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Dear sirs:

We are very pleased to resubmit manuscript 44687, "the natural history of children with mild Crohn's disease treated without immunomodulators or Biologics, to the world Journal of gastroenterology. We would like to thank the reviewer's further thoughtful comments, and would like to reply enough point by point manner to these comments. We also attach the revised manuscript, both with and without the edits.

However before we reply to the comments, I would like to reply to an issue with the "review check" that was performed by the Journal. Prior to submission to the World Journal of gastroenterology, we had submitted to another journal (an LWW journal, as identified by the Review check), and it appears the "review check" picking up words and phrases from the abstract from our prior submission. We have decided to submit the work to the world Journal of gastroenterology instead of the LWW journal, this is an original manuscript, and is not replicating previously published work. If there are any issues or concerns, please contact Dr. Bousvaros directly at 617-355-2962, or by email at [Athos.Bousvaros@childrens.harvard.edu](mailto:Athos.Bousvaros@childrens.harvard.edu).

Point by point reply to the reviewer comments:

Reviewer 01557050 (Japan)

1. We have inserted page numbers as suggested by reviewer 1.
2. We have defined inflammatory disease in the results section as disease Crohn's disease that presents without fibrostenosing or perforating complications. This is the same method that is utilized in standard classifications of inflammatory bowel disease, such as the Montreal or Paris classifications.
3. We have now defined Z score in the methods section, as requested by the reviewer.
4. Thank you for emphasizing that we needed to clarify this point. When we utilized the term "immunomodulators", we typically refer to either azathioprine, mercaptopurine, or methotrexate. These are small molecules, that have modest

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efficacy in the treatment of inflammatory bowel disease. When we utilized the term "Biologics" we refer to the anti-TNF agents for purposes of this paper. The data from this paper were gathered before newer Biologics such as ustekinumab or vedolizumab were developed. We have clarified these terms in the introduction of the manuscript. We also have reemphasized the definition of immunomodulators and biologics in the discussion on page 9.

5. Given that the top of the table says "months," using the abbreviation "mo" in the table cell was redundant, so we simply eliminated it. Thank you for this observation.

Reviewer 00503587

1. The author makes the important point that we have not formally assessed quality of life using questionnaires during this retrospective study. In fact, during most clinical visits, quality of life is not formally assessed in questionnaires, but rather subjectively assessed by the physician and patient during a conversation. Based on our chart review, we did not identify any obvious quality of life impairment in our patients (such as hospitalization or school absence). We have modified the manuscript to reflect the reviewer's point that quality of life questionnaires were not utilized.

2. Thank you for making the point about modifying the abstract to include the control group. We have made included a new sentence in the abstract to emphasize that we did use a case control method.

3. We have made the CD abbreviation more consistent as respected by the reviewer.

4. "The authors use the term mild and limited CD. While they subsequently acknowledge that this term is not clearly defined, the nature of this work is such that a definition (even a working definition) is required. Subsequently, the authors mention that patients with mild CD may have growth impairment - this seems contradictory.

**Response:** As outlined in the paper, a small group of patients with Crohn's do not have the clinical symptoms or disease severity to warrant immediate

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escalation of therapy to immunosuppressive drugs. This paper in part attempts to characterize that phenotype, and we believe we have done so, and identifying that most of these patients have either very limited ileal disease, or mild colonic disease that can be treated with amino salicylates antibiotics or diet. The point about growth impairment is important however, because it does suggest that even patients with clinically mild Crohn's disease clinically or endoscopically may have low-grade inflammation that may impair growth. This paper will allow better communication to families, that if they opt for treatment that avoids immunosuppression, that growth impairment may be a potential risk.

5. We have made the change as requested by the reviewer.
6. Since this was a retrospective study, going back many years before vitamin D levels were measured routinely in patients, we do not have the ability to assess vitamin D status. In addition, no formal disease activity scores were obtained on these patients at the time of their initial evaluation.
7. We feel repetition is helpful in the manuscript in this area, because given the nature of the manuscript it is important to highlight the groups we are comparing.
8. The patient the reviewer refers to here was actually followed for 25 months past diagnosis. In other words, the patient did well for 24 months without immunosuppression, then was followed for another month and then subsequently lost to follow-up.
9. The control group was primarily used to evaluate disease location compared to the reference group (see table 1).
10. Thank you for identifying an area the reader could misinterpret. The denominator in this section refers to the total number of patients in the cohort, not those with ileal disease. The total number with ileal disease is 20, as shown in table 1. We have modified the manuscript for clarity on page 8.
11. The RISK study is referred to in reference 5.
12. We have formatted the bacterial names (aka italicized *Clostridium difficile*).

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13. All antibiotics were utilized short term (1 month or less) based on our chart review. The review cannot ascertain exactly how many days of antibiotics were prescribed.
14. We have clarified our use of the word "macroscopic".
15. The term indeterminate colitis is still widely used by clinicians, though technically IBDU is the term used by researchers. I have included both terms in this revision at the reviewer's suggestion.
16. References have been updated.
17. Well stated and thank you. We have revised the title of figure 1 to "Probability over time of avoiding treatment escalation in children with mild CD"
18. We revised the title of the abstract for clarity.

We hope we have addressed all the concerns, and that this manuscript now is ready for publication. Please do not hesitate to contact us if we can be of any further help.

Sincerely,

Yamini Sharma, MD

Athos Bousvaros MD

