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LEADING ARTICLE

Pain Management in Chronic Pancreatitis: Summary of Clinical Practice, Current Challenges and Potential Contribution of the M-ANNHEIM Classification

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Abstract
Abdominal pain, diarrhea with weight loss, and endocrine insufficiency represent the dominant symptoms of chronic pancreatitis (CP). High intensity of pain and constant pain have been shown to reduce quality of life in CP and may result in disability and increased health resource utilization. Various basic challenges and unanswered questions still exist regarding the treatment of pain in CP. Recently, limited evidence has been gained that early surgery for painful disease might be associated with better treatment results. Thus, timing of pancreatic surgery in painful disease represents a major issue that needs to be clarified in future studies. In this context, surveillance of patients is necessary in clinical practice. It appears that a generally accepted classification of the disease represents a major requirement for inter-institutional comparison of data with future progress in clinical research. Among recently proposed classification systems, the M-ANNHEIM classification system of CP with its recently presented M-ANNHEIM Surgery Score might be a useful tool to picture the course of the disease and to monitor treatment results. Future research is required to clarify the possible role of this system in the management of pain in CP. In the present article, we provide an overview of current status, challenges, and unanswered questions in the treatment of pain in CP, and we demonstrate the potential benefits of the M-ANNHEIM classification system in the management of painful CP.

Key Points

Pain in chronic pancreatitis appears to be of neuropathic origin.

Treatment for pancreatic pain is based on the sequential introduction and titration of medications with increasing analgesic capacity, and on endoscopic and surgical treatment approaches.

Several issues with regard to the management of patients with painful chronic pancreatitis have not yet been clarified. These issue include the clinical description and measurement of pancreatic pain, the surveillance of patients with painful chronic pancreatitis, and the timing of surgery for the treatment of pancreatic pain.

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1 Introduction

Chronic pancreatitis (CP) represents 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]. In recent decades, much progress has been achieved in understanding the molecular basis of the disease and the evolution of pancreatic fibrosis. However, diagnosis and treatment of CP remains a difficult issue since the morphological destruction of the organ does not match with the loss of pancreatic function [6, 7]. A standardized clinical classification of CP appears essential for future progress in clinical treatment and research of the disease [8].

In most patients, nonspecific abdominal pain represents the first presentation of CP and is the leading symptom. Pain may present with short relapsing episodes separated by pain-free intervals lasting for up to several years, or it may be characterized by prolonged periods of either persistent pain or clusters of recurrent severe pain [5]. Kempeneers et al. recently demonstrated that patients alternated between pain patterns regardless of any endoscopic or surgical intervention [9]. High intensity of pain and

constant pain have been shown to reduce quality of life in CP and may result in disability and increased health resource utilization [10, 11]. In contrast, pancreatic exocrine or endocrine loss of function is diagnosed in about 10% of individuals with alcoholic CP that have previously never experienced pancreatic abdominal pain [1, 3]. Typically, the initial phase of the disease is characterized by abdominal pain and may last for several years. In the later phase of the disease, pancreatic exocrine and endocrine insufficiency occurs [1–5]. It has been suggested that abdominal pain completely dissolves in the final phase of the disease after a disease duration of more than 10 years [5, 12]. However, pain relief over time has also been observed in other studies [2, 3], but the general concept of a 'pancreatic burn-out' has been challenged [2]. Recent studies found that pain does not resolve over time in most patients [11, 13]. In line with this observation, there is no convincing evidence that endocrine and exocrine pancreatic insufficiencies are associated with pain relief [10].

The origin of pain in CP is not fully understood but might be multifactorial [14]. Of note, various pancreatic and extra-pancreatic causes of pain need to be investigated and treated (e.g., peptic ulcers, other comorbidities with an increased prevalence in CP, morphological changes such as pseudocysts, obstruction of the duodenum or the common bile duct, pancreatic duct strictures, inflammatory masses) [14, 15]. Effects in response to medical treatment such as opioid-induced bowel syndrome or endoscopic and surgical complications may also contribute to pain [10]. In a large group of patients, no clear source of pain is identifiable, and in the absence of morphological changes such as dilated pancreatic ducts, these patients are often labelled as 'minimal change CP' [16, 17]. Of note, a lack of correlation between radiological findings and pain has been described in patients with CP [11, 18]. In the past, it has been suggested that pancreatic pain originates from local tissue hypertension due to fibrotic changes in the pancreas such as pancreatic stones or duct strictures [16, 19]. This concept of the development of pancreatic pain might be accurate, especially in the early phase of the disease. Recent evidence rather suggests that changes in the pancreatic nerves are associated with the development of pancreatic pain [20]. These changes of the pancreatic nerves appear to stimulate the central nervous system with subsequent further neuroplastic changes. Thus, pancreatic pain appears to be of 'neurogenic' origin in CP [10, 21, 22], and a progressive development might exist from the initial phase of the disease with 'true visceral pain' to the later phase of the disease with 'neuropathic pain' and irreversible central sensitization [10, 21].

The present article provides an overview of the current status of pain management in CP. The manuscript also aims to summarize challenges and unanswered questions regarding the treatment of pancreatic pain. Finally, the M-ANNHEIM classification system of CP is presented as a tool to monitor treatment results, to picture the course of the disease, and to guide clinical decision making in the management of pain in CP [8].

2 Current Status of Pain Management

2.1 Medical Treatment

Medical analgesic treatment of CP follows the principles of the 'pain relief ladder' that was initially proposed by the World Health Organization (WHO) to treat pain related to different forms of cancer [23]. The system has been adapted for the treatment of pain in CP and has been expanded with level IV, which represents surgical and interventional approaches. The adapted system consists of various levels (levels I–IV) and is based on the sequential introduction of medications with increasing analgesic capacity that need to be titrated until pain relief is achieved (Fig. 1) (reviewed in [24]). Fig. 2 represents an algorithm for pharmacological treatment of pain in CP that has been proposed by Drewes et al. in the international consensus guideline for the understanding and management of pain in CP [21].

Acetaminophen represents the major analgesic that is used in *level I*. Side effects of this drug are limited. Nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used but should be avoided due to their gastrointestinal toxicity [10, 21]. In individuals who are at high risk for peptic ulcers, proton-pump inhibitors should be prescribed. Metamizol represents another potent non-opioid analgesic that also has spasmolytic effects that can be helpful for painful CP. A major adverse effect of metamizol is the risk of agranulocytosis. Therefore, this drug is not approved in various countries (e.g., USA, UK) [24].

Tramadol appears as the preferred analgesic in *level II* and was superior to morphine in patients with CP, with less gastrointestinal side effects [10, 25].

The analgesic medication in *level III* represents strong opioids such as morphine [10, 21]. These drugs are usually used in individuals with CP and severe pain. These medications are associated with high rates of dependency and side effects [26, 27]. Treatment in patients with alcoholic CP can be challenging due to the addictive risk in this group of patients [21]. Treatment is further challenged by the metabolism of many opioids that is based on a preserved liver and gut function that might be reduced in many patients [28]. Of note, experimental and clinical investigations suggest that some drugs (e.g., oxycodone) may be more effective in the treatment of pain in CP [10, 29, 30]. Opioid rotation should be applied in the case of treatment failure [10, 28]. In general, treatment in patients with CP should be applied

World Health Organization pain ladder adapted for the treatment of pain in chronic pancreatitis

Pain ladder step 1:	Nonopioid analgesic
Pain ladder step 2:	Step 1 and mild opioids
Pain ladder step 3:	Previous steps and potent opioids
Pain ladder step 4:	Surgery and other interventional procedures
Additional treatment at each step:	Adjuvant drugs (such as tricyclic antidepressants, psychotherapy, abstinence from alcohol and nicotine

Fig. 1 World Health Organization pain ladder adapted for the treatment of pain in chronic pancreatitis. Pain relief ladder of the World Health Organization. In the absence of clinical trials, recent recommendations for conservative treatment of pain in chronic pancreatitis have adapted the three-step pain relief ladder of the World Health Organization originally developed for the treatment of cancer pain (reviewed in [8, 24]). Endoscopic ductal decompression therapy and surgical intervention remain treatment options if satisfactory pain relief with conservative approaches is not achieved

according to guidelines for chronic opioid therapy with the lowest possible dosage [10, 27]. Opioid medication should preferably be taken orally to avoid as far as possible dose escalation and addiction [10, 27]. However, in up to 50% of patients, opioids fail and treatment should be stopped [10]. Transdermal administration of opioids is not recommended and should be reserved for patients with malabsorption and problems with tablet ingestion [10, 21]. Opioids may cause constipation, reflux disease, gas, bloating, and abdominal distension, which may also be painful [26]. Thus, opioid tapering or administration of opioid antagonists with restricted local effects in the gut may improve these side effects and abdominal pain [10, 27]. Finally, 5% of patients undergoing opioid therapy may develop 'narcotic bowel syndrome,' which represents a paradoxical increase in abdominal pain with enhanced opioid dosage requiring opioid tapering [31, 32].

In *level IV*, interventional endoscopic procedures and surgical approaches are applied.

Adjuvant analgesics represent a group of drugs that have been developed for diseases other than pain and that are administered additionally at each level. These drugs are antidepressants, anticonvulsants (such as gabapentinoids), and anxiolytics [10, 21]. However, only the gabapentinoid, pregabalin, has been investigated in a placebo-controlled randomized trial and was shown to induce moderate pain relief with few side effects [22]. Anti-depressive drugs might be helpful in treating pain in selected patients with CP [10]. These drugs should be administered in a low dose, and drugs with serotonin–noradrenaline reuptake inhibition should be used due to their reduced side effects. In the group of patients with a severe pain presentation, opioids need to be combined with adjuvant analgesics [33].

2.2 Endoscopic Treatment

Briefly, endoscopic treatment (ET) is effective in patients with painful CP with an obstructive type of CP and in patients with a pancreatic duct dilatation due to strictures and intraductal stones, and appears as a beneficial bridge to surgery [10]. However, endoscopic drainage is less effective and has a shorter-term effect compared with surgery [10, 17, 21, 34–39]. Extracorporal shock wave lithotripsy (ESWL) therapy represents another treatment option in painful CP and is indicated for disintegrating stones obstructing the main pancreatic duct, when endoscopic stone removal is not possible [34]. Other options for selected cases with painful disease include endoscopic ultrasound-guided plexus block, splanchnic nerve block, spinal cord stimulation, transcranial magnetic stimulation, and acupuncture [10, 21]. In general, the currently assumed pathophysiological mechanisms in CP contradict the rationale for invasive treatment options such as celiac plexus block and splanchnic nerve block (reviewed in [17]). Neuropathic changes represent the origin of pain in CP and are observed at all levels of the nervous system, and their expression correlates with the intensity of pain. The ongoing sensitization of central nociceptive pathways is accelerated by acute inflammatory changes and may result in an autonomous and self-perpetuating pain state, which finally is independent of the peripheral nociceptive input. In the setting of such an autonomous pain state, it appears unlikely that any local neuroablative procedure will succeed. Invasive treatments such as neuroablative procedures may

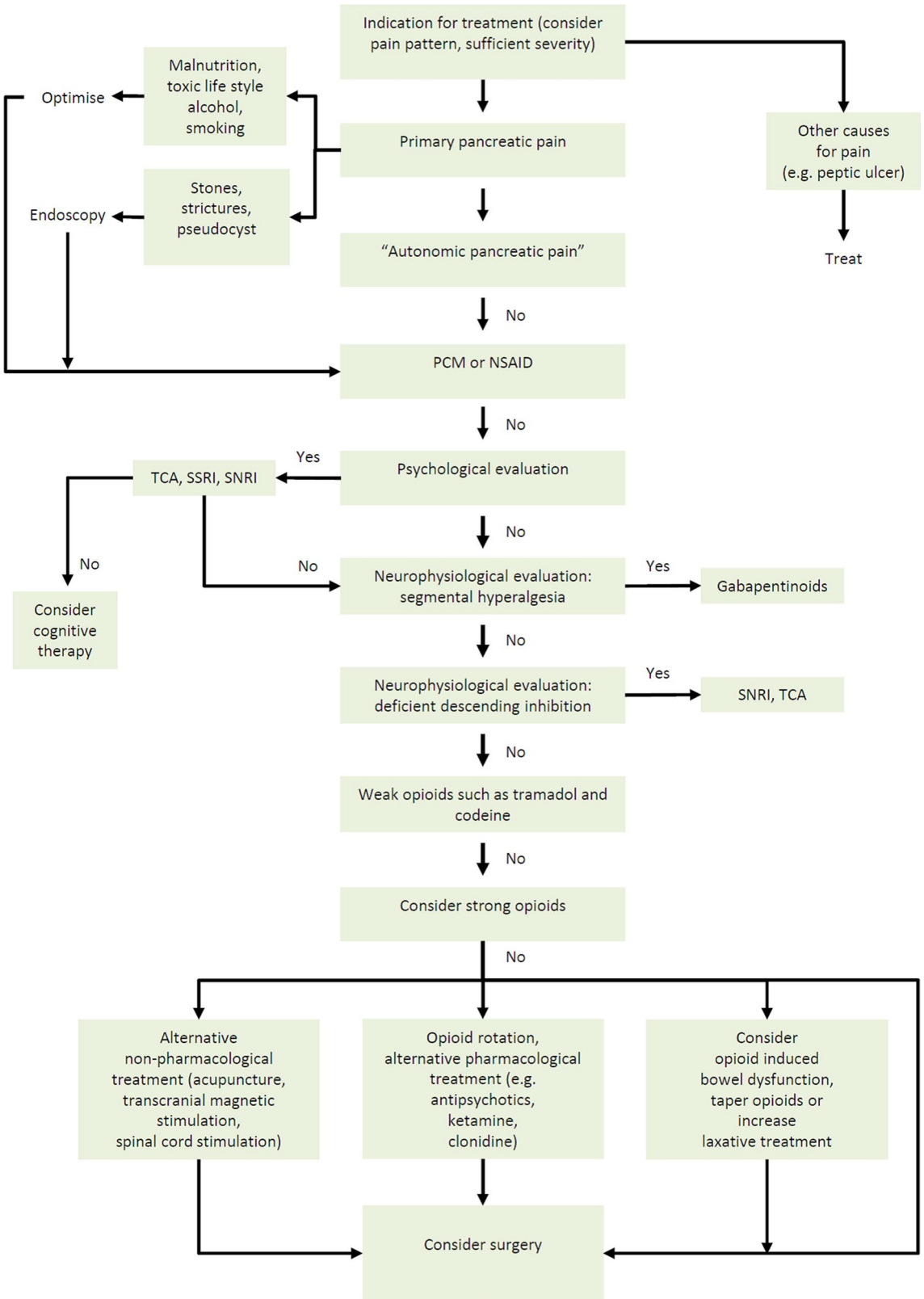


Fig. 2 Algorithm for pharmacological treatment of pain in chronic pancreatitis (CP) that has been proposed by Drewes et al. in the international consensus guideline for the management of pain in CP [21]. *Yes* indicates sufficient effect, positive testing; *No* indicates insufficient effect. *NSAID* non-steroidal anti-inflammatory drugs, *PCM* paracetamol, *SNRI* serotonin-noradrenalin reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressives

remove the source of neuropathic pain and might reduce the signal input and pain severity since neural blocks are effective for peripheral nerve injury. However, the success occurs temporarily, and pain relief is only short term with a risk for side effects such as postural hypotension and diarrhea. After initial alleviation of pain, the procedures finally may promote spontaneous activity of peripheral afferent nerves due to disinhibition and upregulation of ion channels. As a consequence, further pathological changes are pushed ahead in the central nervous system that again worsen pain. This phenomenon was formerly known as 'deafferentation pain' (reviewed in [17]). As a result, celiac plexus block and splanchnic nerve block are nowadays rarely applied in CP and have been almost abandoned in recent guidelines [10, 21]. However, a detailed overview about these different invasive, but non-surgical treatment options is beyond the scope of the present article and is given elsewhere [40, 41].

2.3 Surgical Treatment

Various surgical options for the treatment of pancreatic pain have been developed and consist of three categories: decompression due to ductal hypertension, resection due to inflammatory masses in the pancreatic head, and mixed techniques [10, 17, 21, 42]. Briefly, these techniques achieve pain relief that is maintained over time in about 80% of patients, but drainage surgery associated with duodenum-preserving pancreatic head resection currently appears to be the most promising surgical strategy [10, 42]. Of note, all surgical studies compared different procedures, were not sham-controlled, and neglected the natural course of the disease and any placebo effects [17]. Moreover, the high rate of pain relief with success in up to 90% of patients in surgical series suggests a biased effect due to selection of patients [10]. It is clear that correct patient selection in a multidisciplinary approach and appropriate timing for referral to surgery are major issues for a successful outcome [10, 17, 21]. Evidence is missing for detailed recommendations for managing pain relapse after surgery, but any kind of surgical treatment may fail due to irreversible neuropathic alterations after previous surgical interventions [21, 43]. Thus, a total pancreatectomy currently represents a salvage approach and should only be considered in subjects without ductal dilatation, who are resistant to conventional medical, endoscopic, and previous surgical treatment and who have severe pain [10]. However, a detailed review of the different surgical treatment options is not the purpose of the present article and is provided elsewhere [42].

2.4 Other Treatment Approaches

Other treatment options for pancreatic pain include lifestyle modifications such as cessation of alcohol intake and smoking. Several studies revealed that cessation of alcohol consumption has beneficial effects on pain in alcoholic CP [10, 44, 45], and that smoking accelerates disease progression and is also associated with increased pain in CP [45, 46]. At present, pancreatic enzyme supplementation is not recommended for pain relief in CP in the European guideline [10], but has been suggested as an initial treatment option in another international guideline [21]. Nevertheless, beneficial effects clearly exist with enzyme replacement therapy on abdominal discomfort such as gas and bloating related to exocrine insufficiency [10, 21]. Antioxidant therapy was associated with significant and prolonged pain relief in a randomized placebo-controlled trial from India [47], but the findings were not confirmed in a subsequent study from North America [48]. Thus, current guidelines are also contradictory with regard to the recommendation of antioxidants for treatment of pain in CP [10, 21].

3 Problems and Unanswered Questions in Treatment of Pancreatic Pain

The medical management of pain in patients with CP has not changed in the past decades. Current guidelines basically summarize the knowledge that was already summarized in reviews and guidelines three decades ago and still refer to the adapted WHO pain ladder [24]. As already mentioned in the past, only very few studies have been performed that compare different treatment regimens in patients with CP [17]. As a consequence, treatment statements in current guidelines must remain rather vague and still cannot provide detailed recommendations for special patient groups such as alcoholic versus hereditary disease [49].

Pain in CP appears to belong to the clinical entity of neuropathic pain [10, 21, 22]. It has been demonstrated that the clinical entity of neuropathic pain appears to be heterogeneous regarding its etiologies and different nerve lesions, but it presents a strong clinical consistency [50]. These findings suggest that selecting patients according to their disease or neural lesion might not be a promising approach to succeed in treatment studies [50]. Negative results of clinical trials of drugs for neuropathic pain might reflect flawed study designs rather than the lack of efficacy of the drugs under investigation [51]. In line with these findings, pharmacological trials reveal similar efficacy of most medications for neuropathic pain of different etiologies, including painful polyneuropathies and central pain [50]. Thus, it might be that pharmacological pain management with central effects that is proven to be successful in, for example, musculoskeletal pain may also be effective in pancreatic pain. In general, improvements in clinical classification schemes of diseases and study designs are required, otherwise helpful drugs may not enter the clinical stage and may not reach the

patient despite being highly efficacious in defined subgroups of patients [51].

Moreover, in clinical practice, adherence to guideline recommendations appear to be limited. A recent nationwide investigation from the Netherlands revealed that adherence to the United European Gastroenterology evidence-based guidelines (HaPanEU) recommendations for the management of CP is only moderate to low for all non-invasive domains [52]. In their study, health care issues showing the lowest adherence to the guidelines were—among several other clinical issues—structured evaluation of abdominal pain and quality of life. The authors concluded that their results may indicate suboptimal care for patients with CP [52].

In this context, experts recently summarized several points that future research projects should investigate in painful CP [49]. Future research should include development of (i) a simple quantitative sensory testing approach for assessment of pain chronification and guidance of treatment, (ii) prospective surveys with assessment of pain biomarkers to predict treatment outcome (e.g., quantitative sensory testing, clinical and psychological variables, biopsies, pancreatic juice and urine, genetics, pharmacological challenge), (iii) clinical tools to differentiate between pancreatic and non-pancreatic pain to guide treatment of peripheral and central sensitization, (iv) longitudinal pain studies, (v) studies to explore opioid use with its complications, (vi) new technological treatments with pain self-management interventions to improve pain, associated brain manifestations, and quality of life, and (vii) studies demonstrating that etiology rather than morphology may determine the best treatment [49]. However, all these ambitious goals appear to be significantly hindered by three major questions that could not be solved in recent decades.

These three major questions that could not be solved regarding pancreatic pain management can be summarized as follows:

The first question represents the controversial debate about the disease status that requires pancreatic surgery for the treatment of painful CP and that is associated with optimal treatment results [17]. A few retrospective studies suggest that rather early surgery for painful disease is associated with better treatment results [53–60]. A single prospective controlled study recently confirmed better outcomes in patients with early pancreatic surgery compared with patients under an endoscopic treatment approach [61]. However, after exclusion of patients with unsuccessful endoscopy, there remained no differences in pain score measurements and quality of life between the groups. In addition, the nerve damage associated with surgery may outbalance the possible benefit of early surgery in preventing central sensitization. Thus, this study did not clarify whether early surgery can dampen pancreatic pain. Of note, current guidelines support performance of early surgery in painful CP [10, 21, 62], but evidence with clear clinical information about the required disease status remains limited.

The second question refers to the clinical description and measurement of pancreatic pain and its response to treatment. Pain in CP should be assessed using a multidimensional approach, including evaluation of pain intensity, pain pattern, and its impact on daily function and quality of life (QoL) [10]. Overall, scientific evidence is vague regarding this issue. Guidelines summarize that *Subjective Verbal Reports* from the patients might be used to describe the individual pain presentation [21]. *One-Dimensional Scales* grade selected features of pain and are simple methods to self-report the magnitude of pain in individual patients [21]. These scales usually employ numeric (e.g., 0 to 10), verbal or visual gradings to describe the pain or its relief. However, these scales may oversimplify the extent of pain [21]. The visual analog scale (VAS) represents the most often applied numerical scale in patients with CP. Of note, these scales need to be used together with a standardized recording of the pain pattern over time for a more detailed description of pain [11]. The occurrence of pain with constant versus intermittent pain, and the rate of pain exacerbations, need to be registered [11, 63]. In individuals with CP, pancreatic disease appears to influence various issues of QoL [64–66]. Patients with CP experience a significant increase in symptoms of depression compared with the general population [64]. In another study, 60% of patients reported a negative impact on their social lives, 43% demonstrated a negative effect on their spouse and other relationships, and 63% were unemployed due to the disease [65]. Thus, based on the obvious interaction of symptoms with QoL, any treatment of the disease may also have an impact on this interaction in patients with CP. Importantly, the reduction of QoL in individuals with CP appears only partly explained by pain, but also by other features of the disease such as exocrine and endocrine insufficiency with its possible consequences. However, only pain significantly impaired all eight domains of a questionnaire for QoL (Medical Outcome Study 36-Item Short-Form Health Survey [SF-36]), thus confirming that pain control is the main therapeutic approach (reviewed in [67]). Indeed, several questionnaires have been applied to determine the effect of pain on QoL, but only the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the recently developed Pancreatitis Quality of Life Instrument (PANQOLI) questionnaire have been validated in individuals with CP [66, 68]. *Multidimensional scales* measure several aspects of pain, including its intensity, nature and location, and impact on mood or activity level. The Izbicki pain score has been developed to capture these pain dimensions and provides a score based on pain attack frequency, pain intensity score (VAS), analgesic use, and duration of disease-related inability to work

[69]. Although this score has never been strictly validated in patients with CP, its value has been confirmed by application in important studies in CP [53–55, 61]. The Brief Pain Inventory (BPI) quantifies intensity as well as pain's interference with mood and ability to work and correlates with QoL in CP patients [63]. The McGill Pain Questionnaire is another survey that assesses sensory, affective, and evaluative dimensions of pain [70]. The comprehensive pain assessment tool (COMPAT) questionnaire has been recently developed and validated for pain in CP [71, 72]. Although its current version appears too cumbersome for daily clinical practice, this tool represents a promising approach that addresses all relevant aspects of pain in CP [71, 72]. Finally, pain sensitivity can be reliably assessed and quantified using *Quantitative Sensory Testing (QST)* [73]. These techniques summarize various calibrated and standardized signals that are generated under controlled conditions and that stimulate the peripheral nervous system. These techniques have been applied to evaluate and characterize the sensitivity to pain in CP [74, 75] and to predict outcome of treatment in individuals with CP [76–79]. In patients with painful CP, techniques of QST predicted the analgesic effect of pregabalin [76], demonstrated that pregabalin inhibited central sensitization [77], revealed subgroups of individuals with altered pain processing [78], and that oxycodone was more effective than morphine in the treatment of visceral pain [79]. Thus, techniques of QST might be used to determine and monitor treatment approaches based on individual sensory profiles [76–79], and might be of major importance for management of pain in CP. Finally, several consensus meetings have been held under the auspices of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and identified six core outcome domains (pain, physical functioning, emotional functioning, participant ratings of treatment, symptoms and adverse events, participant disposition) [80, 81]. In a recent statement from this group of experts, measurable phenotypic characteristics of individual patients or subgroups of patients have been established that increase or decrease the response to a specific analgesic treatment, and measurement tools have been proposed that are best suited to evaluate these characteristics [82]. We emphasize that this approach also needs to be considered in research and treatment of pain in CP since chronic pancreatic pain probably does not differ from other painful diseases.

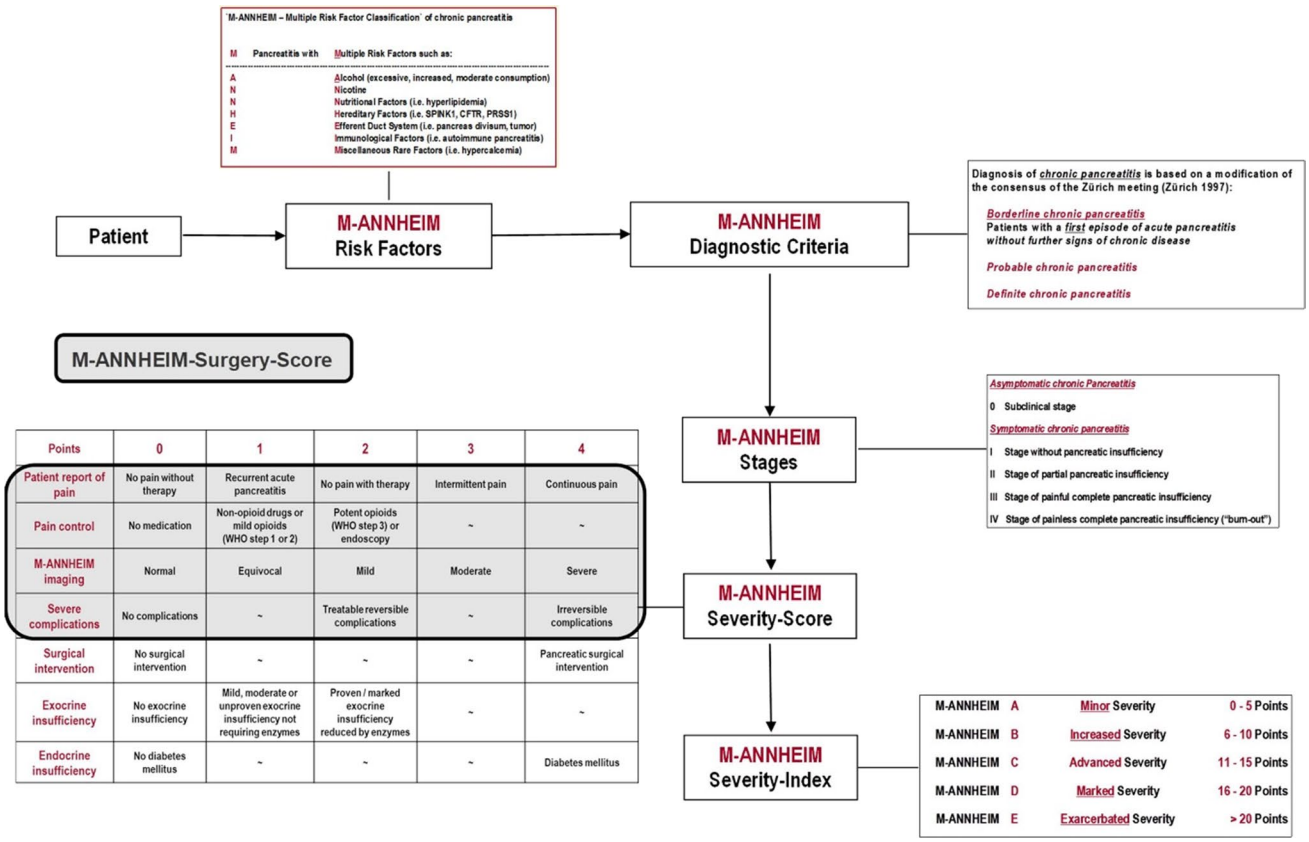
The third challenging question represents the need for the best clinical strategy to monitor the treatment of CP. Here, a generally accepted classification of disease might clearly help to meet this requirement. This issue has been recognized in the field of pancreatology, and several classifications of CP have been proposed in recent years [8, 83–88]. However, even an international panel of experts recently failed in reaching agreement about the definition of early CP [89]. In other words, the basic question that physicians and researchers are talking about could not be answered. In line with this discouraging observation, it is not surprising that none of the international guidelines clearly commit to a single clinical classification for CP, but rather suggest the performance of prospective studies to clarify this issue [10, 17, 21, 34–39]. It is obvious that a unified disease description is important for further progress in treatment of pancreatic pain.

4 M-ANNHEIM Classification and Its Potential Contribution to Pain Management

4.1 M-ANNHEIM Classification of Chronic Pancreatitis

A disease classification should be useful in monitoring the disease, directing clinical practice, and comparing inter-institutional data. In an attempt to fulfill these requirements, we developed the M-ANNHEIM classification system of CP based on a comprehensive review of the literature [8]. Figure 3 summarizes this classification. The M-ANNHEIM classification was developed in Mannheim, Germany, and is based on the assumption that CP results from the interaction of multiple risk factors. Thus, we named the classification multiple (M) risk factor classification and grouped 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 classification includes a clinical staging system and provides a scoring system of clinical features for an overall score of clinical severity.

The M-ANNHEIM classification system is in accordance with the clinical demands for a classification of CP (reviewed in [8]). First, the system orders all different etiologies of CP since this information appears essential for treatment and surveillance of patients [45, 46, 90–93]. Second, the detailed disease description of the system considers various difficulties with the clinical presentation of CP (reviewed in [8]). Third, the system includes recent consensus statements for pancreatic imaging in CP [8, 35, 85]. Endoscopic ultrasound represents the major imaging investigation for diagnosis of CP [8, 85, 94]. However, diagnosis of early CP with EUS still remains a clinical challenge since the method is extremely operator dependent and EUS findings reflecting minimal pancreatic changes have limited sensitivity and specificity for the diagnosis of early CP [95]. The German guidelines of CP established a consensus for the correlation of imaging



Points	0	1	2	3	4
Patient report of pain	No pain without therapy	Recurrent acute pancreatitis	No pain with therapy	Intermittent pain	Continuous pain
Pain control	No medication	Non-opioid drugs or mild opioids (WHO step 1 or 2)	Potent opioids (WHO step 3) or endoscopy	~	~
M-ANNHEIM imaging	Normal	Equivocal	Mild	Moderate	Severe
Severe complications	No complications	~	Treatable reversible complications	~	Irreversible complications
Surgical intervention	No surgical intervention	~	~	~	Pancreatic surgical intervention
Exocrine insufficiency	No exocrine insufficiency	Mild, moderate or unproven exocrine insufficiency not requiring enzymes	Proven / marked exocrine insufficiency reduced by enzymes	~	~
Endocrine insufficiency	No diabetes mellitus	~	~	~	Diabetes mellitus

Fig 3 M-ANNHEIM classification and the M-ANNHEIM Surgery Score. The M-ANNHEIM classification includes a clinical staging system which provides subcategorization into asymptomatic (stage 0) and symptomatic (stages I, II, III, IV) phases of chronic pancreatitis. Of note, the concept of a 'pancreatic burn-out' is reflected by stage IV, but recent lines of evidence challenge this hypothesis and suggest that this phenomenon does not frequently occur. The disease onset and diagnosis was based on several widely accepted criteria. For the grading of morphological changes, the M-ANNHEIM classification introduces imaging criteria that consider any information from abdominal ultrasound, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasound (EUS). These criteria are based on previous consensus statements. Finally, the M-ANNHEIM classification includes a scoring system of clinical features that grades the presence of abdominal pain, therapeutic approaches for pain control, pancreatic surgical interventions, exocrine and endocrine insufficiency, morphological status of the organ, and the occurrence of additional severe organ complications. These various features are linked to corresponding amounts of points. Depending on the presence of these features, the points are added to an overall score of clinical severity. The M-ANNHEIM Surgery Score (grey) represents a simplified scoring system to predict the risk of pancreatic surgery in an individual patient

findings by EUS with the well accepted criteria of the Cambridge classification [35]. The Rosemont classification later established a reference standard of EUS findings for the diagnosis of CP [85]. Of note, the M-ANNHEIM classification remains in line with these recent consensus developments.

The M-ANNHEIM classification has been applied in numerous research projects from throughout the world (e.g., [96–100], reviewed in [101]) and has been frequently cited. Most studies utilized only single parts of the M-ANNHEIM classification instead of the complete system [101]. Thus, it currently appears that the system—at least partially—is generally well accepted in pancreatic research, but has not yet found acceptance in clinical routine work. In recent years, we performed various studies to validate the M-ANNHEIM classification [13, 102–105]. We categorized a patient cohort from Romania to describe the clinical course of CP in patients with SPINK1-mutations [102]. We retrospectively investigated the course of CP in two studies with up to 741 individuals [13, 105]. We applied the M-ANNHEIM classification and similar systems from throughout the world in a well-defined cohort of patients with autoimmune pancreatitis [104]. This investigation revealed that the M-ANNHEIM classification is the most beneficial system to describe pancreatic inflammation [104]. In all these studies, we obtained rational data reflecting the previously described and generally accepted clinical course of CP [13, 102, 104,

105]. Thus, we clearly assume that an analysis based on the M-ANNHEIM system provides meaningful results.

4.2 Disease Surveillance and Timing of Pancreatic Surgery

We performed a retrospective multicenter analysis in our patient cohort of 741 individuals with CP and we demonstrated that the M-ANNHEIM classification might be used to monitor the course of the disease and might help to predict the timing of pancreatic surgery [103]. Briefly, we classified 12% ($n = 89/741$) of patients immediately preceding pancreatic surgery. These patients revealed a higher severity according to the M-ANNHEIM scoring system than patients that were not scheduled for an operation. In a next step, we performed a logistic regression analysis with all variables of the M-ANNHEIM Severity Score and established the M-ANNHEIM Surgery Score, which was shortened to the variables of pain with corresponding pain medication, pancreatic imaging, and pancreatic complications (Fig. 3, *grey area*). This simplified score may serve as a new tool to identify patients that may require surgery. A receiver operating characteristic analysis revealed a cut-off value of 9 points within the M-ANNHEIM Surgery Score to identify these individuals (sensitivity 78.7%, specificity 91%). We defined three risk categories for surgery and found frequencies of pancreatic operations of 1.6% ($n = 7/440$) in the 'Baseline-Risk' category, 7% ($n = 12/172$) in the 'Low-Risk' category ($p < 0.0001$, Chi-square-test, odds ratio [OR] 4.6, confidence interval [CI] 1.8–12), and 54% ($n = 70/129$) in the 'High-Risk' category ($p < 0.0001$; OR 73; CI 32–167). Patients that presented with a Surgery Score for the 'High-Risk' category, but were not operated on, had a significantly increased ratio of clinical features that hamper performance of surgery ($p < 0.001$, Chi-square test). Thus, the differentiation of patients into different risk categories for pancreatic surgery with the M-ANNHEIM Surgery Score supports a prognostic evaluation of patients and may be used for clinical disease surveillance [103].

Close surveillance of patients with CP and abdominal pain appears crucial. Although evidence for this approach is only based on a few observational studies, delayed surgery might be associated with limited postoperative pain reduction, increased risk of pancreatic insufficiency, and frequent re-intervention rates [58, 60]. Individuals in the 'High-Risk' category should be advised to undergo an accurate monitoring with more frequent medical consultations. As an example, a patient with 7 points in the M-ANNHEIM Surgery Score (e.g., patient with intermittent pain, pain medication with peripheral analgesics, and moderate pancreatic imaging findings) serves to describe the usefulness of the system. This individual would not be prepared for surgery. However, if this patient's disease progressed towards 10 points (e.g., intermittent pain, pain medication with opioids together with development of a biliary stricture), the patient would be a candidate for a surgical intervention. Recently, Kempeneers et al. convincingly showed that patients move frequently between different pain patterns during the course of the disease [9]. Such frequent changes in the clinical presentation of the disease clearly demonstrate that a close monitoring of patients is required not to miss major changes in the clinical course of the disease. The stages in the M-ANNHEIM classification are clearly separated by the presence of pancreatic exocrine or endocrine insufficiency, and on a subordinate level by the presence of pain [8]. Thus, the M-ANNHEIM classification system with its stages is robust enough to closely monitor patients with CP.

A few retrospective studies suggest that early surgery for painful disease is associated with better treatment results [53–60]. A retrospective Dutch study revealed that early surgery within 3 years after onset of symptoms was associated with better results with regard to pain relief and development of endocrine insufficiency [58]. The authors developed a nomogram to predict pain relief after pancreatic surgery based on the duration of pain, the number of endoscopic interventions, and preoperative use of opioids [58]. Furthermore, prolonged treatment with opioids may result in narcotic dependency with associated social problems, and may promote central sensitization and hyperalgesia with further limitations on surgical success [58, 106, 107]. A recent prospective trial confirmed the superiority of treatment with early surgery compared with an endoscopic approach, but, as already discussed, this study has limitations [61]. Based on limited evidence, current guidelines suggest that surgery should be performed (i) within the first 2–3 years after diagnosis or symptom onset, (ii) in patients who have had five or fewer endoscopic procedures, and (iii) in patients who have not yet required opioid analgesics for medical pain treatment [10, 21]. It currently appears that, especially in patients with obstruction of the duct system, timing of surgery may be decisive for the outcome [10, 21]. Of note, these recommendations are vague with regard to this major point and are based on a few retrospective studies without control observations. Thus, further research is clearly required, and a generally accepted classification would help to compare inter-institutional data. However, consensus is difficult to achieve, and further improvement of the current version of the M-ANNHEIM classification might be necessary.

4.3 Current Limitations and Suggestions for Further Implementation into Clinical Practice

The M-ANNHEIM classification has obtained worldwide attention and has been mentioned in various national and international guidelines [10, 35–37, 39, 108, 109]. In these guidelines, the M-ANNHEIM classification has been listed

among other recently published systems, and no classification has been preferred. All available systems were recommended to be evaluated in randomized prospective trials. It is our opinion that such recommendations hamper progress since long-term prospective trials regarding the outcome of patients with CP need decades, seemingly impossible regarding modern standards of research. The detailed M-ANNHEIM classification unifies the description of patients with CP and offers a tool to unambiguously describe the status of a patient with CP during communication in clinical conferences and research projects. However, various limitations of the M-ANNHEIM classification system need to be mentioned. The system might be too detailed for routine use of the clinical severity score in clinical practice. The system does not incorporate nutritional status. It is clear that the decision to perform surgery cannot be solely driven by fulfilment of a category within this scoring system. The M-ANNHEIM classification represents a tool to monitor the disease for general practitioners or doctors in out-patient clinics rather than for surgeons during their decision-making [103]. The M-ANNHEIM classification categorizes abdominal pain by combining the clinical presentation of pain with the corresponding therapeutic approaches. This approach has not been validated and does not follow pain guidelines that recommend for the monitoring the inclusion of psychosocial and cognitive aspects of pain. Thus, the system should be validated, extended, and combined with other frequently used or validated tools that have been established for pain management (e.g., the Izbicki pain score [69], QoL score [63, 66, 68]) as recommended in pain guidelines.

5 Summary

Various challenges and unanswered questions exist regarding the treatment of pain in CP. Timing of pancreatic surgery in painful disease represents a major issue that needs to be clarified in future studies. In this context, the M-ANNHEIM classification system together with other established tools for surveillance of pain and QoL might be used to picture the course of the disease, to monitor treatment results, and to guide clinical decision making in the management of CP.

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