

Point-By-Point Response to Reviewer Comments

To
The Editors
World Journal of Hepatology

Dear Editors,

We would like to thank you for considering our manuscript for publication in the *World Journal of Hepatology*. We would also like to thank the reviewers for taking the time to review our manuscript and helping us improve the quality of our work. Please note that all the reviewer comments have been addressed in the re-submitted version of the manuscript and a point-by-point response has been provided for the reviewer comments. The changes are highlighted in red in the main revised manuscript. The manuscript has also been thoroughly revised again to ensure data accuracy and reporting. All authors agree to the resubmitted version of the manuscript and have no conflict of interest to report.

Please feel free to reach out to me at any time regarding this manuscript at dush.dahiya@gmail.com

Sincerely,
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Reviewer Comments

Reviewer #1

P1. Authors can add some relevant researches on the efficacy of FMT in different types of HE, which may make the article more complete.

Author Response: We would like to thank you for taking the time to review our manuscript. We appreciate your effort, hard work, and enthusiasm in helping us improve the quality of our work. Please note that we have revised the manuscript according to your comments. The changes are highlighted in yellow in the main manuscript. We have discussed the results from studies that have checked the efficacy of fecal microbiota transplant in different types of HE.

“ There are a few studies that have assessed the efficacy of HE based on the severity. Of these studies, the study by Metha et al. on 10 patients treated with FMT for recurrent over HE (≥ 2 episodes of WHC criteria II–IV HE in 6 months as previously described in Table 2) showed that 6 patients had sustained clinical response as well as significant improvement in ammonia levels, Child–Turcotte–Pugh Score (CTP) and model end–stage liver disease score (MELD). On the other hand there were two readmissions for spontaneous bacterial peritonitis and three patients with overt HE.⁸¹ The case report by Kao et al. showed improvement in ammonia levels, Inhibitory Control Test (ICT), and Stroop test after FMT enema in a patient with Grade I-II HE which later worsened after stopping the treatment.⁹

To sum up, significant progress has been achieved in the potential application of FMT as a therapeutic option for HE among cirrhotic patients and careful selection of the donor can lead to improved outcomes in patients with HE. Prospective studies are required to compare the efficacy of FMT in patients with different stages of HE.”

P2. FMT is one of the microbial therapies for treating HE, it would be better if the review could briefly supplement the advantages and disadvantages of other microbial therapies, such as prebiotic, probiotic, and so on.

Author Response: Thank you for raising this excellent point. We have added information regarding other microbiome targeted therapies like probiotics, prebiotics, and synbiotics in the management of hepatic encephalopathy. We have also discussed the advantages and side effects of these therapeutic options.

“The microbiome targeted therapies that have been proposed as a therapeutic option in the management of patients with hepatic cirrhosis include prebiotics, probiotics, FMT, antibiotics, and synbiotics.¹⁵ Probiotics are live microbial supplements of human origin which have shown to benefit the host by improving intestinal microbial balance when consumed adequately.^{15,16} Prebiotics are non digestible food ingredients that can selectively stimulate the growth of beneficial bacteria in the human gut and thereby improving the host’s health.¹⁶ Synbiotic is the synergistic combination of

prebiotics and probiotics.¹⁶ A meta-analysis of 9 randomized control trials showed that prebiotics and probiotics were associated with significantly reduced relative risk of no improvement in minimal hepatic encephalopathy without any significant adverse events.¹⁶ There are no studies in the literature that have compared the direct outcomes and adverse events of prebiotics, probiotics, synbiotics, and FMT.”

P3. Most FMT is aerobically prepared, and thus anaerobes are not administered. Many probiotics, such as *Faecalibacterium prausnitzii*, are lost with aerobic stool processing and preserved with anaerobic processing. Therefore, different preparation methods of FMT may affect the efficacy of hepatic encephalopathy. This section can be described in the article.

Author Response: Thank you for pointing out this excellent point. We have discussed aerobic and anaerobic methods for preparation of fecal microbiota transplant and discussed the potential of anaerobically processed fecal microbiota transplant in the treatment of hepatic encephalopathy due to preservation of probiotics like *Faecalibacterium prausnitzii*. We have also discussed various methods of preparation of fecal microbiota transplant along with their advantages and disadvantages.

“Fresh FMT is readily can be immediately transferred from a donor and it has higher microbial load and diversity but it is logistically challenging to find a donor and transfer stool immediately.⁴⁰ On the other hand frozen FMT can be conveniently stored and transported but it can lose efficacy if appropriate preservation and storage techniques are not maintained.^{15,40} Lyophilized is the easiest to store and administer as it does not warrant invasive procedures for administration.”

“The method of preparation of FMT can also impact the outcomes. Several studies in patients with ulcerative colitis have shown improved outcomes with anaerobically processed FMT as compared to aerobically processed FMT as many probiotics like *Faecalibacterium prausnitzii* are lost with aerobic stool processing.⁴² Similarly, patients with HE might also benefit from anaerobically processed FMT.”