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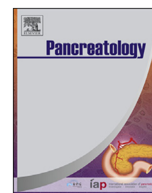

Guidelines for the understanding and management of pain in chronic pancreatitis☆

Asbjørn M. Drewes [a, *], Stefan A.W. Bouwense [b], Claudia M. Campbell [c], Güralp O. Ceyhan [d], Myriam Delhaye [e], Ihsan Ekin Demir [d], Pramod K. Garg [f], Harry van Goor [b], Christopher Halloran [g], Shuiji Isaji [h], John P. Neoptolemos [g], Søren S. Olesen [a], Tonya Palermo [i], Pankaj Jay Pasricha [j], Andrea Sheel [g], Tooru Shimosegawa [k], Eva Szigethy [l], David C. Whitcomb [m], Dhiraj Yadav [m], for the Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis

[a] Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark
[b] Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
[c] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, USA
[d] Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[e] Department of Gastroenterology, Erasme University Hospital, Brussels, Belgium
[f] Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India
[g] Institute of Translational Medicine, University of Liverpool, United Kingdom
[h] Department of Surgery, Mie University Graduate School of Medicine, Japan
[i] Seattle Children's Hospital Research Institute, Washington School of Medicine, USA
[j] Center for Neurogastroenterology, Johns Hopkins University School of Medicine, Baltimore, USA
[k] Department of Gastroenterology, Tohoku University Graduate School of Medicine, Japan
[l] Visceral Inflammation and Pain Center, Division of Gastroenterology, University of Pittsburgh and UPMC, Pittsburgh, PA, USA
[m] Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh and UPMC, Pittsburgh, PA, USA

A R T I C L E I N F O

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A B S T R A C T

Abdominal pain is the foremost complication of chronic pancreatitis (CP). Pain can be related to recurrent or chronic inflammation, local complications or neurogenic mechanisms with corresponding changes in the nervous systems. Both pain intensity and the frequency of pain attacks have been shown to reduce quality of life in patients with CP. Assessment of pain follows the guidelines for other types of chronic pain, where the multidimensional nature of symptom presentation is taken into consideration. Quantitative sensory testing may be used to characterize pain, but is currently used in a research setting in advanced laboratories.

For pain relief, current guidelines recommend a simple stepwise escalation of analgesic drugs with increasing potency until pain relief is obtained. Abstinence from alcohol and smoking should be strongly advised. Pancreatic enzyme therapy and antioxidants may be helpful as initial treatment. Endoscopic treatment can be used in patients with evidence of ductal obstruction and may be combined with extracorporeal shock wave lithothripsy. The best candidates are those with distal obstruction of the main pancreatic duct and in early stage of disease. Behavioral interventions should be part of the multidisciplinary approach to chronic pain management particularly when psychological impact is experienced. Surgery should be considered early and after a maximum of five endoscopic interventions. The type of

☆ Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club.

* Corresponding author. Centre for Pancreatic Diseases & Mech-Sense, Department of Gastroenterology and Hepatology, Clinical Institute, Aalborg University Hospital, Mølleparkvej, 9000 Aalborg, Denmark.

E-mail address: amd@rn.d (A.M. Drewes).

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surgery depends on morphological changes of the pancreas. Long-term effects are variable, but high success rates have been reported in open studies and when compared with endoscopic treatment. Finally, neurolytical interventions and neuromodulation can be considered in difficult patients.
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In 2016, John P Neoptolemos, David C Whitcomb and Tooru Shimosegawa embarked on a joint venture to produce the first truly International Guidelines on chronic pancreatitis (CP) with endorsement from the four International Societies and support from their respective Presidents and members in general. Although different guidelines exist such as the recent European consensus [1], the aim was to create a fresh clinical approach to the most important complications of CP; not only to assist a more pragmatic basis for patient diagnosis and management, but also to help accelerate the assessment and hence the development of newer therapies. The guidelines follow a new mechanistic definition of chronic pancreatitis and conceptual model of disease initiation and progression [2], which has been adopted by major international societies. Producing guidelines on CP is unquestionably a considerable task. Therefore the core committee for the working group decided to divide the work into more manageable sections. Each section focused on the key topics of CP, which were felt would benefit from consensus statements. The core committee identified International experts to ensure multidisciplinary representation from most regions of the world, and they were invited to contribute work to their respective areas. Calls for volunteers to participate in the process were also circulated around the four International Societies.

Prior to the process starting, the core committees were asked to vote on their preferred system for rating the quality evidence, which would be used as the basis for the International CP guideline recommendations. The consensus was in favor of adopting a GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach for topics lending themselves to evidence based statements. The guideline development process evolved over several milestone meetings at subsequent society conferences hosted throughout 2016.

The members of the Pain Management Working Group were appointed to represent worldwide specialists in treatment of pancreatic pain with representatives from gastroenterology, endoscopy, surgery and psychiatry/psychology. This was done to ensure an appropriate balance between the different regions and specialties in order to achieve the most comprehensive evaluation and recommendations. AMD was appointed as chairman of the group. First the following questions (Q) thought to be the most urgent and clinical relevant were made and authors assigned to answer them. These were (author initials in brackets):

Q1. What is the natural history and burden of pain in CP (in relation to treatment)? (DY, CMC)
Q2. Are there different types of pain in CP? (PJP, SSO, ES)
Q3. Which methods are available to assess pancreatic pain and its response to treatment? (CMC, PJP)
Q4. What is the role of smoking and alcohol on pain treatment in CP? (ES, PKG)
Q5. Do enzymes and antioxidants influence pain in CP? (PKG, ES)
Q6. How can analgesics be used to treat pain in CP? (SSO, AMD, ES)
Q7. Is endoscopic therapy effective for pain treatment in CP? (MD, SI, SAWB)
Q8. Is ESWL effective for pain treatment in CP? (CH, MD)
Q9. Are other treatments (psychological, neurolytical etc.) of value for pain treatment in CP? (HvG, ES, TP)
Q10. What is the optimal surgical approach to release pain in CP? (GOC, HvG, SAWB)
Q11. When is the optimal time for surgery in painful CP? (GOC, IED)
Q12. How to manage pain "relapse" after surgery or endoscopy? (IED, SI)
Q13. What are the indications for referral to a specialist center for further investigation of pain (CH, DY)

The working group then provided a structured format for systematic reviews for the different questions, and included instructions on how to evaluate the level of evidence and clinical implications according to the GRADE guidelines, as adapted for “UpToDate” (http://www.uptodate.com/home/grading-tutorial). In the absence or limited availability of literature, the Pain Management Working Group decided if a recommendation would be included in the consensus report. The quality of evidence supporting the different statements was graded as (i) “high” if there was very low probability of further research completely changing the presented conclusions, (ii) “moderate” if further research may completely change the conclusions, (iii) “low” if further research is likely to change the presented conclusions completely. The term “very low” (iv) could be used if new research will most probably change the presented conclusions completely; however, the term was not used in the present work.

The strength of the recommendation was classed as “weak/conditional”, “strong” or “not applicable”. This took into account the quality of evidence, the translation of evidence into clinical practice, and any relevant uncertainties relating to population risk.

Finally, to gauge the level of objective support from the participating international expert panel, the members of the Pain Management Working Group voted using a nine-point Likert scale on their level of agreement with the recommendations and their GRADE score. Voting results were classified under “agreement” as either; strong ($\geq$80% of votes were 7 or above), conditional ($\geq$65% of votes were 7 or above), and weak (<65% of votes were 7 or above).

All authors reviewed the final manuscript to ensure the general relevance and applicability of the conclusions. The European Pancreatic Club conference in July 2016 hosted the first milestone meeting for the process of developing the International CP guidelines. AMD presented the outcomes of “the Pain Management Working Group” to the meeting and the work is summarized in this manuscript.

In the present document, the recommendations are listed with a summary of the most relevant information and references. However, due to word limits *most* information could not be included and the reader is encouraged to see the Appendix where the full text and references are found.

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