

November 22, 2018

Professor Ya-Juan Ma
Scientific editor
World Journal of Clinical Cases

Dear Prof. Ya-Juan Ma,

Many thanks for the letter dated November 15, 2018, regarding our manuscript entitled "Safety of Fecal Microbiota Transplantation in Chinese Single-center Children: a Retrospective Analysis" (Manuscript NO. 42761). We appreciate the valuable comments of the reviewers. Based on the reviewers' comments and suggestions, we have revised the manuscript. Our specific responses to the reviewers' comments and suggestions are as follows:

Reviewer (code: 02537353)

The authors investigated the safety of fecal microbiota transplantation (FMT) in children, by a retrospective study, including 49 patients. The Title reflects the main subject of the manuscript, the Abstract well summarizes the described study and the Key words reflect the focus of the manuscript. ...the Methods have well been described...

1. About the manuscript the Background is too short and very general, in addition the author declare that " is also much clinical research focusing on FMT to treat different diseases" but the references ??

Response: We thanks for the valuable suggestion of the reviewer. We had revised the introduction and added the references after "is also much clinical research focusing on FMT to treat different diseases" (see page 5, line 119).

2. The authors declared that the immune state was an independent risk factor for AE occurrence but which type of the immune state, immunodeficiT ? or ? Did The authors evaluated the the distribution of T cells' subsets ? and the inflammatory status ?

Response: We fully agree with this important concern from the reviewer. Three of our primary immunodeficiency patients were determined by the next-generation sequencing test after FMT, which included VEO-IBD with IL10Ra gene mutation, IPEX with FOXP3 gene mutation and DNA ligase IV syndrome with LIG4 gene mutation listed under the Table 1. Another 3 primary immunodeficiency patients were diagnosis for their repeatedly infection and development retardment after birth. They were under severe, chronic, intractable diarrhea beyond antibiotic control, which were in line 281, and most of them were in inflammatory status (with WBC, CPR elevated). Some did not have clinical lab test for further diagnosis and distribution of T cell due to some their personal reasons. It is important to test the distribution of T cell for further diagnosis in the future.

3. In addition, is absent the number of the local ethical endorsement.

Response: We appreciated the suggestion of the reviewer. We have added the information in the revised manuscript (see page 6, line 142-144).

Reviewer (code: 00742196)

In this retrospective observational study, Dr. Zhang et al reported their experience with 49 children who underwent fecal microbiota transplantation (FMT) treatments. There were a total 114 FMT treatments performed on those 49 patients in a single center. They evaluated the adverse events (AEs) in short-term (48 hours) and long-term (up to 3

months). They noted that the incidence of short-term AEs was 26.32% (30/114). The most common short-term AEs were abdominal pain, diarrhea, fever and vomiting. All short-term AEs were all self-limited and symptom-free within 48 hours. There were 2 cases with severe AEs presented with GI bleeding. One patient with primary immunodeficiency died due to sepsis and liver failure 4 weeks after FMT. Other than this, there were apparently no relevant long-term AEs during 3 months' follow up. AEs were more common in immunodeficient patients. This is an important field which clearly needs more clinical experience and reports about FMT in children, especially the criteria of patient selection, efficacy, and safety. ...

1. While authors present their data about the safety of FMT in children, they did not present the criteria for patient selection and efficacy. I think that additional data should be added into the paper.

Response: We thanks for the valuable comments from the reviewer. We added the information of patients underwent FMT in "Study population" in Method (see page 5, line 135-141). FMT cured all the pediatric patients with RCDI, and we reported it in another previous study (Li, et al., *Front Microbiol.* 2018 Nov 2; 9: 2622). For other disease types, FMT temporary alleviated the GI symptoms in short term, however, FMT was not helpful to cure the primary disease during the follow-up period.

2. Table 1 should be divided into 2-3 tables. The table 1 can be patient demographics and others may be presented in other tables and presented in a different way. For example, AEs are more common in patients with immunodeficiency, therefore, AEs may be analyzed and presented in patients that divided into 2 groups: the group with immunodeficiency and those not immuno-compromised. Furthermore, AEs from different route of administration (enema vs. upper GI administration) may be interesting to know as well.

Response: We have divided the Table 1 into two tables to indicate patients and donors characteristic (see Table 1), and the number of AEs compared with different category in 114 times of FMT (see Table 2). Also, we add the times of AEs in different way, such as age, route of administration, number of FMT infusions and immune state (see Table 2). Although the rate of AEs in different route of administration showed no difference in statistics, in our practice we do feel the patients would complain more with the upper GI administration, especially nasogastric tube. But most of our patients were too young to keep their position and hold the bacterial liquid inside the gut after FMT so that we tried more Nasal jejunal tube. We added the information of AEs from different route of administration in the revised manuscript (see page 9, line 235-239).

3. As mentioned above, the data in the current table 2 may be presented for 2 different groups and 2 different way of FMT administration.

Response: We divided the Table 1 into two tables and presented the number of AEs in different way of FMT administration. We also added the information of AEs from different route of administration in the revised manuscript (see page 9, line 235-239).

Reviewer (code: 00742108)

1. The manuscript is about a trend topic recently all over the world. The originality and speciality of the study comes from the following reasons; it is obtained in childhood, some of the donors are relatives, a considerable follow-up duration. 2. The manuscript is well, concisely and coherently organized and presented. Also the number and content of the tables are sufficient. 3. The manuscript adequately describes the background, present status and significance of the study. 4. The manuscript interprets the findings

adequately and appropriately, highlighting the key points concisely, clearly and logically.
5. The manuscript meets the requirements in terms of ethics, biostatistics and informed consent. ...

1. *The title should be better if it is arranged as follows or any other type: "Safety of Fecal Microbiota Transplantation in Chinese Children: a single-center and retrospective study".*

Response: We thank for these valuable comments from the reviewer. We have changed the title to "Safety of Fecal Microbiota Transplantation in Chinese Children: A single-center retrospective study".

2. *The authors should correct the highlighted words in terms of English grammar listed below:*

"Staphylococcus aureus, Vibrio parahaemolyticus, Vibrio cholerae), ova and" in "line 136".

- *"Preparation the bacterial liquid" in line 142.*

- *Description of this abbreviation "SAEs" has not been defined in the text anywhere; "FMT beyond mild or moderate AEs. AEs and SAEs were determined to be" in line 178, "not considered an SAE. The patient was diagnosed with chronic active EBV" in line 284.*

- *"Table 1 shows the characteristics of all patients and donors" in line 191. "Table 1" should be placed at the end of the sentence.*

Response: Thanks for such detailed advice. We have corrected the highlighted words below:

- We have corrected "ova" to "parasitic ovum" (see page 6, line 157).

- We have corrected "Preparation the bacterial liquid" to "bacterial liquid Preparation" (see page 6, line 163).

- We have described the abbreviation "SAEs" so that all the following "SAEs" make sense (page 8, line 198).

- We have changed the sentence "Table 1 shows the characteristics of all patients and donors" into "The characteristics of all patients and donors were listed in Table 1" (see page 8, line 212).

We hope that our revised manuscript is now suitable for publication in **World Journal of Clinical Cases**.

Sincerely Yours,

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