

August 15, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4605-review.doc).

Title: Exocrine Pancreatic Insufficiency in Adults: A Shared Position Statement of the Italian Association For the Study of the Pancreas.

Author: Pezzilli R, Andriulli A, Bassi C, Balzano G, Cantore M, Delle Fave GF, Falconi F, Frulloni L, and the Exocrine Pancreatic Insufficiency collaborative (EPIc) Group*.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4605

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1

First of all I would like to thank the Authors for this position paper focused on the treatment of PEI. The topic of the paper is very important even if other recommendations are already published on this argument.

Anyway I think the authors should review the paper in some parts before publication.

1. The paper is too long. The manuscript is something in between a review of the literature and a position paper. I think the Authors should drastically reduce the length of the text.

Answer. We agree with the comments of the reviewer: the title has been modified and the main text of the manuscript has been also shortened of five pages.

2. The Methodology of the consensus meeting and of the paper preparation is very superficially described. I think the authors should provide a more detailed description of the methods.

Answer. We agree with the comment of the reviewer and a section on methodology has been added to the text (page 3, lines 9-22).

3. The “mechanisms of exocrine pancreatic insufficiency” paragraph is not adequate to explain the problem. I think more comprehensive information should be done, including the extra pancreatic causes (Dominguez-Munoz et HPB 2009, 11 (suppl.3), 3-6).

Answer. We have reported for brevity the other non-pancreatic causes of maldigestion in Table 2.

4. In the “Pancreatic Enzyme Replacement Therapy” part, the authors conclude that a dose of 25000-40000 units of lipase per meal is generally recommended. This is not the tendency of the last year literature where a dose of 40000-50000 units per meal and 25000 per snacks are generally recommended.

Answer. We completely agree with the comment of the reviewer, and the text has been modified accordingly.

5. In “Dietary and drug recommendations” the authors recommended a reduction in fat intake if steatorrhea impact the QOL. This is a controversial point and there is no evidence in literature about that (Sikkens et al. J Gastrointest Surg 2012; 16: 1487-1492). Not only, there are completely opposite position on this specific argument. Generally in these patients there is a problem of enzymes dose or compliance with the treatment. I think the authors should remove this indication from the text.

Answer. We agree with the comment of the reviewer and the sentence has been deleted.

6. The same indication of fat restriction in the diet is repeated in other parts of the paper. I suggest to remove these parts.

Answer. Done.

7. Regarding the recommendations for specific diseases, I suggest to add a paragraph or add in the gastric surgery one, on PEI in esophageal surgery (Huddy et al. Diseases of the Esophagus 2012)

Answer. Done (page 15, lines 27-29).

8. In the pancreatic surgery chapter the authors discriminate between pancreas cancer and benign disease in terms of risk of post-operative PEI. This perspective is very interesting but, in my knowledge, not supported by any kind of evidence. For this reason I think that the authors should underline that this is just a consensus reached by some experts and not data coming from literature. If it's true that pre-neoplastic lesions and other malignancies of periampullary area are not generally associated to chronic pancreatitis, is also true that in the long run, many of the patients will lose the pancreas stump function due to other problems, like for example the stricture of the pancreas anastomosis (Nordback I et al. Scandinavia Journal of Gastroenterology 2007; 42: 263-270).

Answer. We agree with the comment of the reviewer and the sentence suggested has been added underlying that the consensus reached on this topic is that of experts and not from data coming from literature (page 16, lines 16 and 17).

9. No information regarding the “Exocrine Pancreatic Insufficiency collaborative group is offered to the reader. I think an appendix with all the names of the expert involved will be very useful. As recommendation of a National Society, I think that the number of participants to the consensus meeting is a relevant aspect.

Answer. The members of the panel and their affiliation were already reported in the Appendix of the manuscript and as described in the Methods section was discussed during the AISP National meeting in October 2012. The complete list of 130 participants is too long and we reported in the Appendix the EPIC members, as well as those of the Association Council.

Reviewer 2

1. This article is original since it is unclear whether this is a review of the literature, the result of a consensus conference or an original article concluded with standard definition by an international expert group. The title does not clearly announce it. But all is very accurate, and very informative. I have only minor remarks, especially concerning the problem of the plan making it difficult to read the manuscript.

Answer. We thank the reviewer for the comments on our manuscript. This is a position paper and the conclusions underwent to a consensus by a national expert group. This has been now better explained in the new section Methods (page 3, lines 9-22). The title has been also modified.
2. Introduction, page 3, the methodology chapter must be distinguished from the introduction and the introduction should state what is the purpose of this work.

Answer. We agree with the comment of the reviewer and a new section (Methods) has been added to the text (page 3, lines 9-22).
3. Page 4 mechanisms of exocrine pancreatic insufficiency, make a primary / secondary distinction as in the corresponding table. - Paragraph investigation is less clear

Answer. We agree with the comment of the reviewer and section has been revised (Page 4, lines 23-25).
4. Page 5. The plan is very difficult to follow. Specify exactly what are the direct of indirect tests. - New tests appeared page 6 (in which group do they belong?), - What are the parameters that reflect the nutritional status ? bioelectrical impedance ? the coefficient of fat absorption ? It is not clear to what class the various tests belong to?. I will propose to modify this chapter in this form: o the list of direct and indirect tests o the most common definition of exocrine pancreatic insufficiency o the recommended test associated with normal values and application conditions o clarify what is defined as a severe pancreatic insufficiency o also identify / clarify predisposing factors for exocrine pancreatic insufficiency that appear in Figure 8, which are not specified before in the text.

Answer. We agree with the comment of the reviewer and section has been revised (Page 5, lines 21-22). We have clearly indicated in the text (see “Pancreatic resection” section) and in Figure 8 the surgical factors predisposing to pancreatic insufficiency.
5. Page 9, I think you should individualize a chapter focusing about treatment: nature of the enzymes, differences between gastro-protected and non gastro-protected microgranule ... You have to propose it on time, “in book” dealing completely with this subject instead of speaking about treatment with new informations at each page of the manuscript.

Answer. We do not agree with the comment of the reviewer because the differences on the various enzyme preparations have been reported in “Pancreatic enzyme replacement therapy” section.

6. Page 11, clarify what is the “Phase angle Obtained” which is also used in Figure 3, which is not specified in the text.
Answer. We agree with the comment of the reviewer and the technique description has been completely reworted (Page 6, lines 25-32 and Page 7, line 1).
7. Page 21, ref. 154, pancreatico-jejunostomy is not a pancreatic resection but a diversion and the title of the article talks about pancreatic resection.
Answer. We apologize for the incomplete information; in this study patients underwent a pancreatic resection with longitudinal pancreaticojejunostomy. This is now specified in the text (Page 16, line 15; reference is now 152).
8. The references are complete
Answer. We thank the reviewer for the comment.
9. Figures: harmonize the figures, there are 8 figures and 8 different presentations and polices
Answer. The algorithms reflect the present knowledges on the treatment of exocrine pancreatic insufficiency in the various pancreatic and non pancreatic diseases and they cannot be similar; however, we have attempted to harmonize the figures according to the comment of the reviewer.

Reviewer 3

1. I would like to congratulate the authors for the thorough and accurate report. The authors could give more details about de dedicated meeting during which the recommendations were discussed, i.e., number of days and number of participants of the meeting.
Answer. We thank the reviewer for the comments. According to the reviewers 1 and 2 we have completely revised these details (see Method section, page 3, lines 9-22).

Reviewer 4

This is a very interesting article on an important topic. Only minor points have to be clarified.

We thank the reviewer for the comments which increase the readability of the manuscript.

1. It is not clear if the study is a systematic review of the literature or reflects experts' opinion.
Answer. This is a position paper and the conclusions underwent to a consensus by a national expert group. This has been now better explained in the new section Methods (page 3, lines 9-22). The title has been also modified.
2. The number and names of all experts paticipating to the EPIC Group should be added.
Answer. The members of the panel and their affiliation were already reported in the Appendix of the manuscript and as described in the Methods section was discussed

during the AISP National meeting in October 2012. The complete list of participants is too long (130 AISP members) and we reported in the Appendix the EPIC members as well as the Association Council members.

3. reference nr. 157 is not cited in the text.

Answer. Reference 157 (now reference 155) is cited in Table 1.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Raffaele Pezzilli'.

Raffaele Pezzilli

Department of Digestive Diseases and Internal Medicine
Sant'Orsola-Malpighi Hospital
Via Massarenti 9,
40138 Bologna (Italy)
Tel./Fax +39 051 636 4148
e-mail: raffaele.pezzilli@aosp.bo.it