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# The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease

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***Background.*** Several classification systems of chronic pancreatitis have been proposed to provide a basis for treatment and research. All of these previous classifications were designed at the height of pancreatic research of their respective times; thus, each represented the most current knowledge available to pancreatologists at the time. However, none of these classifications provide simultaneously a simple standardized system for the clinical classification of chronic pancreatitis according to etiology, clinical stage, and severity of the disease, nor are they consistently useful for directing clinical practice and comparing interinstitutional data. Thus, we aimed to develop a new classification system of chronic pancreatitis to provide a framework for studying the interaction of various risk factors on the course of the disease. ***Methods.*** We reviewed the literature on the clinical course of all different forms of chronic pancreatitis, and we reviewed all previous classification systems of the disease. This approach provided a basis for the development of a new and unifying classification of chronic pancreatitis. ***Results.*** We established the M-ANNHEIM multiple risk factor classification system based on the current knowledge of acute and chronic pancreatitis. This classification allows patients to be categorized according to the etiology, clinical stage, and severity of their disease. The severity of pancreatic inflammation was assessed using a scoring system that takes into account the clinical symptoms and treatment options of chronic pancreatitis. Finally, four hypothetical patients were categorized according to the M-ANNHEIM classification system to provide examples of its applicability in clinical practice. ***Conclusions.*** The M-ANNHEIM multiple risk factor classification system is simple, objective, accurate, and relatively noninvasive, and it incorporates etiology, different stages of the disease, and various degrees of clinical severity. This new classification system will be helpful for investigating the impact and interaction of various risk factors on the course of the disease and will facilitate the comparison and combination of interinstitutional data.

**Key words:** chronic pancreatitis, classification, CFTR, SPINK1, PRSS1, alcoholic pancreatitis

## Introduction

Chronic pancreatitis is an inflammatory disease of the pancreas characterized by abdominal pain, repeated episodes of acute pancreatitis, and fibrotic destruction of the organ, resulting in exocrine and endocrine insufficiency.[1–5] During the last decade, several reports have provided evidence that repeated attacks of acute pancreatitis may progress to chronic pancreatitis.[4,6–10] However, several questions remain unanswered. It has been noted that a marked variability exists in the progression of alcoholic chronic pancreatitis,[10] that nonalcoholic chronic pancreatitis presents with delayed progression compared with alcoholic chronic pancreatitis,[3,11] and that a lack of pancreatic dysfunction, ductal dilatation, and calcification are present in a subgroup of patients with nonprogressive alcoholic pancreatitis.[12] Although our knowledge regarding the molecular basis of the disease (reviewed by Etemad and Whitcomb[13] and Schneider[14]) and the development of pancreatic fibrosis[15–17] has improved considerably in recent years, chronic pancreatitis remains a disease that is impervious to investigation and intervention.

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This classification was first presented on the occasion of the 60th anniversary of Professor Manfred V. Singer to honor his research in the field of pancreatology.

More rapid expansion of medical knowledge has been hampered by various factors. Researchers and clinicians must face a lack of suitable animal models.[18] Difficulties exist in obtaining biopsy specimens of the human pancreas owing to its rather inaccessible location in the retroperitoneal space and the often focal damage of the pancreas in chronic pancreatitis. Only a limited correlation exists between morphological damage seen on pancreatic imaging and the severity of functional impairment.[19,20] During the early stages of the disease, detection of chronic pancreatitis is extremely difficult owing to the low sensitivity of exocrine pancreatic function tests and pancreatic imaging techniques.[21,22] The lack of a simple standardized system for clinical classification of the disease has been an obstacle to the comparison of treatment schedules and research studies among different institutions.[21] However, several classifications of chronic pancreatitis have been proposed in the past.

Each of these previous classifications represented the knowledge available to pancreatologists at that time. Table 1 summarizes previous classifications of chronic pancreatitis. In 1946, the first definition of chronic pancreatitis was introduced by Comfort and colleagues,[23] who described the progressive course of the disease with recurrent attacks of acute pancreatitis and noted the association with chronic alcohol consumption. In 1963, a symposium was held in Marseille, France, to establish a classification of acute and chronic pancreatitis.[24,25] The participants differentiated pancreatic inflammatory diseases into the distinct forms of acute and chronic pancreatitis and, at that time, concluded that acute pancreatitis did not progress to chronic pancreatitis.[24,25] The initial classification was revised and further improved in 1984[26] and 1988.[27] However, these classifications were based on histology of the pancreas, thereby limiting their application in clinical practice. In 1983, the Cambridge classification established a diagnostic system designed to grade the severity of pancreatic damage according to the changes observed by pancreatic imaging techniques using endoscopic retrograde cholangiopancreatography (ERCP), abdominal ultrasound (US), and computed tomography (CT).[28–30] The problem with this classification remains the limited correlation between pancreatic morphology and symptoms, especially during the early stages of the disease.[19,31] In addition, more recently established imaging techniques such as magnetic reso-

**Table 1.** Previous classifications of chronic pancreatitis

| Classifications of chronic pancreatitis | Major objectives, definitions, and criteria |
|---|---|
| Clinical description 1946[23] | Description of the clinical presentation of chronic pancreatitis and its association with increased alcohol consumption |
| Marseille 1963[24,25] | Description of morphologic characteristics and etiological factors of the disease; no discussion of the correlation between anatomic and functional changes; no categorization according to disease severity or clinical presentation; no inclusion of pancreatic imaging findings |
| Marseille 1984[26] | Further description and subclassification of morphological changes; "obstructive chronic pancreatitis" listed as distinct form; no discussion of the correlation between anatomic and functional changes; no categorization according to disease severity or clinical presentation; no inclusion of pancreatic imaging findings |
| Marseille-Rome 1988[27] | Further description of "chronic calcifying" and "chronic inflammatory" pancreatitis as distinct forms; description of etiological factors; no further elaboration of clinical, functional, or imaging criteria |
| Cambridge 1984[28–30] | Classification of disease severity based on pancreatic imaging criteria (US, CT, ERCP); further discussion of etiological factors, pancreatic function, and testing for pancreatic insufficiency; morphologic characteristics not clearly defined |
| Clinical stages 1994[21] | Detailed subclassification of chronic pancreatitis with correlation of etiological factors with different morphological forms of the disease; differentiation of clinical stages of the disease; linkage of pancreatic imaging findings and functional testing with stages of the disease |
| Japan Pancreas Society 1997[33] | Description of clinical presentation and classification of disease in "definite" and "probable" chronic pancreatitis according to imaging findings, functional testing, and histological examination |
| Zürich Workshop 1997[32] | Description of clinical presentation and classification of disease in "definite" and "probable" chronic pancreatitis according to imaging findings, functional testing, and histological examination |
| TIGAR-O 2001[13] | Detailed categorization of etiological risk factors |
| ABC grading system 2002[34] | Disease grading according to clinical criteria, but limited separation of different disease severities; not all clinical presentations can be categorized |
| Manchester system 2006[35] | Disease grading according to clinical criteria, but limited separation of different disease severities; not all clinical presentations can be categorized |

US, ultrasonography; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography

nance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) have not yet been incorporated into the Cambridge grading system. In 1997, another symposium, in Zürich, Switzerland, introduced a clinically based classification system of alcoholic pancreatitis that differentiated between "probable" and "definite" chronic pancreatitis on the basis of various clinical features.[32] At the same time, a similar system of diagnostic criteria for chronic pancreatitis was proposed by the Japan Pancreas Society.[33] At that time, a classification system had already been suggested that included different etiologic forms and different stages of the disease.[21] However, none of these three classification systems referred to the various degrees of disease severity, and they could not consider insights gained from recent genetic studies. In 2001, a classification system was introduced that summarized all etiologic risk factors that have been associated with the development of the disease.[13] In 2002, the ABC grading system of chronic pancreatitis was proposed, which categorizes patients without pain into the A group, individuals with pain but without complications into the B group, and patients with pain and complications into the C group.[34] Unfortunately, this system does not clearly differentiate between different degrees of disease severity within a given category, nor does it allow categorization of all possible clinical presentations of chronic pancreatitis. More recently, the Manchester classification, which differentiates mild, moderate, and end-stage chronic pancreatitis, has been suggested.[35] However, this classification system again is imprecise, owing to its rather rough categorization of chronic pancreatitis into different severities and stages, and its limitations in classifying all possible clinical pictures of the disease. In summary, each of these previous classifications presents limitations, and none of the systems simultaneously distinguishes among different forms of chronic pancreatitis according to etiology, clinical stage, and degree of clinical severity.

The ideal disease classification system of chronic pancreatitis would be simple, objective, accurate, and noninvasive and should incorporate etiology, staging, and severity of the disease.[13,21,36] Similar scoring systems already developed for Crohn's disease[37] and liver disease[38,39] are widely used to guide treatment decisions and to predict the prognosis of the disease. An ideal classification of chronic pancreatitis should incorporate a severity index that refers to the different conditions of pancreatic morphology and pancreatic function and that includes clinical features of the disease such as various patterns of pain and the impact of conservative, endoscopic, and surgical treatment interventions.

Therefore, we developed the M-ANNHEIM classification system of chronic pancreatitis to fulfill these criteria. Our suggested classification is based on previous in-depth work on the various classifications of pancreatitis, and on recent epidemiological, genetic, and experimental insights into the development of the disease. We aimed to establish a classification of chronic pancreatitis that standardizes the clinical description of the disease and provides a new tool for obtaining further insights into the development and progression of the disease according to different disease etiologies.

## Methods and definitions of the M-ANNHEIM classification system

### *Review of the literature in support of the M-ANNHEIM classification*

The development of the M-ANNHEIM multiple risk factor classification was based on a comprehensive review of the literature. In general, the classification is based on current knowledge of the etiology of chronic pancreatitis (reviewed by Etemad and Whitcomb[13] and Lankisch and Banks[40]), epidemiological studies,[41–48] clinical long-term observations of the natural course of the disease,[1–5,10,46,49–52] hypothetical concepts of the development of chronic pancreatitis,[7,9,53–57] recent genetic findings,[6,58–77] insights gained from experimental studies and investigations revealing the mechanisms of fibrotic destruction of the organ,[15–18,78–81] and studies dealing with pancreatic imaging techniques.[28–30,82–90]

### *Previous classifications of chronic pancreatitis*

The M-ANNHEIM classification encompasses key features of previous classification systems. We reviewed the Marseille classification of acute and chronic pancreatitis of 1963,[24,25] the revisions from 1984[26] and 1988,[27] the Cambridge classification of 1984,[28–30] the classification into clinical stages, different etiologies, and morphological forms of 1994,[21] the diagnostic criteria for chronic pancreatitis proposed by the Japan Pancreas Society in 1997,[33] the Zürich classification of 1997,[32] the TIGAR-O classification of 2001,[13] the ABC grading system of chronic pancreatitis from 2002,[34] and the recently suggested Manchester classification.[35] Table 1 provides an overview of all previous classifications of chronic pancreatitis and the major features of each classification system.

### *M-ANNHEIM definition of onset of chronic pancreatitis*

In accordance with previous studies, the onset of chronic pancreatitis is defined as when one of the following criteria is fulfilled: first clinical presentation of abdominal pain, first episode of acute pancreatitis, or first manifestation of exocrine or endocrine insufficiency.[2–5]

*M-ANNHEIM definition of severe complications*

Several severe complications frequently occur during the course of chronic pancreatitis and have an impact on the prognosis of the disease.[91] We divided the severe complications listed by Lankisch and Banks[91] into possibly reversible features (such as the presence of stenosis of adjacent viscera, e.g., duodenal stenosis, colonic stenosis, common bile duct stenosis; gastrointestinal bleeding; development of ascites; occurrence of pleural effusion; osseous lesions; pseudoaneurysm, pancreatic fistula) and irreversible complications (portal or splenic vein thrombosis with or without portal hypertension; occurrence of pancreatic cancer). It is noteworthy that these severe complications are not included among the morphological imaging features of the Cambridge classification system.

## Results: the M-ANNHEIM classification system of chronic pancreatitis

*M-ANNHEIM multiple risk factors*

The M-ANNHEIM classification is based on the assumption that, in the majority of patients, chronic pancreatitis results from the interaction of multiple risk factors. Thus, we named our classification the multiple (M) risk factor classification and grouped possible risk factors into the major subcategories of alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic (M) factors. The M-ANNHEIM risk factor classification is based roughly on the prevalence of each of these major subcategories of pancreatic risk factors (Table 2).

Alcohol consumption (A) and classification of past drinking history

Based on clinical observations, the Zürich conference on alcoholic chronic pancreatitis agreed to define alcoholic chronic pancreatitis as chronic pancreatitis that occurs following a daily intake of alcohol equal to or greater than 80 g per day for several years in men.[32] However, the intake of smaller amounts of alcohol may also result in pancreatic damage and may influence the course of the disease.[52] In an attempt to consider the risk associated with a lower intake of alcoholic beverages, we modified the consensus of this conference and grouped alcohol consumption into patterns of moderate (<20 g pure ethanol per day), increased (20–80 g pure ethanol per day), or excessive (>80 g pure ethanol per day) intake of alcohol for several years (Table 2). This additional stratification of past alcohol intake may facilitate the comparison of different drinking histories, particularly in patients with low to moderate alcohol intake.

Nicotine consumption (N)

Smoking has been recognized as an independent risk factor for the development of chronic pancreatitis and pancreatic calcifications.[46,48–50,92,93] We suggest summarizing past cigarette consumption according to the accepted stratification of cigarette smoking by pack-years (PY).[94,95] The number of pack-years is equal to the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.[94,95]

Nutritional factors (N)

The consumption of a diet rich in fat and protein may play an important role in the development of pancreatic inflammation.[45] Additional support for a role of nutritional factors in the development of chronic pancreatitis is to be found in the association of hyperlipidemia with recurrent acute pancreatitis and, in exceptional cases, with chronic pancreatitis (reviewed by Etemad and Whitcomb[13]). However, retrospective descriptions of daily nutritional habits and retrospective determination of the body mass index present extremely difficult problems. Thus, it appears impossible to provide a simple description of past daily nutrition in the majority of patients with (alcoholic) chronic pancreatitis.

Hereditary factors (H)

During the last decade, several genetic mutations in the cationic trypsinogen (*PRSS1*) gene, the serine protease inhibitor kazal type 1 (*SPINK1*) gene, and the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene have been identified that predispose to the development of various forms of chronic pancreatitis.[6,13,14,58–64,66–71,75–77] An overview of currently described genetic mutations in the *PRSS1* and *SPINK1* genes is available at www.uni-leipzig.de/pancreasmutation, and a summary of *CFTR* variations is presented at www.genet.sickkids.on.ca.

Hereditary pancreatitis refers to otherwise unexplained pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern.[96] Familial pancreatitis refers to pancreatitis that occurs in a family with an incidence that is greater than would be expected by chance alone, given the size of the family and incidence of pancreatitis within a defined population. Thus, familial pancreatitis may also be caused by a genetic defect.[96] Idiopathic pancreatitis is defined as isolated cases of pancreatitis within a family and in which other causes of the disease have been ruled out. We listed idiopathic chronic pancreatitis, including the clinical entities of early-onset and late-onset idiopathic pancreatitis,[3,11,97]

**Table 2.** The M-ANNHEIM multiple risk factor classification of chronic pancreatitis

| | **M** Pancreatitis with **M**ultiple risk factors |
|---|---|
| **A** | **A**lcohol consumption |
| | Excessive consumption (>80 g/day) |
| | Increased consumption (20–80 g/day) |
| | Moderate consumption (<20 g/day) |
| **N** | **N**icotine consumption |
| | (In cigarette smokers: description of nicotine consumption by pack-years) |
| **N** | **N**utritional factors |
| | Nutrition (e.g., high caloric proportion of fat and protein) |
| | Hyperlipidemia |
| **H** | **H**ereditary factors[a] |
| | Hereditary pancreatitis (defined according to Whitcomb[96]) |
| | Familial pancreatitis (defined according to Whitcomb[96]) |
| | Early-onset idiopathic pancreatitis |
| | Late-onset idiopathic pancreatitis |
| | Tropical pancreatitis |
| | (possible mutations in the *PRSS1*, *CFTR*, or *SPINK1* genes) |
| **E** | **E**fferent duct factors |
| | Pancreas divisum |
| | Annular pancreas and other congenital abnormalities of the pancreas |
| | Pancreatic duct obstruction (e.g., tumors) |
| | Posttraumatic pancreatic duct scars |
| | Sphincter of Oddi dysfunction |
| **I** | **I**mmunological Factors |
| | Autoimmune pancreatitis |
| | Sjögren syndrome-associated chronic pancreatitis |
| | Inflammatory bowel disease-associated chronic pancreatitis |
| | Chronic pancreatitis with autoimmune diseases |
| | (e.g., primary sclerosing cholangitis, primary biliary cirrhosis) |
| **M** | **M**iscellaneous and rare metabolic factors |
| | Hypercalcemia and hyperparathyroidism |
| | Chronic renal failure |
| | Drugs |
| | Toxins |

The M-ANNHEIM classification is based on the assumption that, in the majority of patients, chronic pancreatitis results from the interaction of multiple risk factors (M). The different risk factors are grouped into the major subcategories of alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic factors (M)

[a] Hereditary and familial pancreatitis are defined according to Whitcomb.[96] Hereditary pancreatitis refers to otherwise unexplained pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern.[96] Familial pancreatitis refers to pancreatitis due to any cause that occurs in a family with an incidence higher than would be expected by chance alone, given the size of the family and incidence of pancreatitis within a defined population. Thus, familial pancreatitis may or may not be caused by a genetic defect.[96] Idiopathic pancreatitis is defined as pancreatitis in isolated cases within a family, in which all other causes of the disease have been excluded

as well as tropical pancreatitis, among the subgroup of hereditary factors owing to the recent identification of genetic risk factors in these forms of chronic pancreatitis.[13,14]

Efferent duct factors (E), immunological factors (I), and miscellaneous and rare metabolic factors (M)

In addition, several rare risk factors for the development of chronic pancreatitis have been described. We summarized in the subgroup of efferent duct obstruction (E) etiologic entities that have been linked to obstructive chronic pancreatitis, which has been recognized as a pathologically distinct form of chronic pancreatitis.[17] Various reports have demonstrated that among patients with acute or chronic pancreatitis the incidence of pancreas divisum is increased compared with control populations.[98–100] However, patients undergoing ERCP investigations represent a select group, and pancreas divisum is the most frequent congenital ductal anomaly of the pancreas and is found in approximately 9% of autopsy studies.[100] Therefore, the association of pancreas divisum with chronic pancreatitis remains controversial.[100] Finally, we grouped autoimmune pancreatitis among the category of immunological factors (I), and we added a subgroup for miscellaneous and metabolic factors (M).[13,40]

Table 2 provides an overview of the identified risk factors for the development of chronic pancreatitis. The possible interaction among the various risk factors on the development of chronic pancreatitis and during the course of the disease is illustrated in Fig. 1.

*M-ANNHEIM clinical stages*

Nonspecific abdominal pain is the leading symptom in the majority of patients and may present as short relapsing pain episodes separated by pain-free intervals lasting for up to several years, or this condition may be characterized by prolonged periods of either persistent pain or clusters of recurrent severe pain.[5] About 10% of patients with alcoholic chronic pancreatitis are diagnosed without prior abdominal pain at the onset of exocrine or endocrine insufficiency.[1,3] The initial painful phase of the disease may last for several years and is usually followed by a late phase characterized by the additional development of exocrine and endocrine insufficiency.[1–5]

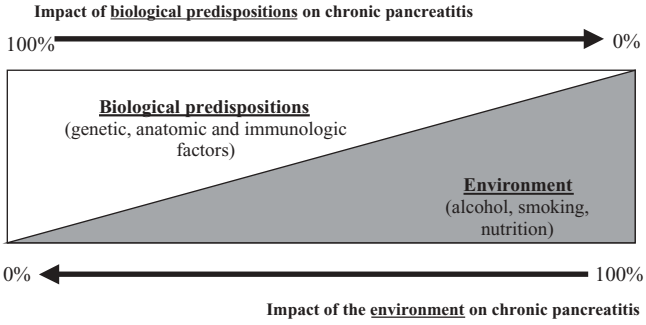


**Fig. 1.** Interaction of biological predispositions with the environment in chronic pancreatitis. The M-ANNHEIM classification is based on the assumption that chronic pancreatitis results from the interaction of multiple risk factors in the majority of patients. This interaction may be summarized as a continuum of various biological factors and environmental factors. Currently, an exact grading of the impact of each of these various risk factors on the development of the disease does not appear possible, as sufficient clinical and epidemiological data are not available. The M-ANNHEIM classification aims to provide a clinical tool to reveal the as yet unknown interactions of these risk factors with the development and course of chronic pancreatitis

The M-ANNHEIM classification includes a clinical staging system adapted from a previous classification of chronic pancreatitis.[21] The M-ANNHEIM staging is subcategorized into an asymptomatic phase (stage 0) and a symptomatic phase (stages I, II, III, IV) of chronic pancreatitis (Table 3). Each stage offers the possibility of classifying patients according to the presence of severe complications.

The poorly defined asymptomatic and early phase of chronic pancreatitis, during which clinically recognized symptoms are not present (stage 0 a), can be estimated only retrospectively. In a few patients, the diagnosis might be established by chance at this early stage, for example, during surgical intervention or by autopsy. We included in this phase of chronic pancreatitis a first episode of acute pancreatitis (stage 0 b), since it has been hypothesized that any episode of acute pancreatitis in individuals at risk may cause the later development of chronic pancreatitis.[4,7,9,56,57]

**Table 3.** M-ANNHEIM clinical staging of chronic pancreatitis (modified from Chari and Singer[21])

| | |
|---|---|
| ➢ **Asymptomatic chronic pancreatitis** | |
| 0 | Stage of subclinical chronic pancreatitis |
| a | Period without symptoms (determination by chance, e.g., autopsy) |
| b | Acute pancreatitis—single episode (possible onset of chronic pancreatitis)[a] |
| c | Acute pancreatitis with severe complications[b] |
| ➢ **Symptomatic chronic pancreatitis** | |
| I | Stage without pancreatic insufficiency |
| a | (Recurrent) acute pancreatitis (no pain between episodes of acute pancreatitis)* |
| b | Recurrent or chronic abdominal pain (including pain between episodes of acute pancreatitis) |
| c | I a/b with severe complications[b] |
| II | Stage of partial pancreatic insufficiency |
| a | Isolated exocrine (or endocrine) pancreatic insufficiency (without pain) |
| b | Isolated exocrine (or endocrine) pancreatic insufficiency (with pain) |
| c | II a/b with severe complications[b] |
| III | Stage of painful complete pancreatic insufficiency |
| a | Exocrine and endocrine insufficiency (with pain, e.g., requiring pain medication) |
| b | III a with severe complications[b] |
| IV | Stage of secondary painless disease (burnout) |
| a | Exocrine and endocrine insufficiency without pain and without severe complications[b] |
| b | Exocrine and endocrine insufficiency without pain and with severe complications[b] |

[a] A patient with a single episode of acute pancreatitis (without other symptoms of chronic pancreatitis) and with risk factors for chronic pancreatitis (e.g., a history of increased alcohol consumption) would be classified as "0 b" without morphological or functional signs of chronic pancreatitis. In contrast, the patient would be categorized as "I a" in the presence of chronic pancreatitis features (e.g., calcifications).
[b] Severe complications are defined as severe organ complications not included in the Cambridge classification. Reversible severe complications include development of ascites, bleeding, pseudoaneurysm, obstruction or stricture of the ductus choledochus, pancreatic fistula, and duodenal stenosis. Irreversible severe complications are portal or splenic vein thrombosis with or without portal hypertension and pancreatic cancer

The symptomatic phase represents the period of clinically recognized chronic pancreatic inflammation. The clinically recognized progression of the disease[1–5] is reflected by categorization into stages I, II, III, and IV. Stage I is characterized by abdominal pain without pancreatic insufficiency.[1–5] Stage II is determined by the presence of partial pancreatic insufficiency with or without abdominal pain.[2–5] In this stage, patients present with either exocrine or endocrine insufficiency, but not both. The presentation of endocrine insufficiency in the absence of exocrine loss of function appears extremely rare in individuals with alcoholic chronic pancreatitis or other forms of the disease in industrialized countries, but might be more frequent in patients with tropical pancreatitis.[101] Stage III is characterized by the presence of both exocrine and endocrine insufficiency.[2–5] Finally, in stage IV, abdominal pain may subside and permanent pain relief may typically occur after a disease duration of more than 10 years and may reflect the natural course of the disease with fibrotic destruction, progressive functional insufficiency, and, finally, burnout of the gland with permanent relief of pain.[5,102] Although a decrease of pain has been observed in other studies as well,[2,3] the concept of a progressive functional burnout resulting in lasting pain relief has been questioned.[2]

### *M-ANNHEIM diagnostic criteria*

The Zürich workshop on alcoholic chronic pancreatitis proposed a classification of chronic pancreatitis into "probable" or "definite" chronic pancreatitis, depending on the presence of several different diagnostic features of the disease.[32] A similar grading has been suggested by the Japan Pancreas Society.[33] We included the consensus of the Zürich workshop in our new M-ANNHEIM classification system, but we decided to include smaller amounts of alcohol intake as risk factors for the development of chronic pancreatitis than was agreed on by this workshop, and we included a subgroup of "borderline" chronic pancreatitis into our classification system. This subgroup summarizes patients with typical symptoms of chronic pancreatitis (i.e., recurrent episodes of acute pancreatitis) or with a first episode of acute pancreatitis who present without any morphological damage visible by means of pancreatic imaging techniques or detectable functional insufficiency suggestive of chronic pancreatitis. The possible progression from acute to chronic pancreatitis and the underlying pathological mechanisms have not been clarified and remain a topic of controversial discussion.[1,4,7,9,12,56,57,103,104] The classification of patients into this relatively loose category of yet to be proven chronic pancreatitis provides a new framework for monitoring these patients more intensively in clinical practice (e.g., with endoscopic ultrasound imaging[105]), and for revealing clinical features that are associated with the progression from early pancreatic changes toward the later stages of the disease. The M-ANNHEIM diagnostic criteria of chronic pancreatitis are presented in Table 4.

### *M-ANNHEIM imaging criteria of the pancreas based on the Cambridge classification*

The Cambridge classification established clear-cut criteria for the description of equivocal, mild, moderate, and severe changes by imaging with ERCP (Table 5).[28–30] The Cambridge classification also categorized pancreatic imaging findings on CT and abdominal US similar to the grading of ERCP changes.[28–30] However, the grading according to CT and US did not clearly differentiate between mild and moderate changes (Table 5).

In recent years, MRI and MRCP have been increasingly accepted as the primary imaging techniques for the morphological diagnosis of chronic pancreatitis.[86–88,90] The MRI technique is helpful in detecting early signs of chronic pancreatitis,[88] and MRCP after secretin stimulation improves visualization of the pancreatic main duct and pancreatic duct side branches, thereby providing significant support in the detection of early and mild changes of chronic pancreatitis.[87] In general, morphologic findings of chronic pancreatitis on MRI/MRCP are analogous to those seen on CT.[90] However, no consensus exists concerning the grading of MRI/MRCP imaging according to the Cambridge criteria.

EUS has added considerably to the diagnosis of chronic pancreatitis and pancreatic cancer since the early 1980s. Several characteristic findings have been described that are detectable by EUS in patients with chronic pancreatitis[82,84,85,89] (Table 6). A good correlation exists between the presence of abnormal ERCP findings and the detection of chronic pancreatitis features by EUS.[83] In another study, the presence of more than six EUS criteria allowed diagnosis of moderate or severe chronic pancreatitis with a positive predictive value of greater than 85%, whereas the presence of fewer than three criteria excluded moderate or severe chronic pancreatitis with a negative predictive value of more than 85%.[85] A similar investigation revealed a good correlation between moderate and severe chronic pancreatitis according to ERCP findings and the presence of EUS criteria (moderate pancreatitis with three to five EUS criteria, severe pancreatitis with greater than five EUS criteria).[84] In contrast, mild chronic pancreatitis present on ERCP demonstrated only poor agreement when adjusted to the presence of one or two EUS criteria.[84] In summary, there is discus-

**Table 4.** M-ANNHEIM diagnostic criteria of chronic pancreatitis (modified from Ammann[32])

The diagnosis of chronic pancreatitis requires a typical clinical history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis)
Based on these features, three forms of chronic pancreatitis

***Definite chronic pancreatitis*** is established by one or more of the following additional criteria:
1. Pancreatic calcifications
2. Moderate or marked ductal lesions (according to the Cambridge classification)
3. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
4. Typical histology of an adequate histological specimen

***Probable chronic pancreatitis*** is established by one or more of the following additional criteria:
1. Mild ductal alterations (according to the Cambridge classification)
2. Recurrent or persistent pseudocysts
3. Pathological test of pancreatic exocrine function (such as fecal elastase-1 test, secretin test, secretin–pancreozymin test)
4. Endocrine insufficiency (i.e., abnormal glucose tolerance test)

***Borderline chronic pancreatitis*** is already established and is defined by a typical clinical history of the disease but without any of the additional criteria required for definite or probable chronic pancreatitis. This form is also established as a first episode of acute pancreatitis with or without (1) a family history of pancreatic disease (i.e., other family members with acute pancreatitis or pancreatic cancer) or (2) the presence of M-ANNHEIM risk factors

***Pancreatitis associated with alcohol consumption*** requires in addition to the above-mentioned criteria for definite, probable, or borderline chronic pancreatitis one of the following features:
1. History of *excessive* alcohol intake (>80 g/day for some years in men, smaller amounts in women) or
2. History of *increased* alcohol intake (20–80 g/day for some years) or
3. History of *moderate* alcohol intake (<20 g/day for some years)

The Zürich workshop on alcoholic chronic pancreatitis proposed a classification of chronic pancreatitis into "probable" or "definite" chronic pancreatitis, depending on the presence of several distinguishing diagnostic features of the disease.[32] We included a subgroup of "borderline" chronic pancreatitis in the M-ANNHEIM classification system, and we introduced a subclassification for the amount of alcohol consumed

**Table 5.** Cambridge classification of pancreatic morphology in chronic pancreatitis[28–30]

Pancreatic morphology evaluated by ERCP

| | Main duct | Abnormal side branches | Additional features |
|---|---|---|---|
| Normal | Normal | None | |
| Equivocal | Normal | <3 | |
| Mild changes | Normal | ≥3 | |
| Moderate changes | Abnormal | >3 | |
| Marked changes | Abnormal | >3 | One or more of the following: large cavity, obstruction, filling defects, severe dilatation, or irregularity |

Pancreatic morphology evaluated by computed tomography and ultrasound

| | |
|---|---|
| Normal | Main pancreatic duct <2 mm, normal gland size and shape, homogenous parenchyma |
| Equivocal | One only of the following signs: Main pancreatic duct enlarged (between 2 and 4 mm), slight gland enlargement (up to 2 x normal), heterogeneous parenchyma, small cavities (<10 mm), irregular ducts, focal acute pancreatitis, increased echogenicity of the main pancreatic duct wall, irregular head / body contour |
| Mild changes | Two or more of the above listed criteria |
| Moderate changes | As with mild changes (not differentiated) |
| Marked changes | As above, with one or more of the following: large cavities (>10 mm), gross gland enlargement (>2× normal), intraductal filling defects or calculi, duct obstruction, structure or gross irregularity, contiguous organ invasion |

The Cambridge classification established clear-cut criteria for the description of equivocal, mild, moderate, and severe changes of chronic pancreatitis using the imaging technique of ERCP.[28–30] The Cambridge classification also categorized chronic pancreatitis according to pancreatic imaging findings on CT and abdominal US, similar to the grading of ERCP changes.[28–30] However, the grading according to CT and US did not clearly differentiate between mild and moderate changes

**Table 6.** Endoscopic ultrasound criteria of chronic pancreatitis[82,84,85,89]

| |
|---|
| Parenchymal features |
| ➢ Gland size |
| ➢ Cysts |
| ➢ Echo-poor lesions (focal areas of reduced echogenicity) |
| ➢ Echo-rich lesions (>3 mm in diameter) |
| ➢ Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by hyperechoic strands) |
| Ductal features |
| ➢ Increased duct wall echogenicity |
| ➢ Irregularity of the main pancreatic duct (e.g., with narrowing of the duct) |
| ➢ Dilation of the main pancreatic duct |
| ➢ Visible side branches (e.g., with dilation) |
| ➢ Calcification |

**Table 7.** M-ANNHEIM pancreatic imaging criteria for US, CT, MRI/MRCP, and EUS based on imaging features as defined by the Cambridge classification

| Cambridge grading | CT, US, MRI/MRCP[a] | EUS[b] |
|---|---|---|
| Normal | Quality study depicting whole gland without abnormal features (0 points)[c] | |
| Equivocal | One abnormal feature (1 point)[c] | Four or fewer abnormal features (no differentiation between equivocal and mild) (1 point)[c] |
| Mild changes | Two or more abnormal features, but normal main pancreatic duct (2 points)[c] | |
| Moderate changes | Two or more abnormal features, including minor main pancreatic duct abnormalities (either enlargement between 2 and 4 mm or increased echogenicity of the duct wall) (3 points)[c] | Five or more abnormal features (no differentiation between moderate and marked) (3 points)[c] |
| Marked changes | As above with one or more of the required features of marked changes (4 points)[c] | |

The Cambridge classification did not differentiate between mild and moderate changes according to CT and US findings, nor could it consider recent developments in MRI/MRCP-imaging and EUS-imaging for the grading of ductal and parenchymal damage (Table 5). Thus, we suggest applying these additional criteria for the grading of parenchymal changes according to the Cambridge classification

MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; US, abdominal ultrasound

[a] Abnormal features on pancreatic imaging with CT, US, MRI/MRCP are imaging criteria defined in the Cambridge classification[28–30] (Table 5)

[b] Abnormal features on EUS are based on previous reports[82,84,85,89] (Table 6). A good correlation exists between the presence of abnormal ERCP findings representing moderate and marked stages of the disease (Cambridge III and IV) and the detection of chronic pancreatitis features by EUS.[83] However, no accepted consensus exists as to the threshold number of EUS findings and their reference standards to establish the diagnosis of chronic pancreatitis

[c] The points in parentheses refer to the M-ANNHEIM scoring system (Table 8) for calculation of the M-ANNHEIM Severity Index (Table 9)

sion as to whether the total number of changes is more predictive than the presence of an individual criterion, and currently no accepted consensus exists as to the threshold number of EUS findings or regarding reference standards to establish the diagnosis of chronic pancreatitis.[89]

We suggest that, within the M-ANNHEIM classification, any imaging information obtained by abdominal US, CT, ERCP, MRI/MRCP, or EUS should be considered for the stratification of patients according to the Cambridge criteria. It should be noted again that the Cambridge classification did not differentiate between mild and moderate changes according to US and CT findings, and it could not consider recent developments in MRI/MRCP techniques and EUS imaging for the grading of parenchymal damage[28–30] (Table 5). Therefore, we suggest differentiating between mild and moderate disease according to the presentation of the main pancreatic duct on US, CT, and MRI/MRCP (Table 7). In addition, we suggest a slightly differing grading for EUS findings, as an internationally accepted consensus regarding EUS imaging in chronic pancreatitis is not currently available (Table 7). Table 7 summarizes our suggestions for grading morphological changes by features of the various imaging techniques based on the recommendations of the Cambridge classification.

### *M-ANNHEIM score and M-ANNHEIM severity index*

The M-ANNHEIM classification system includes a scoring system to determine the severity of the disease. Similar scoring systems have been developed for

**Table 8.** M-ANNHEIM scoring system for the grading of clinical features of chronic pancreatitis

| Clinical features | | Points |
|---|---|---|
| **Patient report of pain**[a] | | |
| No pain without therapy | (patient reports requiring no pain medication) | 0 |
| Recurrent acute pancreatitis | (patient reports freedom from pain between attacks of acute pancreatitis) | 1 |
| No pain with therapy | (patient reports freedom from pain with pain medication or endoscopic intervention) | 2 |
| Intermittent pain | (patient reports intermittent pain-free episodes, either with or without therapy; possibly additional attacks of acute pancreatitis) | 3 |
| Continuous pain | (patient reports absence of pain-free episodes, either with or without therapy; possibly additional attacks of acute pancreatitis) | 4 |
| **Pain control**[a] | | |
| No medication | | 0 |
| Use of nonopioid drugs or use of mild opioids (WHO step 1 or 2) | | 1 |
| Use of potent opioids (WHO step 3) or endoscopic intervention | | 2 |
| **Surgical intervention**[a,b] | | |
| Pancreatic surgical intervention for any reason | | 4 |
| **Exocrine insufficiency**[c] | | |
| Absence of exocrine insufficiency | | 0 |
| Presence of mild, moderate, or unproven exocrine insufficiency not requiring enzyme supplementation (including patient reports of intermittent diarrhea) | | 1 |
| Presence of proven exocrine insufficiency (according to exocrine function tests) or presence of marked exocrine insufficiency defined as steatorrhea (>7 g fat/24 h), normalized or markedly reduced by enzyme supplementation | | 2 |
| **Endocrine insufficiency** | | |
| Absence of diabetes mellitus | | 0 |
| Presence of diabetes mellitus | | 4 |
| **Morphologic status on pancreatic imaging** (according to the Cambridge classification) | | |
| Normal | | 0 |
| Equivocal | | 1 |
| Mild | | 2 |
| Moderate | | 3 |
| Marked | | 4 |
| **Severe organ complications**[b] (not included in the Cambridge classification) | | |
| Absence of complications | | 0 |
| Presence of possibly reversible complications[d] | | 2 |
| Presence of irreversible complications[d] | | 4 |

[a] The classification of pancreatic pain according to the severity index is done by combining the observed pain patterns together with their treatment interventions. For example, potent opioids (2 points) resulting in intermittent occurrence of abdominal pain (3 points) is 5 points on the severity index

[b] Any surgical intervention and any severe complication are included in the calculation of the severity index starting from their first occurrence and continuing during the later course of the disease. Thus, if a patient has two different severe complications, both must be included separately in the calculation of the severity index

[c] As tests for pancreatic exocrine function are relatively insensitive for detecting mild or moderate exocrine insufficiency, the presence of intermittent diarrhea and a typical description of the stool, suggestive of chronic pancreatitis, given by the patient (e.g., white, bulky, voluminous, with undigested food present), together with normal test results of exocrine function, are consequently classified as partial pancreatic exocrine insufficiency (1 point)

[d] Reversible severe complications: development of ascites, bleeding, pseudoaneurysm, obstruction or stricture of the ductus choledochus, pancreatic fistula, duodenal stenosis. Irreversible severe complications: portal or splenic vein thrombosis with or without portal hypertension, pancreatic cancer

Crohn's disease[37] and liver disease[38,39] to guide clinical treatment decisions and to predict the prognosis of the disease.

The M-ANNHEIM scoring system of clinical features of chronic pancreatitis grades the presence of abdominal pain, therapeutic approaches to pain control, pancreatic surgical interventions, exocrine and endocrine insufficiency, morphological status of the pancreas, and the occurrence of severe organ complications. The various diagnostic and therapeutical features are linked to appropriate numbers of points. Table 8 provides an overview of the M-ANNHEIM scoring system.

Abdominal pain and its therapeutical management represent dominant features in clinical practice. However, pain associated with chronic pancreatitis is a highly variable phenomenon that is difficult to quantify, and it may be difficult to treat, owing to ongoing alcohol abuse or a developing addiction to narcotics.[106] Therefore, we placed special emphasis on the scoring of abdominal pain. We classified pain according to its presentation, and we assessed its severity by combining the presence of pain with the corresponding therapeutic approaches (Table 8; see also Table 10). However, well-defined prospective trials comparing nonsurgical treatment proce-

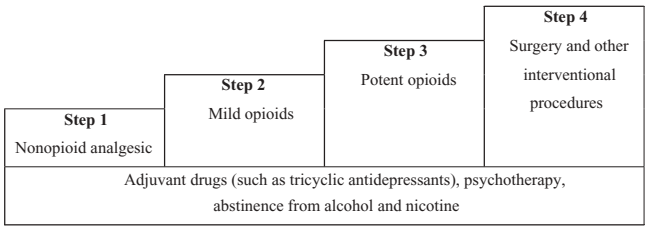


**Fig. 2.** World Health Organization pain ladder adapted for the treatment of pain in chronic pancreatitis. In the absence of clinical trials, recent recommendations for conservative treatment of pain in chronic pancreatitis[107,108] have adapted the three-step pain relief ladder of the World Health Organization originally developed for the treatment of cancer pain.[109] Endoscopic ductal decompression therapy and surgical intervention remain treatment options in patients in whom satisfactory pain relief employing conservative approaches is not achieved

dures do not exist, and no consensus has been reached regarding surgical intervention in patients with painful chronic pancreatitis.[106] Recent recommendations for conservative treatment of pain in chronic pancreatitis[107,108] have adapted the three-step pain relief ladder of the World Health Organization (WHO).[109] Endoscopic ductal decompression therapy is another useful approach for pain relief in chronic pancreatitis.[110] Surgery remains an option for patients in whom other forms of pain relief have not been successful. Figure 2 presents a therapeutic ladder for the treatment of pain in chronic pancreatitis.[107,108]

The assessment of exocrine pancreatic insufficiency represents a diagnostic challenge. There are two different means of testing exocrine pancreatic function. Noninvasive tests of pancreatic function are simple to perform, but they are relatively insensitive in detecting pancreatic insufficiency.[22] In contrast, invasive tests of pancreatic exocrine function (e.g., secretin–pancreozymin test) are considered the gold standard for diagnosing exocrine insufficiency, but these tests are offered only in a few specialized centers around the world. They are difficult to compare owing to the administration of different stimulants of the gland and the measurement of different parameters.[13] Finally, with the development of new classes of pancreatic enzymes, many patients receive enzyme supplementation based on their clinical description of exocrine insufficiency rather than on test results of pancreatic function. It currently appears that these tests are no longer frequently performed in many centers anywhere in the world. A grading system for mild, moderate, and severe pancreatic insufficiency has been suggested by Lankisch and colleagues.[111] In this context, mild to moderate pancreatic insufficiency means compensated function that does not require enzyme substitution, whereas severe insufficiency signifies decompensated function with steatorrhea requiring enzyme supplementation.[111] This grading of pancreatic function is reflected in our scoring system. We suggest grading pancreatic insufficiency as "mild or unproven" in patients who report intermittent diarrhea but who have not been tested pancreatically insufficient by exocrine function tests. In contrast, patients describing features of steatorrhea, reporting improvement of exocrine insufficiency with enzyme supplementation but without prior testing of exocrine function, or presenting with any test result showing loss of exocrine function should be graded as "proven" pancreatically insufficient.

**Table 9.** M-ANNHEIM severity index of chronic pancreatitis

| Severity index | Severity level | Point range |
|---|---|---|
| M-ANNHEIM A | **Minor** | 0–5 points |
| M-ANNHEIM B | **Increased** | 6–10 points |
| M-ANNHEIM C | **Advanced** | 11–15 points |
| M-ANNHEIM D | **Marked** | 16–20 points |
| M-ANNHEIM E | **Exacerbated** | >20 points |

M-ANNHEIM scoring system points are added together, and the sum is used to categorize a patient's disease according to the M-ANNHEIM severity index

Endocrine insufficiency and subsequent diabetic complications with a poorer prognosis are frequently recognized in patients with chronic pancreatitis.[2–4,112] Therefore, we assessed pancreatic exocrine insufficiency as a much milder event than pancreatic endocrine insufficiency within the scoring system (Table 8). The diagnosis of endocrine insufficiency should be based on the diagnostic criteria of WHO[113] and the American Diabetes Association.[114]

The manifestation of severe organ complications and surgical interventions represent major events during the course of the disease, as loss of pancreatic function often results from surgical interventions, and severe organ complications may exert an influence on the prognosis of the disease.[91] Within the M-ANNHEIM scoring (Table 8), we linked irreversible complications with a higher score, since these complications are more likely to influence the long-term prognosis of the disease. Therefore, from the first occurrence onward, these features need to be rescored each time a new severity index is calculated.

Depending on the presence or absence of clinical features as reflected by the M-ANNHEIM scoring, the points are added together to yield an overall score of clinical severity, which allows the categorization of patients according to the M-ANNHEIM severity index (Table 9).

Figure 3 summarizes major developments in pancreatology and their integration into the M-ANNHEIM classification system. Figure 4 summarizes the different steps and the corresponding tables necessary to classify

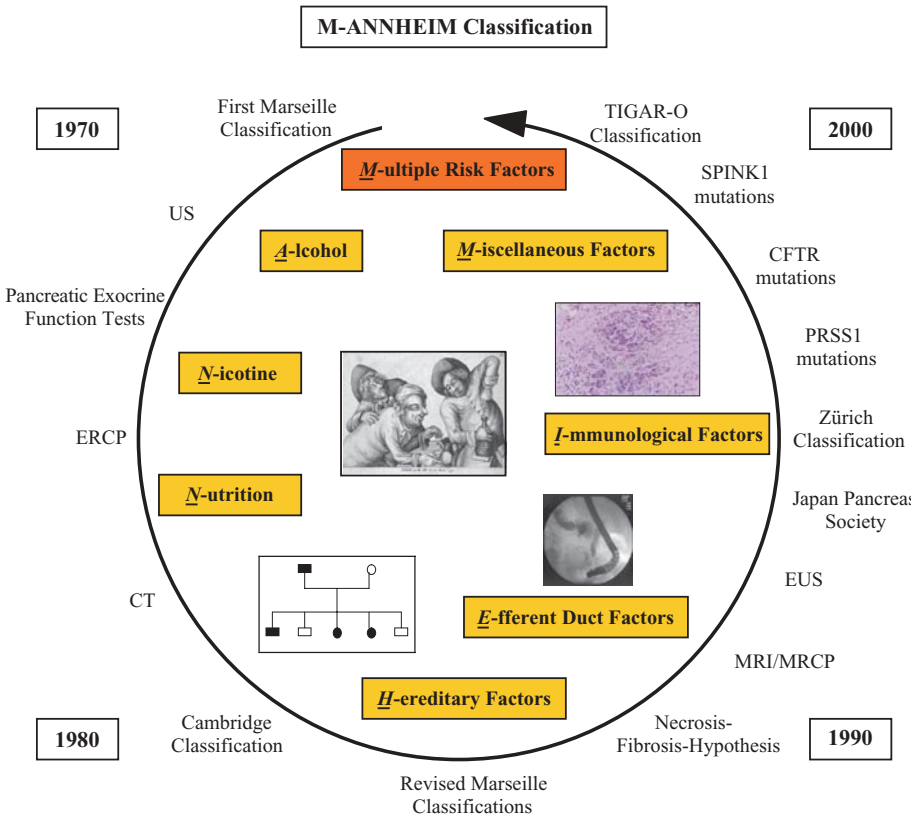


**Fig. 3.** The M-ANNHEIM classification as a new tool for further progress in pancreatology. In the past, major insights have been gained into the etiology and the clinical presentation of chronic pancreatitis. Several classifications and hypothetical concepts of the disease have been developed, which have reflected the available knowledge in pancreatology at a given time. However, several questions have not yet been answered. The M-ANNHEIM classification may serve to standardize the clinical description of chronic pancreatitis and may provide an important tool for obtaining further insights into the clinical presentation of the disease according to different disease etiologies. EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography

patients according to the M-ANNHEIM classification system.

## Examples of the M-ANNHEIM classification system in clinical practice

We classified four hypothetical archetype patients according to the M-ANNHEIM multiple risk factor classification system to demonstrate the use of the system in clinical practice. We chose a similar disease duration in each patient to highlight the advantages of our new classification system in comparing different courses of the disease. Table 10 provides an overview of the classification of each patient according to the individual risk factors, the hypothetical course of the disease at various stages of chronic pancreatitis, and the corresponding severity score and severity index. Figure 5 compares the different courses of the disease in these patients.

All patients presented with abdominal pain severe enough to result in treatment with potent opioids, and endoscopic interventions were performed in patients A, B, and C to achieve pain relief. Surgery was performed in all patients either for pain relief (patients A and C) or owing to severe complications (B, C, and D). All patients developed pancreatic exocrine dysfunction during the course of the disease. Progression toward pancreatic endocrine insufficiency was demonstrated in patients A, B, and C. Pancreatic surgery immediately preceded the development of endocrine insufficiency in patient A. Severe organ complications were present in two patients. In patient B, bleeding from a pancreatic pseudocyst occurred, and patient C revealed a splenic vein thrombosis and pancreatic cancer. Patients A, B, and C showed fading pain after long duration of the disease in line with the so-called burnout of the organ.

The M-ANNHEIM system also grades improvements and aggravations in the clinical presentation of the disease with corresponding changes in the M-ANNHEIM score and the severity index, as demonstrated in these patients. Therefore, this new classification system may also be helpful in guiding treatment decisions in chronic pancreatitis.

In summary, these four hypothetical individuals presented with very similar clinical features of chronic pancreatitis. However, the M-ANNHEIM severity index demonstrated considerably different courses of the disease with different degrees of severity, thereby supporting the usefulness of this new tool in the clinical characterization of patients with chronic pancreatitis.

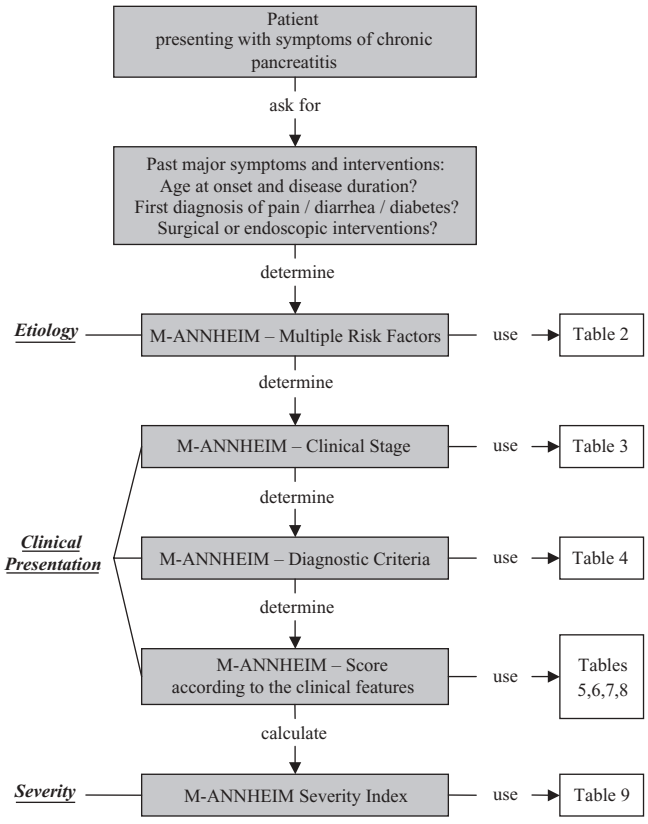


**Fig. 4.** Practical approach toward the M-ANNHEIM classification. Overview of the different steps and the various tables of this manuscript, which are to be used for categorization of patients according to the M-ANNHEIM system

## Discussion

The M-ANNHEIM classification system offers the opportunity to categorize patients according to disease etiology (Table 2) and to compare clinical courses of chronic pancreatitis according to stages (Table 3) and severity (Table 9) of the disease. Previously, several other classification systems of chronic pancreatitis have been proposed to provide a basis for treatment and research of chronic pancreatitis.[13,21,24–30,32–35] All of these classifications were devised at the height of pancreatic research of their respective times and reflect the most current knowledge available to pancreatologists during those years. However, none of these classifications provided a standardized system for clinical classification of chronic pancreatitis simultaneously employing the factors of etiology, clinical stage, and severity of the disease, nor did they suggest a scoring system for clinical comparison of patients with chronic pancreatitis. Thus, none of these classifications was consistently useful in directing clinical practice and comparing interinstitutional data.

During the past decade, new insights have been obtained regarding the mechanisms of pancreatic fibrosis during chronic inflammation.[15,16] Genetic variations in the *PRSS1*,[6,62,75] *CFTR*,[58,59,64,76,77] and *SPINK1* genes[60,61,63,66–71] have been associated with the development of chronic pancreatitis. It has been suggested that recurrent episodes of acute pancreatitis may progress towards chronic pancreatitis following a necrosis–

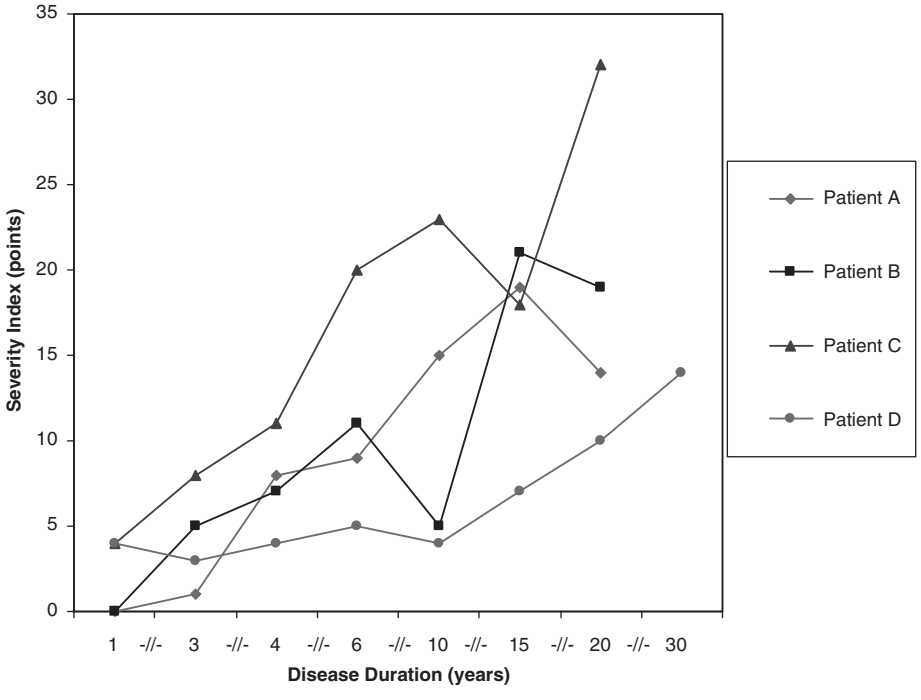


**Fig. 5.** Different courses of chronic pancreatitis in four hypothetical patients. An overview of the various courses of the disease in the four hypothetical patients is given in Table 10. The M-ANNHEIM severity index appears to be a valuable tool for comparison of different stages of the disease and various degrees of clinical severity in patients with chronic pancreatitis

**Table 10.** Examples of typical patients with chronic pancreatitis classified according to the M-ANNHEIM classification

| Age | Disease duration (years) | Clinical characteristics | M-ANNHEIM severity index (points) | M-ANNHEIM diagnostic criteria | M-ANNHEIM clinical staging |
|---|---|---|---|---|---|
| **Patient A, male, Caucasian, pancreatitis with multiple risk factors (M): excessive alcohol intake (A), and smoking (N)** | | | | | |
| 35 | 1 | Onset of disease at age of 34 years with acute pancreatitis, alcohol consumption of 100 g/day since the age of 26 years, smoker since the age of 16 years | A Minor severity (0 points) | Borderline | 0 b |
| 37 | 3 | Another episode of acute pancreatitis within the last 12 months, no pain between the episodes of acute pancreatitis, no signs of pancreatic insufficiency, still smoking | A Minor severity (1 point) | Probable | I a |
| 38 | 4 | Intermittent pain, medication with potent opioids, according to the patient, rare occurrences of intermittent diarrhea, no enzyme supplementation necessary, normal test results for exocrine and endocrine function, ERCP with mild changes, stopped drinking, still smoking | B Increased severity (8 points) | Probable | II b |
| 40 | 6 | Under medication with potent opioids no pain, ERCP with moderate changes, proven exocrine insufficiency | C Increased Severity (9 points) | Definite | II b |
| 44 | 10 | Again intermittent pain, potent opioids every 4 h without sufficient pain relief, ERCP showing marked changes, endoscopic interventions without successful pain relief, still no endocrine insufficiency, finally surgical intervention for pain relief | C Advanced severity (15 points) | Definite | II b |
| 49 | 15 | Since surgery, again intermittent pain; medication with potent opioids; after surgery onset of endocrine insufficiency; still smoking | D Marked severity (19 points) | Definite | III a |
| 54 | 20 | In recent years fading pain, currently no pain, no pain medication necessary, still smoking | C Advanced severity (14 points) | Definite | IV a |
| **Patient B, female, Caucasian, pancreatitis with multiple risk factors (M): moderate alcohol intake (A) and genetic predisposition (H)** | | | | | |
| 21 | 1 | Onset of disease at age 20 with acute pancreatitis, grandfather with pancreatic cancer as cause of death, alcohol consumption of 20 g/day since the age of 18 years, no pain since the episode of acute pancreatitis, no signs of pancreatic insufficiency | A Minor severity (0 points) | Borderline | 0 b |
| 23 | 3 | Intermittent pain, no pain medication necessary, another episode of acute pancreatitis, ERCP with equivocal changes, normal test results for exocrine and endocrine function, rare bouts of diarrhea but no steatorrhea, no enzyme supplementation necessary, stopped consumption of alcohol, genetic testing with heterozygous *PRSS1* mutation | A Minor severity (5 points) | Probable | I b |
| 24 | 4 | Pain pattern unchanged, according to the patient intermittent diarrhea now more often, proven mild exocrine insufficiency, now enzyme supplementation, normal endocrine function, MRCP without significant changes, ERCP with mild changes | B Increased severity (7 points) | Probable | II b |
| 26 | 6 | Continuous pain, potent opioids without sufficient pain relief, CT with moderate changes, endoscopic interventions for pain relief | C Advanced severity (11 points) | Definite | III a |
| 30 | 10 | Since endoscopic interventions no pain, currently no pain medication necessary, recent resumption of moderate alcohol consumption | B Minor severity (5 points) | Definite | III a |
| 35 | 15 | Again intermittent pain, unsatisfactory relief with potent opioids, ERCP with severe changes, repeated endoscopic interventions without successful pain relief, now proven endocrine insufficiency, development of a large pseudocyst, gastrointestinal bleeding from a vessel in the wall of the pseudocyst resulting in an emergency situation with surgical intervention | E Exacerbated severity (21 points) | Definite | III b |
| 40 | 20 | In recent years fading pain, currently no pain, still medication with mild opioids on a regular basis, no alcohol consumption | D Marked severity (19 points) | Definite | III a |

| | | | | | |
|---|---|---|---|---|---|
| **Patient C, male, Caucasian, pancreatitis with multiple risk factors (M): excessive alcohol intake (A), smoking (N) and genetic predisposition (H)** | | | | | |
| 36 | 1 | Onset of disease at age of 35 years with intermittent diarrhea and intermittent abdominal pain, alcohol consumption of 140 g/day since the age of 26 years, smoker since the age of 18 years, no episodes of acute pancreatitis | A<br>Minor severity<br>(4 points) | Borderline | II b |
| 38 | 3 | First diagnosis of chronic pancreatitis with proven exocrine insufficiency, ERCP with mild changes, intermittent pain, pain medication with nonopioid drugs, brother with infertility due to absence of vas deferens | B<br>Increased severity<br>(8 points) | Probable | II b |
| 39 | 4 | Intermittent pain, medication with potent opioids, ERCP with marked changes, stopped drinking, still smoking, panel testing for *CFTR* mutations with mild mutation | C<br>Advanced severity<br>(11 points) | Definite | II b |
| 41 | 6 | Continuous pain, potent opioids no longer sufficient for pain control, proven endocrine insufficiency, ERCP with marked changes, endoscopic intervention without successful pain relief, surgical intervention for pain relief | D<br>Marked severity<br>(20 points) | Definite | III a |
| 45 | 10 | Intermittent pain, again medication with potent opioids, again excessive alcohol intake, development of splenic vein thrombosis | E<br>Exacerbated severity<br>(23 points) | Definite | III b |
| 50 | 15 | In recent years fading pain, since 12 months no pain, no pain medication necessary, still smoking, splenic vein thrombosis unchanged | D<br>Marked severity<br>(18 points) | Definite | IV b |
| 55 | 20 | Since 2 years development of diabetic nephropathy and coronary heart disease, now weight loss, again continuous abdominal pain, medication with potent opioids not sufficient, splenic vein thrombosis unchanged, diagnosis of a pancreatic mass in the head of the pancreas, surgical intervention, histology reveals pancreatic cancer | E<br>Exacerbated severity<br>(32 points) | Definite | III b |
| **Patient D, male, Caucasian, sporadic idiopathic pancreatitis (H): probably a yet unidentified genetic predisposition** | | | | | |
| 7 | 1 | Onset of disease at age of 6 years with intermittent abdominal pain for 2 weeks every 6 months, no pain medication necessary | A<br>Minor severity<br>(3 points) | Borderline | I b |
| 10 | 3 | Still intermittent abdominal pain, now occurring every 4 months, still no pain medication necessary | A<br>Minor severity<br>(3 points) | Borderline | I b |
| 10 | 4 | Still intermittent abdominal pain, pain medication on demand with nonopioid drugs, now first episode of acute pancreatitis | A<br>Minor severity<br>(4 points) | Borderline | I b |
| 12 | 6 | Intermittent abdominal pain every 6 months and intermittent diarrhea. No steatorrhea. Pain medication on demand with nonopioid drugs. Normal test results for exocrine and endocrine function. No more episodes of acute pancreatitis | A<br>Minor severity<br>(5 points) | Borderline | II b |
| 16 | 10 | Still intermittent diarrhea, no steatorrhea, intermittent abdominal pain every 6 months. According to the patient no pain medication necessary. Recently another episode of acute pancreatitis, still normal test results for exocrine and endocrine function | A<br>Minor severity<br>(4 points) | Borderline | II b |
| 21 | 15 | Smoking since 2 years, intermittent pain every 6 weeks, pain medication on demand with nonopioid drugs, intermittent diarrhea every 2 months, no steatorrhea, normal test results for exocrine and endocrine function, ERCP with mild changes | B<br>Increased severity<br>(7 points) | Probable | II b |
| 26 | 20 | Intermittent pain, medication with potent opioids, ERCP with moderate changes, proven exocrine insufficiency, no enzyme supplementation necessary, normal endocrine function | B<br>Increased severity<br>(10 points) | Definite | II b |
| 36 | 30 | Intermittent pain every 2 months, medication with potent opioids, slight weight loss, diagnosis of a mass in the head of the pancreas, suspicion of pancreatic cancer, ERCP still with moderate changes, surgical intervention with exclusion of pancreatic cancer, demonstration of an intense chronic inflammatory reaction with a fibrotic mass. Still normal endocrine function following surgery | C<br>Advanced severity<br>(14 points) | Definite | II b |

fibrosis sequence.[7,9] On the basis of these findings, new hypothetical concepts of the disease have been proposed.[56] Recently, the TIGAR-O classification of chronic pancreatitis incorporated genetic, immunologic, and epidemiologic findings and suggested a framework for categorizing patients according to the different etiologies of the disease.[13] However, the TIGAR-O classification again did not consider the different stages and degrees of severity of the disease. Thus, we felt that a revised classification of chronic pancreatitis was clinically demanded, and we developed the M-ANNHEIM classification system to facilitate the investigation of several hitherto unanswered questions.

The clinical course of pancreatic disease demonstrates a marked variability.[3–5] Epidemiological reports also suggest a high degree of heterogeneity with respect to susceptibility to chronic pancreatitis. Patients with alcoholic chronic pancreatitis present with consumption of alcohol ranging from 80 g to more than 500 g per day for several years before onset of the disease.[41–44,47] There appears to be no precise threshold of toxicity below which alcoholic pancreatitis does not occur, and an increased risk of developing the disease has also been reported in patients with moderate amounts of alcohol consumption, such as 20 g per day.[42] A strong relationship between alcohol consumption and chronic pancreatitis appears not to exist, as only about 10% of heavy alcohol drinkers ever develop clinically recognized pancreatic inflammation.[115] The incidence of alcohol-induced pancreatitis varies considerably, ranging from 38% to 94%, among different cohorts of patients in industrialized countries,[3,42–44,47,116,117] and differences in racial susceptibility may exist between patients of African origin and Caucasians.[118]

Patients with chronic pancreatitis have been categorized so far into clusters of patients with alcoholic, nonalcoholic or idiopathic, and hereditary pancreatitis. With increasing knowledge of the genetic background, these clusters no longer reflect the complexity and possible interactions of the different risk factors. It is likely that the interaction of different genetic variations or the presence of different risk factors explain the observed variability in epidemiological and clinical presentation of the disease.[52] Within this context, the impact of smoking has not been conclusively clarified,[13] and the influence of recently identified genetic risk factors on the course of the disease has only been studied in a limited number of patients.[65,71–75] Preliminary reports already suggest a role for interactions between different genes or associations between genes and additional factors such as pancreas divisum.[64,119,120] These findings highlight the need for stratification of patients according to our new classification system.

Indeed, the M-ANNHEIM classification offers a completely new approach to investigation and treatment of patients with chronic pancreatitis. The categorization of disease severity according to our system may reveal the impact and the interaction of different risk factors on the clinical presentation of the disease. Chronic pancreatitis is a relatively rare disease, and it remains extremely difficult for single institutions to obtain significant numbers of patients with rare genotypes or risk factors for performing meaningful statistical analysis. In this context, the M-ANNHEIM classification provides a framework for combining and comparing interinstitutional data. Our classification requires clinical information that can easily be obtained from the patients. The suggested staging of the disease (Table 3) and the prioritization of clinical and therapeutic features (Table 8) closely reflect the clinical presentation of the disease and clearly distinguish between different grades of disease severity (Tables 9 and 10). The M-ANNHEIM system extends the consensus of the Cambridge classification and incorporates imaging information obtained from EUS and MRI (Table 7). The clinically recognized onset of chronic pancreatitis is correctly remembered by the majority of patients. Thus, the disease duration together with the stage and severity of the disease provide key features for the comparison of different courses of chronic pancreatitis. Although our classification is organized to reflect the clinical presentation at a given point in time, it may also be useful for retrospective analysis, since the required clinical features for categorization represent major events during the course of the disease. The severity score also captures aggravation as well as recovery from the disease (Table 10) and allows comparison of treatment results and prospective monitoring of patients. It is our assumption that the use of the M-ANNHEIM system will reveal subgroups of patients requiring special treatment options, or which are associated with a particular prognosis. The M-ANNHEIM system also includes patients with a first episode of acute pancreatitis, thereby facilitating the prospective investigation of patients who may progress toward chronic disease.

In conclusion, the M-ANNHEIM multiple risk factor classification system for chronic pancreatitis incorporates etiology, different stages of the disease, and various degrees of clinical severity. The M-ANNHEIM classification represents a simple, objective, accurate, and noninvasive tool in clinical practice and may be helpful in investigating the impact and interaction of various risk factors on the course of the disease. Future studies with large patient cohorts are required to validate the M-ANNHEIM classification in clinical practice.

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