

Dear Editor,

Great thanks to you and the anonymous referees for the time and efforts you spent on our manuscript entitled " Postoperative diarrhea in Crohn's disease: Pathogenesis, diagnosis, and therapy" and the potential consideration for publication it in World journal of clinical cases.

According to the comments, we have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

Best wishes.

Yours sincerely,

Zhen Guo, MD, PhD

Corresponding author

We would like to express our sincere thanks to the reviewers and editors for the constructive comments. We believe that the comments have been very useful to improve the quality of the manuscript.

## **Replies to Editors and Reviewers**

### **Reviewer 1**

Authors presented the important topic, postoperative issue in Crohn's disease. It is interesting, however, it has some serious concerns.

1. Authors suggested several reasons of diarrhea. it may be complicating when each issue is simply described. Please summarize them using new Table 1.

#### **Answer:**

Thanks. We added a table to summarize the causes, and treatments according to your suggestion.(Table 1)

2. I would like to read Crohn's disease related issues in more detail.

**Answer:** Thank you for the comment. We modified the manuscript to make the CD related issues more detail (Page 3 ,Line 79-88; Page 3 ,Line 114-118; Page 4 ,Line 131-139; Page 4 ,Line 155-162; Page 4 ,Line 179-181; Page 7 ,Line 237-262)

3. A few images of these issues to express the details may be recommended.

**Answer:** Thanks. An image focusing on Mechanisms of bile acid (BA)-related bowel dysfunction in irritable bowel syndrome with diarrhea was added to the manuscript. (Fig 1)

## Reviewer 2

In this paper, authors propose a list of situations or “causes” which may be more or less frequently associated with diarrhea in patients who had surgery for Crohn’s disease. Their second (and short) paragraph concerns “evaluation of diarrhea” and the third paragraph (also very short) lists some of the treatments but not how to choose them and associate them. Many patients have diarrhea after surgery for Crohn’s disease. However, the situation is heterogeneous. Different surgeries can be performed, the most frequent one being “short” ileocecal resection. A short ileocecal resection does not have the same consequences, risk of diarrhea, and mechanisms for diarrhea that a long ileal resection or a colonic resection. Authors should describe these situations separately (for example with description of the consequences on the bile acid metabolism). Diarrhea may be transient or permanent, it may occur immediately after surgery or after a while. Specific comments

1. Abstract: The term “postoperative Crohn’s disease” does not correspond to a disease and should be avoided

**Answer:** Thank you. We corrected this term in the manuscript. (Page 1 ,Line 5-6)

2. Introduction: reference 2 presents total colectomy and other references should be used to describe the frequency of diarrhea after the various surgeries

**Answer:** This had been corrected. (Page 1 ,Line 22-24)

3. Introduction: I am not sure that the authors are right when they claim “proper treatment of postoperative diarrhea may affect the risk of postoperative recurrence” Do they have references to quote there?

**Answer:** Thanks for the comment. Postoperative CD recurrence in CD may be characterized by symptoms such as abdominal pain, weight loss, diarrhea. We want to emphasize the importance to treat postoperative diarrhea. In deed, “proper treatment of postoperative diarrhea may affect the risk of postoperative recurrence” is not appropriate confirmed by previous studies, thus, we had deleted this sentence.

4. Chapter 1.1: The following sentence could be rephrased “It is well known that CD usually occurs in the ileocecal region”.

**Answer:** Thanks. As suggested, We rephrased this sentence. (Page 2 ,Line 41)

5. Chapter 1.1: the link between the dysbiosis observed after ileocecal resection for CD and SIBO is not established and the reference provided here (a review on SIBO) is not accurate enough.

**Answer: Thank you.** There was a retrospective observational cohort research showed that SIBO was highly prevalent in patients with CD, and was independently linked to clinical relapse in quiescent patients. (PMID: **35965806**) As you mentioned, this study did not report the influence of surgery on SIBO in CD. We modified the sentence to make the statement more accurate. (Page 2 ,Line 45-47)

6. Chapter 1.1: 3 lines before end : which hormones ?

**Answer:** Thanks. The hormones should be glucocorticoid. We also changed this in the

manuscript. (Page 2 ,Line 57)

7. One line below: Which specific bacteria?

**Answer:** Thanks. We added the information about specific bacteria. (Page 2 ,Line 52-53)

8. Chapter 1.2: what do authors mean by "stimulation of high colonic amplitude?"

**Answer:** Thanks. This sentence was modified to "BA could induce colonic high- amplitude propagated contractions in colon" (Page 2 ,Line 65-66)

9. Chapter 1.2: Where are the "BA levels significantly reduced in patients with IBD" please clarify the site of sampling and the type of BA (primary, vs secondary, conjugated?, sulfated?)

**Answer:** Thank you for the comment. We rephrased these sentence to make this issue more clear. (Page 3 ,Line 79-88)

10. Chapter 1.3: the frequency of "edema due to malabsorption, lipase deficiency and lactase deficiency" should be expressed.

**Answer:** Thank you for the comment. We added the information about frequency to make this issue more clear. (Page 3 ,Line 114-118)

11. Chapter 1.5: Discussion of early recurrence of CD after ileocecal resection should be presented in more details. How do you define it? ("early" vs "late" How do you diagnose it? How do you treat it?

**Answer:** We modified this paragraph to make the information more clear. (Page 5 ,Line 155-162)

12. Chapter 1.6: The frequency of short bowel syndrome in CD should be provided as well as the specific management of this situation

**Answer:** Thank you. The information about frequency and management was added to the manuscript. (Page 5 ,Line 179-181)

13. 1.7: I am not sure that "infection at the incision site may slow down recovery of intestinal function". Authors should provide details on the frequency of the problem and the ways to handle it when it occurs.

**Answer:** Postoperative ileus is a common and costly complication after elective surgery. A study showed that postoperative infection was associated with ileus. ( PMID: **34210525**) We want to show that Infection may cause pain at the incision site, Infection may slow recovery of intestinal functions which causes postoperative ileus. When the infection occurs, it is important to take measures to control it such as using antibiotics or changing medicine.

14. Reference 14 is incomplete

**Answer:** Thanks. We corrected this error.

### Reviewer 3

This is an interesting and comprehensive review that explores the causes, underlying mechanisms, and management of postoperative diarrhea in patients operated on for Crohn's disease. The review is expected to assist the clinician in making the correct diagnosis and taking appropriate therapeutic decisions in the operated Crohn's disease patients.

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I would like the authors to mention some data regarding the risk of post-operative endoscopic recurrence in CD (90% by one year, Buisson et al 2012;35:625-633), the few symptoms appearing in the early stages, 35-50% developing clinical manifestations including diarrhea by five years (Rutgeerts et al Gastroenterology. 1990;99:956-963) and that histological disease activity in an endoscopically normal neoterminal ileum may occur as early as one week after surgery (Rutgeerts et al Gastroenterology 1990;99:956-963, Olaison et al, Gut 1992;33:331-335).

**Answer:** Thanks, We added these data to the manuscript. (Page 5 ,Line 157-158; Page 5 ,Line 158-159; Page 5 ,Line 160-161)

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I would like the authors to outline (in a relevant figure) the underlying mechanisms of diarrhea in cases of bile salt malabsorption.

**Answer:**Thank you. The figure was added according to your suggestion

The term diversion colitis (DC) is usually used in cases of resection of descending and/or sigmoid colon, in which the remaining rectum is either buried in the abdomen or externalized as a mucinous fistula. As a consequence of the absence of feces, SCFAs (which are the source of the left colon mucosa cells) are absent in the rectal or rectosigmoid energy stump, resulting in the appearance of an inflammatory process which may not substantially differ from the inflammation appearing in ulcerative colitis. I would like the authors to refer in more detail and more precisely to this interesting entity both, from a clinical and a therapeutic point of view (e.g. acetic, propionic, and butyric acid solution enemas).

**Answer:** Thanks a lot. We added these information to the manuscript. (Page 4 ,Line 131-138)

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Is there any role for pro/pre/synbiotics in the treatment of postoperative diarrhea in Crohn's disease?

**Answer:** Thanks. We added these information to the manuscript. (Page 7 ,Line 260-262)