CHAPTER 84

Chronic pancreatitis

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Chapter menu

Introduction, 1702
Definition, 1702
Epidemiology, 1703
Etiology and risk factors, 1703
Pathogenesis, 1705
Clinical presentation and natural history including prognosis, 1705
Diagnosis, 1707
Differential diagnosis, 1713
Therapy and management of complications, 1713
Prevention and follow-up, 1729
Acknowledgment, 1730
Further reading, 1730

Introduction

To provide detailed knowledge on chronic pancreatitis, it seems reasonable to rely on the latest S3-consensus guidelines on definition, etiology, diagnosis, and management of this disease [1–3]. These guidelines were developed by the German Society of Digestive and Metabolic Diseases (DGVS) in cooperation with other societies. For most of the following statements, the level of scientific evidence will be provided as detailed in Box 84.1.

In 1761, Jean-Baptista Morgagni reported on the first autopsy case of chronic pancreatitis, but it took another 60 years before Kuntzmann made the connection between fatty stools (steatorrhea) and this disease of the pancreas. Even in the 21st century, the time lag between onset of symptoms and establishing the diagnosis of chronic pancreatitis remains disproportionately long. The reasons for this delay may be the absence of specific laboratory parameters and the nonspecific symptoms that often characterize the clinical picture. The first modern method of establishing the diagnosis of pancreatic disorders originated in 1929, when Elman introduced the measurement of serum amylase [4]. Following this discovery, Comfort and coworkers succeeded in describing the natural course of chronic pancreatitis, based on clinical observations, surgical procedures, and autopsy studies [5]. Henri Sarles from Marseille, France and Rudolf Ammann from Zurich, Switzerland reported an association with prolonged alcohol consumption, the frequent occurrence of the disease in the third and fourth decades of life, and typical complications such as loss of the exocrine and endocrine function of the pancreas [6–8].

Since the formulation of the first German consensus recommendations [9], our understanding of chronic pancreatitis, from its basic principles to its management, has improved considerably. Significant advances have been achieved in the clarification of pathogenetic mechanisms responsible for the disease. Furthermore, a larger number of validated epidemiological observations as well as prospective, therapeutic trials are available. This chapter will summarize, evaluate, and provide practical recommendations based on the current level of knowledge with respect to definition, etiology, diagnosis, and management of all forms of chronic pancreatitis in adults.

Definition

Chronic pancreatitis is a disease in which pancreatic parenchyma is replaced by fibrotic tissue as a result of recurring inflammation. Abdominal pain is the leading symptom in patients with chronic pancreatitis. Complications include the formation of pseudocysts, pancreatic duct stenosis, duodenal

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Box 84.1 Evidence levels.

1a	Systematic review of randomized controlled trials (RCT)
1b	One appropriately planned RCT
1c	All-or-none principle
2a	Systematic review of well designed cohort studies
2b	One well designed cohort study/RCT of mediocre quality (e.g., <80% follow-up)
2c	Outcome research studies
3a	Systematic review of well designed case–control studies
3b	One case–control study
4	Case series/cohort– and case–control studies of mediocre quality
5	Expert opinion without critical evaluation or opinion based on physiological models, laboratory research results or "first principles"

stenosis, vascular complications, compression of the distal bile duct, malnutrition, and a chronic pain syndrome. Chronic pancreatitis is also a risk factor for the development of pancreatic cancer. Chronic pancreatitis reduces both the overall quality of life and life expectancy.

Epidemiology

The incidence of chronic pancreatitis increases proportionally with alcohol consumption in the general population [10]. The incidence worldwide is reported to be between 1.6 and 23/100 000 with an increasing prevalence in countries with a high alcohol consumption [11]. Although most patients with chronic pancreatitis are treated as outpatients, in the year 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 acute pancreatitis due to an acute exacerbation of chronic pancreatitis (50 673 cases). These data substantiate the high socioeconomic burden of the disease.

Etiology and risk factors

Ethanol is a proven cause of chronic pancreatitis (evidence 3b). Patients with chronic pancreatitis who smoke should be urged to enroll in a nicotine abstinence program, because nicotine abuse accelerates the progression of the disease (evidence 3b). Retrospective case–control studies with sufficient case numbers are available, which suggest a causal relationship between alcohol abuse and chronic pancreatitis [6,7,12–18]. In a study from Marseille in 1978, a logarithmic relationship between the relative risk of developing pancreatitis and the quantity of consumed alcohol and protein has been demonstrated [19]. 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. However, it is not possible to specify a threshold value. The type of consumed alcohol has no influence on the increased risk. The time between the start of excessive alcohol consumption and the development of pancreatitis is around 18 ± 11 years. The prevalence of chronic pancreatitis correlates with the amount of alcohol consumed in the society [8,20].

Smoking accelerates disease progression. However, at present smoking cannot be regarded for certain as a sole initiating cause of the development of the disorder. Large cohort studies involving up to 695 patients show that smoking leads to exacerbation of pancreatic pain and to calcifications [8,16–18,20–25]. Even with abstinence of alcohol, continued smoking results in a more rapid progression of chronic pancreatitis [22]. Yadav et al. showed that patients without a history of alcohol but with 21–35 pack years of smoking have an increased risk of chronic pancreatitis ($P < 0.05$, odds ratio [OR] 3.26) [26]. Thus, it is probable that in future studies smoking will become established as an independent risk factor.

Chronic pancreatitis is generally not caused by cholecystolithiasis or choledocholithiasis (evidence 4). However, gallstones have been linked to acute pancreatitis, and cholecystectomy is indicated in patients with proven gallstone pancreatitis or when otherwise unexplained pancreatitis develops in a patient who has gallstones after an episode of acute pancreatitis [27,28]. Untreated microlithiasis/sludge in the common bile duct can result in recurrent episodes of pancreatitis. Signs of chronic pancreatitis, such as calcifications or higher-grade ductal changes, have so far not been reported in this setting [19,29].

Primary hyperparathyroidism (pHTP) can lead to chronic pancreatitis, with or without calcifications (evidence 4). Case series of patients with pHTP substantiate an increased rate of pancreatitis (acute and chronic). A causal connection is assumed to exist with raised serum calcium levels [30]. According to one study, about 1% of patients with pancreatitis also have pHTP and 12% of patients with pHTP also have pancreatitis [31]. Overall, patients with pHPT seem to have a 28-fold increased risk of developing pancreatitis [30,31].

Diabetes mellitus type 1 or 2 is not an independent risk factor for chronic pancreatitis. Diabetes (sometimes described as type 3c) can be a consequence of chronic pancreatitis (evidence 4). 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 is the result of chronic pancreatitis, but not its cause [32].

Whether pancreas divisum is a risk factor for the development of chronic pancreatitis is controversial. The presence of pancreas divisum without additional risk factors tends not to lead to chronic pancreatitis (evidence 3b). Pancreas divisum develops from an incomplete fusion of the dorsal (ductus Santorini) with the ventral (ductus Wirsungianus) main pancreatic ducts 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 [33–42]. If a further risk factor is present (e.g., alcohol or *SPINK-1* mutations), then chronic pancreatitis frequently occurs. Those cohorts that attribute an increased risk for chronic pancreatitis to pancreas divisum were often not examined for other risk factors (e.g., genetic). Endoscopic intervention may be appropriate in individual cases. The occurrence of an acute idiopathic pancreatitis during childhood should prompt an etiological search for abnormalities of the hepatopancreaticobiliary system [37].

Individual case reports show an association between a papillary tumor and recurrent exacerbations of pancreatitis. Resection of papillary tumors that trigger attacks of pancreatitis may prevent chronic disease [43], although chronic pancreatitis has so far not been reported in this setting.

Up to 66% of patients with hereditary pancreatitis have a mutation of the *PRSS1* gene. The prevalence of hereditary pancreatitis is approximately 0.3/100 000 (for further details please see Chapter 85 and reference [44]). Mutations of the trypsinogen gene lead to chronic pancreatitis (penetrance rate of up to 80%; autosomal dominant inheritance) (evidence 1c). Three analyses published in 1996 demonstrated linkage between a locus on chromosome 7q35 and hereditary pancreatitis [45,46]. Further genetic analyses revealed an association of the disease with mutations in the trypsinogen gene (*PRSS1*) (p.N29I and p.R128H) [45]. Clinical data from the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) collaborative register substantiate an association between trypsinogen mutations and the occurrence of the disease [47]. Several studies established an autosomal inheritance in the causal relationship between *PRSS1* mutations and the development of chronic pancreatitis [45–51]. Mutations within the *SPINK1* gene (serine protease inhibitor type Kazal) also predispose to idiopathic (sporadic) chronic pancreatitis (evidence 1a). A metaanalysis of 2431 patients and 4857 controls published in 2008 substantiated with an OR of 11.0 that the N34S mutation in the gene encoding SPINK1 is associated with chronic pancreatitis. The OR for idiopathic pancreatitis is reported to be 14.97. More rare mutations in the *SPINK1* gene are also associated with the development of chronic pancreatitis. It is possible that *SPINK1* mutations provide additional risk in those who consume excess alcohol. 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 all patients with idiopathic chronic pancreatitis [52,53], but only in 1%–2% of the general population.

Approximately 25%–30% of patients with idiopathic pancreatitis carry germline alterations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene as compared to about 15% in the healthy population [54,55]. Thus, *CFTR* mutations confer risk for the development of chronic idiopathic pancreatitis (evidence 1a), even in the absence of clinical signs of cystic fibrosis. Cystic fibrosis, a disease with an autosomal recessive inheritance pattern and an estimated incidence of 1:2500 amongst Caucasians, is characterized by pancreatic insufficiency and chronic lung disease. Pancreas involvement varies from a complete loss of exocrine and endocrine function to an almost normal pancreatic function. Recurrent episodes of pancreatitis are observed in 1%–2% of pancreatic-sufficient patients and are also extremely rare in pancreatic-insufficient patients [56]. In comparison with the normal population, patients with idiopathic pancreatitis have about twice as many molecular changes in their *CFTR* gene [55,57–60]. While a study suggests that *CFTR* as risk factor for chronic idiopathic pancreatitis may have been overestimated [61], the evidence overall indicates that *CFTR* mutations are one of the most important risk factors for this disease.

Patients with chymotrypsin C (*CTRC*) mutations have an elevated risk to develop chronic pancreatitis (evidence 3b). Since the first report of mutations of the chymotrypsin C gene [62], the association with idiopathic chronic pancreatitis, alcoholic chronic pancreatitis, and hereditary pancreatitis has been reproduced in independent cohorts [63,64]. 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 in acinar cells, which is considered to be the cause of the cell damage [63,64]. Endoplasmatic reticulum stress is also a pathogenetic factor in chronic pancreatitis associated with mutations of carboxypeptidase A 1 [65].

Autoimmune pancreatitis is a systemic fibrosing inflammatory disease in which the pancreas is one of the affected organs. Autoimmune pancreatitis was first reported by Henri Sarles in 1961 [66]; the concept of the clinical entity "autoimmune pancreatitis" was first described by Yoshida et al. in 1995 [67]. The largest comparative study comprised 731 cases [68]. Men are affected more often than women (2:1) [68]. In Asia, the prevalence of autoimmune pancreatitis is 5%–6% of all patients with chronic pancreatitis. About 5% of patients operated for suspected pancreatic carcinoma had histological confirmation of autoimmune pancreatitis [69]. Clinical symptoms include discrete abdominal pain, jaundice (50%), and recurrent episodes of pancreatitis leading to chronic injury and a form of chronic pancreatitis (see Chapter 83 for complete discussion). Chronic pancreatitis in childhood, its diagnosis, and therapy will not be discussed in this chapter. Besides genetic causes, that is hereditary chronic pancreatitis, and further genetic associations, there are numerous rare causes and associated risk factors for chronic pancreatitis in childhood.

In summary there are no population-based data from Europe on the etiology of chronic pancreatitis. Alcohol abuse is the predominant predisposing cause during adulthood in about 50%–84% of all cases. The second most common group is so called idiopathic, that is sporadic pancreatitis with up to 28%. Genetic susceptibility factors play a role in up to 45% of cases of sporadic pancreatitis.

Pathogenesis

The pathogenesis of chronic pancreatitis is still only partially understood. Up to now there exists no convincing animal model to study the pathogenesis of chronic pancreatitis [70]. Ethanol-induced hyperviscosity of the protein-rich digestive enzyme secretion from the pancreas may be a factor. Protein plaques with secondary calcifications are characteristic for chronic pancreatitis. These protein plaques may lead to ductal hypertension with resulting acinar atrophy. CFTR mutations could be responsible for a decrease of secretion of bicarbonate and water by ductal cells. This may increase the viscosity and acidity of acinar secretions. Activation of zymogens within the ducts is facilitated by a decrease of pH. The genetic abnormalities both in hereditary and sporadic pancreatitis support the hypothesis of premature activation of trypsinogen. Alcohol is the most important risk factor and the most common cause of chronic pancreatitis during adulthood. Alcohol leads to various alterations of metabolic cascades within the acinar cell. However, most alcoholics do not develop chronic pancreatitis. Thus, there must be other cofactors. For progression of chronic inflammation within the pancreas, smoking appears to be an important factor [71,72]. The role of cellular stress due to oxygen-derived free radicals requires further study [73,74]. Both alcohol and smoking increase the concentration of free radicals within the acinar cell. Chronic ischemia due to arteriosclerosis as a consequence of smoking may also be a cofactor. The interplay between genetic and environmental factors in various forms of chronic pancreatitis is shown in Figure 84.1.

Clinical presentation and natural history including prognosis

In alcoholic chronic pancreatitis, the first symptoms usually develop in the fourth decade of life. A minority of patients experience painless chronic pancreatitis and become clinically apparent when exocrine and endocrine insufficiency progresses, resulting in steatorrhea and diabetes.

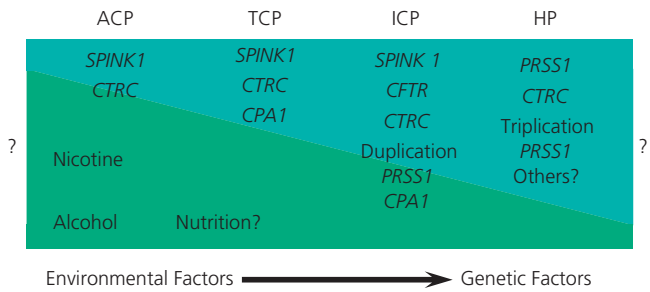


Figure 84.1 Interplay between genetic and environmental risk factors in chronic pancreatitis. ACP, alcoholic chronic pancreatitis; HP, hereditary chronic pancreatitis; ICP, idiopathic chronic pancreatitis; TCP, tropical chronic pancreatitis. Source: Data courtesy of Heiko Witt, MD, Professor of Pediatrics, Technical University of Munich, Germany.

Acute relapse

The most common cause of an acute exacerbation is continued alcohol abuse or dietary triggers. Acute exacerbation of chronic pancreatitis manifests in two forms, irrespective of underlying etiology: acute interstitial edematous pancreatitis (75%–85%) with a mortality of below 1% and acute hemorrhagic necrotizing pancreatitis (15%–25%) with mortality between 10% and 24%. Patients with acute pancreatitis should be admitted to a hospital to ensure adequate treatment. The need for frequent follow-up assessment of clinical findings, the laboratory parameters, and imaging are necessary in patient treatment for optimal care. At the time of admission into hospital, it is often difficult to differentiate between the majority of patients with a mild and uncomplicated course (about 80%) and those patients who will experience a severe course associated with multiple organ complications (about 20%).

Apart from the physical examination by an experienced physician, various parameters have been identified for prognostic assessment. A complicated course is usually to be expected in patients with three or more signs of organ complication 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 in the contrast-enhanced computed tomography (CT) scan. Nowadays, C-reactive protein (CRP), serum urea, hematocrit, and persistent (>48 h) organ failure are considered to be parameters of high prognostic significance for predicting the severity of both acute pancreatitis and an acute relapse superimposed on chronic pancreatitis. Diagnosis and treatment of an acute relapse does not essentially differ from acute pancreatitis (for further details see Chapter 82).

Pain syndrome

Clinical symptoms are often unspecific. Symptoms such as a belt-like upper abdominal pain and vomiting, together with a more than threefold rise in serum amylase or lipase levels above normal, point the way to the diagnosis of either acute pancreatitis or a relapse of chronic pancreatitis. Initially, it may not be possible to differentiate acute alcohol-induced pancreatitis with the potential for full recovery from an attack of previously unrecognized, yet already established chronic pancreatitis. The pain syndrome – either acute relapses of pain, chronic pain, or relapses of pain with decreasing pain severity during the course of the disease – has been extensively described by Rudolf Ammann et al. [24]. In their prospective long-term study, they found that the course of early stage chronic pancreatitis is characterized by episodes of relapsing pain. Chronic pain was often associated with local complications such as pseudocysts. In advanced chronic pancreatitis, all patients achieved complete pain relief. This observation by the Zurich group has not been completely confirmed by others. However, in some patients pain may remit spontaneously due to the chronic inflammatory

destruction of the pancreas ("burn out"). A relief of chronic pain is sometimes achieved by surgery.

Complications

Pseudocysts

Complications are frequent in patients with chronic pancreatitis, and pseudocysts are among the most common. Compression of the duodenum or gastric outlet by a pseudocyst leads to pain and postprandial vomiting. Rupture of a pseudocyst into the abdominal cavity leads to pancreatic ascites; however, rupture of an infected pseudocyst results in peritonitis. A pseudocyst in the pancreatic head may lead to pain and jaundice due to bile duct obstruction; slow development of a pseudocyst may produce painless jaundice. In rare cases, pseudocysts perforate into the duodenum and "heal" spontaneously.

Inflammatory tumor

An inflammatory mass of the pancreatic head may also cause pain and jaundice. Jaundice is accompanied by a dark color of urine and acholic stools. The obstruction of the distal bile duct may be incomplete and detected only by laboratory parameters indicating cholestasis, such as an elevation of alkaline phosphatase and γ-glutamyl transferase, and/or by ultrasound showing dilated bile ducts without clinically evident jaundice.

Obstruction of pancreatic ducts

Obstruction of the outflow of exocrine secretions by an inflammatory mass, calcified protein plaques in pancreatic ducts, or narrowing of ducts by inflammatory scars, usually causes chronic pain. In this setting, some patients try to relieve their pain by using a heat pad. Rarely, this may be reflected in the findings on physical examination of a brownish color of the underlying skin, that is chronic burning (in Latin "erythema ab igne"). This sign (Figure 84.2) is highly specific for chronic pancreatitis.

Bleeding

Rare complications in chronic pancreatitis include severe upper gastrointestinal hemorrhage due to rupture of fundic varices secondary to portal and/or splenic vein thrombosis, resulting from the adjacent pancreatic inflammatory process. Both the pancreatic inflammatory process itself and repeated stenting of the biliary tract (see Section Endoscopic treatment of bile duct obstruction) are risk factors for the development of a portal vein thrombosis. A very rare symptom may be a life-threatening arterial bleeding due to an aneurysm of the splenic artery, which lies immediately behind the pancreas and can be damaged by the pancreatic inflammation. Rarely, one may see endoscopically the presence of blood emerging from the papilla Vateri ("hemosuccus pancreaticus").

Fistula, pleural effusions

Another rare complication is the development of a fistula to the pleura, which can lead to pleural effusions causing dyspnea. The pancreatic etiology of these pleural effusions can be verified by measurement of lipase/amylase in the pleural fluid. Formation of fistulas during acute exacerbations or due to rupture of pseudocysts with connection to the jejunum, ileum, and colon are also possible.

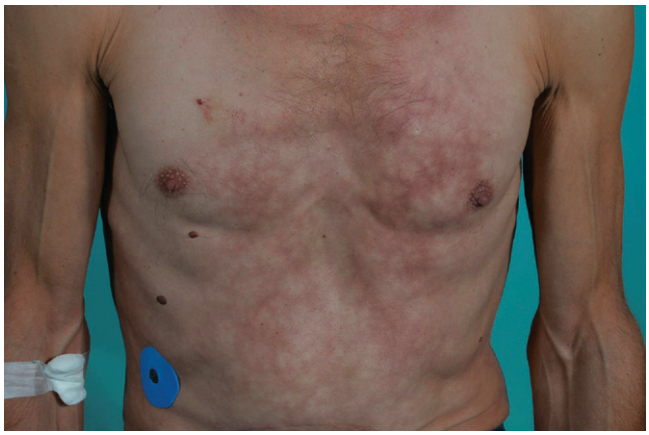


Figure 84.2 Erythema ab igne. Brownish color of the underlying skin due to chronic burning by using a heat pad because of chronic abdominal pain.

Late complications: exocrine and endocrine insufficiency

The clinical symptoms and diagnostic approach to exocrine pancreatic insufficiency are described below in Section Diagnosis. With ongoing destruction of pancreatic acini and pancreatic ducts, the reduction in pancreatic drainages and the inhibition of outflow of digestive enzymes leads to further destruction of the islets of Langerhans, and thus the development of both exocrine and endocrine insufficiency. Destruction of exocrine acini and endocrine islets does not proceed in a uniform or parallel manner. As a result, exocrine insufficiency may precede the development of diabetes or vice versa. However, most patients with long-standing chronic pancreatitis develop so-called type 3c diabetes.

Other diseases due to chronic alcohol and nicotine abuse

The simultaneous presence of both chronic pancreatitis and liver cirrhosis is surprisingly uncommon. However, many patients with chronic pancreatitis due to alcohol also have some parenchymal liver damage, that is fatty liver, which will be aggravated due to cholestasis. Nicotine-related diseases such as lung cancer or cancers of the throat have to be kept in mind. Furthermore, squamous cell cancer of the esophagus due to smoking and chronic consumption of "high percentage" alcoholic beverages is not so rare. Chronic pancreatitis is a risk factor for pancreatic cancer.

Prognosis

Mortality from chronic pancreatitis is reported to be 12.8%–19.8%, with a mean observation period of 6.3–9.8 years [8,75,76].

Total mortality in the same studies was reported to be 28.8%–35%. Continued alcohol consumption results in a significantly reduced survival rate. 33% of patients suffering from chronic pancreatitis are no longer able to pursue their profession [75]. The number of patients who become unemployed due to prolonged periods of illness or continued alcohol consumption or become either unfit for work or enter retirement in the course of the disease amounts to 40% [76]. Mortality is increased 3.6-fold compared to the general population. The 10-year survival rate is approximately 70% and the 20-year survival rate 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, smoking with a HR of 1.4, and cirrhosis with a HR of 2.5 [21]. Smoking-related diseases such as lung cancer or squamous cell cancer of the esophagus have to be considered as well as causes of early mortality.

Diagnosis

The diagnosis of chronic pancreatitis is based on complementary clinical, morphological, and functional parameters. Clinical symptoms such as belt-like upper abdominal pain and vomiting, together with a more than threefold rise in serum amylase or lipase levels above normal, are a prerequisite for the diagnosis of acute pancreatitis or a relapse of chronic pancreatitis. However, relapses of pain in chronic pancreatitis may also be possible without a marked elevation of serum lipase. As mentioned in Section Clinical presentation and natural history including prognosis, there are numerous causes for pain, not only an acute inflammatory process. Thus, with serum lipase values below the threefold normal value, the revised criteria of the Atlanta Classification of 1994 suggest the use of an imaging technique to establish the diagnosis (e.g., contrast-enhanced CT) [77].

Laboratory tests

Serum lipase/serum amylase

As in acute pancreatitis, acute relapses of chronic pancreatitis are usually characterized by increases of serum lipase and amylase that are more than threefold the upper value of normal. Measurement of serum lipase is preferred due to its higher specificity. The degree of elevation of these pancreatic digestive enzymes does not correlate with the severity of the disease. Measurement of serum lipase does not discriminate between acute pancreatitis and a relapse of chronic pancreatitis. In late-stage chronic pancreatitis, values of serum lipase may decrease due to the loss of exocrine tissue. However, serum lipase values do not correlate inversely to the degree of exocrine pancreatic insufficiency. There are no single or combinations of parameters that can be easily measured in serum that provide a reliable correlation to the severity of the disease.

Serum glucose

The criteria to diagnose diabetes in chronic pancreatitis do not differ from other forms of diabetes.

Genetic testing

In 1952, Comfort and Steinberg reported on a hereditary form of pancreatitis with an autosomal dominant inheritance pattern [78]. Patients with chronic pancreatitis and a family history of the same in first- or second-degree relatives should be offered molecular testing to check for mutations of the *PRSS1* gene associated with hereditary pancreatitis, especially in cases when the first manifestations of the disease in relatives started in childhood or adolescence (evidence 3b) (see also Chapter 85). Patients with trypsinogen (*PRSS1*) mutations have an increased risk of developing pancreatic carcinoma [79]. This may not be due to the mutations itself, but rather due to the prolonged chronic inflammatory processes. The cumulative risk of developing pancreatic carcinoma in patients with hereditary pancreatitis is approximately 49% by their 75th year of life, a risk that is significantly higher than for all other known etiologies of chronic pancreatitis. The optimal approach to tumor screening for this high-risk group is remains unresolved, but there are no available blood tests adequate for this purpose, including Ca-19-9.

Mutation analysis of the *SPINK-1*, *CFTR*, and chymotrypsin C genes may be performed, though currently they do not have a major role for clinical management (evidence 3b). There is no proven increased risk of tumor development in patients with mutations in these susceptibility genes as opposed to other etiologies of chronic pancreatitis. It may be assumed that these genetic alterations are susceptibility factors that predispose to the disease, but on their own do not cause it. The detection of mutations in these genes does not allow a definite etiological classification of chronic pancreatitis and does not generally lead to specific therapeutic interventions [47,48,53,59,62]. Aspects regarding healthcare providers should be discussed with the patient or his relatives. Prior to performing the genetic test, a detailed discussion with the patient and/or his relatives is required, so that he or she fully understands the testing procedure, the benefits and limitations of the test, and the possible outcomes and consequences of the test results (i.e., informed consent). Genetic testing of nonaffected family members should not be undertaken outside research projects [80].

Diagnosis of exocrine pancreatic insufficiency

Definition of exocrine insufficiency

Exocrine pancreatic insufficiency results from a decrease of pancreatic enzyme and bicarbonate secretion to the point it is inadequate to fully digest dietary intake. The main causes of exocrine pancreatic insufficiency in adults are chronic pancreatitis, pancreatic carcinoma, and a previous pancreas resection. A functional decrease of exocrine pancreatic function is also expected after subtotal gastrectomy, some forms of bariatric surgery, as well as in patients with marked protein deficiency or cystic fibrosis. Rare causes include Shwachman–Diamond

syndrome, Johanson–Blizzard syndrome, and congenital enzyme deficiencies such as trypsinogen, amylase, lipase, enteropeptidase (enterokinase), or α1-antitrypsin deficiencies.

Development and clinical features of exocrine pancreatic insufficiency

Typical symptoms of exocrine insufficiency are abdominal symptoms such as cramps, gas, bloating, flatulence, steatorrhea, and signs of malnutrition. The development of steatorrhea and other symptoms of exocrine pancreatic insufficiency are to be expected once the diagnosis of chronic pancreatitis has been made. In patients with alcoholic chronic pancreatitis, clinically manifest exocrine pancreatic insufficiency usually appears approximately 10–15 years after development of the first symptoms such as abdominal pain. In patients with early onset of idiopathic or hereditary chronic pancreatitis, exocrine pancreatic insufficiency may develop after even longer periods. The relatively late manifestation of exocrine insufficiency, well after pancreatic tissue destruction has begun, reflects the large functional reserve capacity of the pancreas. It is widely agreed that decompensation associated with steatorrhea and creatorrhea (abnormal excretion of muscle fibers in the feces) does not occur until secretion of the corresponding enzymes has been reduced by more than 90%–95% [81] (evidence 1b–2b). There are patients, however, who present primarily with signs and symptoms of exocrine insufficiency, such as malnutrition and/or abdominal symptoms (diarrhea, steatorrhea, abdominal distension, gas, pain). There is no clinical symptom that unequivocally confirms exocrine pancreatic insufficiency or, conversely, excludes it (evidence 1b–2b). Clinically, steatorrhea cannot be reliably detected. Inspection of the stools can be misleading, even when performed by an experienced practitioner [82]. Absence of clinical symptoms of steatorrhea is even less reliable in making a diagnosis; the negative predictive value is only 31% [83]. Moreover, the etiology of diarrhea and other abdominal symptoms in patients with chronic pancreatitis is often multifactorial, and pancreatic insufficiency is often not the only cause of malnutrition. Additional causes include pain-related reduction of food intake, continued alcohol consumption as well as an increased metabolic rate [84]. Exocrine pancreatic insufficiency, even without symptomatic steatorrhea, can have a negative effect on nutrition parameters such as body weight [85] (evidence 2b). Moreover, there are studies that substantiate reduced absorption of fat-soluble vitamins in patients with only mild to moderate exocrine insufficiency [86–88]. Reports have detected significantly reduced fecal elastase levels in patients with osteoporotic fractures, which correlate with low vitamin D-3 levels [88]. There appears to be a clearly increased risk of osteoporosis and fractures even with subclinical disease, that is mild to moderate exocrine insufficiency.

Exocrine pancreatic function and morphological signs of chronic pancreatitis usually, but not always, run in parallel. However, exocrine pancreatic insufficiency is possible even in the absence of morphological evidence of chronic pancreatitis (evidence 1b–2b). Previous studies have shown a virtually complete concordance between normal morphology and normal exocrine function, but also severe changes with regard to both parameters (evidence 1b) [89]. In the majority of patients with chronic pancreatitis, there is a correlation between the extent of morphological and functional disturbances. Discordant findings with varying degrees of morphological and functional changes are to be found in about one-quarter of patients [90,91]. 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 (evidence 2b) [92,93]. Exocrine pancreatic insufficiency despite normal morphological findings may be particularly common in so-called "small duct disease" type chronic pancreatitis (evidence 1b–2b) [91].

Invasive ("direct") and noninvasive ("indirect") pancreatic function tests (see Chapter 156)

In many countries, the secretin test is the "gold standard" to measure directly exocrine pancreatic function. This test has been used as a reference point for evaluation of new tests (evidence 1b). Noninvasive function tests are often preferred for the initial clinical evaluation and, due to its simplicity, the fecal elastase test (using specific antibodies) has mainly been used [94]. As an alternative, breath tests using ^{13}C-labelled lipids can also be employed (evidence 5). When a diagnosis of chronic pancreatitis is made, a pancreatic function test is recommended (evidence 1b–2b). In cases of new or worsening symptoms suggesting exocrine pancreatic insufficiency, pancreatic function testing should be repeated when a prior function test was normal (evidence 2b). Diabetics have an increased risk for exocrine pancreatic insufficiency. Thus, pancreatic function tests should be performed in cases of symptoms typical for exocrine pancreatic insufficiency (evidence 2b).

Measuring fecal elastase levels in a random stool sample is a widely used pancreatic function test. The following pancreatic function tests are also clinically available: measurement of fecal fat excretion, measurement of chymotrypsin activity in stool, breath test with ^{13}C-labelled substrates (preferentially ^{13}C-labelled mixed triglycerides), and the secretin test. Measuring the quantitative amount of fat secreted in the feces is rarely performed nowadays because of the effort involved and the unpleasant procedure of collecting and processing stool. The secretin–pancreozymin test (or the secretin–caerulein test), while the most exact technique for quantifying exocrine pancreatic function, is no longer practical because the only available cholecystokinin analogue ceruletide (Takus™) has been withdrawn from the market. The remaining option is to perform a tube test, stimulating only with secretin, which normally results in a sharp rise in pancreatic bicarbonate secretion. However, this examination is both expensive and laborious, requiring insertion of a nasoduodenal tube. It is therefore reserved for specialist centers and for strictly selected indications. The endoscopic variation of the secretin test, with repeated endoscopic

Table 84.1 Sensitivity and specificity of the available pancreatic function tests. Source: Siegmund et al. 2004 [99]. Reproduced with permission, © Georg Thieme Verlag KG.

Test	Mild exocrine insufficiency Sensitivity (%)	Moderate exocrine insufficiency Sensitivity (%)	Severe exocrine insufficiency		Level of evidence grade
			Sensitivity (%)	Specificity (%)	
Fecal elastase 1	54	75	95	85	1a/b
Qualitative fecal fat test	0	0	78	70	
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

Direct invasive pancreatic function tests (secretin and secretin–pancreozymin tests) were used as reference methods. Sensitivity and specificity are therefore not stated for these.

aspiration of duodenal juices after secretin stimulation, is increasingly favored in the USA, and can in principle be carried out in any standard endoscopy unit [95]. However, the procedure is rarely used due the cost and invasiveness of the endoscopic procedure, and the rather long examination time (up to 60 min). Magnetic resonance imaging (MRI)-based techniques allow semiquantitative assessment of exocrine pancreatic function by determining fluid secretion into the duodenum during a secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) [96–98]. The sensitivity and specificity of the available pancreatic function tests is listed in Table 84.1 [99].

Following the diagnosis of chronic pancreatitis, a pancreatic function test should be performed (evidence 1b–2b) because even when unequivocal laboratory and imaging findings are sufficient to make the diagnosis, clinical symptoms (history and inspection of the stools) are unreliable for recognizing exocrine insufficiency, and, conversely, the possible causes of diarrhea and other abdominal symptoms are manifold, even in patients with chronic pancreatitis. In the case of new or worsening symptoms, which could be due to exocrine pancreatic insufficiency, diagnostic evaluation of pancreatic function should be repeated if previous results were unremarkable (evidence 2b). The development of symptoms due to exocrine pancreatic insufficiency in a patient with known chronic pancreatitis can occur at any time, even though steatorrhea usually develops several years after the appearance of initial symptoms.

Diabetics have an increased risk of developing exocrine pancreatic insufficiency. Pancreatic function tests, therefore, should be performed for clinical symptoms of exocrine pancreatic insufficiency (evidence 2b). A significant proportion of patients with type 1 and type 2 diabetes mellitus suffer from exocrine pancreatic insufficiency [100,101] due to a deficient insuloacinar axis and extensive exocrine atrophy.

Diagnostic imaging

Transabdominal ultrasound, endoscopic ultrasound, and endoscopic retrograde cholangiopancreatography

A transabdominal ultrasound scan is usually appropriate as the initial imaging modality (Figure 84.3). If signs of pancreatitis are equivocal (i.e., inhomogeneous gland but normal-diameter pancreatic duct), yet there is still a strong clinical suspicion, endoscopic ultrasound (EUS) should be performed (Figures 84.4 and 84.5). In diagnosis of chronic pancreatitis, EUS has generally the highest, or at least equal, accuracy when compared with endoscopic retrograde cholangiopancreatography (ERCP) or MRCP/MRI [102–110]. In a prospective comparison of radial and linear endoscopic ultrasound for diagnosis of chronic pancreatitis, the two methods had a similar sensitivity [111]. EUS-guided fine-needle biopsy can also provide a cytological and/or histological diagnosis of focal lesions. In IgG4-positive autoimmune pancreatitis in combination with autoimmune cholangitis, biopsy of the papilla of Vater may be sufficient for diagnosis. CT and MRI, as well as MRCP, are supplementary diagnostic techniques for equivocal pancreatic changes detected on ultrasound or EUS (Figure 84.6). MRCP should be performed when more detailed information about the pancreatic ductal system is necessary (evidence 2a).

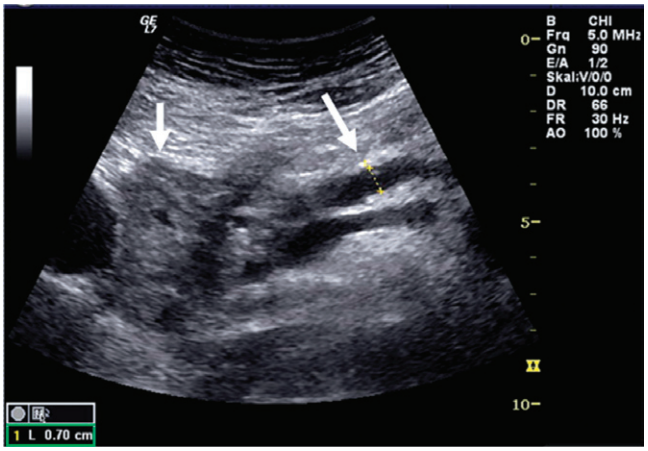


Figure 84.3 Inflammatory tumor of the pancreatic head. Transabdominal sonography: inflammatory tumor of the pancreatic head (short arrow) and dilated main pancreatic duct (long arrow).

Magnetic resonance cholangiopancreatography and computed tomography

In a prospective study comparing MRCP with ERCP, MRCP demonstrated a higher sensitivity (84% vs 70% for ERCP) with

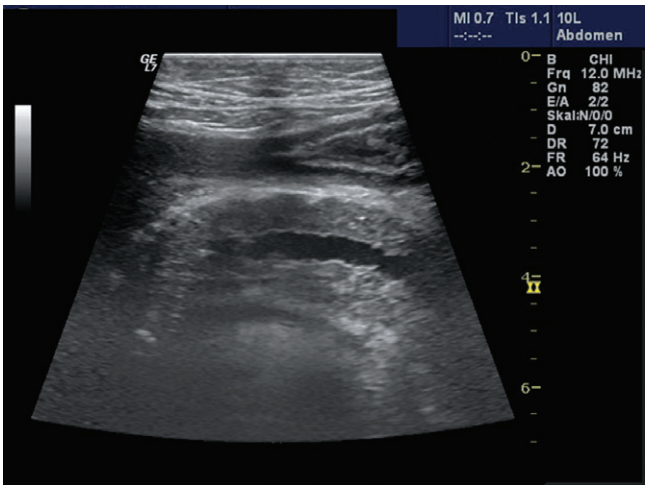


Figure 84.4 Pancreatic duct alterations in chronic pancreatitis. Transabdominal ultrasound: dilated irregular main pancreatic duct.

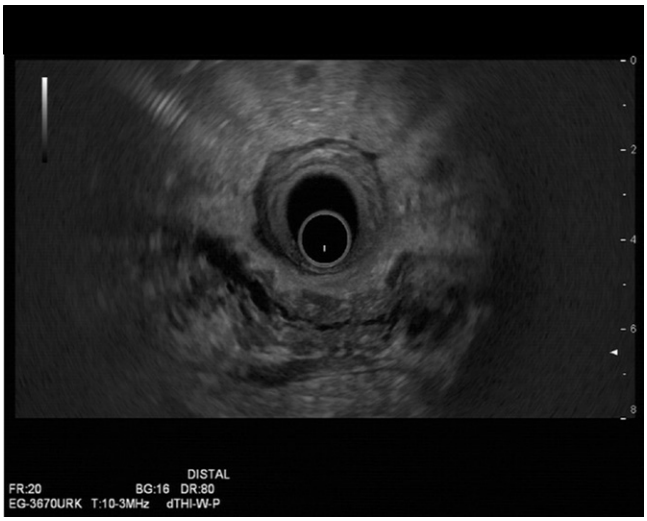


Figure 84.5 Irregularities and slight dilation of the main pancreatic duct. Radial endoscopic ultrasound: slightly dilated irregular main pancreatic duct.

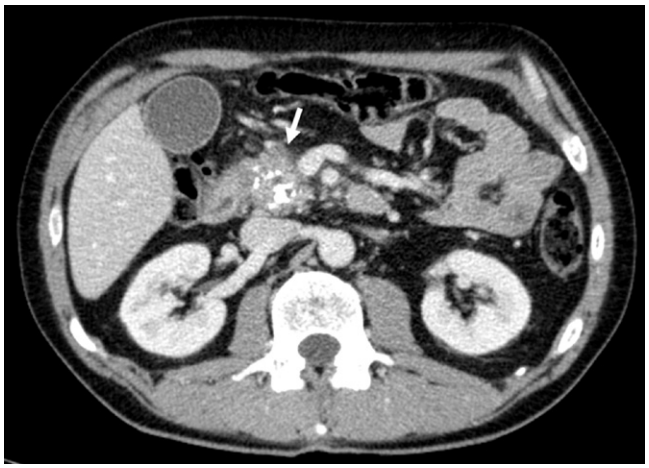


Figure 84.6 Inflammatory mass of the pancreatic head. Computed tomography: inflammatory mass of the pancreatic head with calcifications (arrow). Source: Courtesy of Thomas Kahn MD, Professor of Radiology, Institute of Radiology, University Hospitals of Leipzig.

Table 84.2 Sensitivity and specificity of the individual imaging techniques in diagnosis of chronic pancreatitis.

Examination	Sensitivity (%)	Specificity (%)	Level of evidence	Literature
CT	n/a	n/a	2b	[104]
ERCP	70–80	80–100	2a	[102–105]
MRCP	88	98	2b	[109,112]
Ultrasound	60–81	70–97	2a	[104]
EUS	80–100	80–100	2a	[102–110]

n/a, not analyzed. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

equal specificity (94%) for the diagnosis of pancreatic cancer [112]. Thus, MRCP has generally replaced diagnostic ERCP for this purpose. Comparative studies between MRCP and EUS showed a better discriminatory power for EUS, especially in early forms of chronic pancreatitis [107].

Sensitivity and specificity of the individual imaging techniques for the diagnosis of chronic pancreatitis are listed in Table 84.2. There are no prospective randomized studies comparing EUS, ultrasound, and CT for diagnosing chronic pancreatitis. Prospective comparative studies are only available comparing ERCP with EUS, MRCP with EUS, and ultrasound with ERCP [104–108,111,112]. It has been shown that EUS is superior to ERCP, especially for assessing early forms of chronic pancreatitis. Patients with changes on EUS, but initially an unremarkable ductal anatomy by ERCP, will in time probably develop pathological changes in their ductal system typical for chronic pancreatitis or demonstrate histological changes of chronic pancreatitis [107,108]. Thus, diagnostic imaging starts with transabdominal ultrasound. In cases when ultrasound is either normal or reveals inadequate imaging of the pancreas due to overlying gas, the higher spatial resolution of EUS will enable detection of early parenchymal changes indicative of chronic pancreatitis. CT scanning still has an essential role in preoperative planning.

Elastography

At the moment, elastography cannot be recommended for diagnosing chronic pancreatitis (evidence 4). However, it may be helpful for the differential diagnosis of focal lesions (evidence 3b). So far, single-center studies involving elastography have examined patients with space-occupying lesions of the pancreas [113–115]. Two studies have suggested that elastography is able to differentiate between malignant and benign focal lesions, with rather good sensitivity and specificity [114,115]. The number of patients studied so far is too small and the diseases too

inhomogeneous to allow definitive conclusions on the value of elastography. It remains an unsolved challenge to diagnose early pancreatic cancer arising in chronic pancreatitis. EUS elastography currently has no significant value for diagnosing chronic pancreatitis, although one study suggests that elastography may be helpful in diagnosing autoimmune pancreatitis [116].

Classification of morphological findings

The criteria for diagnosing chronic pancreatitis in adults using different imaging techniques should be applied according to the Cambridge classification (evidence 2a), as outlined in Box 84.2 (Figure 84.7). The Cambridge classification based on ERCP [117,118] and its adaptation for sectional imaging (ultrasound, EUS, CT/MRCP) should be used for diagnosing chronic pancreatitis in adults (evidence 3a). 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. The Rosemont classification is widely accepted for interpreting EUS findings without relying on clinical findings [119,120]. The Cambridge classification is particularly useful for MRCP [118]. Early changes of chronic pancreatitis are only detectable using EUS. Comparisons of the individual imaging techniques render it appropriate to adopt the Cambridge classification for ultrasound, CT, and MRCP in order to achieve a standardization of nomenclature. The morphological findings of chronic pancreatitis can be assessed using the classification systems shown in Box 84.3. The Manchester classification combines imaging findings of chronic pancreatitis with clinical findings and converts them into a simple classification for chronic pancreatitis [121]. In this system, the dominant criterion for the severity of pancreatitis is evidence of exocrine or endocrine insufficiency and/or evidence of complications, while imaging findings play a more minor role.

The ABC system of Ramesh and Büchler represents a comparable form of classification [122,123]. It requires positive imaging findings for all stages, while the presence of exocrine or endocrine insufficiency and/or complications alone is decisive for the severity of chronic pancreatitis.

The M-ANNHEIM classification attempts to characterize patients according to etiology, clinical stage, and severity [124]. The severity of the inflammatory reaction is evaluated using clinical symptoms and therapeutic interventions. Complex classification criteria are used to generate a point system (0–25 points), which defines the severity of chronic pancreatitis.

As yet, these classification systems have not been validated in prospective randomized studies. The target criterion must be the calculation of morbidity and mortality in order to measure the effects of treatment.

Selection of imaging method

The choice of an imaging technique depends largely on the expected complications (evidence: ultrasound 3a; EUS 2a, CT 4, MRI 3a).

Box 84.2 Adaptation of Cambridge Criteria for various imaging procedures. Data from [117,118].

ERCP

Cambridge 0	Good quality imaging of the main pancreatic duct and side branches without any abnormal signs
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 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 2 plus cysts, focal calcifications
Cambridge 4	As 3 plus duct stones, duct obstruction, tumorous enlargement of the gland >2-fold, splenic vein thrombosis

Endoscopic ultrasound:

Cambridge 0	Normal pancreas
Cambridge 1	Lobular honeycomb appearance – duct <3 m
Cambridge 2	Hyperechoic duct, hyperechoic foci, hyperechoic contour, duct <3 mm
Cambridge 3	Lobular honeycomb appearance, septated, hyperechoic foci, duct >3 mm, irregular duct, no duct calculi
Cambridge 4	As 3 plus calcifications, duct calculi, cysts

CT/MRCP:

Cambridge 0	Normal pancreas
Cambridge 1	Not possible to diagnose 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 listed under 2 plus pathological main duct (>4 mm)
Cambridge 4	One of the changes listed 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

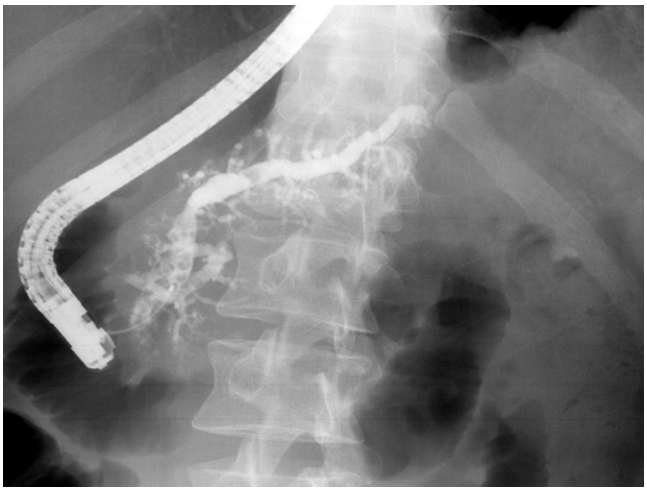


Figure 84.7 Endoscopic retrograde pancreatography, stage 4, according to the Cambridge classification (see Box 84.2).

Necrosis Contrast-enhanced ultrasound is capable of detecting necrosis to the same degree as contrast-enhanced CT. This is of particular advantage in patients with impaired kidney function. However, quantification of the degree of severity is not possible with contrast-enhanced ultrasound [125,126]. An ultrasound- or CT-guided fine-needle biopsy can be performed if infected necrosis is suspected. CT, contrast-enhanced MRI, and echo-enhanced ultrasound can detect necrotic pancreatic tissue [127,128].

Pseudocysts Pseudocysts are well detected with the aid of transabdominal ultrasound [129,130] or EUS (Figure 84.8). Their criteria are clearly defined: echo-free, tangential artefact, and dorsal acoustic enhancement. Pseudocysts with atypical appearances do occur. Here, cystic neoplasm should be included in the differential diagnostic considerations. The most reliable differentiation of cystic pancreatic lesions is achieved by EUS and MRI/MRCP. Cystic neoplasms can be well differentiated from pseudocysts or periintestinal fluid accumulations with the aid of EUS und MRI/MRCP. In ambiguous cases, EUS-fine-needle aspiration (FNA) with sampling of cystic fluid (cytology, lipase, carcinoembryonic antigen [CEA], and CA 19-9 determination) may be the method of choice.

Pseudoaneurysm On detection of cystic changes within the pancreas, ultrasound should be performed in combination with color Doppler ultrasonography in order to reliably detect perfusion in the cyst as an indication of a pseudoaneurysm and is obligatory before any interventions. CT-angiography and MR-angiography are also capable of identifying pseudoaneurysms. There are no studies comparing diagnostic accuracy of imaging studies for detecting pancreatic pseudoaneurysm.

Carcinoma Once chronic pancreatitis has been diagnosed, ultrasound and EUS are only able to distinguish to a limited degree between carcinoma and inflammation. In equivocal cases, EUS-FNA should be performed. Histological and cytological examinations may raise the sensitivity up to 85% with a rather good specificity [131,132]. The probability of false-negative findings is reported to be between 5% and 10%. Thus, in a patient with a suspected tumor, surgery is recommended even without prior FNA. A sensitivity of 84%, with a specificity of 97%, has been reported for MRI combined with MRCP in diagnosing pancreatic cancer. A sensitivity of 93%, with a specificity of 75%, has been calculated for differentiating between chronic pancreatitis and pancreatic carcinoma [133]. However, this does not apply when a carcinoma develops within chronic

Box 84.3 Morphological findings of chronic pancreatitis assessed by various classification systems.

1. Manchester classification [121]:

Mild CP:
ERP, CT, ultrasound, EUS – evidence of chronic pancreatitis, no peripancreatic complications, preserved endocrine and exocrine function; abdominal pain; no regular analgesia

Moderate CP:
ERP, MRI, CT, ultrasound, 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, plus exocrine or endocrine insufficiency

2. ABC system (Ramesh, modified according to Büchler) [122,123]:

Stage A:
Pain, positive imaging on ultrasound, ERP, MRI, 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 with the aid of endoscopic ultrasound [119,120]:

In addition to parenchymal changes (hyperechoic foci with +/– shadowing, honeycomb-type lobularity, cysts, hyperechoic strands), ductal changes (main pancreatic duct calculi, irregular duct, dilated side branches, hyperechoic duct wall) are also described.

4. M-ANNHEIM classification [124]:

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

CBD, common bile duct; CT, computed tomography; ERP, endoscopic retrograde pancreatography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging.

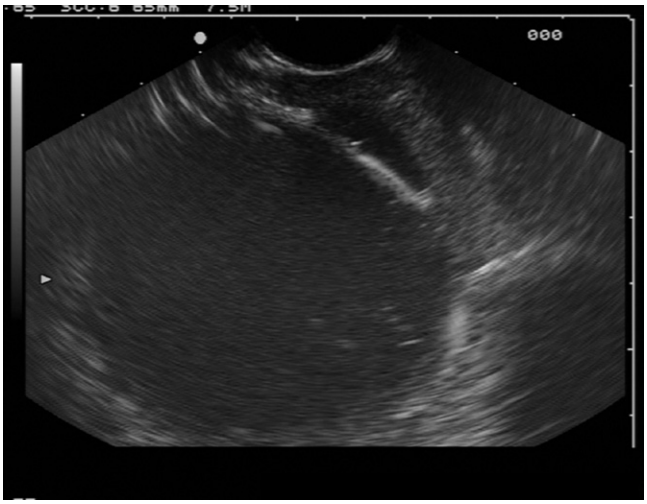


Figure 84.8 Pancreatic pseudocyst. Endoscopic ultrasound: large pancreatic pseudocyst.

pancreatitis. Even after application of all diagnostic techniques, sensitivity for detecting a tumor within the chronically inflamed pancreas is only about 67%, and the specificity only 45%. More recent studies involving contrast-enhanced ultrasound and EUS show that both necrosis and pancreatic carcinoma appear as demarcated as hypoperfused focal lesions [118,119,134–137]. In the presence of chronic pancreatitis, focal necrosis has to be differentiated from carcinoma. An EUS-FNA of the focal lesion may be appropriate, although a considerable rate of false-negative findings has to be expected [138]. Cytological or histological FNA can be recommended to differentiate between autoimmune pancreatitis and other pancreatic diseases (evidence 2c).

In summary, besides history and physical examination, transabdominal ultrasonography is the preferred first-line imaging test. If findings remain inconclusive (inhomogeneous organ, main pancreatic duct not dilated) but there is strong clinical suspicion, EUS should be performed. EUS-guided fine-needle puncture enables cytological and histological evaluation of focal lesions. CT and MRI as well as MRCP are complementary procedures in equivocal findings of ultrasound and EUS. MRCP is the preferred method for evaluation of pancreatic ducts (evidence 2a).

Differential diagnosis

Early in the course of the disease it is often not possible to differentiate between alcohol-induced acute pancreatitis and an attack superimposed on an already chronic inflammatory process. The differentiation between acute relapsing pancreatitis and attacks of chronic pancreatitis is only possible when typical signs of chronic pancreatitis can be detected by imaging, such as an inflammatory tumor of the pancreatic head with calcifications. The most important differential diagnosis is pancreatic cancer. Usually it is not difficult to differentiate chronic pancreatitis (with the exception of autoimmune pancreatitis) from a pancreatic cancer mass at initial diagnosis, which often leads to some patients to undergo surgery to rule out a malignancy. Despite all of the sophisticated imaging techniques available, early diagnosis of pancreatic cancer in preexisting chronic pancreatitis is almost impossible. The development of chronic pancreatitis is very unlikely to result from biliary disorders. In alcohol-associated pancreatitis relapses that occur despite having discontinued alcohol ingestion, the relapses are most likely due to chronic pancreatitis. Relapsing acute pancreatitis rarely may be due to sphincter of Oddi dysfunction, and even after a papillotomy some of these patients may develop chronic pancreatitis [139]. In patients with clinical signs of maldigestion but without abdominal pain, a wide spectrum of diseases has to be considered. Whether so-called "early chronic pancreatitis" in the absence of imaging abnormalities may cause abdominal pain without an elevation of serum lipase is controversial. There is no convincing explanation for the pathogenesis of pain in a patient with normal findings on imaging and without signs of acute pancreatitis, characterized by an elevation of serum amylase/lipase. The argument that in these patients the diagnosis of chronic pancreatitis can only be established by pancreatic exocrine function tests is not persuasive. Furthermore, the specificity of the secretin test in this setting is suboptimal. Irritable bowel syndrome may be the underlying cause of abdominal pain. Thus, in some cases of chronic pancreatitis, a definitive diagnosis requires patient observation to determine the presence of any underlying pathology.

Therapy and management of complications

The same principles are applicable to the management of acute exacerbations of chronic pancreatitis, recurrent acute pancreatitis, and acute pancreatitis, but are less useful for management of chronic calcifying pancreatitis. Management of acute pancreatitis and its complications is addressed in Chapter 82. An acute exacerbation of chronic pancreatitis is one of the most common disorders in gastroenterology.

Intensive care

Rapid and adequate fluid replacement is essential in the management of acute relapses of chronic pancreatitis (evidence 2b) [140–142]. Prerenal kidney failure within the first 48 h after admittance to hospital correlates with increased mortality. Any increase of serum urea levels by 5 mg/dL raises mortality by a factor of 2.2 [143,144]. However, excessive administration of fluid results in local complications, global respiratory failure, and an increased rate of sepsis. In order to establish adequate fluid replacement, the clinical strategy of fluid replacement was examined in a prospective randomized study including patients with severe acute pancreatitis (APACHE-II score >14). One

group received 10–15 mL/kg/h until the fluid deficit was corrected, measured by reaching two or more of the criteria: heart rate <120/min, mean arterial pressure 65–85 mmHg, urine output >1 mL/kg/h, hematocrit <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 that received the more aggressive amount of volume was significantly increased, as were local complications such as abdominal compartment syndrome or sepsis [145]. Volume administration is best monitored by a thermodilution system [146]. When invasive monitoring of fluid deficits is not possible, treatment with 5–10 mL/kg/h is recommended (evidence 1b). Neither hematocrit nor central venous pressure have proven being adequate for assessing volume deficits [147]. Based on the findings of the VISEP study on sepsis management, crystalloid solutions and not colloid solutions should be used for fluid replacement [148]. There is a general consensus that rapid and adequate fluid resuscitation is of prognostic significance [140,141,149,150].

The insertion of a nasogastric tube may not be necessary in the absence of small bowel obstruction or vomiting (evidence 4). The insertion of a nasogastric tube is indicated as prophylaxis and therapy of a paralytic ileus. However, nasogastric suction of gastric juices has no benefit on the pancreas per se [151–154].

Acid suppression for stress ulcer prophylaxis is recommended for the severely ill (evidence 3a). Controlled studies on stress ulcer prophylaxis are not available. Nevertheless, prophylaxis is generally recommended.

Any required intensive care management is based on standardized principles, which apply in particular to the treatment of sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ failure.

Treatment of pain

Adequate pain management is essential (evidence 2b). Patients with an acute exacerbation of pancreatitis often suffer from severe visceral pain. Analgesia is therefore one of the most important and urgent aims of treatment. The argument that morphine or its analogues possibly cause contraction of the duodenal papilla, thus creating an additional obstruction for pancreas secretion, is obsolete (evidence 2b). Papillary contraction either does not occur in the majority of analgesics users or is so inconsequential that it does not play any clinical role [155–157]. Some morphine analogues have been successfully used for pain control both in acute and chronic pancreatitis. Tramadol is generally not preferred because it often causes nausea and vomiting in patients with acute pancreatitis. Some centers have achieved good results by the use of thoracic epidural analgesia (EPA) [158,159]. This not only leads to rapid analgesia but, in addition, prevents or treats paralytic ileus. A prerequisite for the use of EPA is an alert patient and coagulopathy a contraindication.

Nutrition in acute pancreatitis or in acute relapses of chronic pancreatitis

Clinical symptoms may require withholding oral intake (NPO) (evidence 4). Fasting has a positive effect on the course of paralytic ileus that often occurs secondary to acute pancreatitis. Many patients experience some relief from their nausea, vomiting, and pain with fasting. However, studies have found no positive effect of fasting on the clinical course or prognosis of acute pancreatitis itself. Experimental and clinical studies have demonstrated that exocrine secretion is blocked during the course of pancreatitis, thus, contrary to earlier assumptions, there is no additional benefit in terms of suppression of secretion for fasting [160,161].

Enteral tube feeding is superior to parenteral nutrition in acute pancreatitis. Ten prospective randomized clinical studies [162–169] have demonstrated that enteral nutrition is superior to parenteral nutrition in acute pancreatitis. The reasons lie not only in the cost of parenteral nutrition (six times more expensive than enteral tube feeding), but in the potential complications of parenteral nutrition. Apart from the risk of an additional source of infection by the central venous catheter, animal studies have shown the development of intestinal villous atrophy within a few days of exclusively parenteral nutrition (see Chapter 114). Villous atrophy facilitates bacterial translocation. In patients with necrotizing pancreatitis, the translocated bacteria preferentially colonize pancreatic necrosis and cause one of the most serious complications of pancreatitis, that is infected necrosis. Enteral nutrition administered via a nasojejunal tube or, according to most recent studies, with the same effectiveness via a nasogastric tube, may counteract translocation and has proven an alternative to parenteral nutrition [170,171]. The administration of total caloric requirement via an enteral nutrition tube is not possible in all patients with necrotizing pancreatitis, and additional intravenous supplementation is occasionally required to prevent catabolism. Nevertheless, calories should be administered by the enteral route whenever possible to prevent intestinal villous atrophy. Imrie et al. were able to demonstrate that the rate of pulmonary complications is also significantly reduced by enteral nutrition [161]. However, a Dutch trial did not find superiority of early nasoenteric tube feeding as compared with an oral diet after 72 h in reducing the rate of infection [172].

Return to oral nutrition should be initiated as early as possible (evidence 2b). Studies indicate that oral feeding may have a positive effect on the course of mild acute pancreatitis in comparison with fasting. Oral food intake should start as early as possible in the pain-free patient according to a multicenter cohort study on symptom relapse in acute pancreatitis. Levy et al. found that approximately 20% of patients suffer recurrence of pain upon oral refeeding. The probability of recurrence depends on the extent of necrosis [173], a finding confirmed by a metaanalysis of three studies [174]. The value of so-called "pancreas diets" or "bland" diets for pancreas patients is unproven. Indeed, a randomized trial suggested that initial fasting for mild acute pancreatitis is no longer recommended

[175]. Thus, a reduction in the length of hospital stay and a more rapid recovery can be achieved through early oral feeding [176].

Antibiotics

Routine prophylactic administration of antibiotics is not warranted (evidence 1a). Studies have convincingly shown that in general antibiotic prophylaxis does not offer any advantages and only contributes to the selection of resistant organisms. However, patients with proven infected pancreatic necrosis may profit from antibiotic treatment. A metaanalysis of prophylactic antibiotic administration, which also includes the data of the Meropenem Study by Dellinger et al. [177], incorporating seven studies with a total of 467 patients, found no reduction of the rate of infected necrosis [178]. Mortality was also not significantly reduced in the antibiotic therapy group. Numerous older studies and metaanalyses were unable to substantiate in severe pancreatitis a significant advantage of antibiotic prophylaxis with regard to extrapancreatic infection, infected pancreatic necrosis, and mortality. A significant advantage with regard to infected necrosis was demonstrated, however, for the beta-lactam antibiotic imipenem but not for mortality. All of these studies had methodological weaknesses, and most were inadequately powered. Given the high mortality rate of severe necrotizing pancreatitis, the administration of antibiotics that penetrate infected necrotic tissue in the pancreas (e.g., beta-lactams, quinolones, etc.) is still assumed to be beneficial in this subgroup [179–184].

Probiotics should not be given. They tend to have an unfavorable effect on the course of pancreatitis (evidence 1b). Probiotics are living microorganisms, which are assumed by many to have a number of positive effects on health. Olah et al. conducted two randomized controlled studies on the prophylaxis of infected necrosis in patients with acute pancreatitis. Both studies suggested that the use of probiotics lowers the incidence of infectious complications [185,186]. The PROPATRIA study of the Dutch Pancreatitis Study Group did not confirm these positive effects. In a double-blind placebo-controlled study involving 298 patients with severe acute pancreatitis, administration of a probiotic preparation was associated with a significant increase in mortality, caused predominantly by intestinal necrosis [187]. The administration of probiotics for the treatment of acute pancreatitis should therefore no longer be recommended [187–189].

In the absence of symptoms of small bowel obstruction or ileus with vomiting, placement of a gastric tube is not mandatory (evidence 4). Inhibition of gastric acid secretion for prophylaxis of stress ulcers may be recommended in patients with severe pancreatitis (evidence 3a). Adequate therapy of pain is mandatory. Restriction from oral nutrition may be necessary according to the clinical situation (evidence 4). Intensive care may be necessary. Therapy is based on standard principles with emphasis on therapy of sepsis, SIRS, and multiorgan failure (evidence 5). The initiation of oral nutrition should not be delayed (evidence 2b). In severe cases, nutrition should be primarily performed via gastric or jejunal tube feeding (evidence, 2b).

Treatment of necrosis (see Chapter 82)

Physical examination, laboratory parameters, and contrast-enhanced CT together can provide findings suggestive of infected necrosis. Necrotic infection suspected on clinical and/or imaging grounds can be confirmed by FNA and microbiological studies (evidence 2b) [149,190]. Individual parameters, such as procalcitonin, cannot confirm necrotic infection.

Conservative treatment should be followed initially for infected necrosis. Interventional endoscopic therapy should be given preference over an open surgical procedure (see Section Further indications for interventional endoscopic or surgical therapy). When interventional endoscopic or surgical procedures are necessary they should be started as late as possible in the disease course (evidence 1b). A surgical approach for acute necrotizing 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 a rather "conservative", interventional management. Originally, an indication for necrosectomy was assumed once multiple organ failure had occurred. This approach was associated with a mortality rate of up to 65%. Even in 2003, the mortality rate for open surgery was around 47% [190]. Thus, the benefits of a surgical approach have been questioned. Open necrosectomy should therefore be avoided whenever possible because the surgical trauma induces SIRS, which is very difficult to treat [191]. A study by Mier et al. substantiates that a surgical approach within 2 weeks after onset of the disease is associated with significantly higher mortality [192]. A combined conservative and interventional approach is at least equal to the surgical approach, even in the presence of infected necrosis [193]. A number of studies have shown that minimally invasive therapeutic approaches such as percutaneous CT-guided drainage (Figure 84.9) or laparoscopic-assisted necrosectomy can be effective [194,195]. The minimally invasive "step-up approach"

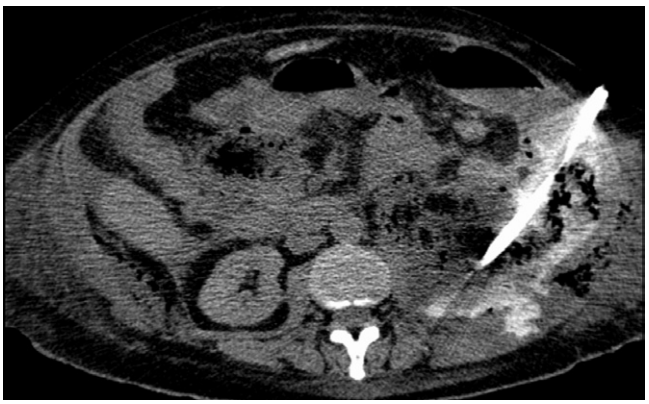


Figure 84.9 Extended pancreatic and retroperitoneal necrosis. Computed tomography-guided drainage of an extended retroperitoneal necrosis due to necrotizing pancreatitis.

results in a significantly better clinical course, as shown in the PANTER study (combined endpoint: mortality and severe complications) [196,197].

Transgastric or transduodenal endoscopic necrosectomy is a new and much less invasive therapeutic approach. To date, approximately 250 treated cases have been reported in the literature. The indication was either confirmed infected necrosis or pancreatic abscess. Technical success rate in this highly selected group of patients was 92.1%, with complications such as colonic fistula, hemorrhage, prosthesis dislocation, pain after more than 24 h, 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 number of interventions was a median of 2.3 [198–201].

Thus, these procedures provide a promising therapeutic approach for some patients [193–206]. Intervention should start between 2 and 3 weeks after onset of disease at the earliest [207].

Further indications for interventional endoscopic or surgical therapy

Band-like upper abdominal pain is a cardinal symptom of chronic pancreatitis, together with weight loss, steatorrhea, and diabetes mellitus. In the absence of therapeutic approaches that are able to address the underlying causation, treatment is restricted to symptom control by means of enzyme replacement, pain therapy, and optimal control of endocrine insufficiency. Between 30% and 60% of patients develop complications of their disease, including strictures of the common bile duct, inflammatory space-occupying masses, pancreatic pseudocysts, or pancreatic ductal stones, which require interventional or surgical treatment.

Interventional or surgical treatment should be undertaken for chronic severe pain requiring analgesics (evidence 2b). Severe pain in chronic pancreatitis that requires analgesics can sometimes be effectively treated by either endoscopic or surgical procedures (evidence 2b/3b) [208]. Surgical procedures (drainage) are superior to endoscopic procedures with regard to long-term pain reduction; however, they are associated with higher mortality but lower morbidity. There have been several studies with a level of evidence grade 2b or 3a that have addressed the treatment of pain from chronic pancreatitis by endoscopy, extracorporeal shock wave lithotripsy (ESWL), thoracoscopic splanchnicectomy, surgical resection, and draining procedures. A direct comparison between surgery and endoscopy was carried out in only two studies, with level of evidence grade 1b [209,210]. Both studies demonstrated a long-term advantage for surgical approaches.

If a resectable pancreatic carcinoma is suspected, then surgery should be performed. (evidence 2b). If a space-occupying lesion of the pancreas is present and suspected (resectable) pancreatic carcinoma cannot be excluded, then surgical resection is indicated. Without surgery, life expectancy for patients with pancreatic carcinoma is less than 1 year; after successful resection it may be more than 5 years in 20%–25% (evidence 1a) [211,212].

Exocrine pancreatic insufficiency as the only presenting symptom of chronic pancreatitis is not an indication for surgical or interventional treatment. Exocrine pancreatic insufficiency is usually treatable with pancreatic enzyme replacement therapy. There are to date no convincing studies showing that exocrine pancreatic function is improved by endoscopic intervention or surgery. Thus, surgical procedures cannot be recommended for the treatment of exocrine pancreatic dysfunction. There are virtually no studies available on endoscopic treatment for exocrine insufficiency. Results of exocrine pancreatic function after Beger's, Kausch–Whipple's, or Frey's procedures are highly variable in their final outcome [213].

Endocrine pancreatic insufficiency as the only presenting symptom of chronic pancreatitis is also not an indication for surgical or interventional treatment of chronic pancreatitis. There are a few case series reporting an improvement in glucose control after resection of a carcinoma, but randomized studies showing a positive effect on diabetes after resection for chronic pancreatitis are not available. Case series do not justify a recommendation for surgery undertaken to improve endocrine insufficiency [214].

Gastric outlet obstruction or duodenal stenosis secondary to chronic pancreatitis should be corrected by interventional or surgical means. Unfortunately, there are no comparative studies available that could answer which modality among resection surgery, bypass surgery, or endoscopic insertion of self-expanding metal stents may be superior [215].

Between 30% and 60% of all patients with chronic pancreatitis will require intervention at some point in the course of their disease. In at least 30% of patients, conservative management, supplemented by endoscopic therapeutic interventions, appears to be sufficient while in 10%–40% of patients, stenosis of the common bile duct (CBD) will develop, which requires intervention (Figure 84.10). In the presence of an inflammatory tumor of the pancreatic head, ERCP for bile duct obstruction with insertion of a stent into the bile duct should be performed followed by duct dilatation. However, if after endoscopic stenting symptoms or cholestasis persist, then surgical resection should be performed (evidence 2b). 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 lasting benefit beyond 1 year [216]. A prospective study showed a poorer long-term effect of stent management of distal bile duct obstruction if calcifications were associated with chronic pancreatitis [217].

Stenosis of the pancreatic duct is another complication that affects many patients with chronic pancreatitis (Figure 84.11). There are no prospective controlled studies available that have demonstrated a positive effect of stent drainage of a dominant stenosis in the duct of Wirsung. Some studies suggest that the insertion of a stent into the pancreatic duct can actually induce secondary changes due to the stent with subsequent fibrosis and stricture [218,219]. Removal of the obstruction of the main

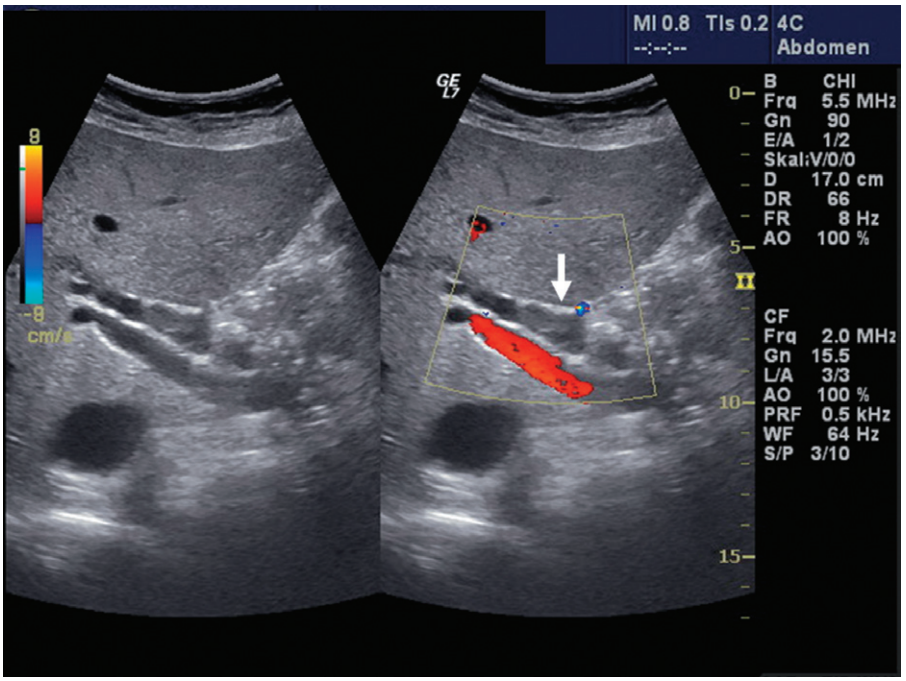


Figure 84.10 Dilated bile duct. Transabdominal ultrasound: dilated bile duct shown at liver hilus (arrow) due to an inflammatory mass of the pancreatic head in chronic pancreatitis.

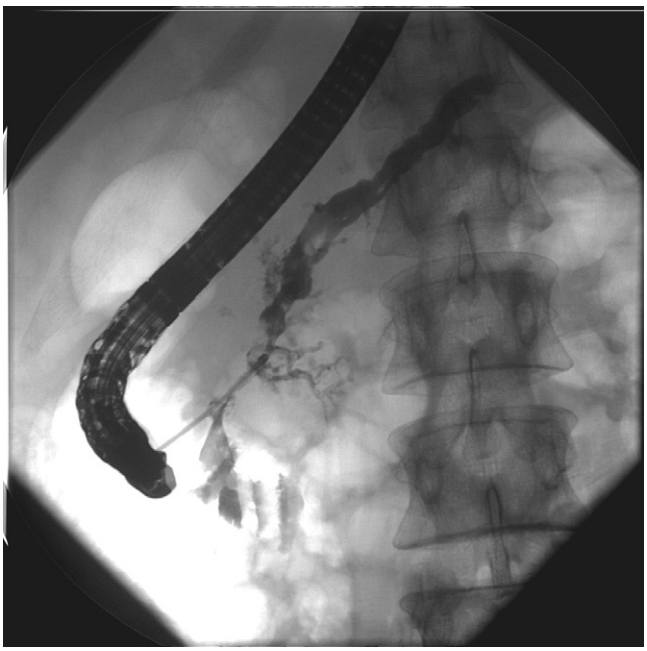


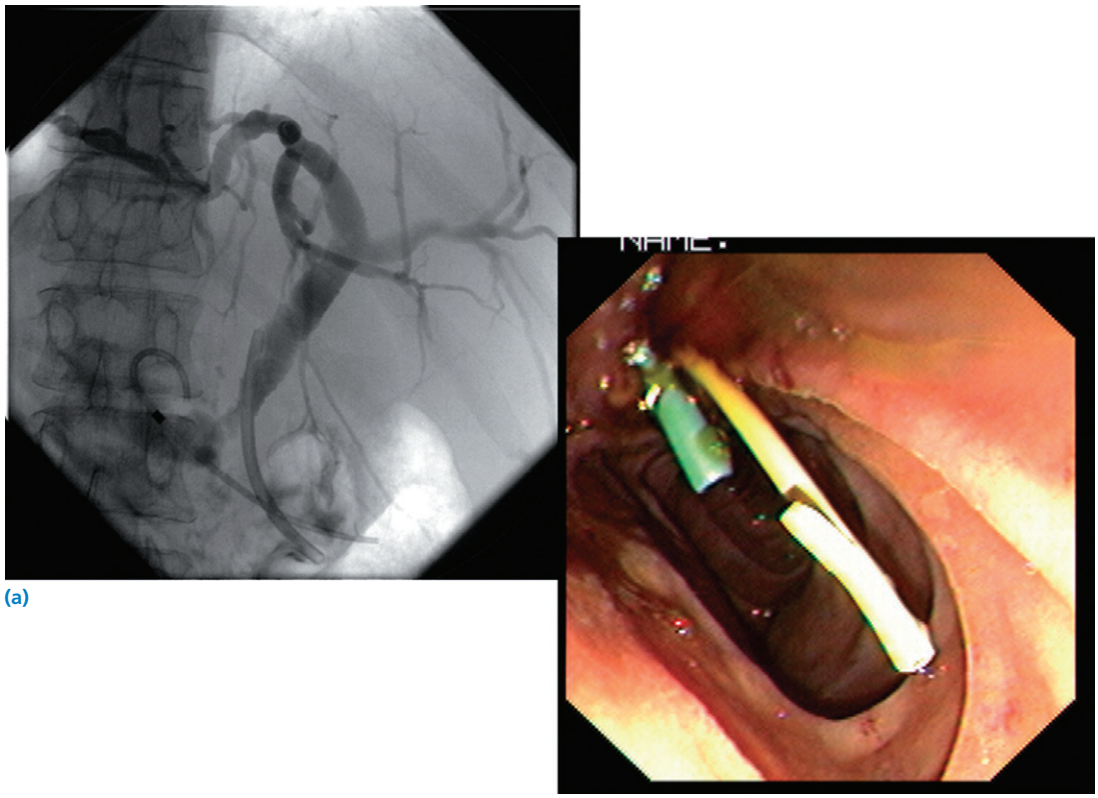
Figure 84.11 Dilated main pancreatic duct with prepapillary stenosis. Endoscopic retrograde pancreatography reveals prepapillary stenosis of main pancreatic duct and a duct stone probably not responsible for duct dilation.

pancreatic duct is often effective for pain management in the shorter term, and success rates of between 37% and 94% are reported [220]. Thus, stenting of a prepapillary stenosis of either the common bile duct or the main pancreatic duct or both as initial treatment is employed by many groups (Figure 84.12). Metabolic side-effects of stenting the pancreatic duct over a longer period of time have not been reported.

ESWL can be used for treatment of stones in the main pancreatic duct. Before the introduction of ESWL in 1989, surgery was often the only option for removing pancreatic duct stones that cannot be removed by endoscopic means. Several retrospective studies have addressed the question of the clinical benefit of ESWL for pancreatic duct stones. For further reading see reference [221].

Therapy of pseudocysts

Pancreatic pseudocysts are a frequent complication of acute and chronic pancreatitis. Symptomatic pseudocysts should undergo treatment. The endoscopic or surgical treatment of a symptomatic pseudocyst should be carried out regardless of its size (evidence 2a). Pseudocysts that have resulted in complications such as gastric outlet obstruction, hemorrhage, pain, cholestasis, or vascular stenosis should undergo endoscopic or surgical treatment. The surgical procedures to treat pseudocysts tend to have higher success rates, but carry a somewhat higher mortality rate than the endoscopic pseudocyst drainage into either the duodenum or more often the stomach. In cases where a pseudocyst is connected to the main pancreatic duct, endoscopic transpapillary drainage may be possible. The decision in whom,



(a) (b)

Figure 84.12 (a, b) Distal bile duct and main pancreatic duct stenosis treated by stents. One plastic stent is placed via endoscopic retrograde cholangiopancreatography after papillotomy into the bile duct and another one in the main pancreatic duct.

when, and by which procedure pancreatic pseudocysts should be treated has been controversial. The prevalence of pancreatic pseudocysts in chronic pancreatitis ranges between 20% and 40% [222]. Pancreatic pseudocysts occur most often in patients with alcoholic chronic pancreatitis (70%–78%) [8] and are less common in idiopathic chronic pancreatitis (6%–16%) and biliary pancreatitis (6%–8%) [222]. Within the first 6 weeks after an acute exacerbation of pancreatitis, 40% of the pseudocysts resolve spontaneously, while in 20% of cases complications such as infection, obstruction of adjacent organs, cystic rupture, or persistent pancreatitis render an intervention necessary. Spontaneous remission of pseudocysts after 12 weeks is very rare, and complications are observed in up to two-thirds of cases. The increase in size of pseudocysts to over 5 cm in diameter is associated with an increased risk of complications. In symptomatic pseudocysts, either surgery or percutaneous or endoscopic drainage can be performed. All of these procedures demonstrate comparable results regarding technical success and recurrence rates. Endoscopic drainage should have first preference because it is less invasive for the patient.

If a pancreatic pseudocyst causes complications, an interventional or surgical form of treatment should be undertaken (evidence 2a). The literature on interventional therapy of pancreatic pseudocysts as a form of pain management is very limited. Most of the data are based on retrospective case series [223–228]. Despite the limited data available, there are three systematic reviews [229–231]. Pain relief will be achieved in a majority of patients, whether treatment is by a surgical, endoscopic, or percutaneous drainage technique. 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 the more effective form of pain management. The relative merits of these different approaches in this setting have not been defined. Thus, it may be assumed from the scant literature available that pseudocyst drainage improves pain. In cases of obstruction of the bile duct or pancreatic duct by pancreatic pseudocysts, the pseudocyst should be treated. When cholestasis does not improve after drainage of the pseudocyst alone, stent placement into the bile duct or a resection procedure may be indicated.

Further complications that render endoscopic or surgical treatment of the pseudocyst necessary include compression of large abdominal vessels, clinically relevant gastric outlet obstruction or duodenal stenosis, infection of a pseudocyst, and pancreaticopleural fistula formation. Nausea and vomiting are quite common symptoms of pancreatic pseudocysts. Endoscopic

interventional therapy of a hemorrhagic pseudocyst is associated with a high risk of further bleeding. Thus, these pseudocysts should be treated surgically.

Initial therapy for symptomatic pancreatic pseudocysts can be endoscopic drainage of the pseudocyst followed by surgery should the pseudocyst recur (evidence 3a). The choice between endoscopic and operative pseudocyst drainage should be determined by the location of the cyst and the type of additional morphological changes (evidence 3b). Endoscopic procedures draining a pancreatic pseudocyst are less prone to complications than surgical procedures. However, not all pseudocysts are successfully treated by endoscopic drainage alone. Studies comparing endoscopy with surgery are not available, but a multidisciplinary approach may be appropriate for long-term patient management [232].

Asymptomatic pancreatic pseudocysts, which have reached the size of more than 5 cm in diameter and which do not resolve within 6 weeks, can be treated (evidence 2a). Pancreatic pseudocysts that show already a fibrous wall of more than 5 mm on imaging are particularly suited for endoscopic or surgical drainage. In a multivariate analysis, a pseudocyst size <4 cm in diameter was the only favorable factor for spontaneous resolution [233]. Untreated cysts larger than 5 cm may have a higher risk of complications such as rupture, infection, jaundice, or hemorrhage [234].

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 (evidence 4). One should select the access route for endoscopic transmural drainage of pseudocysts by endoscopic ultrasound assessment. The access route depends on the size, vessels in the vicinity, and location of the pseudocyst. Comparative studies assessing the optimal superiority of the endoscopic access route, either through the stomach or duodenal wall, are not available. Transcutaneous drainage carries a risk of persistent cutaneous fistula formation, adversely affecting the patient's quality of life. Thus, endoscopic transmural drainage is preferred [232].

Transmural drainage should be done under EUS guidance (evidence 3). EUS is the best measure to assess the appearance of the pseudocyst wall, content, location, and relationship to adjacent blood vessels. EUS guidance possibly reduces the rate of failed puncture attempts and complications [235], although a direct comparison of the complication rate for transmural needle drainage without ultrasound guidance is not available. The success rate in the 1126 published patients with transmural drainage of a pancreatic pseudocyst is reported to be 79.2%, with more recent studies reporting success rates of significantly over 85%. These results are comparable with surgery. The mortality rate in larger series involving over 30 patients was 0.2%. The recurrence rate is reported to be around 8% and the complication rate 13%.

A diagnostic needle aspiration of the cyst may be performed for suspected infection or for suspected neoplasm (evidence 4). If diagnostic needle aspiration of the cyst confirms an infection of its content, then drainage is indicated. Surgical treatment should be carried out not only when malignancy is detected but when suspected as well. Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between cystic malignancies and pseudocysts. When EUS-guided needle aspiration of a cyst reveals a CEA >400 ng/mL, a variably increased or low amylase (lipase), high viscosity, mucin, or epithelial cells in the cyst contents, then the presence of a mucinous cystic neoplasm must be assumed. This kind of tumor is more prevalent in women aged between 30 and 50 years, located usually in the pancreatic tail and demonstrates mural nodules on imaging. A so-called eggshell pattern of calcification is typical. Prognosis after surgery is good in the absence of tumor invasion. A malignant lesion may be assumed with a CEA value >6000 ng/mL. Aspiration biopsy of an mucinous cystic neoplasm differs only little from an intraductal papillary mucinous neoplasm (IPMN). IPMN is regarded as a precancerous lesion. Its malignant potential depends on its location (main duct or side branch duct) and the size of the lesion as well as its solid parts. An IPMN originating from the main pancreatic duct should always be resected because in 52%–92% of cases a carcinoma develops from this lesion within a period of 8 years. For lesions of the side-branch ducts this amounts to 6%–46% [236]. Lesions less than 1 cm on MRI or EUS and originating from a side-branch duct may be followed-up by imaging after 1 year. Side-branch lesions that are between 1 and 3 cm in size and exhibit no solid components should be followed up after 6 months. In contrast, lesions that are larger than 3 cm or exhibit mural nodules or cytology with higher-grade dysplasia should be resected. IPMN may be multifocal, in which case a more aggressive course can be expected [237]. In contrast, a serous cystadenoma is diagnosed as pancreatitis in 30% of cystic lesions and virtually never turns malignant. In this case, aspiration of the cyst is negative for mucin, CEA, and amylase. Cytology reveals glycogen-rich epithelium (see Chapter 86 for more details).

A surgical approach should be chosen for a suspected malignant cystic lesion (evidence 4). In 1% of all CT scans of the abdomen, a cystic lesion of the pancreas is discovered as an incidental finding [238]. More than two-thirds of these lesions are congenital cysts or pancreatic pseudocysts. The prevalence of pancreatic pseudocysts in chronic pancreatitis ranges between 20% and 40%. Of the cystic lesions that 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 tumors or cystic acinar cell carcinoma are rare. In assessing cystic tumors found in asymptomatic patients, a 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) are essential considerations. Diagnostic needle aspiration of a pseudocyst with EUS guidance

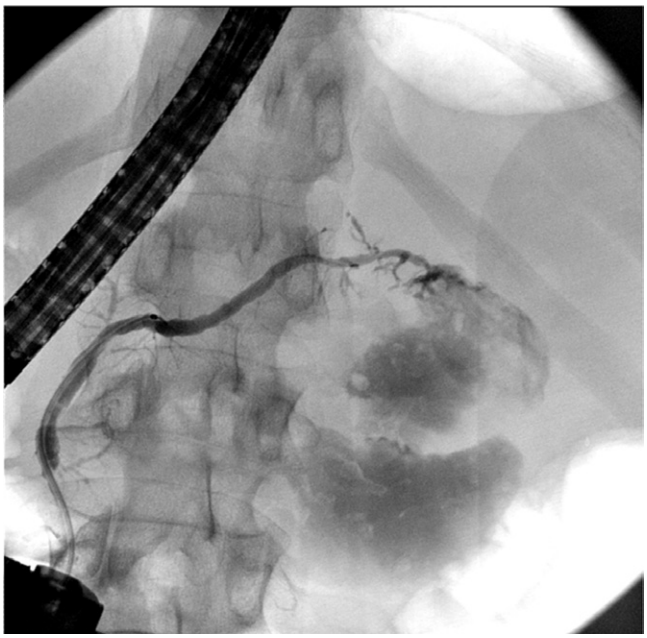


Figure 84.13 Pseudocyst in the pancreatic tail. Endoscopic retrograde pancreatography: visualization of a pseudocyst in the pancreatic tail.

helps in differentiating between premalignant cystic neoplasms, cystic malignancies, and pseudocysts.

Visualization of the pancreatic ducts can be performed before endoscopic or surgical drainage of a pseudocyst (Figure 84.13) (evidence 3b). Whether an ERCP with attempted pseudocyst drainage via the papilla should be performed instead of transgastric or transduodenal drainage is still a matter of controversy. Drainage of the pseudocyst via a stent in the pancreatic duct is the "most physiological" form of drainage. According to one study, 22%–57% of pancreatic pseudocysts have a connection with the pancreatic ductal system [226]. Thus, an endoscopic retrograde pancreatography (ERP) can precede endoscopic transmural drainage in order to detect a connection with the duct or to exclude a rupture of pancreatic ducts (8% after acute necrotizing pancreatitis). Transmural drainage in the presence of an undetected rupture of the pancreatic duct or a connection of the pancreatic pseudocyst with an obstructed pancreatic duct often yields disappointing long-term outcomes. However, the success rate of an attempted transpapillary drainage is usually less than 60%. Furthermore, these attempts carry a risk of ERCP-induced pancreatitis. Direct transgastric or transduodenal cyst drainage is very effective and usually associated with few complications [233]. The procedure-related incidence of an infection of a pseudocyst and the risk of development of a pancreas abscess increases if undertaken without antibiotic prophylaxis [239].

In patients with advanced pancreatic duct changes, especially pancreatolithiasis, any pseudocyst treatment should be part of a general therapeutic plan (evidence 2b). The presence of chronic pancreatitis with respective pancreatic duct anomalies or pancreatic ductal stones is a relative indication for the treatment of pseudocysts, because in these cases the rate of spontaneous regression, even of small cysts, is at most 10%–26% due to continued inflammation [233]. Treatment of pancreatic duct obstruction can be undertaken in patients with a pancreatic pseudocyst, prestenotic duct dilatation or fistula formation (evidence 4). Pancreatic pseudocysts are maintained by pancreatic duct obstruction in the presence of prestenotic duct dilatations or fistulae, if these stenoses impede pancreatic secretions. In these cases, removal of the pancreatic duct obstruction is recommended.

Therapy of vascular pseudoaneurysms

Vascular pseudoaneurysms secondary to chronic pancreatitis should be treated. There are no studies available that compare active treatment of vascular pseudoaneurysms with watchful waiting. Furthermore, there are no studies examining the best time point for treatment of vascular pseudoaneurysms. Both surgical and radiological interventional approaches have been used in the treatment of pseudoaneurysms. Angiographic embolization is the method of first choice for active hemorrhagic pseudoaneurysms (evidence 3a). According to a systematic review of case series available the success rate of angiographic treatment was 66% [240], and the complication rate is lower as compared to surgery and hospital stay is shorter [240]. Surgery should be reserved for patients in whom an operation is also indicated for other complications of chronic pancreatitis.

Therapy of pancreatic duct stenoses and ductal stones

In patients with chronic pancreatitis, the pressure in the pancreatic duct is initially increased, regardless of etiology and dilation of the duct of Wirsung [241]. Ductal and interstitial hypertension and possible relative pancreatic ischemia are thought to play a role in the genesis of pain. 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 outflow (Figure 84.12). Techniques such as sphincterotomy, dilatation, ESWL and stent insertion have been modified for treatment of pancreatic ductal lesions. The endoscopic procedure can precede the surgical procedure, as an alternative to surgery, with low morbidity and low mortality. Endoscopic interventions do not interfere with subsequent surgery. Furthermore, clinical success after endoscopic reduction of the intraductal pressure does provide some indication of the potential effectiveness of surgical drainage or a resection procedure.

Pancreatic ductal stones may cause pain by obstructing the outflow of pancreatic juice, induce recurrent exacerbations, maintain a pseudocyst or fistula, or cause other complications. Stones can be treated by endoscopic or surgical means (evidence 4). Pancreatic ductal stones are typically the result and not the initial cause of chronic pancreatitis. However, they can lead to an obstruction of the outflow of pancreatic secretions in the ducts and duodenum and thus maintain pseudocysts or fistulae.

They can also cause recurrent exacerbations or contribute to the pathogenesis of pain. Under these conditions, treatment of pancreatic ductal stones appears appropriate. However, there are no studies available that have compared the treatment of pancreatic ductal stones with a sham intervention. Case series and one metaanalysis are available that show improvement of pain after treatment of pancreatic ductal stones, although comparative studies involving the spontaneous course or randomized studies have not been published. Endoscopic treatment appears particularly suitable for treating solitary stones and obstructions close to the papilla. Surgical drainage procedures have been shown to be superior for distal obstructions. There are no studies available comparing either endoscopic or surgical procedures with untreated cohorts or in direct comparison with the natural course of the disorder. In two studies, in which endoscopic treatment was compared with surgery, that is drainage operation, the results after surgery were significantly better with respect to long-term pain reduction [209,210].

Pancreatic duct obstructions, which may be responsible for pain, recurrent exacerbations, maintenance of a pseudocyst, fistula, or other complications, can be treated by endoscopic dilatation and stent placement (evidence 4). Studies involving dilatation of pancreatic duct obstructions in comparison with a sham intervention are not available. In a prospective nonrandomized study, rapid improvement of symptoms was achieved by insertion of a pancreatic stent in nonoperable patients, although further interventions were frequently necessary [242]. Some studies report that the insertion of a prosthesis into the pancreatic duct can induce secondary changes due to the stent, including subsequent fibrosis and strictures [218,219]. 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, long-term reduction of pancreas-related pain was achieved in 84% of cases [243]. However, in 79% of the patients, stent therapy for control of pain had to be repeated within 1 year and in 97% within 2 years. Metabolic side-effects have not been examined over the long term.

Endoscopic placement of a stent into the pancreatic duct may be performed if pancreatic ductal stones or stenosis of the pancreatic duct near the papilla causes obstruction to flow. Benign strictures of the duct of Wirsung can develop as a complication of an impacted stone or as the result of acute inflammatory parenchymal changes with compression or stricture of the duct [244]. The success of stent placement has been assessed in several studies [245–252]. Pancreatic stent placement is technically successful in about 70% of patients. Patients in whom a pancreatic fistula or a pseudocyst is maintained by an obstruction especially benefit from this approach. Endoscopic drainage with stone extraction and stent therapy is an effective measure to control pain in some patients with a dilated duct of Wirsung [228]. However, better pain management was achieved by pancreaticojejunostomy in two randomized controlled studies [209,210]. Endoscopic therapy led to pain reduction or complete pain relief in 32% [209] and 65% [210], respectively, whereas this was achieved in 75% [209] and 86% [210], respectively, by pancreaticojejunostomy. The disparate success rates of endoscopic therapy in the two studies are possibly due to the longer duration of stent therapy in the study by Dité et al. There are currently no reliable data available regarding the duration of stent therapy, and thus no general recommendations can be made about the necessary duration of stent therapy (evidence 4). Some authors recommend treatment over 1 year with an exchange of the stent at least every 3 months.

When surgery is not possible, a coated self-expandable metallic stent can be inserted into the duct of Wirsung for pain control (evidence 4), an approach supported by a few case reports and small case series. Their potential advantage versus plastic stents is due to their longer period of patency. Long-term results showing clear benefit are not available. Uncoated self-expandable metallic stents are not recommended due to the rapid proliferation of duct epithelium as a reaction to the metal mesh [253,254].

Pancreatic ductal stones, which cause pain by obstructing the ducts, may be treated by ESWL, which can alleviate the obstruction. There is some evidence that the subsequent endoscopic removal of the pancreatic ductal stones or their fragments is not a prerequisite for the effectiveness of the procedure [255]. The treatment of pain in patients with diffuse calcifications by means of ESWL has not been substantiated in any studies (evidence 2b). A metaanalysis demonstrated significant pain reduction; however, results were highly variable [256]. The metaanalysis included only case studies without untreated or sham-operated control groups. In a cohort study, a better technical result was reported regarding the complete removal of stones by using ESWL with subsequent endoscopic stone retrieval in comparison with ESWL alone [257]. Only one randomized controlled study has been published comparing ESWL with and without subsequent ERP to remove fragments from the main pancreatic duct. In this study, endoscopic stone extraction subsequent to ESWL had no influence on pain relief after 2 years [255].

Endoscopic treatment of bile duct obstruction

Obstruction of the CBD will develop in 10%–44.6% of patients with chronic pancreatitis and require intervention. Indications for endoscopic intervention include significant cholestasis, exacerbations of cholangitis, prevention of secondary biliary cirrhosis, and determining the cause of pain (obstruction of the CBD vs chronic pancreatitis). Several studies have assessed the efficacy and cost effectiveness of endoscopic drainage of the CBD. A long-term success rate was achieved in only a third of the patients. Thus, in most patients endoscopic therapy is only indicated as an interim or temporizing procedure prior to definitive surgery, for example as an acute intervention in septic patients, or in nonoperable patients or in those unwilling to undergo surgery. In principle, there is a risk of developing cholangitis after endoscopic drain placement. The administration of prophylactic antibiotics together with ursodeoxycholic

acid has not been proven effective [258–263]. The most common complications include stent occlusion by cellular detritus, bacteria, or extracellular, fibrillar material.

If chronic pancreatitis causes bile duct obstruction and if there are clinical signs of cholangitis, then immediate endoscopic drainage of the obstruction should be carried out. Treatment of mechanical cholestasis as part of therapy for cholangitis is important and well substantiated by clinical experience. If chronic pancreatitis causes distal obstruction of the bile duct with cholestasis or jaundice, then either surgical treatment or endoscopic stent therapy should be performed (Figure 84.12). If calcifications are present in the pancreas, then surgical treatment should be favored (evidence 4). Cholestasis due to obstruction may be treated by either endoscopic or surgical means, although endoscopic stent therapy has lasting success beyond 12 months in only a third of patients. A prospective study showed an even worse long-term effect of stent management for distal bile duct obstruction in patients with calcifying pancreatitis (long-term effect 9%) [217]. In these cases, surgical treatment is preferred. A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for obstruction of the CBD in patients with chronic pancreatitis has no additional benefit beyond 1 year [216]. Surgical treatment should therefore be pursued for recurrence of CBD obstruction after 1 year of stent therapy.

Treatment by insertion of several plastic stents for distal bile duct obstruction can be recommended (evidence 3b). 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, nonrandomized single-center study, the long-term success rate after insertion of four or five stents into the CBD was higher than after a single stent [264]. The insertion of coated metal stents can be undertaken for distal bile duct obstruction (evidence 4). Good results have been reported for coated metal stents in case series. However, there are no randomized studies comparing coated metal stents with singular or multiple plastic stents [265,266].

Endoscopic treatment for distal common bile duct obstruction should not extend beyond 12 months. Stent exchange should be undertaken every 3 months at most because otherwise occlusion of the stent may cause cholangitis (evidence 4). Long-term success, defined as an exchange of stents no more frequently than at 3-month intervals without recurrence of cholestasis, is achieved in only about a third of patients [252,267–269]. The exchange interval is less critical with the insertion of multiple stents [270].

The management of chronic bile duct obstruction after unsuccessful attempts at endoscopic treatment should be surgical (evidence 1b). Surgical resection to treat bile duct obstruction in patients with chronic pancreatitis is effective and often has lasting success. The long-term results of the various surgical procedures such as Beger, Büchler, Kausch–Whipple, and Frey do not differ from each other with regard to quality of life, exocrine pancreatic insufficiency, endocrine pancreatic insufficiency, pain, and recurrence rate [271–273]. If there is an indication to treat cholestasis by surgery, 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 (evidence 2a). A multicenter prospective randomized study examined the effect of preoperative endoscopic stent insertion into the CBD for mechanical cholestasis secondary to carcinoma of the head of the pancreas before pancreas resection. Preoperative drainage significantly increased the rate of complications [274]. A short individual life expectancy of a patient, a high comorbidity, and a technically difficult operation (e.g., marked collateral circulation secondary to portal hypertension), all favor endoscopic treatment of bile duct obstruction.

Pain management

Pain is the predominant clinical symptom for 80%–95% of patients. Studies on the natural course of the disease reveal that the intensity of pain often declines with increased duration of the disease ("burn-out of pain") [24]. 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 the USA, the annual costs caused by pain due to chronic pancreatitis amounts to $638 million [275]. The cause of pain is multifactorial. Pancreas-related causes of pain include inflammatory infiltration of the parenchyma and nerve sheaths, especially sensory nerves. Obstruction to outflow due to scars and stones can be responsible for a rise in pressure. However, drainage of the duct or reduction of secretion with the aid of drugs (somatostatin analogues) does not always result in adequate pain reduction. Increased pancreatic parenchymal pressure causes pain due to tension in the pancreas, similar to pain due to pancreatic pseudocysts. In addition, neuropathy may contribute [276]. Extrapancreatic causes of pain include concurrent and secondary disorders, such as gastric or duodenal ulcers and meteorism or bloating, caused by gaseous distention due to abnormal bacterial colonization of the intestine secondary to maldigestion.

Pain score

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 (evidence 1b). There are only two studies that have validated a pain scale [277,278]. The older study assessed a pancreatitis-specific pain score [277]. Rated on a scale from 0–100 are: frequency of pain attacks (0 never, 100 daily), intensity of pain on the VAS (1–100), use of analgesics (100 morphine, 1 acetylsalicylic acid), and pain-related absence from work (100 permanent, 0 not in the last year). The more recent study compared the SF-12 with the SF-36 Quality of Life Questionnaire [278]. Both studies included aspects of pain that have an effect on the quality of life. An explicit pain score, assessed independently of the quality of life data, was not

included in the evaluation. Both the SF-12 and the SF-36 have been assessed as valid, albeit only for the assessment of quality of life. The pain score published in 1995 is therefore the only validated score explicitly for pain in patients with chronic pancreatitis.

Pain medication

Pain management in patients with chronic pancreatitis should follow the World Health Organization (WHO) three-step analgesic ladder (evidence 5). There have been four randomized controlled studies published addressing pain management in chronic pancreatitis but these involved only 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 has been examined. Thus, the effectiveness of the WHO pain management plan cannot be answered at present. Analgesics are indicated to treat patients with pain from chronic pancreatitis in order to achieve pain relief or reduction of pain until definitive treatment (e.g., endoscopy or surgery).

The duration of trial therapy with various combinations of pain relievers can be decided on a case-by-case basis. However, reevaluation should be made regularly when treatment remains unsuccessful in order to augment the treatment with an endoscopic or surgical procedure (evidence 5). There are no data to guide the duration of pain therapy using conservative means or when endoscopic or surgical treatment is indicated. Most clinicians 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 [279].

Weaning patients from pain medication can follow the WHO three-step analgesic ladder in reverse order, reassessing the patient's pain relief at each step (evidence 5). Conservative pain management follows the WHO three-step analgesic ladder, although its effectiveness has not been specifically tested in chronic pancreatitis. Superiority or inferiority over another graduated plan or over simply discontinuing pain medication has again not been examined.

A validated pain score, as discussed above, should be used to guide reduction of pain therapy.

Inhibition of exocrine pancreatic secretion by somatostatin analogs

Octreotide should not be used primarily to treat pain associated with chronic pancreatitis (evidence 1b). Because pain may also be due to an increased pancreatic parenchymal and ductal pressure, the approach of reducing exocrine pancreatic secretion and thus lowering pressure seems pathophysiologically reasonable. However, apart from single case reports and retrospective case series, there is one double-blind crossover study [280] and one unblinded crossover study comparing octreotide with octreotide long-acting release [281]. In both studies, pain was measured by the VAS. The double-blind crossover study comparing octreotide with saline administration was unable to detect reduction in pain or analgesic requirement, while effectively blocking pancreatic secretion [280]. The unblinded crossover study showed no difference between octreotide and octreotide long-acting release with regard to pain reduction. Thus, the potential role of octreotide in treatment of pain associated with chronic pancreatitis remains uncertain.

Inhibition of exocrine pancreatic secretion by porcine pancreatic extracts (negative feedback inhibition)

Pancreatic enzymes should not be used primarily to treat pain associated with chronic pancreatitis (evidence 1a) [282,283]. The rationale behind pancreatic enzyme therapy for pain relief is based on the assumption of a negative feedback mechanism for the release of cholecystokinin releasing peptides. This in turn leads to a reduced release of cholecystokinin and in this way 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 [283]. 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 characteristic variables did 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 that quantified analgesic usage reported a reduction in the consumption of analgesics. No study examined long-term effects of the various types of treatment. One may conclude, therefore, that the use of pancreatic enzyme supplements has no proven positive effect on pain symptoms. Furthermore, no improvement in the quality of life was detected. Another randomized controlled study (25 patients with pancreatic enzymes, 29 with placebo) confirmed the lack of an effect of pancreatic extracts on pain reduction [284]. Due to different inclusion criteria, which are in part not clearly explained in the studies, it is not possible to deduce whether the cause of pancreatitis, the presence of exocrine pancreatic insufficiency, or the specific formulation used was responsible for the lack of therapeutic success. Finally, the negative feedback inhibition of exocrine pancreatic secretion may either not exist in humans or does not play a major role in the pathogenesis of pain [285].

Antioxidants

Increased levels of free oxygen radicals have been detected in the serum and pancreatic juice of patients with chronic pancreatitis. Based on this knowledge, treatments using antioxidants could help to reduce cellular damage from pancreatitis and thus in theory prevent pain. One initial study involving patients with recurrent acute and chronic pancreatitis demonstrated a significant improvement in the number of acute exacerbations as well

as in chronic pain. However, per protocol analysis, only 20 of the initial 28 patients could be assessed [286]. In another study, an improvement in pain could also be demonstrated. However, the number of patients that could be analyzed was much too low to draw any firm conclusions [287]. In a double-blind placebo-controlled study from India, 71 patients were treated with antioxidants and 56 with placebo over a period of 6 months. There was a reduction of the days with pain in the treatment arm [288], but these results were not confirmed in a controlled trial carried out in the USA [289]. Thus, convincing evidence that antioxidants have a role in the treatment of pain from chronic pancreatitis is still lacking. Furthermore, in all of the studies mentioned, the preparations used contained beta-carotene; application of beta-carotene may be associated with the development of bronchial carcinoma in smokers who comprise the majority of patients with alcoholic chronic pancreatitis [290,291].

Electroacupuncture and transcutaneous electrical nerve stimulation

Electroacupuncture and transcutaneous electrical nerve stimulation (TENS) is not effective for treatment of pain associated with chronic pancreatitis (evidence 2b). 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 standardized manner. No benefit was observed from electroacupuncture and TENS in a randomized trial [292].

Inhibition of leukotrienes and radiotherapy

Montelukast should not be used to treat pain associated with chronic pancreatitis (evidence 2b). A 3-month treatment with the leukotriene receptor antagonist, montelukast, also showed no significant reduction in pain [293]. Radiotherapy cannot be recommended for treatment of pain (evidence 4). In a pilot study, significant reduction in pain and avoidance of acute exacerbations were achieved with one session of radiotherapy in 12 of 15 patients [294]. However, in view of an increased risk of developing pancreatic cancer in chronic pancreatitis, radiation may have the potential to increase this risk.

Celiac plexus block or thoracoscopic splanchnicectomy

Celiac plexus block or thoracoscopic splanchnicectomy may be considered for treating pain associated with chronic pancreatitis (evidence 4). There are no randomized controlled trials available comparing celiac plexus block with placebo. However, metaanalyses [295,296], which examined the efficacy of celiac plexus block in a large patient population, found reduction in pain in about 50% of patients. This pain reduction did not persist 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 another treatment option. The concept of pancreatic denervation was suggested for the first time in 1943 by Mallet-Guy, and the procedure was introduced in practice in 1993, and modified into a minimally invasive procedure by the introduction of video-assisted thoracoscopy. A prospective long-term study demonstrated adequate pain control by bilateral splanchnicectomy with a perioperative morbidity of 7% in patients who respond well to epidural anesthesia [297]. A case–control study reported that the results of splanchnicectomy after previous use of opioids are worse than in therapy-naive patients, although thoracoscopic splanchnicectomy showed significantly better results as compared with control patients with purely symptomatic treatment [298].

In conclusion, celiac plexus block for pain associated with chronic pancreatitis is only effective in the short term (a few months at most) and is clearly inferior to surgical management. Splanchnicectomy is, to a certain extent, a modification of celiac plexus block, which can be performed by thoracoscopy. It showed good results in individual cases, albeit the data are sparse. Thus, celiac plexus block should only be pursued in patients who cannot be offered a reliable long-term effective pain control, that is patients who cannot be operated on due to various reasons such as an unfavorable prognosis or a worse general condition. If there are no contraindications, celiac plexus block should be done as a bilateral injection under endoscopic ultrasound guidance (evidence 1b). In a randomized controlled study comparing endoscopic guidance with CT-guided plexus block, superiority of the endoscopic ultrasound guidance has been demonstrated with 30% of patients still benefiting from it after 24 weeks as opposed to 12% after CT-guided injection [299]. When celiac plexus block is compared with pancreaticogastrostomy, the latter provides superior pain relief [300]. Endoscopic ultrasound guidance is superior to needle guidance using fluoroscopy [301]. A cohort study examined the central single endoscopic ultrasound-assisted plexus block in comparison with the bilateral approach. Pain reduction after bilateral injection was better after 7 days than after a single central injection (70% vs 46%) [302].

Surgery for treatment of pain

Surgical treatment should be performed as the most effective long-term form of pain therapy for chronic pancreatitis (evidence 1a) [303,304]. Randomized controlled trials achieved better pain management by surgical treatment such as pancreaticojejunostomy or pancreatic head resections in comparison with endoscopic treatment (for further literature see ref. [305]).

Therapy of exocrine pancreatic insufficiency

The indication for pancreatic enzyme replacement therapy is weight loss of more than 10% of body weight, steatorrhea with fecal fat excretion of more than 15 g/day, or dyspeptic symptoms with severe gas or diarrhea. The majority of enzyme supplements contain pancreatin, a pulverized extract from porcine pancreas with four main components: lipase, amylase, trypsin, and chymotrypsin. Pancreatin is not absorbed from the

gastrointestinal tract, but is inactivated by enteric bacteria and digestive juices and eliminated in the feces. Encapsulated microsphere formulations, which protect the enzymes from gastric acid, clearly improve efficiency of these replacement enzymes. The measure of success of treatment is improvement of the disease symptoms.

Pancreatin supplements should be given to patients who experience unequivocal steatorrhea or in whom it is assumed (evidence 1b). The indication for pancreatic enzyme replacement is established for steatorrhea with fecal fat excretion of more than 15 g/day. Pancreatin supplements should also be given even when the increase in fecal fat excretion is modest (7–15 g/day) if there are signs of malabsorption (e.g., weight loss) or if the patient presents with abdominal symptoms that can be attributed to maldigestion and malabsorption (evidence 1b) [59]. As quantitative measurements of fecal fat are often no longer performed, the indication for replacements include an abnormal pancreatic function test in combination with clinical signs of malabsorption [81,306–308], which might include weight loss, dyspepsia, severe gas, or diarrhea. Therapy with pancreatin as an empiric trial for up to 4–6 weeks may also be beneficial if the source of symptoms is uncertain.

During replacement therapy, reducing malabsorption by sufficient oral nutrition (essential nutrients and vitamins) and treatment of the abdominal symptoms should be pursued. Complete normalization of digestion and absorption of nutrients is usually not attainable (evidence 2b). Untreated severe exocrine pancreatic insufficiency results in a severe malabsorption syndrome. Clinically, this manifests itself mainly in the form of steatorrhea, deficiency of fat-soluble vitamins together with its sequelae, and weight loss, even to the extent of cachexia [83–88,309]. Malabsorption itself can also lead to abdominal symptoms, and these symptoms may also be the consequence of intestinal motility disorders caused by maldigestion and malabsorption [307].

The success of pancreatin replacement therapy should be monitored primarily using clinical parameters (weight gain, long-term normalization of the vitamin status, disappearance of abdominal symptoms) (evidence 2b). If there is doubt as to whether persistence of symptoms can be explained by a lack of efficacy of enzyme replacement, then fecal fat excretion or pancreatic function tests to measure nutrient digestion under therapy (e.g., breath tests with ^{13}C-labelled lipids) should be applied (evidence 2b). The disappearance of clinical signs of malabsorption is the most important criterion for the success of pancreatic enzyme therapy, and is associated with an overall improvement of the quality of life [310]. Several studies have shown that breath tests with ^{13}C-labelled lipids provide a good measure of fat digestion and fecal fat excretion and are therefore suitable for monitoring the effectiveness of pancreatin therapy [311–313]. Success of replacement therapy cannot be assessed by measuring the fecal concentration of elastase, because only the natural human enzyme and not the therapeutically administered enzyme are measured.

Pancreatin should be taken with meals (evidence 1b). The effectiveness of pancreatic enzyme supplements presupposes mixing of pancreatin and chyme. If more than one capsule/tablet per meal is to be taken, it may be beneficial to take one part of the dose immediately at the beginning of, and the rest distributed throughout, the meal [314].

Preparations with acid protection should be used in patients with preserved gastric acid secretion, owing to the acid instability of pancreatic enzymes (evidence 2b). Lipase activity in particular is irreversibly destroyed at pH values below 4 [315]. 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. Without concomitant acid suppression, preparations with acid protection lower fecal fat excretion more than those without [316]. Because mixing of chyme and pancreatin is required for optimal effectiveness, preparations should be chosen that consist of acid-protected particles with a diameter of $\leq$2 mm (evidence 2b). This critical value is in principle only relevant for patients with a preserved pylorus [307]. However, small particle sizes may also facilitate and/or accelerate gastric emptying. The release of enzymes from small particles may be accelerated even after distal gastric resection. However, there are no double-blind, prospective, randomized trials comparing the efficacy of acid-protected microtablets or microspheres with larger acid protected tablets/capsules. In a randomized study of patients with chronic pancreatitis and steatorrhea, the coefficient of fat absorption was measured after application of either acid-protected minimicrospheres (>90% diameter <1.25 mm, range 0.7–1.6 mm) with minispheres (>70% diameter >1.25 mm, range 1–2 mm). Both preparations were efficacious and roughly equivalent [317]. The number of patients studied was not large enough to determine whether minimicrospheres are superior to minispheres.

The administered pancreatin dose should contain adequate enzymatic activity for the digestion of one meal (evidence 1b). The dose 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; approximately 10 000 (to 20 000) lipase units for the digestion of smaller in between meals (evidence 1b). The enzyme dose should be doubled, and if necessary tripled, if the effect is inadequate. Pancreatin powder or granulate should be combined with a PPI (proton pump inhibitor) if the effect is still inadequate (evidence 2b). If this does not result in the desired treatment outcome, then another cause of the persistent symptoms should be sought. The clinical efficacy of pancreatin preparations is determined by the administered dose, the time point 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 to the gastrointestinal anatomy (e.g., after gastric resection); concomitant medications can also affect efficacy (e.g., treatment with

PPIs in patients taking nonsteroidal antiinflammatory drugs) [283,284,307,312,314,316–323]. The recommended initial dose is about 5%–10% of the cumulatively secreted lipase activity into the duodenum after a normal meal and should therefore suffice to prevent malabsorption and steatorrhea. However, some patients will require doubling or tripling this dose. If secretion of gastric acid is suppressed, then unprotected pancreatin can be administered. This may be particularly beneficial because action of digestive enzymes is not delayed by the time needed for the protective coat to dissolve. Patients with chronic pancreatitis frequently have an abnormal bacterial colonization [324], which may be another cause of persistent symptoms.

Almost all pancreatic enzyme supplements available contain porcine pancreatin. 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 favorable biochemical properties (higher acid stability, but rapid deactivation in the presence of low bile acid concentrations) and are therefore of only limited clinical value. Bacterial enzymes and human lipase produced using gene technology are not yet of relevance in the treatment of exocrine pancreatic insufficiency. Given that some religions prohibit the consumption of pork, the patient should be made aware of the origin of the preparations.

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 (evidence 3b). Very high doses of enzymes (>10 000–20 000 units of lipase per kg body weight per day) should be avoided if possible. Fibrosing colonopathy, a rare disorder, has been reported to occur after the administration of extremely high doses of pancreatin in children with cystic fibrosis [325], but an association has not been established and is unlikely [326–329].

In patients with diabetes mellitus and newly initiated or increased pancreatic therapy, blood glucose levels should be monitored more closely for a short time because the improved uptake of carbohydrates can result in hyperglycemia (evidence 2b). 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 hypoglycemia developed during placebo treatment and ketoacidosis after recommencing pancreatic therapy [330].

Therapy of endocrine insufficiency

Endocrine insufficiency in chronic pancreatitis has been designated diabetes type 3c. Endocrine insufficiency will eventually develop at some point in most cases as the inflammatory processes progress. There is some correlation with the development of exocrine insufficiency. Therapy of this type of diabetes is often more difficult due to several reasons: (1) besides a lack of insulin due to the inflammatory destruction of islets, there is also a lack of counter-regulatory islet hormones such as glucagon and somatostatin; (2) postprandial serum glucose levels depend on adequate food digestion, which is dependent on the efficiency of treatment with porcine pancreatic enzymes; and (3) lack of compliance, especially in alcoholics, may compromise efforts to control blood sugar. Thus in patients whose daily food intake varies due to their life style or to abdominal pain, treatment with insulin has to be done carefully. The risk of late complications as a consequence of insufficient treatment of diabetes has to be counterbalanced by the risk of severe hypoglycemia. Intensified insulin therapy by self-monitoring of fasting serum glucose and individual selection of the appropriate dosage of insulin may not be possible in many of these patients. However, in patients with good adherence, as is usually the case in patients with hereditary and idiopathic chronic pancreatitis and patients with a rather stable disease course, may be managed with an intensified diabetic regimen. The life expectancy of heavy smokers with alcoholic pancreatitis is usually not determined by late complications of diabetes. Unfortunately, there are no evidence-based data regarding treatment of diabetes type 3c in patients with alcohol induced chronic pancreatitis.

Nutrition for patients with chronic pancreatitis

Malnutrition in patients with chronic pancreatitis may not only be the result of exocrine pancreatic insufficiency, but is also complicated by reduced food intake secondary to pain or continued alcohol consumption. In addition, some patients have an increased basal metabolic rate (evidence 3b). Patients with chronic pancreatitis and clinically manifest exocrine pancreatic insufficiency, that is weight loss, should receive pancreatic enzyme replacement therapy together with an individually tailored nutritional support in order to prevent further deterioration of their metabolic status. Nutritional treatment should try to provide an adequate supply of nutrients, vitamins, and trace elements, as well as an individual match for their daily energy requirements, in order to avoid a catabolic state (evidence 5). Malnutrition and underweight in chronic pancreatitis are associated with increased mortality [331]. Patients should in principle receive a normal isocaloric diet together with adequate pancreatic enzyme replacement. To improve the response, the nutrition intake should be distributed over appropriately four to six smaller meals (evidence 2b). A normal balanced, isocaloric diet according to patient's preferences is recommended; there is no established or pancreas-specific diet [84]. 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 [332]. A low-fat diet cannot be generally recommended. Only when clinical symptoms of fat maldigestion occur with further progression of exocrine pancreatic insufficiency, despite adequate oral enzyme replacement, should the amount of oral fat may be reduced, depending on tolerability (evidence 5). Fat is important as a central source of energy for avoiding and treating catabolism. If the fat intake has to be reduced for reasons of intolerability, despite adequate

enzyme replacement therapy, it is necessary to ensure that subsequently the compensatory oral supply of other sources of energy (carbohydrates, proteins) are appropriately increased to maintain isocaloric nutrition.

Medium-chain triglycerides (MCT) can be absorbed without prior digestion by lipase. MCT may improve fat absorption in patients with exocrine insufficiency not receiving enzyme replacement therapy. However, MCT should not be recommended in conjunction with enzyme administration (evidence 2b). In a small study on patients with severe steatorrhea, MCT alone were not superior to regular fat intake together with pancreatic enzyme application [333].

Additional nutritional supplements given either orally via an enteral tube or parenterally may be necessary for patients with advanced exocrine pancreatic insufficiency (evidence 2b). Supplementary oral liquid nutrition 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 [84]. The indication is usually not for treatment of exocrine pancreatic insufficiency, but rather for patients with complications of the disease, such as gastric outlet obstruction or enteric fistula. This is usually a temporary measure before definitive surgical management.

Alcohol consumption should as a rule being avoided in chronic pancreatitis (evidence 2b). Alcohol consumption is an important pathogenetic factor for the progression of exocrine pancreatic insufficiency [334]. As there are currently no data on the question of whether in the presence of existing chronic pancreatitis the consumption of small amounts of alcohol (e.g., daily amount <20 g/day) is damaging, it would be appropriate to recommend complete abstinence from alcohol.

Deficits of vitamins and trace elements should be specifically replaced (evidence 2b). Patients with chronic pancreatitis and exocrine pancreatic insufficiency usually have an intake of vitamins and trace elements less than recommended for daily consumption. Thus, deficiencies of the fat-soluble vitamins A, D, E, and K as well as of calcium, magnesium, zinc, thiamine, and folic acid are often detected. A reduced intake has also been reported for riboflavin, choline, copper, manganese, and sulfur. The ingestion of vitamin C and selenium was within the recommended daily doses, but was less than in healthy controls [84,335]. The indication to replace vitamins and trace elements should be established in adults primarily according to clinical symptoms of deficiency. Additional monitoring of serum levels is only required in individual cases. A routine monitoring of these parameters in adults cannot be recommended due a lack of data. In children, the indication for replacement should be established before development of clinical deficiency symptoms. In children, subclinical deficiency states can develop and be a cause for failure to thrive.

Surgical procedures and their indications

Surgery is indicated for some patients with chronic pancreatitis suffering from intractable pain and/or local complications [208,336]. Because endoscopic techniques may also be applied for these indications, an early interdisciplinary discussion is essential to determine the best-suited therapeutic approach for the individual patient. The ideal time point for surgery is difficult to determine and remains controversial. Evidence is increasing that timely surgical intervention may delay progression to pancreatic insufficiency. Apart from the success rate, complications and in particular mortality of the therapeutic procedures should also be included in the decision-making process. Historically, pancreatic surgery was associated with a high morbidity and mortality rate, but has made dramatic improvements in recent decades by advances in surgical techniques, perioperative management, and the development of "high volume" pancreas centers of excellence [336–341].

Surgery should be undertaken when malignancy is suspected in a patient with known pancreatitis. Surgery is indicated after failed endoscopic or interventional therapy for ongoing pain, or local complications such as symptomatic obstruction of the pancreatic ducts, bile duct or duodenum. Surgery can be recommended for pseudocysts with concomitant ductal alterations (evidence 3). There is no therapeutic potentially curative alternative to surgical resection for suspected malignancy. Whereas the median survival rate in the presence of pancreatic carcinoma is merely 6 months, a 5-year survival rate of over 20% and a median survival rate of approximately 24 months can be achieved by resection [212,341]. Resection of the pancreatic head seems also to be the most effective therapeutic option for treating pain associated with pancreatitis and local complications [336,342].

The standard surgical procedure for chronic pancreatitis associated with an inflammatory pseudotumor of the pancreatic head is pancreatic head resection. A variation of the duodenum-preserving pancreatic head resections (Beger, Frey, Berne, Hamburg procedures) or the Kausch–Whipple procedure (in the classical or pylorus-preserving variation) should be performed (evidence 1a). Pancreatic head resection is the most effective surgical procedure for an inflammatory mass of the pancreatic head and is superior to a mere surgical drainage or endoscopic interventions. Duodenum-preserving pancreatic head resections (DPPHR) seem to be superior to the Whipple procedure in the short and medium term over a follow-up observation period of up to 2 years [339,340,342,343]. The three variations of DPPHR are equal in their treatment effectiveness [344]. The long-term outcomes after Whipple procedure and after DPPHR seem to be comparable. Intraoperative internal drainage of the CBD is indicated in preoperative cholestasis (evidence 1c). Whereas in the classical and pylorus-preserving Whipple procedure a choledochojejunostomy anastomosis is always performed to drain the bile duct, this is not routinely done in DPPHR. By resecting the pancreatic head, the bile duct is freed of pancreatic substance in all DPPHR variation procedures (Beger, Frey, Berne, Hamburg). The bile duct should be opened within the pancreatic head 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-drain to divert bile during the postoperative phase until the anastomosis has healed can be placed. However, a Whipple [345] procedure (classical or pylorus-preserving) should be performed if malignancy of the pancreatic head is suspected (evidence 1c).

Frey's procedure or a drainage operation can be undertaken if there is no inflammatory mass of the pancreatic head but the pancreatic duct is obstructed (evidence 3). Pure drainage procedures such as the lateral pancreaticojejunostomy (Partington–Rochelle procedure) or Frey's procedure with limited pancreatic head resection have good primary success rates [346–348]. Drainage operation is better than endoscopic therapy, but yields less-good long-term outcome in comparison with pancreatic head resection procedures [349,350]. Furthermore, drainage procedures seem to be only successful if a very wide ductal system (>7 mm) without inflammatory tumor of the pancreatic head is present. They are therefore an option for less than 10% of cases [350]. However, the majority (>85%) of patients present with an inflammatory enlarged pancreatic head and a secondary obstruction of the pancreatic duct. These patients hardly ever experience improvement of their clinical symptoms from a pure drainage procedure. Thus resection procedures are preferable.

In patients with portal hypertension and formation of venous collaterals, the various modifications of DPPHR, which do not presuppose division of the pancreas, may be employed (evidence 4). In the DPPHR procedure of Beger et al. [351], the pancreas is transected above the portal vein and the inflammatory space-occupying mass in the pancreatic head resected, leaving behind a 5–8 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 Whipple procedure, although this usually does not succeed due to the chronic obstruction. However, Bloechle et al. have shown that, in segmental nonocclusive portal hypertension secondary to chronic pancreatitis, portal venous flow can be restored by a decompressing removal of the obstruction [352]. Reconstruction is achieved by 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 cored out pancreatic head. A precondition 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 et al. developed a modification of the Beger procedure in which a circumscribed "coring out" of the pancreatic head is combined with a longitudinal pancreaticojejunostomy, corresponding to Partington–Rochelle drainage operation [347,348]. This procedure appears appropriate in the absence of a large inflammatory space-occupying mass in the pancreatic head combined with ductal obstructions in the left-sided pancreas. The Hamburg and Berne variations are a technical simplification of Beger's DPPHR [353,354]. In patients with portal venous thrombosis and cavernous transformation of the portal vein, procedures that do not transect the mesentericoportal axis are preferred (such as Hamburg, Berne). The indication for surgery in this situation requires especially an interdisciplinary discussion because the mortality rate is significantly increased. Nevertheless, complete pain relief and return to work can also be achieved in this group of patients [352,354,355].

In patients with segmental inflammatory pancreatic changes (e.g., traumatic lesions of the head), segmental pancreatic resection or, if necessary, even a left-sided pancreatic resection may be performed (evidence 4). 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 lies in the lower postoperative morbidity in comparison with partial pancreaticoduodenectomy. Because less viable pancreatic parenchyma is removed, the development of postoperative diabetes mellitus or exocrine pancreatic insufficiency is also less frequent [356–365].

Very rarely, cases of chronic pancreatitis are also seen in which the main pancreatic duct is not dilated. These cases are defined as so-called "small duct disease". The frequency of this disease manifestation is very controversial. In recent years, an increasing number of patients are being diagnosed with autoimmune pancreatitis, which is characterized morphologically by inflammation of the parenchyma without dilatation of the duct. It is therefore important in these cases to exclude autoimmune pancreatitis. Surgical therapy of "small duct disease" by pancreatic head resection or a pure duct drainage procedure does not lead to satisfactory results [366,367], so the technique of the V-shape excision was developed for this clinical situation (evidence 3) [353,368]. 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 [368].

A Whipple procedure or one of the various forms of DPPHR may be performed for obstruction of the superior mesenteric vein or even portal vein (evidence 4). A 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. Success depends on the degree and duration of obstruction. The technical operability depends on the formation of collaterals and inflammatory adhesions [213].

Suspected malignancy secondary to chronic pancreatitis often cannot be excluded preoperatively. Therefore, if pancreatic cancer is suspected, surgery should be undertaken (evidence 1b). A thorough preoperative medical history should be obtained and any new symptoms such as weight loss, fever, or night sweats (B-symptoms) noted. CT or MRI and the results of previous examinations should be available. Laboratory parameters should include baseline CA19–9 for postoperative

follow-up measurements. Endoscopic ultrasound should be performed because it provides better local resolution. Bearing in mind that the indication for surgery for suspected pancreatic carcinoma in chronic pancreatitis is an absolute one and the surgical technique is predetermined, preoperative diagnostic investigations should not be prolonged. There is an indication for a Whipple procedure or a pylorus-preserving pancreatic head resection [369–371]. A DPPHR should not be performed for suspected pancreatic carcinoma as dissemination of the tumor could occur from incision of the tumor, thus precluding any potential cure.

Treatment of postoperative complications

Pancreas surgery has progressed from high-risk operations, which in earlier days were often regarded as heroic interventions, to operations with a manageable perioperative risk [372,373]. Mortality has also been reduced in recent years at highly specialized centers. This is especially the case for surgical treatment of chronic pancreatitis because a fibrotic hard pancreas is less vulnerable and reconstructions tend to heal better. A standardized surgical technique and improved perioperative management of the patients have contributed significantly to this. Pancreatic fistulae development remains a potential complication, but the majority of patients can be treated conservatively or endoscopically. The choice of therapy depends on the clinical state of the patient (evidence 3). The critical operative steps during a pancreaticoduodenectomy or left-sided pancreatic resection are pancreatic anastomosis and pancreatic stump closure [343]. The consensus definition for postoperative pancreatic fistula (POPF) of the International Study Group for Pancreatic Fistula (ISGPF) is dependent 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 84.3). An initial validation and a multicenter study performed a retrospective calculation that the prevalence of POPF as defined by the ISGPF is approximately 30%, with grade A fistula [374–377]. 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 in rare cases develop after pancreatic head resection are potentially more dangerous. Diagnostic examinations for fistulae are performed by determining amylase and lipase levels via an intraabdominal drain, CRP measurements, as well as ultrasound sectional imaging.

Table 84.3 International Study Group for Pancreatic Fistula consensus definition of postoperative pancreatic fistulae. Source: Data from [369].

Grade	Clinical state, CT result	Adjustment of management, intervention	Hospital stay
A	Well, no fluid accumulation	No, consider CT investigations	Not prolonged
B	Often well, peripancreatic fluid	Yes, no invasive intervention	Usually prolonged
C	Critical, peripancreatic fluid	Yes, percutaneous drainage or revision laparotomy	Prolonged
Definition	Output via an operatively placed drain of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than 3 times the upper normal serum value		

Prevention and follow-up

Follow-up after surgical management

Interventional or surgical therapy may be indicated with recurrent cholestasis after surgery (evidence 3). CBD obstruction after a Whipple procedure is defined as recurrent cholestasis and is usually the result of a bile duct leak that has healed with scar formation. Whereas initially an endoscopic or interventional dilatation and/or stent therapy may be appropriate, revision surgery is necessary for persistence of the problem [378]. Persistent postoperative pain should be treated according to the WHO pain treatment ladder (evidence 2a). Postoperatively, pain is significantly reduced in approximately 90% of all patients after pancreatic head resection. Postoperative persistent pain is treated as for preoperative pain with analgesics according to the WHO pain plan. Causes of persistent pain reflect a chronic pain syndrome unrelated to further pancreatic inflammation. Recurrence of pain after initial pain relief can, however, also develop as a result of a recurrence of the inflammatory pancreatic tumor and renewed pancreatic duct obstruction. In these cases, revision surgery is possibly indicated, involving renewed DPPHR or Whipple's procedure [379]. Residual pancreatectomy is not indicated for persistent pain or completely atrophic or calcified pancreas [373]. Residual pancreatectomy is only indicated as a last resort for postoperative septic complications after unsuccessful interventional therapy (evidence 3) [380,381].

However, revision surgery may be undertaken if medication or endoscopic procedures to treat recurrence following primary surgery fail (evidence 3a). Revision operations belong to the most difficult abdominal operations. If pain persists or recurrent cholestasis cannot be successfully treated by percutaneous transhepatic cholangiographic drainage or endoscopic means, the most promising therapy is resection surgery.

Monitoring and follow-up of chronic pancreatitis

During chronic pancreatitis, treatable complications may develop, such as endocrine or exocrine insufficiency, acute exacerbations, pseudocysts, cholestasis, and an increased risk of pancreatic carcinoma. For this reason, monitoring/follow-up should be undertaken after establishing the diagnosis. Prospective studies, which substantiate the benefits of follow-up reviews,

are not available. Mortality in patients with chronic pancreatitis is increased by 38.4% 20 years after establishing the diagnosis in comparison with an age-adjusted control cohort [21]. The risk of developing pancreatic carcinoma is increased 16-fold in patients with chronic pancreatitis and by 25-fold in those who also smoke. The relative risk for developing pancreatic carcinoma as calculated in a recent metaanalysis for chronic pancreatitis is 13.3 (95% CI 6.1%–28.9%) and 69 for hereditary pancreatitis (95% CI 56.4–84.4) [382]. The lifetime risk for developing pancreatic carcinoma in patients with chronic pancreatitis is at a maximum of 5% (evidence 2b) [21,382–384]. Clinical experience supports the value of yearly follow-up (clinical findings, transabdominal ultrasound, laboratory tests including HbA_{1c}).

The risk of hypoglycemia is increased in patients with diabetes due to injury or removal of the pancreas (so-called pancreoprivic diabetes type 3c). This results in increased mortality. Glucose metabolism should therefore be monitored (evidence 3b). Eight years after establishing the diagnosis of chronic pancreatitis, 50% of patients suffer from diabetes mellitus requiring therapy. Episodic hypoglycemia occurs in up to 79% and severe hypoglycemia in up to 41%. Patients with diabetes type 3c may also develop late complications such as retinopathy [385–389]. Mortality in patients with diabetes mellitus is significantly increased. Median survival is 8.7 years after establishing the diagnosis of pancreoprivic diabetes. The various difficulties to treat diabetes in chronic pancreatitis adequately have already been discussed above (see Section Therapy of endocrine insufficiency).

The development of exocrine insufficiency leads to malnutrition and secondary complications such as osteoporosis. A regular check-up to prevent or detect early these problems have also already been discussed (see Section Therapy of exocrine pancreatic insufficiency).

Follow-up evaluations should be undertaken at intervals of 6–12 months (evidence 5). The aim of follow-up includes diagnosis and treatment of exocrine or endocrine insufficiency, intervention for patients with cachexia or pain, as well as treatment of local complications (gastric outlet obstruction, pseudoaneurysms, pseudocysts). However, medical adherence of chronic alcoholic pancreatitis patients is often problematic. One study showed that even patients with bile duct stents did not show up for regular stent replacement [390].

Apart from clinical and laboratory examinations, patients may benefit from several transabdominal ultrasounds as a noninvasive technique to monitor the disease (evidence 2b). The sensitivity of the case history, physical examination, and transabdominal ultrasound reaches 94%. Specificity can be increased by subsequent examination techniques such as EUS, MRCP, or CT. Transabdominal ultrasound therefore appears suitable as an initial examination. An additional imaging modality may be necessary to confirm the diagnosis [391]. The "gold standard" for detecting complications of chronic pancreatitis is contrast-enhanced CT. However, none of the actual imaging techniques can exclude operable cancer within preexisting chronic pancreatitis with reasonable certainty. A combination of imaging techniques may be necessary if there is clinical suspicion. Currently, endoscopic ultrasound appears to be superior to other imaging techniques, such as MRI and CT. Tumor markers should not be used for follow-up controls (evidence 2a). Tumor markers are unsuitable as screening tests for the presence of pancreatic carcinoma in patients with chronic pancreatitis. Falsely high values are often seen in patients with cholestasis. Diagnostic sensitivity and specificity of tumor markers for differentiating a space-occupying mass in the pancreas are not adequate to justify its use. Further diagnostic work up is necessary to evaluate unexplained weight loss, new-onset diabetes mellitus, change in pain character, cholestasis without an acute painful episode, and recurrent exacerbations of pancreatitis of unknown origin (evidence 4). Unfortunately, there are no controlled studies evaluating the significance of an early diagnosis of the disease or its complications and early intervention [392,393] (see Chapter 87).

Prophylactic total pancreatectomy in patients at high risk of pancreatic carcinoma (hereditary pancreatitis) should not be performed (evidence 4). No prospective studies on total pancreatectomy for prevention of cancer are available. Median survival following total pancreatectomy in patients with benign disease is only around 8 years. The average 5-year survival rate seems to be only 50% [394].

Acknowledgment

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References are available at www.yamadagastro.com/textbook

Further reading

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