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Responses to the reviewer's comments

Name of journal: World Journal of Gastroenterology

Manuscript NO: 66118

Title: Frontiers in antibiotic alternative for *Clostridioides difficile* infection

Dear Editor,

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We edited the paper according to the reviewer's comments. Please find enclosed the revised manuscript in Word format (file name " 66118-Manuscript File"). Each comment has been answered accordingly in the manuscript and each text that has been altered was highlighted yellow in the revised manuscript.

We hope that the revised version will fulfill the requirements for publication in the World Journal of Gastroenterology.

Thank you for your consideration. We look forward to hearing from you.

Sincerely yours,

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Responses to the reviewer's comments

Reviewer #1:

The manuscript submitted by Pranchana and cols., aims to critically overview and discuss alternatives to antibiotic to treat *Clostridioides difficile* infection. In general, the text is well written and structured. Further, the review presents a broad and in-depth critical analysis of data besides debating pros and cons of each suggested approach.

Our response: We thank the reviewer 1 for his/her valuable comments and suggestions.

Major concerns:

- The authors must address the concept of eubiosis and dysbiosis rather than solely stating that “microbiota is perturbed” or “healthy microbiota”

Our response: Thank you for your suggestion. We included the concept of eubiosis and dysbiosis in Introduction section of the revised manuscript.

- It is of utmost importance to describe/discuss the contribution of multidrug-resistant microorganisms to safety and feasibility of FMT

Our response: Thank you for your suggestion. We included this point in our revision.

Minor concerns:

- Please, replace the term “flora” by “microbiota”;

Our response: We edited the text accordingly.

- There are some typos throughout the text e.g : “synbiotic”

Our response: We used the term ‘synbiotic’ deliberately to refer to ‘a mixture of prebiotic and probiotic’ as defined by the International Scientific Association for Probiotics and Prebiotics or ISAPP. However, we replaced some synbiotic with ‘pre- and probiotic’



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where they are not meant to be together. We thank the reviewer for pointing this out.

Reviewer #2:

This is an overall good and comprehensive review. I just have a few suggestions:

1. Use of certain antibiotics including clindamycin, cephalosporins, quinolones, and penicillins has been reported to increase CDI risk - This statement requires citation and further explanation.

Our response: We included a sentence that further explains this statement and citations.

2. The pathogenesis and toxins of *C. difficile* can be further elaborated and make it into a section.

Our response: We included a statement that directs readers to appropriate reviews on the pathogenesis and toxin and CDI as we think including this section is beyond the scope of the manuscript.

3. Findings should be added into Table 1

Our response: Due to the extensive length of chemical clustering result, we think including the whole table to the main text would be too lengthy. Therefore, we retained the complete result in the table S1 and included the mentioned clusters and representative structures in Table 1 as the reviewer's suggestion.

4. Authors should add in a section on the efficacy of different antibiotics available in treating *C. difficile* infection which can justify the need of alternatives to antibiotics.

Our response: We included the information on efficacy of antibiotics in the text.