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Barros LL, Farias AQ, Rezaie A. Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment

Thank you for the opportunity to respond to the reviewers. We have carefully revised the present manuscript and addressed their thoughtful comments. Please find the responses to their specific comments and suggestions below.

Reviewer Comments

1. Reviewer number: 02544416

I read with great pleasure the manuscript entitled "Gastrointestinal motility disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment". In my opinion this review is of great clinical importance. Mainly, researchers are focused on development and introduction of new biological treatment for IBD patients, but clinicians are very often confronted with such conditions and this review will raise awareness about the presence and all possible non-IBD reasons of GI complaints in IBD patients.

Response: We would like to thank the reviewer for the careful reading of this manuscript and supportive insights. We agree with the high relevance of this review to clinical practice.

2. Reviewer number: 03474080

The manuscript has interesting topic. It has been written with well presentation. I have no additional recommendation. Thanks in advance.

Response: Thank you for your review and valuable comment.

3. Reviewer number: 00503545

In this paper, the authors reviewed the prevalence, diagnosis and treatment of GI motility disorders in patients with IBD in detail. This review is well written and the contents of the paper are clinically important and useful in the treatments with IBD patients.

Response: We thank the reviewer for this encouraging comment.

4. Reviewer number: 02529464

This is a well-organized review on possible causes of bowel symptoms in patients with IBD in remission. The title "gastrointestinal motility disorders in IBD" seems to me too restrictive since in the present review SIBO (including fungal overgrowth), pancreatic insufficiency and else are considered. Just a few corrections: Page 4, first line: stenosis and enteric fistulas...change to Enteric stenosis and fistulas...Next line: in these scenario...better scenarios. Page 6: cromolyn sodium...please mention also the term "disodium cromoglycate". Page 7, last para: as the Rome criteria ... is based on, change to ... are based on.

Response: Thank you for your comment on this manuscript. The reviewer is correct to point out that not all disorders described in the manuscript are motility-related. Hence, we have revised the text and modified the title to "Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment". We agree with the reviewer regarding the appropriate form to write the sentences "enteric stenosis and fistulas", "scenarios" and we have reconstructed as suggested. Furthermore, we have included disodium cromoglycate as a therapeutic option for MCAS and corrected the grammar in the sentence "Rome criteria is" to "Rome criteria are".

5. Reviewer number: 00009064

It is a very timely and informative review. The subject is well covered and I have nothing add. However, I would suggest modifying the title of the review to include pathophysiological conditions like bacterial or fungal overgrowth, pancreatic insufficiency, bile acid malabsorption and mast cell activation syndrome. These do not fit in the generic term of 'motility disorders'. Perhaps, simply adding 'absorptive' after motility in the title may rectify the discrepancy.

Response: Thank you for this review and for the discerning observations. We agree with the reviewer that the title of the manuscript might not represent all above conditions described. Therefore we have accepted the suggestion and we have modified the title to "Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment"

6. Reviewer number: 00055108

It is a well-written manuscript, just some minor Language errors to correct. Please stick to on the metric system, preferable the SI-system. However, I do struggle to some extent with the title of the manuscript. GI-motility disorders in pat....I do think that it would be more appropriate to say: Gastrointestinal transit and motility disorders in pat...One small question regarding the

conclusion in the abstract: "Therefore, in this review we describe the prevalence, diagnosis and treatment of GI motility disorders in patients with IBD". You should indicate that the patients are in IBD remission - limited inflammatory activity.

Response: Thank you for your positive and constructive comments. We have revised the text and have corrected English and grammatical errors. The reviewer is correct regarding the restrictive title of this manuscript. Thus, we have agreed to rewrite to "Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment" Additionally, we have included the term "quiescent IBD" in the conclusion of the abstract as it was suggested.

7. Reviewer number: 02549032

This is a well-written and interesting review article on non-IBD related disorders in IBD patients. The authors reviewed 91 articles and concluded that: <<motility disorders are highly prevalent in IBD patients, particularly in those with persistent GI symptoms despite quiescent disease>>. The review is suitable for publication. However there are some major issues: 1. Motility disorders refers to muscle layer disease and neither to endoluminal disease such as (SIBO SIFO, chronic pancreatitis, bile acid malabsorption etc) nor to mucosal disease such as (celiac disease, giardiasis, inflammation, etc): So the title should be changed, because celiac disease or chronic pancreatitis, or IBS etc are not pure motility disorders. 2. The examination of choice to study GI motility disorders is manometry. The authors reported only one study (ref 85) referred to antroduodenal manometry which, however as the authors themselves stated, its usefulness is limited and it is only available in selected centers. 3. Another mode of study for GI motility disorders especially small and large bowel motility is the orocecal and oroanal time studied by specific radiomarkers. No such reference is reported in order to prove the exact motility disorder in IBD patients. 4. Many if not all of the issues reported in this review, are already known and are reported in classical books for many years (such as IBS, SIBO, bile acids malabsorption, chronic pancreatitis, celiac disease, autoimmune pancreatitis, CIPO, rectoanal dysfunctions, etc). 5. Pure motility disorders in small or large intestine are difficult to diagnose or study in IBD patients especially after surgical interventions. The authors reported no limitations in their review nor future issues remained to be solved."

Response: We would like to express our appreciation for the detailed and thoughtful review. The reviewer is correct to highlight that not all conditions reported in the manuscript are classified as pure motility disorders. For this reason we have modified the title to "Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment" We agree and estimate your suggestion to include orocecal and oroanal transit time as a diagnostic tool to detect motility disorders in

IBD population. However, there is limited data in the literature to recommend the use in this setting, especially due to the formal contraindication of this test when stenosis or fistulas are suspected^[1-3]. We have added a section in the conclusion in regards the limitations of our manuscript and deficiencies of the current literature.

8. Reviewer number: 03478404

The manuscript contains very useful and very much needed data. Both pediatric and adults guidelines regarding IBD mention that in symptomatic patients, other conditions with similar manifestations should be excluded, before escalating therapy. Since data regarding diagnosis and therapy of these conditions are not presented in the guidelines, this paper is of outstanding importance, covering a huge gap. Truly impressive! Minor comments: 1. Among these conditions, the authors mention celiac disease, giardiasis, exocrine pancreatic insufficiency, carbohydrate intolerance, eosinophilic gastroenteritis and others, which are not really classified as "Gastrointestinal motility disorders". Sure, they can manifest with symptoms of dysmotility. Therefore, I would suggest the title to be changed. Maybe "Gastrointestinal disorders with dysmotility symptoms" or something similar. 2.a "Irritable Bowel Syndrome (IBS) - like symptoms" - I would suggest the title of this paragraph to be changed to "Conditions with persistent non-bloody diarrhea", to be entirely correct and to avoid any potential confusion. 2b. The sentence "Treatment for active disease demands therapy optimization either with escalation of anti-inflammatory drugs or surgery." should include also immunomodulators and biologic agents. Not all "drugs" act as anti-inflammatory agents. 3. All described conditions include therapy in the main text, except for celiac disease and giardiasis. They are mentioned in Table 2, but it would be better to have a uniform presentation. Therapy of these two conditions would require only 2 lines of full text. 4. Anti-endomysial antibodies should also be mentioned (after anti-tissue transglutaminase antibodies, which are more sensible, but less specific; anti-endomysial are more specific) 5. Maybe one line about specific probiotics in IBS 6. 5-ASA and JAK should be written as full words, before the abbreviation, for readers with less knowledge. 7. Table 2 contains "Eosinophilic gastroenteritis" and "Intra-abdominal adhesions", but they are not addressed in the text. Table 2 should have a Figure legend with abbreviations. 8. Minor language corrections: "An IBD flare maybe recognized when" - please change to "may be"; "Presence small intestinal bacterial overgrowth" - please insert "of"; "As the Rome criteria for diagnosis of IBS is based on clinical symptoms, it" - please change to "are" and "they", since "criteria" are plural; reference 35 - please correct "Amercian"; "Non-pharmacological interventions such as exercise, increased fluid intake or soluble fiber have modest efficacy in general population and may considered in IBD patients" - please insert "be"; "Safety of these medications are" - please replace with "is".

Response: Thank you very much for the thorough review of our manuscript. We agree that the title of this manuscript is not the most appropriate to summarize our text. Thus, we have rewritten to “Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment. As suggested by the reviewer the sentence “Irritable Bowel Syndrome (IBS) - like symptoms” has been modified to “Conditions with persistent non-bloody diarrhea”. We have added immunomodulators and biologic agents as therapeutic options of drug optimization. The reviewer is correct to indicate the treatment of celiac disease and giardiasis was not addressed in the text. We have included both and have mentioned anti-endomysial antibodies for diagnosis of celiac disease. We understand the important role of the microbiome in all gastrointestinal and liver diseases. In the present manuscript we have approached IBS treatment in IBD population and the available data have not yet shown benefit in this context⁴. We have rewritten 5-ASA and JAK as full words accordingly and have included a legend with abbreviations at Table 2. We apologize for the grammar mistakes. They are all revised and corrected now.

1. Castiglione F, Del Vecchio Blanco G, Rispo A, Petrelli G, Amalfi G, Cozzolino A, et al. Orocecal transit time and bacterial overgrowth in patients with Crohn's disease. *J Clin Gastroenterol*. 2000;31(1):63-6 [PMID:10914780]
2. Tursi A. Delayed orocecal transit time and bacterial overgrowth in Crohn's disease. *J Clin Gastroenterol*. 2001;32(3):274-5 [PMID:11246364]
3. Rana SV, Sharma S, Malik A, Kaur J, Prasad KK, Sinha SK, et al. Small intestinal bacterial overgrowth and orocecal transit time in patients of inflammatory bowel disease. *Dig Dis Sci*. 2013;58(9):2594-8 [PMID:23649377 DOI: 10.1007/s10620-013-2694-x]
4. Parker EA, Roy T, D'Adamo CR, Wieland LS. Probiotics and gastrointestinal conditions: An overview of evidence from the Cochrane Collaboration. *Nutrition*. 2018;45:125-34 e11 [PMID:28870406 DOI: 10.1016/j.nut.2017.06.024]