Cover letter for revision of the manuscript

March 5, 2020

Dear Editor,

Thank you for giving me the opportunity to revise and resubmit the manuscript number 53475 entitled "Nutrition Management in Acute Pancreatitis" I appreciate the careful review and constructive suggestions provided by each reviewer and editor. The manuscript has certainly benefited from these insightful revision suggestions. I look forward to hearing from you regarding our submission and to respond to any further questions and comments you may have.

Following this letter are the reviewers' comments and the editor's comments with our specifically responses to each suggestion in italics, including how and where the text was modified. Changes made in the manuscript are marked using yellow highlighted text.

Please address all correspondence concerning this manuscript to me at Narisorn.L@chula.ac.th

Sincerely,

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Reviewer: 1

Comments to the Author

(1) The text is very long, with many abbreviations: could you reduce the number of abbreviations and the text length?

Answer: *Thank you for your valuable comment. The text length has been reduced by more than 400 words while more scientific evidence, explanations, underlying mechanisms, and practical recommendations have been added (please see the answer to the second question from reviewer 3 below). Additionally, all unnecessary abbreviations have been removed from the manuscript.*

(2) You could discuss the role of antisecretory drugs, as Octeotride, during enteral nutrition.

Answer: *The role of antisecretary medications during enteral nutrients in acute pancreatitis has been discussed on* ***page 11*** *as follow:*

"Given that pancreatic enzymes stimulated by enteral nutrients may lead to pancreatic autodigestion, the role of antisecretory agents, including somatostatin and its analogues (octreotide), has been investigated in several studies. However, the result remains inconclusive. A RCT and recent Cochrane review revealed no benefit among treatment group with respect to mortality, complications, and duration of pain.[1, 2] *This may be due to a dramatic decrease in pancreatic secretion during AP."*

Reviewer: 2

Comments to the Author

To Authors: The Abstract contains all the content of the paper. The Introduction shows the well-known general data on the AP and the aim of the study. The development of the pathophysiology of malnutrition in course of AP is clear and complete, analyzing the various components of this complex clinical problem. The analysis of the evolution of the nutrition procedures used in the AP shows the steps that have followed over time. This section is well presented. The plan of nutrition management in AP i salso complete and explores the clinical characteristics and the nutritional need of each degree of severity of AP, mild, moderate severe and severe. It's correct to analyze the various ways of administration of nutrients, with the examination of the detailed clinical characteristics. It's also justified to evaluate the possible use of some nutritional supplements. Very interesting the insertion of cases of practical clinical experience. The Conclusion contains synthetically the themes developed in the study. The References are up-to-date. The Tables and Figures are clear and appropriate. In summary this review is a very good work.

Answer: *Thank you for your opinion. We hope this review will help improve and guide nutrition management in acute pancreatitis in real-life practice.*

Reviewer: 3

Comments to the Author

This manuscript entitled “Nutrition Management in Acute Pancreatitis” is a comprehensive and timely review that emphasizes the importance of nutrition interventions for alleviating the inflammation and complications in patients with acute pancreatitis. The practical considerations provided in this review may help to improve the management of acute pancreatitis. However, some concerns remain.

(1) The novelty and impact of this work seem limited since no dramatic progress has been made in this field in the recent couple of years, and similar review papers have been published in other journals.

Answer: *Thank you for your valuable comment. We also concern about this issue. Although no dramatic change has been made, valuable information has been provided by several studies that were recently published (e.g., the association between obesity and clinical outcomes, the efficacy of enteral glutamine, and the efficacy of nutrition assessment tools to predict clinical outcomes in acute pancreatitis).*[3-10] *Additionally, in this review, we aim not only to comprehensively review the latest evidence but also to recommend practical managements and to give an example of clinical scenarios in order to improve understanding of nutrition management in real-life practice. As a result, we hope this review will help emphasize the crucial role of nutrition treatment and provide additional knowledge and practical recommendations for nutrition management in acute pancreatitis to the audiences.*

(2) The review appears to be general and descriptive, lacking clear explanation and deep discussions of underlying mechanisms.

Answer: *Thank you for your suggestion. We have added more explanations and discussions of underlying mechanisms as follows:*

1. “Resting energy expenditure (REE) in patients with AP is generally higher than healthy individuals because of inflammation-induced hypermetabolism and/or septic complications.” This is described on ***page 5*** *in order to give the reasons why resting energy expenditure usually increases in acute pancreatitis.*

2. “Amino acids released from protein catabolism provide substrates for the production of acute-phase protein.” This is described on ***page 5****. The purpose is to explain the underlying cause of protein catabolism in patients with acute pancreatitis.*

3. “Hyperglycemia is often found in patients with pancreatitis. It is a result of insulin resistance, increased glucose production from liver (gluconeogenesis), and impaired insulin secretion

caused by beta-cell damage." This is described on ***page 5 and 6****, helping explain the etiologies of hyperglycemia in acute pancreatitis.*

4. "Patients with chronic alcoholism require special attention to evaluate clinical signs and/or biochemical levels of the micronutrients (vitamin B1, B2, B3, B12, C, A, folic acid, and zinc). [11]*" This statement is showed on* ***page 8****. The purpose is to give a detailed recommendation regarding the micronutrients that should be evaluated in chronic alcoholism.*

5. "As for dietary composition, even though a low fat diet (<30% of total energy) has been used in previous studies [12, 13]*, this diet does not support by good scientific evidence and may lead to inadequate energy intake." This statement is showed on* ***page 9****. The aim is to give the reason why low fat diet is unnecessary in patients with mild acute pancreatitis.*

6. "Tube feeding is only recommended when oral nutrition is not feasible for more than 5 days. [14] *An example of this is patients with poor oral intake resulting from persistent nausea, vomiting, and abdominal pain." This is described on* ***page 9*** *in order to give an example of conditions that tube feeding is required in mild acute pancreatitis.*

7. "Estimated protein requirements are higher than healthy individuals (1.2-1.5 g/kg/day). This may improve nitrogen balance and is related to a decrease in 28-day mortality in critically ill patients. [15]*" This is described on* ***page 10****. The aim is to explain the underlying causes why high-dose protein is recommended in acute pancreatitis.*

8. "Local complications (necrosis, fistulas, ascites, and pseudocyst) are not contraindications for enteral feeding" This statement is described on ***page 10.*** *The purpose is to clarify that patients with local complications are able to receive enteral nutrition.*

9. "Better feeding tolerance and fewer interruptions of EN delivery due to elevated residuals and vomiting were found in continuous infusion compared with bolus group. [16, 17] *This is described on* ***page 11****, which helps explain the reasons why continuous tube feeding is recommended over bolus feeding.*

10. Traditionally, it is believed that small bowel feeding was associated with less pancreatic stimulation and autodigestion. Nevertheless, a meta-analysis found that nasogastric feeding was not inferior to nasojejunal feeding in terms of exacerbation of pain, aspiration, meeting energy balance, and mortality "This is predicated by lack of impact on pancreatic secretion regardless of feeding route during acute pancreatitis." This is described on ***page 11*** *in order to discuss the mechanism why small bowel feeding is not superior to gastric feeding.*

11. "Its depletion has been demonstrated in critically ill patients because of the increased demand during metabolic stress. [18]*" This is described on* ***page 13****. The purpose is to explain the underlying mechanism why glutamine is depleted in severe pancreatitis.*

12. "Intestinal barrier dysfunction may induce bacterial translocation and infected necrosis, being the major cause of morbidity and mortality in severe pancreatitis. Probiotics may help improve gut integrity and immune function, and thus prevent bacterial translocation. [19, 20] *" This statement is described on* ***page 14*** *in order to illustrate the mechanisms why probiotics may be associated with beneficial effects in acute pancreatitis.*

13. "This condition is directly related to the degree of pancreatic parenchymal injury" This sentence is described on ***page 15*** *in order to explain why pancreatic exocrine insufficiency is more common in alcoholic, severe, and necrotizing pancreatitis.*

14. "Patients should be monitored for symptoms of maldigestion (diarrhea, steatorrhea) and/or non-invasive pancreatic function test (e.g., fecal fat and fecal elastase) [21] *" This is described on* ***page 15****. The purpose is to give a clear explanation about methods for monitoring of pancreatic exocrine insufficiency in patients with acute pancreatitis.*

(3) The figures could be made clearer and more intuitive, and the writing could be improved as well.

Answer: *The figure 3 has been changed to table 3 in order to make it more understandable and more intuitive. The writing is also edited.*

Editor

Comments to the Author

(1) Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information. The accepted formats are mp3 or wma.

Answer: *We already provided the audio core tip with mp3 format in the uploaded file.*

(2) Your manuscript should be prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.

Answer: *The manuscript was prepared by Microsoft Word with 12 pt Book Antiqua font and 1.5 line spacing with ample margins.*

(3) Please revise and perfect your manuscript according to peer-reviewers' comments. Please upload the required files on the system.

Answer: *The manuscript was revised according to the reviewers' comments. We have responded to all comments clearly and specifically, and this will improve the overall quality of our article. All of the required files were already uploaded as well.*

(4) Running title

Answer: *The running title "Nutrition management in acute pancreatitis" was added in page 1 of the manuscript***.**

(5) Please rearrange all the authors' affiliations with Department, University or Institute, City, Postcode, Country, etc. (without any symbol or figure like * or 1, postcode must be there)**.** Are Chulalongkorn University and King Chulalongkorn Memorial Hospital two institutions?

Answer: *The affiliations of all authors were rearranged according to your suggestion in page 1. Chulalongkorn University and King Chulalongkorn Memorial Hospital are two different institutions, and therefore we removed King Chulalongkorn Memorial Hospital from the affiliation.*

(6) Corresponding author: Author names (unabbreviated) should be followed by the author's title in bold, and the affiliation, complete name of institution, present address, city, province/state, postcode, country, and E-mail.

Please add your title, such as MD, PhD, Professor, etc.

Please provide your organization real-name mailbox here

Answer: *We already edited this part and added the present address and title in page 1.*

(7) Please correct all cited references number like [number], then keep them superscript. There are no spaces before [number].

Answer: *All cited references have been corrected according to the required format.*

(8) Please distinguish between the title of the article series. Three levels of subtitles are allowed: (1) First subtitle: All in bold and capital; (2) Second subtitle: All in bold and italic; and (3) Third subtitle: All in bold.

Answer: *All subtitles have been edited to three levels according to the suggestion.*

(9) Please check and confirm that there are no repeated references!

Please correct all cited references number like [number], then keep them superscript.

Please download the reference templete.

Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) (Please begin with PMID:) DOI (http://www.crossref.org/SimpleTextQuery/) (Please begin with DOI: 10.**)

Answer: *We confirm that there are no repeated references in our manuscript. All cited references were edited according to the recommendation, and we already downloaded the reference template. In addition, PMID and DOI were added in all journal articles containing these data, and PMCID was already removed. Regarding one article without PMID and DOI (reference 36), we already uploaded the first page of that article in the system.*

(10) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published. Otherwise, we will withdraw the paper or delete this figure.

Answer: *We have tried to contact and ask for the permission to use and adapt the figure 1 from the original publication, but there is no response from the publisher yet. However, the purpose of this figure is only to emphasize the role of gastrointestinal tract and enteral nutrition in acute pancreatitis, which already stated in several parts of our review. Therefore, this figure has been removed from the review.*

(11) Please make table without number before sentences

Answer: *The number before each recommendation in the table 3 has been removed (page 32).*

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