

March 26, 2020

RE: Manuscript NO: 04383168 – WJG – Manuscript No 53335

In addition to our initial responses to the Reviewers (see below), we have addressed the residual requests regarding 1) providing the audio core tip, 2) providing figures in editable format and 3) editing the references to comply with WJG specifications.

Thank you for considering our manuscript revision.

Sincerely,

Amanda Ricciuto

We would like to thank the Reviewers and Editors for their time in reviewing our manuscript and for their thorough review, including very useful comments/suggestions. We incorporated all of the suggestions. Indeed, several of the sections were extensively reworked to address the issues raised by Reviewer #2 and both a Table and Figure summarizing the microbiota changes in PSC were created and added.

Reviewer #1:

1. The title reflect the main subject/hypothesis of the manuscript.
2. The abstract summarize and reflect the work described in the manuscript.
3. The key words reflect the focus of the manuscript.
4. The manuscript adequately describe the background, present status and significance of the study.
5. The manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings and their applicability/relevance to the literature stated in a clear and definite manner. The discussion accurate and discuss the paper's scientific significance and/or relevance to clinical practice sufficient.
6. The manuscript meet the requirements of use of SI units.
7. The manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections.
8. The manuscript well, concisely and coherently organized and presented. The style, language and grammar are accurate and appropriate.
9. The author prepare the manuscript according to the appropriate research methods and reporting?

We thank Reviewer #1 for his overall very favourable review. In response to point #9, we would like to indicate that, as this work represents a narrative review, it does not require compliance with any particular guidelines for reporting (<https://www.equator-network.org/>).

Reviewer #2: The topic of the review is very relevant. In general, the review deserves publication, but only after a major revision.

We would firstly like to thank Reviewer #2 for his very comprehensive and helpful review. We have made considerable effort to incorporate the suggestions and feel that the manuscript is much improved as a result.

1. Some very important studies are not mentioned, e.g. study by Rühlemann M. et al., 2019, suggesting that PSC itself drives the faecal microbiota changes.
 - a. *We have now included all of the studies on the fecal and mucosal microbiota studies in PSC that we could identify. Based on a subsequent recommendation, we created a summary table to present the results from each of these, including the one referenced above. In addition, we felt it would be helpful to add a bit more of a discussion of individual studies to the body of the*

manuscript, so we have done this, again including the study mentioned above. The fact that PSC itself may drive the fecal microbiota changes, as raised by this study, is now explicitly acknowledged. We would also like to highlight that we added the just recently published study by Quraishi et al. 2020, which is the first to apply an integrative multi-omics approach (including the microbiome) to a comparison of PSC-IBD and UC cohorts.

2. In the section on microbial metabolites, information is presented incorrectly and abounds with general phrases (both for bile acids and for SCFAs) that are not related to PSC.
 - a. *We have made efforts to improve this section by reviewing more recent literature and updating the section accordingly. An effort was also made to simplify/shorten the section by removing statements/data that were not directly related to PSC or mechanisms that might be pertinent in PSC. The SCFA section was rewritten as well. As the intention was to focus on bile acids rather than SCFAs, this section was shortened and simplified.*
3. The practically unused and misleading term 'Endobiome' is not referenced.
 - a. *We opted to remove this term, as we too felt it was misleading and was only mentioned once.*
4. Phrases that 'the Gram-negative bacteria, BSH has only been identified for Bacteroides fragilis' (all Bacteroides spp., and some other Gram-negative bacteria, such as Alistipes, Fusobacteria, etc., are BSH containing!) and that 'The process of dehydroxylation ... found only in anaerobic gut bacteria, mainly Clostridium (clusters XIVa and IX) and Eubacterium of the Firmicutes phylum' (not Clostridium genus, but clostridial clusters!) are outdated and incorrect.
 - a. *As per point 1, we have reworked this section to correct the above. The section was purposefully kept a bit more general, as the degree of detail previously was not felt to be necessary given the purpose of the review.*
5. Only one no longer relevant reference for BAs is given (Wahlstrom A. et al., 2016). It is recommended that you either omit this information or update it.
 - a. *We omitted this reference and instead drew on alternate, more recent reviews/original studies to inform this section.*
6. Changes in the gut microbiome in PSC are recommended to be presented in the table.
 - a. *Thank you for this suggestion. We created such a table and added it to the manuscript (Table 1).*
7. It is desirable (but not necessary) to add a figure reflecting the role of the gut microbiome and its changes in PSC.
 - a. *We created a figure summarizing the taxa that are increased and decreased in PSC vs healthy controls and IBD patients (Figure 1).*

Reviewer #3:

This paper focuses on the possible mechanisms about gut microbiome and its metabolites in primary sclerosing cholangitis (PSC) and PSC-IBD, especially the role of bile acids, which provides potential target for clinical treatment of PSC. And an expanded knowledge of the gut microbiome as it relates to PSC offers critical insight into the development of microbe altering therapeutic interventions, such as antibiotics, nutritional interventions and fecal microbial transplantation.

1. The author reviews the literature comprehensively. However, there are a few English spelling mistakes in this paper.

We thank Reviewer #3 for his overall favourable review. The document has been reviewed for spelling errors and these corrected. We opted to employ American English spelling, and this is now consistent throughout.