail a diameter of 1.0 ± 0.4 to 2.0 ± 0.4 cm. The main growth of the pancreas takes place in the first years and is subject to high variation. Determining the size of the pancreas, therefore, does not allow any conclusion to be drawn on the presence of chronic pancreatitis [473].

12.3: Summary of chronic pancreatitis in childhood

Statement 12 – 3-1

In childhood, apart from undertaking a genetic analysis of chronic pancreatitis, a number of underlying disorders must be excluded, especially cystic fibrosis, hypertriglyceridaemia and hypercalcaemia.
[*Level of evidence grade 4, recommendation grade B, consensus*]

Comments

Epidemiological data for chronic pancreatitis in childhood are sparse. There are, however, a number of case reports for the following causes, which must therefore be clarified in children and adolescents.

- Chronic inflammatory bowel diseases: Several case reports exist on this in childhood [474].
- Coeliac disease: Epidemiological data (Swedish register).
- No increased incidence in childhood, but in adult patients [475].
- Haemolytic-uraemic syndrome: common association with acute pancreatitis, rarely with chronic pancreatitis. Other autoimmune diseases: Case reports exist on lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis and chronic pancreatitis in childhood.
- Hypertriglyceridaemia: Case reports exist of patients with lipoprotein lipase deficiency and apolipoprotein CII deficiency and very high triglyceride levels. There does not appear to be an association between chronic pancreatitis and hypercholesterolaemia in childhood.
- Two percent of patients with cystic fibrosis present symptoms of chronic pancreatitis [55].
- Children with organoacidopathies can present as recurrent acute pancreatitis. Hypercalcaemia is also a risk factor for pancreatitis in childhood. There is no association with alpha-1 antitrypsin deficiency [476].
- Data available in the literature on parasitic infections and chronic pancreatitis in childhood are inconclusive.
- There is a proven association between medications and chronic pancreatitis for cytostatic agents, e. g., asparaginase or immune modulators (azathioprine) and valproate, although the data available for childhood is sparse [477, 478].
- A connection between abdominal trauma and chronic pancreatitis in childhood has not been proven. A precise statement cannot be made about the frequency distribution of the various aetiologies for chronic pancreatitis in childhood.

Statement 12 – 3-2

A sweat test should be performed to exclude cystic fibrosis as part of the aetiological elucidation of chronic pancreatitis in childhood.
[*Level of evidence grade 1c, recommendation grade A, strong consensus*]

Comments

Pancreatic-sufficient patients with cystic fibrosis often suffer from recurrent pancreatitis [55]. Furthermore, mutations on the CFTR alleles are commonly found in patients with so-called idiopathic chronic pancreatitis [479, 480].

12.4: Acute episodes of chronic pancreatitis in childhood

Statement 12 – 4-1

Nutrition for children during an acute episode of chronic pancreatitis can be administered in a manner analogous to nutrition in adult patients with chronic pancreatitis.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments

No controlled studies exist on nutrition during an acute episode of chronic pancreatitis in childhood. In principle, early enteral nutrition should be pursued, as for adults, in order to maintain the intestinal barrier function. Oral nutrition is possible in almost all cases due to the usually milder course in childhood. There are no studies available comparing oral nutrition with gastric or jejunal administration in childhood. Complete parenteral nutrition in children with chronic pancreatitis is indicated only in severe cases of an acute episode associated with vomiting and (sub-)ileus.

Statement 12 – 4-2

A general use of antibiotics in children with an acute episode of chronic pancreatitis cannot be recommended.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments

There are no studies on the controlled use of antibiotics during an acute episode of CP in childhood; treatment analogous to that of acute pancreatitis in adulthood, however, appears acceptable.

Statement 12 – 4-3

After exhausting conservative therapeutic measures (pharmacotherapy, interventional therapy), surgical therapy may be indicated in children with chronic pancreatitis, especially if chronic pain persists.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments
Using the literature available, it is not possible to answer the question regarding the indication for surgery of the pancreas in paediatric patients with chronic pancreatitis, timing of an operation or the choice of surgical technique.

12.5: Endoscopic, interventional and surgical treatment of chronic pancreatitis in childhood

Statement 12 – 5-1

It is not possible to provide an evidence-based recommendation on the interventional approach in children with chronic pancreatitis. Given the corresponding symptoms and obstruction or stones in the region of the pancreatic duct or the presence of biliary or duodenal obstruction, therapeutic intervention (stent insertion, sphincterotomy, duct dilatation, stone extraction) using ERCP is possible. Pertinent randomised studies on this are lacking for childhood.
Besides surgery, an interventional, i. e. internal, drainage after endoscopic ultrasound-guided puncture may be indicated for a symptomatic pancreatic pseudocyst.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments
There are individual retrospective case series [470, 472, 481] and one prospective case series [468], which not only describe the diagnostic use of ERCP and EUS, but also their application as interventional therapy in paediatric patients with chronic pancreatitis. Sphincterotomy, stent insertion, stone removal and balloon dilation have been described for ERCP, and the endoscopic ultrasound-guided internal drainage of symptomatic pancreatic pseudocyst for EUS.
This kind of interventional therapy in children demands appropriate staff and facilities and is usually performed under general anaesthesia.

Statement 12 – 5-2

It is not possible to provide an evidence-based recommendation on the surgical approach in children with chronic pancreatitis.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments
The literature does not provide any guidelines for the surgical approach for chronic pancreatitis in childhood. In principle, particular emphasis is placed on organ preservation of pancreas and spleen in children, but there is no evidence for this, given the extremely small number of patients.

Statement 12 – 5-3

No recommendation can be provided with regard to selecting a particular surgical procedure in children with chronic pancreatitis.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments
Given the extremely low number of surgical interventions for chronic pancreatitis in childhood, there are on the whole no valid results on the outcome of specific surgical procedures. In a retrospective study, data on 25 patients were collected over 34 years, in whom six different surgical procedures were employed. It therefore not possible to provide a statement on the validity of an individual surgical procedure in children [481].

12.6: Pain therapy of chronic pancreatitis in childhood

Statement 12 – 6-1

There is no specific pain management for chronic pancreatitis in childhood. Treatment may proceed in a similar manner to pain management in adults.
[*Level of evidence grade 5, recommendation grade D, strong consensus*]

Comments
Pain management in children follows the experience gained in adults. Studies on pain management in children are lacking. The general principles of pain management in children can also be applied to abdominal pain due to pancreatitis.

12.7: Enzyme replacement for chronic pancreatitis in childhood

Particularly in childhood, replacement therapy should be undertaken for exocrine insufficiency. Although secretion of all enzymes is affected in exocrine pancreatic insufficiency, it is fat maldigestion that plays the decisive pathophysiological role. The following mechanisms interact: earlier and greater reduction of lipase secretion in comparison with other enzymes; acid denaturation of lipase due to duodenal pH (bicarbonate deficiency!); associated fat malabsorption due to denaturation of bile acid by low intraduodenal pH levels; more rapid proteolytic breakdown of lipase; absence of effectively compensatory enzymatic systems. The digestion of protein and starch is not usually disturbed to a significant degree or is taken over by other enzymes of saliva, the stomach and the duodenal mucosal brush border. Flatulence is possible in certain cases.

Statement 12 – 7-1

Side effects can develop in children during oral pancreatic enzyme replacement therapy. If necessary, treatment can be changed to an alternative enzyme supplement.
[*Level of evidence grade 4, recommendation grade D, strong consensus*]

Comments
Allergic sensitisation, oral mucosal excoriation and fibrosing colonopathy may develop in children and adolescents during oral pancreatic enzyme replacement therapy.
Only individual case reports exist on this, however, from which no details regarding frequency may be inferred. Sensitisation as diagnosed in the skin-prick test is not observed more often in patients with cystic fibrosis than in healthy controls [482 – 484]. Fibrosing colonopathy or oral mucosal excoriation has so far only been reported in patients with cystic fibrosis.

Statement 12 – 7-2

In children and adolescents with chronic pancreatitis and insufficient physical development, inadequate pancreatic enzyme replacement should be diagnostically excluded.
[*Level of evidence grade 5, recommendation grade B, strong consensus*]

Comments

Frequent voluminous stools, fatty stools, increased flatulence, excessive appetite and reduced growth rate are indications of inadequate pancreatic enzyme replacement therapy and should therefore receive special attention during childhood and adolescence. The substitution of a pancreatic lipase preparation by a delayed-release formulation is effective and may be advantageous given poor compliance [484].

Statement 12 – 7-3

Children and adolescents who continue to show signs of severe maldigestion despite regular oral pancreatic enzyme replacement should receive a therapeutic trial with acid-suppressive proton pump inhibitors.
[*Level of evidence grade 1b, recommendation grade A, strong consensus*]

Comments

Various trials have shown that children and adolescents who have signs of maldigestion with steatorrhoea, despite regular replacement with non-encapsulated or microencapsulated pancreatic enzymes, thrive better under acid-suppressive therapy [359, 484, 485]. This English language version of the guidelines represents a translation of the original version in German [486].

Appendix: Participating authors (⊙ Table 6)

Table 6 Participating authors.

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