

October 30th, 2016

Dear Dr. Qi,

We previously submitted a manuscript entitled “Fecal Microbial Transplant for the Treatment of Pediatric Inflammatory Bowel Disease [Manuscript ID: 29234]” to World Journal of Gastroenterology, for which we received comments on September 23rd, 2016.

Thank you for providing us with your insightful feedback and further direction regarding our manuscript. We greatly appreciate the opportunity to revise our manuscript, and we thank all the reviewers for their helpful comments. We trust this revised version is in keeping with the changes requested.

We hereby submit this revised manuscript for your evaluation. The concerns of all three reviewers have been addressed in the attached point-by-point reply and also in the revised manuscript.

Thank you for your time and consideration and we look forward to your response and publication of this review.

Yours sincerely,

Nikhil Pai,
BSc MD FAAP FRCPC
Assistant Professor, Division of Gastroenterology & Nutrition, Department of Pediatrics
McMaster Children's Hospital (McMaster University Medical Center)

1. RESPONSE TO REVIEWERS

Reviewer 1 (Reviewer Code: 00503545): In this review, the authors summarize existing literature on the role of fecal microbial transplant (FMT) in IBD, and discuss current trials, challenges, and opportunities for this treatment in the future. This paper has been well written and the theme of the review is a topic of note in this field. Although the contents of the review are interesting, the authors should address the following points.

1. The authors should number the references according to the citation order in the text.

Response: The references have been appropriately formatted according to journal requirements.

2. Cited reference number also should be shown in the Tables.

Response: The cited reference numbers of studies included in the tables have been included and updated in our tables.

3. Style of the Tables should be revised.

Response: The style of the tables have been formatted according to the journal requirements.

Reviewer 2 (Reviewer Code: 00158526)

General comment: This is a well-done review about the potential role of fecal microbial transplant in IBD treatment in children.

1. There is insufficient data about possible theoretical backgrounds for treating patient with stool transplantations. What are the possible mechanisms?

Response: We inserted more information regarding the hypothesized mechanism of FMT in IBD under the subheading “FMT Preparation and Administration Techniques.”

- “A potential mechanism for the observed benefits of FMT in the treatment of IBD is its colonization of the recipient’s intestine with donor flora [23]. In RCDI, several studies have compared the microbiota composition pre- and post-FMT and have shown that fecal bacterial composition of the recipient was highly similar to that of the donor and was accompanied by resolution of symptoms [24] [25]. In a small pilot study of FMT in adult IBD patients, previously undetected donor bacteria were detected in patients during and after FMT. However, the relative abundance of these bacteria, and persistence of these changes, was highly variable between patients and generally transient [26]. Change in clinical symptoms did not correlate with timing of when the host’s microbiome reverted back to resemble their pre-FMT state.” (Page 4, Line 27)

2. The author should discuss more about possible ways to deliver fecal samples (advantages, disadvantages), the possible treatment regimens (amount of stool sample, protocols to prepare the samples), the possible adverse events.

Response: We have modified/incorporated sections to reflect these specific points. In particular, to address the possible disadvantages/advantages of fecal sample delivery and possible treatment regimens, we inserted:

- “This may also reflect the relative degradation of microbial material from gastric acid exposure during proximal upper gastrointestinal tract delivery techniques [35]. Further studies clarifying the impact of gastric acid suppression on FMT may further delineate this.” (Page 6, Line 13)

To address possible adverse events of FMT, we created a new heading entitled “Potential Risks and Side Effects of FMT” that reads,

- “The long term risks of FMT are unknown. Animal models have described transmissibility of obesity, metabolic syndrome, and possible neuropsychiatric phenotypes through FMT [14] [15]. A 2014 case report described a patient who used her daughter as a fecal transplant donor for treatment of RCDI, and developed obesity (BMI change from

26kg/m² to 33kg/m²). The patient's 16 year-old daughter had a BMI at the time of stool donation between 85-97% for age. This was the first reported case of obesity developing after fecal microbial transplant in a clinical setting, a finding that has been well-described in animal models [50]. A previous study conducted on RCDI noted transient abdominal cramping, diarrhea, or nausea immediately upon FMT administration and throughout the 13-week follow-up [27]. Furthermore, increased blood in the stool, and infections of the urinary and respiratory tract were noted weeks after treatment, however these results were deemed unrelated to the therapy [27]. A review of the pediatric experience of FMT for UC described no serious adverse events, and self-limited, mild to moderate adverse events (transient vomiting, mucoid stools, and transient fevers) reported [32] [51]. No directly associated infectious complications have been described in adult or pediatric FMT studies [36] [52].” (Page 8-9, Line 34)

3. The references in the text should be changed with numbers, in addition, the citations numbers should be showed in the tables.

Response: The references in the text and citations in the tables have been formatted according to the journal requirements.

4. All tables in the manuscript are adopted, maybe the author should search trough PubMed and make his own data for tables.

Response: We have revised Table 4 and added in Table 3 to contain data that reflects our own literature search.

Reviewer 3 (Reviewer Code: 00503590)

The focus of the present manuscript is effects of FMT in pediatric IBD. In this area well designed and properly powered studies are particularly scant, and thus the review is based on four open label non-controlled case series with a total of 25 patients. Only one of these case series had more than clinical response as measure of effect – this totals 3 patients which were evaluated by endoscopy and histology.

1. There are several ways this is problematic: - A major problem with case series in general is that only the successful cases are likely to be published – thus there is (potentially) a lot of unsuccessful cases that were never reported. - As the hype around FMT as a ?wonderdrug? is quite large, participants in case series and open label studies will probably be prone to report improvement in the follow-up. Therefore double-blinded RCTs are especially important, as the placebo-effect will be huge. - Harder endpoints than clinical scores (UCCS, partial MAYO etc) are also necessary, and endoscopic evaluation and a proper blinding protocol is very important.

Response: We have inserted several key points that reflect the possible placebo effect and increased probability of reporting improvement in follow up, the possibility of publication bias and additional protocol that will be necessary to ensure future studies are of high quality:

- “Studies of clinical response demand a blinded study protocol, particularly given that many patients who enrol in FMT studies are a self-selected group, who implicitly believe in the therapeutic value of “natural” treatments. Further, inflammatory bowel disease has established linkages between clinical symptoms, mucosal disease and underlying stressors; thus, patient bias may have a significant influence on self-reported PUCAI/PCDAI (Pediatric Crohn’s Disease Activity Index) scores when measuring clinical response. (Page 6, Line 22)
 - “In addition, it is also important to note that success of FMT for IBD reflected in the aforementioned studies may reflect a propensity for studies with positive results to be published and unreported, unsuccessful studies may exist.” (Page 6, Line 26)
2. Looking over the presented tables, most of the studies mentioned are either solely based on clinical evaluation or do not have a control group, or both. Moving on to the only RCTs published in adult IBD, one study did not show any difference between active and placebo, and the other showed a significant effect however the effect size was quite small and may represent a type I error. Taken together, these results are quite disappointing regarding further exploration of FMT

effects in IBD. Based on the criticism above I feel that the conclusion is overly optimistic towards FMT in IBD. I truly support the need for well designed RCTs in this field.

Response: We have updated our conclusion to comment on the paucity of well-designed and properly powered studies and reflect the need for well-designed RCTs for FMT in pediatric IBD. Specifically, we have inserted under the “Conclusion” subheading:

- “The use of FMT as a therapeutic option for IBD in adults and children is an active and emerging area of research. Well-designed, pediatric randomized controlled trials are needed, and available safety data suggests fecal transplant has low rates of mild-moderate, short-term adverse effects.” (Page 9, Line 10)
- “As patients increasingly embrace “natural” therapies, it is time we dedicate the funding and resources that have traditionally gone towards multi-center RCTs on immune modulators and explore microbial therapeutics for IBD care.” (Page 9, Line 11)