Peer Review File

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Reviewer A

Comment 1:
Thank you for submitting this elaborate review on a very relevant topic. The review is rather long and needs to be more focused on the topic at hand- which is motility disorders in CF rather than an exhaustive review of motility studies in general. The reader at times forgets that you are even writing about cystic fibrosis in the first place.
The intro starts by describing digestion with little info about CF. For example, discussion of GALAXY study and Tabori et al studies should be much earlier – ie in intro rather than in your conclusions. Prevalence of GI symptoms in CF has been now well-documented by recent studies from US therefor it is worth being in intro prior to discussions of organ system involvements.

Reply 1: The authors would like to thank the reviewer for their excellent comments and suggesting to improve the manuscript. While we recognize that our article is extensive, we have attempted to summarize the key concepts and evaluation tools for each segment of the GI tract, and worked to incorporate the existing CF literature into each corresponding section. We also recognize that although it may, at times, appear generalized, this is also reflective of the paucity of literature within the CF population – we are hoping this review will raise awareness of this scarcity of data. We have followed the reviewer's suggestions to restructure the introductory paragraphs to include discussion of GALAXY and similar Gi specific studies.
Changes in the text: Line 160-166

Comment 2/3:
I would propose to authors that for each section you have labeled, you minimize discussion of actual testing and focus instead on the why someone with CF may have those specific motility disorders, how that impacts their nutrition and pulmonary disease- ie how reflux could lead to rejection in patient with CF or aspiration or coughs etc.
You could organize this review into what we know in CF and gaps in knowledge with only a brief discussion of motility testing. Readers can read a motility-based book or journal for the latter.

Reply 2/3: We would like to thank the review for their insightful suggestions. The objective of our manuscript was to provide a comprehensive review of diagnostic modalities available in the evaluation of patients with CF, sectioned based on segment of the GI tract. We also aimed to highlight the available literature, or lack thereof, particularly for patients with CF. Beyond these endeavors, it is our hope

that this manuscript will inspire and direct future CF-specific motility research. We should like to create a follow-up manuscript aimed at addressing the reviewers suggestions of focusing the pathophysiology behind these motility disorders and their significance regarding nutrition and pulmonary disease in patients with CF.
Changes in the text: N/A

Additional comments:
Comment 4:
1.Intro first paragraph and a lot of the first two pages should be abbreviated.

Reply 4: Thank you for this comment. The authors have worked with all reviewers' suggestions to revise the first two paragraphs and truncate.
Changes in the text: Lines 88-104 and 124-170

Comment 5:
2.Table 2- a lot of this is exhaustive and not correctly labeled and perhaps could be omitted and instead just discussed in the body of paper instead of this large table that is not useful.

Reply 5: Thank you for this suggestion. The authors understand the reviewer's reservation given length; however, wanted to provide the reader an centralized compilation of CF-specific motility literature as a readily-available reference. The authors have worked to make the table as succinct as possible as a way to easily disperse CF-specific literature to the reader.
Changes in the text: N/A

Comment 6:
3.Figure 1 is really nice- would omit endoflip as for evaluation of secondary peristalsis since this right now has no clinical relevance.

Reply 6: The authors would like to thank to the reviewer for their comment and suggestion. We recognize the current limitations of EndoFLIP; however, were attempting to provide a comprehensive assessment of the tests and technology available for as the clinician's disposal. We would also like to make the reader aware of all available technology for future use, although recognize there is no CF-specific literature currently available. For those reasons, we would prefer to retain EndoFLIP within the figure.
Changes in the text: N/A

Comment 7:
4.Shorten section 3

Reply 7: Thank you for your suggestion. Section 3 has been shortened and restructured to incorporate the reviewer's earlier suggestions regarding GALAXY

literature.
Changes in the text: Lines 124-170

Comment 8:
5.Small bowel section talks about DIOS but doesn't really address SIBO and why breath testing is not useful in CF – perhaps.

Reply 8: The authors appreciate this comment, and have updated the text accordingly to address SIBO and the utility of breath testing in patients with CF.
Changes in the text: Lines 343-347 and 368-372

Comment 9:
6.Antroduodenal manometry figure shown doesn't state if this is fasting state or postprandial. Please specify as this has implications for the findings shown.

Reply 9: The authors would like to thank the reviewer for this comment, and are happy to clarify this within the figure description. The antroduodenal manometry tracing shown is in a fasting state for both a) and b).
Changes in the text: Line 618

Comment 10:
7.Omit WMC- or shorten discussion of this although we have more data in CF on this study as technology is no longer available.

Reply 10: Thank you for this comment and suggestion. The authors have truncated the discussion of WMC throughout the text and clarified that this product is no longer available for use.
Changes in the text: Lines 292-297 and 374

Comment 11:
8.Esophagus section- talk about aspiration, lung tx and nissen and whether pH testing should be done- even if expert opinion right now. Talk about Prakash G. Gut paper published with Lyon 2.0 consensus. This does talk about on PPI parameters so you can now update this review.

Reply 11: The authors appreciate the reviewer's insight and suggestions. We have added additional text to address the suggestions above and have included discussion of the updated Lyon 2.0 consensus.
Changes in the text: Lines 197-208 and 227-229

Comment 12:
9.Why is balloon expulsion testing not on Figure 1 list or discussed as way to rule out dyssynergic defecation.

Reply 12: Thank you for this excellent suggestion. Figure 1 has been updated to reflect balloon expulsion testing, and brief discussion has been added to the manuscript text.
Changes in the text: Lines 463-467

Comment 13:
10.I don't think we need a table on what each of these tests rule out- I think we need it for specifically in CF- what testing can help rule out. Ie ARM and Hirschsprung's for example can be omitted since this doesn't pertain to CF.
For each of the tests please keep in mind we are talking about pts with CF.

Reply 13: The authors thank the reviewer for their comment and suggestion. The authors have aimed to correlate each particular manometry test with a Cystic Fibrosis diagnosis. Although some of the diagnoses or indications listed may not be particularly common within patients with CF, the authors believe it may not be ideal to discount particular indications. The authors believe that a comprehensive list of indications will also prove useful in guiding the clinician should these less common scenarios arise in their patients with CF.
Changes in the text: N/A

This review needs a lot of revision but it is an important topic and so if done well could be very informative.

Reviewer B

This article provides a detailed review of the current state of investigating Gastrointestinal Motility in cystic fibrosis. It is based on a comprehensive review of the literature with critical analysis highlighting the problems of investigations, of defining reproducibility of tests, and of identifying normative values. It indicates the limited number of studies available, and the sometimes inconsistent results obtained. Gastrointestinal symptoms and pathology have been identified as a key current topic in cystic fibrosis and an area requiring further research.

Suggestions:

Comment 1:
Consider including a paragraph on the role of validated gastrointestinal Patient Reported Outcome Measures (PROMs) such as the Reflux Symptom Index (RSI), Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM),, Patient Assessment of Constipation Symptoms (PAC-SYM) or the CF Abdomen score. These PROMS are being widely used in clinical assessment of gastrointestinal symptoms in CF, and are being used in research studies such as the GALAXY Study and the PROMISE study, which are referred to in this article.

Reply 1: The authors would like to thank the reviewer for their comment and suggestion. We have updated the manuscript to reflect discussion of GALAXY and the associated PROMs in patients with CF. A more in-depth discussion of these PROMs, which the authors believe would be an excellent addition to a general GI evaluation manuscript, was not undertaken given the aims of our manuscript.
Changes in the text: Lines 160-166

Comment 2:
Consider placing more emphasis in the introduction or discussion on the effect of CFTR-modulator drugs (Elexacaftor-Tezacaftor-Ivacaftor) The initiation of ETI has provided the opportunity to investigate how an increase in CFTR function affects the pathophysiology of CF, including gastro-intestinal symptoms.

Reply 2: The authors appreciate this excellent suggestion from the reviewer. We have made changes within the manuscript to reflect the reviewer's suggestion.
Changes in the text: Lines 125-129 and 135-138

Comment 3:
Consider emphasising the potential adverse effect of Gastro-esophageal reflux on the lung allograft after lung transplantation in CF

Reply 1: The authors appreciate the reviewer's suggestion, and have updated the manuscript accordingly.
Changes in the text: Lines 197-205

Reviewer C

Comment 1:
Please insert briefly into the introduction the definition of cystic fibrosis and the GI complications expected.

Reply 1: The authors appreciate the reviewer's suggestion and have updated the manuscript accordingly.
Changes in the text: Lines 93-97

Comment 2:
The last sentence of the introduction does not justify the importance of the review or give some hypothesis. Please consider to reformulate it. Consider taking it from lines 127-128.

Reply 2: The authors would like to thank the reviewer for this comment and suggestion. The manuscript has been updated with the suggested changes.
Changes in the text: Lines 97-103

Comment 3:
In general, Google Scholar is not a good database for scientific papers. I rather put it as grey literature than a valid database.

Reply 3: The authors appreciate this comment and have updated the manuscript accordingly. All publications were cross-referenced within PubMed to ensure equivalent search results.
Changes in the text: Line 108 and Methods tables

Comment 4:
It would be important to show all the details of the selection of articles. Please consider putting it in a flowchart.

Reply 4: The authors appreciate the reviewer's comment and suggestion. Given that our review is narrative rather than systematic, we have formatted the selection algorithm and table to align with Translational Gastroenterology and Hepatology's formatting guidelines for narrative review.
Changes in the text: N/A

Comment 5:
Please consider inserting into the Small intestine part of the process of nutrient digestion in pwCF with the reposition of enzymes orally.

Reply 5: The authors appreciate the reviewer's comment and suggestion. In order not to deter the reader from motility to digestion, and given the vast literature discussing the topic, the authors have selectively refrained from in-depth discussion of nutrient digestion. The authors understand that there are also not many ways to determine the relation of dysmotility and nutrient absorption. Moreover, there are no functional correlations between a stool marker of absorption and the GI tract motility, making it difficult to make a connection between the two topics. This discussion would be an excellent topic for research within the field of GI motility in patients with CF.
Changes in the text: N/A

Comment 6:
Consider to detail about steatorrhea and its effect into GI transit.

Reply 1: The authors appreciate the reviewer's suggestion. We have added discussion within the text. The effect of steatorrhea on GI transit within humans, and patients with CF, remains unclear however. There are animal studies evaluating alterations in GI transit; however, there is uncertainty within the literature for humans.
Changes in the text: Lines 358-360

Comment 7:
Please insert the inference of CFTR modulators in GI motility. If there are no references to the topic, please make it clear.

Reply 1: The authors appreciate the reviewer's suggestion. The manuscript text has been updated accordingly.
Changes in the text: Lines 135-138

Reviewer D

I would commend the authors for this detailed review of gastrointestinal motility in Cystic Fibrosis. Given the paucity of reviews on this topic, this comprehensive review will be very useful for CF clinicians. The article is well-written, nicely structured into individual sections based on the anatomy, and also inclusive of updated literature on all currently available motility evaluation techniques. The motility tracings are also very well illustrated.

Comment 1:
I have the following comment. in Table 1(Indications). For antroducodenal manometry and colonic manometry, the listed indications give the impression that these tests are routinely indicated for patients with these issues. In fact, most of these motility tests are often offered to patients with refractory symptoms. For example, feeding intolerance is listed as an indication of antroduodenal manometry. In fact, practically, antroduodenal will be most likely done in patients with severe feeding intolerance refractory to medical management. You could modify the indications and provide details with the appropriate severe symptoms.

Reply 1: The authors appreciate the reviewer's excellent comment. The authors agree with the reviewer and have added a footnote to Table 1 to reflect this suggestion.
Changes in the text: Sentence added to the footnote of Table 1