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Dear Editorial Board,

My coauthors and I would like to thank you and the reviewers for your time and review of our manuscript, **"Review: Management of Inflammatory Bowel Disease with Clostridium Difficile Infection".** Comments are numbered and our responses are in red.

If there is any additional information you require, please do not hesitate to contact us.

Sincerely,

Julie D'Aoust

Reviewer No. 03658374

Overall this is a well written and research systematic review. I have minor points that would improve the article.

1. Would include hospitalisation as one of the increased morbidities noted in the abstract. The higher incidence of CDI in hospitalised patients is noted in the text

Thank you. We have now included hospitalization as one of the increased morbidities of CDI in IBD in the abstract.

2. In the conclusion the authors state that "it is likely reasonable to initiate or resume immunosuppressive therapy after 48-72 hours". This time frame does not seem to be supported by any specific literature and constitutes the authors opinion. Perhaps better to leave room for more clinical discretion.

Thank you. We have now rephrased the conclusion in both the abstract and manuscript to reflect the dearth of evidence that exists on this topic and that a formal recommendation on the timing of initiation of immunosuppressive therapy, at this point in time, is primarily based on expert opinion and a few case reports of corticosteroid use in CDI. We therefore now use the phrase "may be considered".

3. Would be helpful to discuss test performance characteristics in the text – i.e. sensitivity, specificity, PPV and NPV for PCR, EIA, GDH etc.
Thank you. We agree that these would be important points to discuss. Unfortunately, we could not identify any data specifically discussing test performance in the IBD population. We chose not to include test performance characteristics in the general population in this manuscript as this has been reported on at length in other publications.

4. In the introduction would be good to include a discussion of antibiotics as the classic risk factor for CDI and link to microbial diversity.
Thank you. We agree that this is an important point to discuss. We have now included a sentence in the introduction regarding antibiotic use as a traditional risk factor for the development of CDI, likely mediated by an alteration in gut microbial diversity.

5. Is it known what the CDI rate in patients with IPAA for non-IBD reasons is? Would be nice to include.
Thank you. We agree that this is an important point to address. The patients who underwent IPAA and developed CDI who have been included in studies reviewed in this manuscript did so for IBD reasons. Although very interesting, the scope of our literature search and manuscript did not yield information on the CDI risk in patients who underwent IPAA for non-IBD reasons.

6. Could the increased risk for CDI associated with steroids and infliximab be related to underlying disease activity? Was this controlled for in the studies cited? Could this be discussed by the authors?
Thank you. We agree that this is an important point to address. The data for an increased risk of CDI with steroids is primarily from two studies: (REFERENCES 44 and 49).
Both are observational studies and did not control for underlying disease activity. We agree that this may be a confounding factor in the identification of risk factors.
This is now addressed on page 8 "However, when analyzing CDI risk in IBD patients using corticosteroids, studies were observational and did not control for underlying disease activity."
With regards to biologic therapy, the evidence as to whether or not it truly constitutes a risk factor for the development of CDI or rCDI is also unclear. Studies are conflicting (REFERENCES 24, 30, 34, 35, 43, 44-47, 49). This is now reflected on page 8 ("Most studies demonstrate ongoing steroid, biologic, or immunomodulator therapy does not increase the risk of CDI in IBD patients[30,34,35,43,45-47], however, some contradictory evidence exists")

7. Figure 2 is very helpful. Could the to box be re-labelled "New onset diarrhea in IBD patient". Also for severe colitis patients I don't know if the flow chart is appropriate.

These patients often require upfront treatment for their colitis and C. dif, and waiting 72 hours could increase the risk of colectomy in these patients. Either the figure needs to be updated to reflect this or severe patients should be excluded from this proposed algorithm.

Thank you. We agree that this is important to address. We have relabeled Figure 2 as suggested. We agree that in those patients with severe colitis who do not improve with the initiation of appropriate C. difficile therapy, waiting 48-72 hours prior to changing management may endanger the patient in question. For this reason, we have altered the wording of the item in the algorithm. Instead of "after 72 hours", we now use, "within" 72 hours. We also have included in the algorithm that regardless of how long the patient has been on appropriate C. difficile therapy, in the event of deterioration, surgical consults should be obtained early.

Editor comments

1. All files must be signed by the corresponding author and provided in PDF format.

Thank you. We have included the biostatistics statement, data sharing statement, conflict of interest statement, and scientific research process statement.

All authors are native English speakers and as such, we have not provided a language certificate.

2. Please reformat reference numbers.

Thank you. All reference numbers have been reformatted throughout the text.

3. Please complete the "Comments section"

Thank you. The comments section has been completed as per instructions included.

4. Please provide decomposable figures, whose parts and movable.

Thank you. We have included versions of Figures 1 and 2 that are decomposable, as a Word document.