

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Chinese Physicians' Perceptions of Fecal Microbiota Transplantation" (ID: 24411). Those comments are all valuable and very helpful for revising and improving our article. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in green in the paper. The main corrections in the paper and the responses to the reviewer's comments are as flowing: Responses to the reviewer's comments:

Reviewer 03474674:

1. Response to comment: The poor written English: special attention should be given to the scientific writing and grammar.

Response: We have corrected the incorrect spelling and grammar and have polished the language with help from a professional English language editing company.

2. Response to comment: Introduction is too long and I would suggest summarizing or deleting the historical part concerning FMT as it is not important to understand the main goal of the manuscript.

Response: We have shortened this paragraph.

3. Response to comment: Please provide a more accurate information in the sentence "FMT was recommended by American CDI guideline in 2013 as an alternative to standard antibiotic therapy for recurrent CDI [10]." According to those guidelines, FMT should be reserved in cases of multiple recurrences of CDI despite antibiotics, rather than an alternative.

Response: We have made the following correction according to the reviewer's comments: "FMT was recommended by the American CDI guidelines in 2013 if there was a third recurrence after a pulsed vancomycin regimen<sup>[10]</sup>."

4. Response to comment: Delete the sentence "As of January 2015, there were 53 registered clinical trials of FMT, including 22 for CDI, 17 for IBD, 3 for IBS, 2 for chronic constipation, 2 for pancreatitis, 1 for metabolic syndrome, 1 for type 2 diabetes mellitus, and so on." Both sentences of the same paragraph are repetitive.

Response: We have deleted the sentence according to the reviewer's comments.

5. Response to comment: Matherial and Methods: A copy of the questionnaire sent to physicians should be included in the manuscript.

Response: We have added the questionnaire to the manuscript according to the reviewer's suggestion.

6. Response to comment: The authors should specify which criteria were adopted to select the physicians who entered in the study.

Response: We apologize for our negligence in specifying the recruitment criteria.

We added the following information to the “Materials and Method” portion. The participants were a convenience sample of physicians working in hospitals and practicing gastroenterology; other specialists, such as those physicians working in endocrinology, pediatrics, general surgery, and neurosurgery, were also included in the study. These physicians were recruited through gastroenterology associations and their subspecialty groups in different provinces.

7. Response to comment: Discussion: Although nicely summarized, the last paragraph of discussion starting on “Chinese physicians especially gastroenterologists showed tremendous interest in FMT and showed a certain awareness and a high degree of acceptance for it. (...)” and ending on “(...) The keen interest, high acceptance and well understanding of FMT provide grounds and conditions for development of this novel treatment in China. (...)” should be deleted as throughout the “results” and “discussion” these information was already detailed and provided. Moreover, similar to introduction, discussion is too long.

Response: We have deleted these sentences and shorted the discussion according to the reviewer’s suggestion.

Special thanks to you for your helpful comments.

Reviewer 03478404:

1. Response to comment: The main drawback is the English language, with many errors, both of grammar and spelling, requiring revision of the full paper, including the questionnaire. Some examples of the many – “On the base of understanding, FMT indications physicians preferred were”, “attitude of FMT by physicians”, “restoring the construction of intestinal flora”, “be aware of FMT / no awareness of FMT” in the Figure 1 etc. The questionnaire is well structured, with interesting questions, however it should be written in proper English.

Response: We have corrected the incorrect spelling and grammar and have polished the language with help from a professional English language editing company.

2. Response to comment: The questionnaire sent to physicians should be included in the paper, not as supplementary material. This is very important. Readers should know what was asked, since the answers are provided (in the Results) and Discussed.

Response: We have added the questionnaire to the manuscript in accordance with the reviewer’s suggestion.

3. Response to comment: The authors stated that the questionnaire was anonymous. However, they asked for the address and hospital location. If there was only 1 response from a given address, then the questionnaire would not be anonymous anymore.

Response: We regret our negligence of this situation. However, there were always several responses from each address, and we really don’t know which is which, so we consider this questionnaire to be anonymous.

4. Response to comment: In the questionnaire, the definition of FMT should be revised (replace “sick” person).

Response: We apologize for this issue, and we have replaced the term “sick person” with “patient”.

5. Response to comment: What do the authors understand by “intimate friends” in the questionnaire, in the results and in the Figure 6?

Response: Intimate friends mean friends that are always together and have similar lifestyles and environments, such that their intestinal microbiota may be more similar than volunteers of no relation.

6. Response to comment: (1) how the physicians included in the study were chosen?

Response: We apologize for our negligence in specifying the recruitment criteria. We added the following information to the “Materials and Method” portion. The participants were a convenience sample of physicians working in hospitals and practicing gastroenterology; other specialists, such as those physicians working in endocrinology, pediatrics, general surgery, and neurosurgery, were also included in the study. These physicians were recruited through gastroenterology associations and their subspecialty groups in different provinces.

(2) The vast majority of them are gastroenterologists (76.9%) – almost 4/5. Do GIs represent most physicians in China? I doubt it. Only a minority are not GIs in the study. Is then the study representative for all physicians in China?

Response: As the reviewer suggested, a vast majority of gastroenterologists and a minority of non-GIs were included in our sample, so we compared their perceptions on FMT, and we didn’t consider the GIs’ opinions as representative of all physicians.

(3) Another issue: Another related issue: only 2/3 provinces of China are included in the study. Again, is it really representative for China?

Response: We apologize for our inaccurate descriptions. While our survey covered 2/3 of the provinces from six different regions of China according to the common geographical zones, our sample is still not representative of all of China. We corrected this text as follows: “this survey is representative to some extent”.

(4) How many physicians are in China and the 844 physicians who responded represent what percentage? Sure, the number of respondents appears impressive; however the total number of physicians should be mentioned, even if approximately.

Response: We added the total number of Chinese physicians in the text per the reviewer’s suggestion in the discussion section (marked in green).

7. Response to comment: From the questionnaire, it could be guessed that only physicians working in hospitals were chosen. Then the title and the abstract should mention this, as well as the conclusions.

Response: In consideration of the reviewer’s suggestion, we have stated this information in the “methods” section of the abstract and text (marked in green).

Additionally, we think including “Chinese physicians” in the title and conclusion sections provides a general sense of the sample. “Chinese hospital physicians” may not be appropriate. If the reviewer still has a different opinion on this problem, we will be happy to correct it.

8. Response to comment: As it appears further in the results, most physicians were working in TERTIARY HOSPITALS (87.6%) and this should be also mentioned in the abstract.

Response: We have made correction according to the reviewer’s comments and mentioned this in the abstract (marked in green).

9. Response to comment: The ancient history of fecal therapy in China is interesting; however this paragraph could be shortened.

Response: We have shortened this paragraph.

10. Response to comment: The phrase “FMT was recommended by American CDI guideline in 2013 as an alternative to standard antibiotic therapy for recurrent CDI [10] is not correct.

Response: We have made correction according to the reviewer’s comments: “FMT was recommended by the American CDI guidelines in 2013 if there was a third recurrence after a pulsed vancomycin regimen<sup>[10]</sup>.”

11. Response to comment: The following results require more attention and comments: “Physicians with increased comprehension of FMT were more likely to accept it (OR = 3.265, 95%CI 1.555-6.855, P = 0.002). The higher the level of hospital physicians worked at, the less they accepted FMT (OR=0.359, 95%CI 0.134-0.961, P = 0.041).” That means that physicians from higher level hospitals had less comprehension?

Response: This is a very good question, and we noticed this fact as well. We tried to explain this result as follows. It is possible that the relationship between the two factors is not linear, and physicians in the higher level hospitals with more knowledge of FMT were more rigorous and cautious in the administration and implementation of new technologies, so their acceptance of FMT was lower.

12. Response to comment: Please insert “recurrent” in the following sentence “Indications: The majority of physicians (86.7%) selected Clostridium difficile infection (RCDI)”.

Response: We are very sorry for our incorrect writing and we have made correction.

13. Response to comment: Some data presented in the Results are redundant (both in the text and tables/figures). Maybe this paragraph could be shortened.

Response: Considering the reviewer’s suggestion, we have shortened this paragraph. “North West (211, 32.7%), North (152, 23.6%), East (100, 15.5%), North East (83,

12.9%), South West (68, 10.5%), and South Central (31, 4.8%)” in “characteristics of respondents” and “chronic constipation (43.7%), irritable bowel syndrome (IBS,39.1%), obesity (28.1%) and type 2 diabetes (23.9%)” in the “indications” were deleted (marked in green).

14. Response to comment: Discussion could be shortened as well, so that the conclusion appears interesting, not as a repeat of what was already mentioned.

Response: As the reviewer suggested, the discussion was too long. We deleted “Except that, results of multivariate analysis revealed a better awareness of FMT among physicians with higher education and higher professional level. Furthermore, geographical region was another factor affecting the perception of FMT” “Physicians in South Central and North China demonstrated higher awareness than those in the other four regions. Physicians working in the Northwest had the lowest levels of FMT awareness” in paragraph 2, “Unexpectedly, physicians in other departments had no difference in acceptance of FMT from gastroenterologists” in paragraph 3, “For donor selection, most physicians preferred donors possessing similar gut flora environment to patients, including blood relatives, non-blood relatives and intimate friends”, “The second selection was healthy volunteers” in paragraph 6, “The lower GI approach to FMT is favored over the upper route according to our survey. However, there are many unanswered questions regarding the best route of administering FMT, which requires additional studies” in paragraph 7, and “Chinese physicians, especially gastroenterologists, showed tremendous interest in FMT and demonstrated awareness and a high degree of acceptance for FMT. Better awareness was confirmed among physicians who had more education, were gastroenterology specialists and worked in more developed regions. Better acceptance was confirmed in physicians who had awareness of FMT and who worked in lower level hospitals. Physicians in different regions showed different levels of acceptance. Efficacy, safety and a therapeutic alternative for refractory diseases were the three most frequent reasons for choosing FMT as a treatment. Primary concerns related to clinical barriers included patient’ acceptance, the absence of guidelines, administration and ethics. The preferred indications were RCDI, IBD, chronic constipation, and IBS, among others, and preferred donors were healthy individuals with similar gut flora environments as the recipients. The preferred route of delivery was the lower GI tract, and an equal number of physicians considered FMT low risk” in the last paragraph of the discussion section.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for editors and reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Thank you and best regards.

Yours sincerely,

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