המרכז הרפואי ת"א ע"ש סוראסקי

המכון למחלות דרכי העיכול והכבד
Department of Gastroenterology and Hepatology

To: Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, World Journal of Clinical Cases

Re: World Journal of Clinical Cases revisions of manuscript ID 68214

We thank the editor and reviewers for the opportunity to submit our revised manuscript (Manuscript ID: 68214) now entitled: "**Management of pouch related symptoms in patients who underwent ileal pouch anal anastomosis surgery for adenomatous polyposis"**.

The manuscript has been corrected in accordance with the reviewer's comments.

Attached is a point-by point reply to the reviewers and editor.

Sincerely,

Ophir Gilad, MD

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Reviewer 1:

The authors assessed clinical, endoscopic and histologic response to various treatments in the pouch related disorders of APS patients. Thirty-three APS patients were identified. Intervention was associated with symptomatic relief, mainly decreasing abdominal pain and daily bowel movements. Dietary modifications decreased abdominal pain, daily bowel movements, overall PDAI and clinical PDAI. Probiotics decreased daily bowel movements, overall and clinical PDAI histologic scores. The authors suggested pouch-related symptoms a functional rather than inflammatory disorder. I have some comments:

1. How to define pouch related symptoms? Bloody stools usually indicated an inflammatory problem. It could be better to exclude the patients with pouchitis in the cohort, while only analyze the patients with IPS.

Response: We thank the reviewer for this important comment. We considered the wide range of any symptom that could be attributed to pouch dysfunction – be it due to a functional dysfunction or an anatomic or inflammatory process. The main symptoms we encountered were increased daily bowel movements, abdominal pain, and also a few patients with rectal bleeding. The small group of patients with pouchitis was separately analyzed. Even when we include the patients who satisfy the criteria for pouchitis (PDAI≥7) we see that the standard therapy that is taken from the world of inflammatory bowel diseases, does not cause symptomatic improvement. This finding implies that even in these patients the main pathophysiology of pouch related symptoms is probably not inflammatory and thus therapy that addresses inflammation is not effective.

2. I cannot see the tables and figures in the Manuscript file.
Response: We regret that due to a technical error the tables and figures were not attached to the original manuscript. We have attached them in the current version in the same file as the main text.
3. As you stated that average 3 different therapies were used per patient, how can you separate the effects of individual therapies from another?
Response: We thank that the reviewer for this comment. Due to the retrospective nature of this study, we were not able to separate the different treatment modalities when they were given at the same time, and since most patients were treated with lifestyle modifications including diet and probiotics in addition to symptomatic therapy – this was not possible in the majority of patients.
4.In the conclusion, the authors suggested pouch-related symptoms in APS a functional rather than inflammatory disorder, again you should separate pouchitis from IPS
Response: We thank the reviewer for this comment. Indeed, we have analyzed the group of patients with overt pouchitis (PDAI≥7) separately and noticed that there was no significant change in clinical symptoms or PDAI. Although this is a small subgroup in a small cohort to begin with, we hypothesize that that fact that this subgroup did not show any significant change after anti –inflammatory treatment may indicate the fact that the basic pathophysiologic changes of pouch related symptoms in APS patients is not inflammatory at its basis. We have emphasized this in our discussion.

Reviewer 2:

it is a very interesting and well written manuscript, presenting data about management of pouch related symptoms in patients with adenomatous polyposis. However, this study has several limitations, such as the small number of patients and only four patients with identified pouchitis (>7 PDAI). However, data about this subgroup of patients with ileal-pouch anal anastomosis are very limited. Furthermore the authors analyze their findings and compare them with current literature and this is an attractive feature of the manuscript.

Response: We thank reviewer for his evaluation of our manuscript. Indeed we have mentioned the small number of patients in our cohort as one of the limitations of our study. Since Adenomatous polyposis syndromes are rare, cohorts of these patients tend to be naturally small. We think that the rarity of this entity – pouch management in APS patients, rather than IBD patients, and the fact that very few other studies devoted themselves to only APS patients – makes our study unique and opens up the way to further prospective studies.

Reviewer 3:

The study has mentioned about dietary modifications but what kind of dietary modification was done is not elaborated. It is difficult to establish that just symptomatic treatment or dietary modifications improved patients' symptoms.
Response: We thank the reviewer for his comments and we have added an elaboration of the dietary modification. We advised our patients to switch to a dietary regimen that is low in poorly digested carbohydrates and low in fiber, as fermentation of dietary carbohydrates or fiber by small intestinal bacterial overgrowth in the pouch can cause increased stool frequency and bloating.
The PDAI should have been tabulated to compare different treatment groups.
Response: We regret that due to a technical error the tables and figures were not attached to the original manuscript. We have attached them in the current version in the same file as the main text.

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Reviewer 4:

The manuscript addresses an important aspect in the management of IPS in a rare subset of patients with APS who have undergone IPAA. The authors have nicely elaborated the issue and have suggested some definitive management strategies. The authors have extrapolated their work retrospectively from their own prospective observational study which was a "by chance" finding. It was perhaps an accidental result rather than a pre-planned study with definite parameters. Though the results and statistical analysis favors some definitive management strategies based on treatment according to lines of IBS, a well-defined cohort based prospective study could help in generating definitive treatment protocol. Though the study opens up a new avenue in the management of IPS but acceptance of treatment based on the conclusions of the Author's needs further research before being implemented into clinical practise.

Response: We thank the reviewer for his important comments. We whole heartedly agree that future prospective research in the field of pouchitis and pouch-related symptoms in APS patients is warranted. We hope that the data we present here can serve as a basis for future research.

Reviewer 5:

Thank you very much for the opportunity to review this paper.
Major comments: The title, abstract and the key words reflect the study described by the authors. I have some trouble to understand the Methods. You need to describe data analysis in detail, and how do you make your analysis.

Response: We thank the reviewer for this comment. We have collected clinical data including number of daily bowel movements, abdominal pain and rectal bleeding in clinic visit before and after therapy was initiated. We also noticed endoscopic and histologic findings found in endoscopy before and after therapy. We then compared whether there was significant change in symptoms or PDAI score and its subscores after treatment was started. We have now emphasized the PDAI calculation in our method section. We have also included the tables and figures that were unfortunately missing from the original manuscript due to a technical error, and we hope this will make our methodology clearer.

On the other hand, the authors referred to the tables 1 and 2, but I never found the tables in your manuscript. Do you compared the different types of treatment? Do you only analyzed the outcomes of every treatment compared by themselves? The results are very difficult to follow A diagram of the different treatment need to be created in the methods. You have a good manuscript, with good information but the information need to improved. Finally it is important that you stated: this is a retrospective work.

We thank the reviewer for these comments. We regret that due to a technical error the tables and figures were not attached to the original manuscript. We realize that the data presented can be difficult to follow, and we hope that table 2 and figure 1 that show the differences in clinical symptoms and PDAI scores will show more clearly the differences between the different treatment modalities.

We did not directly compare the different treatment modalities (as many patients received more than 1 treatment), but rather examined the effect each treatment had on the different clinical outcomes and PDAI scores and discussed the different results. We have emphasized in our discussion that the study was retrospective.

Reviewer 6:

Thank you for allowing me to review this article. It is indeed in any unexplored area in which research is certainly needed especially as it greatly impacts quality of life for patients with FAP who have had a TPC-

IPAA. The study is majorly flawed, however, and there are multiple issues that need to be addressed before it can be considered for publication. I am happy to re-review once this has been done. - I do not fault the authors for a study with 33 individuals since FAP is rare and such studies understandably will have a small overall n. That being said, and though it is understandably retrospective, the numbers for each intervention are too small to make conclusions. The statistics of this will invariably influence readers to think that certain interventions are successful but may instead be due to chance alone. I think all interventions can only be presented as "grouped together." Though a table can be provided with number treated by each intervention, conclusions of the effect of each should not be teased out.
Response: We thank the reviewer for his comments. We have indeed mentioned that one of the limitations of our study is its retrospective nature and our inability to separate completely the different treatment modalities from one another. We have now added a reservation in the result section, at the end of the paragraph regarding the effects of individual therapies that states that data regarding individual treatments should be considered with caution.

The pathophysiology of pouchitis in IBD is completely different than that in FAP. IBD is driven by an inflammatory process, while as the authors astutely mention, FAP pouch issues likely by an IBS-related process. The PDAI, developed for IBD, thus cannot be used in this study. Instead, the authors should evaluate symptoms individually. This is further supported by the fact that only n=4 had overt pouchitis and there was minimal non-significant response to anti-inflammatory therapies.
Response: We thank the reviewer for this important comment. The PDAI was indeed developed to identify and quantify pouchitis mainly in IBD patients. However, since there are no guidelines regarding management of pouchitis and pouch-related symptoms in APS patients, we used the PDAI as a tool to quantify symptoms, endoscopic and histologic changes. The use of PDAI allows us to show more clearly that most patients indeed do not fulfill criteria for pouchitis, since their pathophysiology is more functional rather than inflammatory. Thus, the "standard" therapy used for IBD patients does not seem to work in APS population

-On a related note, there are no tables (not sure if I didnt receive any but I dont see a supplemental document).
Response: We regret that due to a technical error the tables and figures were not attached to the original manuscript. We have attached them in the current version in the same file as the main text.
I suspect that the greatest impact from the PDAI comes from number of bowel movements. Again, symptoms should be described individually and PDAI is inappropriate to use here. -The lack of a placebo control group as well as inability to describe why each intervention was used makes this a descriptive study. -This study comes from a tertiary referral center. How many professionals made medical decisions to treat these patients and pick individual interventions? How were medications chosen? More details should be provided - was there an algorithm, was it provider specific, etc?
Response: We thank the reviewer for his important comments. Two gastroenterologists treated the patients in our cohort. Since there are currently no evidence-based data to guide management of neither IPS nor pouchitis in APS patients, physicians administered therapies that were extrapolated from the management of UC-related pouchitis and irritable bowel disease . Indeed, there was no therapeutic algorithm – which is exactly why we conducted this study. There is no data regarding pouch management in APS patients, and we believe that our data support taking on a more IPS oriented approach rather than using treatments used for IBD related pouchitis. Further prospective trials in APS patients are needed as we emphasized in our discussion.

-The difference between statistical significance and clinical significance should be emphasized and elaborated upon. A decrease in DBM from 10.3 to 9.3 is clinically insignificant even though it reaches statistical significance. If readers conclude that interventions will significantly reduce bowel movements, the point will be lost. A patient with 9 BMs is no different than one with 10.
Response: We thank the reviewer for this comment. We absolutely agree that a decrease from 10 to 9 bowel movements per day is probably not clinically significant. However, we further analyzed the results and demonstrated that a third of our cohort had a significant mean decrease of 3 daily bowel movements – which is more clinically significant, and that major

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decrease is the reason for the statistically significant results. We hope that figure 2 which was absent from the previous version (due to a technical error) will show this more clearly.

For the patients with overt pouchitis, did any have IBD?
Response: We thank the reviewer for this comment. None of the patients suffered from IBD.

Reviewer 7:

I have read the manuscript carefully. Current topic. Usually, ileal pouches packaged for familial polyposis have a lower incidence of pouchitis than patients operated on for ulcerative colitis. Comprehensive introduction. There is no information on the type of ileal pouch. No information is reported on whether patients had a protective ileostomy. No information on ileostomy closure. I think the authors should clarify these aspects. Further information on the surgical act is absent.
We thank the reviewer for this comment. We have elaborated on the surgical technique that was used: All patients underwent creation of a J-pouch in an open surgical approach and stapled anastomosis. Nine patients (27.2%) underwent a single stage procedure, and the other 24 patients underwent a 2 stage procedure with a protective ileostomy that was closed after a few months.

Reviewer 8:

Please, advise the corresponding author to adjust the title of the paper reflecting its contents. I suggest the title should read *Management of pouch related symptoms in patients who underwent ileal pouch anal anastomosis surgery for adenomatous polyposis*. The findings reported in the paper that the dietary modifications and probiotics seem to confer the greatest benefit for pouch-related symptoms than antibiotics and anti-inflammatory modalities is very reasonable.
We thank the reviewer for this comment. We have changed the name of the manuscript accordingly.

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