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Original article

# Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group

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ABSTRACT

*Description:* Pain in patients with chronic pancreatitis (CP) remains the primary clinical complaint and source of poor quality of life. However, clear guidance on evaluation and treatment is lacking.
*Methods:* Pancreatic Pain working groups reviewed information on pain mechanisms, clinical pain assessment and pain treatment in CP. Levels of evidence were assigned using the Oxford system, and consensus was based on GRADE. A consensus meeting was held during *PancreasFest 2012* with substantial post-meeting discussion, debate, and manuscript refinement.
*Results:* Twelve discussion questions and proposed guidance statements were presented. Conference participates concluded: *Disease Mechanism*: Pain etiology is multifactorial, but data are lacking to effectively link symptoms with pathologic feature and molecular subtypes. *Assessment of Pain*: Pain should be assessed at each clinical visit, but evidence to support an optimal approach to assessing pain character, frequency and severity is lacking. *Management*: There was general agreement on the roles for endoscopic and surgical therapies, but less agreement on optimal patient selection for medical, psychological, endoscopic, surgical and other therapies.
*Conclusions:* Progress is occurring in pain biology and treatment options, but pain in patients with CP remains a major problem that is inadequately understood, measured and managed. The growing body of information needs to be translated into more effective clinical care.
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## Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disorder of the pancreas that is complicated by severe, constant and disabling pain in nearly half of all patients [1] and leads to some of the worst quality of life (QOL) scores for any chronic disease [1–3]. Chronic pancreatitis was considered a disease of alcoholism until the discovery that smoking, complex genotypes, and other factors accounted for the underlying etiology in over half of all cases of this disease [4–6]. Studies of patients with CP and pain indicate that there are multiple pain patterns, characteristics and severity levels, and that morphology on abdominal imaging may not correlate with pain features [7]. The strongest predictor of poor quality of life and disability among complications of CP is constant pain [1]. Recent studies have addressed the quality of life [2,8], and comparative effectiveness of treatment for neuropathic pain [9,10] and outcomes of both endoscopic and surgical treatments [11,12]. Finally, there is growing use of total pancreatectomy with islet autotransplantation (TPIAT) for control of pain [13–15].

Several recent guidelines for the general management of pain in CP have been published [15–18]. In addition, specific guidelines for the endoscopic treatment of pain were published by consensus of a working group supported by the European Society of Gastrointestinal Endoscopy (ESGE) [19]. These documents carefully addressed several clinical questions from existing literature and by discussion. The evolving literature on pancreatitis-associated pain, advances in the neuroscience of pain [3], various methods for assessing pain and new treatment options, including total pancreatectomy with TPIAT justify a comprehensive review, identification of knowledge gaps and recommendations for future research.

## Guideline focus

The clinical recommendations guide the evaluation and management of pain in adult patients with recurrent acute pancreatitis (AP) and chronic pancreatitis. Inadequate data on pediatric groups precluded inclusion of this important population in the current review.

The problem of pain in CP is well recognized, and represents a major area of emphasis by the clinical–translational working groups meeting at PancreasFest. In addition to regular working group meetings, a comprehensive, multidisciplinary review of the problem of pain in CP was undertaken over a three-year period at the annual *PancreasFest* meeting, as previously described [15,20].

The *PancreasFest* working groups were organized by academic physicians and scientists associated with the North American Pancreatitis Study Group (see NAPS2 [4]) and the Center for Pain Research, University of Pittsburgh (www.paincenter.pitt.edu) who had an interest in pancreatic pain. The Pain Working Group was further developed by inviting content experts to participate in the process. *Ad Hoc* sub-groups were organized to develop and frame discussion questions and guiding statements in three areas: 1) mechanisms of pain in CP; 2) the assessment of pain; and 3) the treatment of pain, including TPIAT.

## Evidence review and grading

Levels of evidence were ranked based on the Oxford Center for Evidence-Based Medicine's system [21]. Consensus was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) grid for the clinical guideline statements [22].

## Evidence and discussion

The working group included physicians and scientists who regularly attend PancreasFest, expressed a primary interest in pancreatic pain, and met as a group during break-out sessions. Primary areas of interest and need were identified by discussion and presentations in year one. The *ad hoc* group was encouraged to invite the participation of other experts, and to organize and prioritize the state-of-the-art and state-of-the-science, and present their priorities to the larger group at the subsequent PancreasFest meeting. Dr. Anderson organized the PancreasFest working groups, and the process of developing discussion questions was initiated, with refinement and focus during the third year.

The final discussion questions presented to attendees of *PancreasFest 2012* were followed by one or more guidance statements intended to provide a concise summary and, if indicated, a clinical recommendation or guidance. The initial recommendations were presented to the audience and projected onto a screen on a statement-by-statement basis. The audience, which was approximately 90% MD or MD-PhD, 4% PhD and 6% others, such as study nurses (Appendix), responded to the draft guidance statements for specific clinical questions and then indicated their level of agreement based on a 5-point scale (strong positive, weak positive, uncertain or equivocal, weak negative, strong negative) using digital voting devices. Conference attendees discussed the initial questions and guidance statements of the working group. The responses were tabulated and projected for the entire conference to discuss and revise in real-time. The conference participants then voted again on the level of agreement with each statement that, after discussion, required more information or clarification. The participants sent additional comments to the study members by email to be considered in the final discussion.

The working groups revised and extended the evidence and discussion sections for each question over a two-year period with updated references. The focus was to improve accuracy and specificity in each statement, improve clarity, and re-review controversial areas. In addition, common ground and agreement of experts from different disciplines with different approaches was sought throughout the manuscript writing, review and rewriting process. All working group members reviewed each major version of the document, and all participants who participated in the discussion and reviewed and approved the final document are included as co-authors.

## Results

### *Part 1. Mechanisms of pain in chronic pancreatitis*

Three broad discussion questions were developed. Question 2 was subdivided to address specific issues.

**Discussion Question 1**: What causes pain in chronic pancreatitis?

**Guidance Statement 1**: Pain in CP may arise from mechanical (intraductal pressure/obstruction), inflammatory, malabsorptive or neurogenic/neuropathic changes in the pancreas and/or surrounding organs.

Evidence Level: 2b
Grade of recommendation: B
Level of Agreement: A 89%; B 9%; C 0%; D 0%; E 2%.

**Evidence and Discussion**: Pancreatic duct obstruction, strictures, and/or peri-pancreatic fibrosis may cause ductal hypertension or ischemia from a stricture or a compartment syndrome leading to pain [23–26]. However, when measured, pancreatic duct

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