ANSWERING REVIEWERS

August 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12903-review.doc).

Title: Fecal microbiota transplantation broadening its application beyond intestinal disorders

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) "This is an interesting review about the effectiveness and possible broad applications of fecal transplants to different type of diseases. I have a couple of minor concerns one is that I would like to see documented if available adverse effects reported for FMT so that can help also in developing this therapy further."

Response: We appreciate the Reviewer for pointing out this important issue. FMT entered the medical community and became a relatively hot therapeutic strategy in recent years, bringing with it both promise and controversy. According to the published articles, transient adverse responses after FMT have been reported, including mild fever, abdominal pain, diarrhea, exhaust, flatulence and fatigue (J Pediatr Gastroenterol Nutr. 2013; 56: 597-601). However, these adverse effects are self-limited. De Leon reported a UC patient had been quiescent for more than 20 years who developed a flare of UC after FMT (Clin Gastroenterol Hepatol. 2013; 11:1036-1038). This case gives us a caution of FMT in treating CDI with UC. Moreover, a recent paper reported a UC patient had a CMV infection after performing home FMT without donor screening (N Engl J Med. 2014;371:668-675). As extracts of feces are mediators between the donor and recipient, FMT has the potential for transmitting occult infections even by strict donor screening. Anyhow, we considered evaluation of its pros and cons is necessary when facing a specific clinical issue. We have added the contents in page 6 and 7. Changes in the revised manuscript are highlighted in blue font.

(2) The second concern of the reviewer is about the use of words, if possible change them or just not include them in the review. Some specific examples are the following: heroic page #3; raveled and presented in page #4; delightful in page #10; provocatively, certified and sensational in page 11.

Response: We completely agree with your suggestion that it is important to use words scientifically. We invited a professional language editor to help us revise the manuscript in terms of language. We have revised the words in the revised manuscript (Page 4, 5, 12 and 13). Changes in the revised manuscript are highlighted in blue font.

(3)**"I advice the authors change the tittle to: "Fecal microbiota transplantation broadening its application beyond intestinal disorders"**

Response: We totally accept your advice. Indeed, we have been considering the title for a long time and chose the title of "Fecal microbiota transplantation: it's not just for intestinal disorders anymore"

finally when submitting this article. However, the data of FMT in extra-intestinal disorders is limited, and most of the studies are case reports or basic researches. More high-quality clinical trials are needed. The title (Fecal microbiota transplantation broadening its application beyond intestinal disorders) the reviewer suggested is much better as it not only reflects the theme we were talking about but is more appropriately and scientifically. Thanks for your suggestion.

(4) **"There are some statements that need to be re-written in order to be more clear. Specifically: In the abstract the paragraph about clinical observations; the protective effect of Bacteroides in page #4 is not clear enough; page #8 marked increasing number of researchers; in page 9 the word mainly does not make sense in the first paragraph of autoimmune diseases; page #11 what is a complicated flora, explain."**

Response: We appreciate the Reviewer to point out this issue. In the abstract the paragraph about clinical observations we changed it to "Case reports of FMT have also shown its favorable outcomes in Parkinson's disease, multiple sclerosis, myoclonus dystonia, chronic fatigue syndrome and idiopathic thrombocytopenic purpura"(Page 2); the protective effect of Bacteroides in page #4, we rewrote it as "Bacteroides fragilis, the prominent human gut commensal, can prevent and cure inflammatory disease by the effect of its symbiosis factor (polysaccharide A, an immunomodulatory bacterial molecule) on the activation of Toll-like receptor 2 pathway, inducing regulatory T cells and interleukin-10 production"(Page 5); page #8 marked increasing number of researchers, we revised it as follows: Autism is another condition in which intestinal microbiota is implicated. The onset of autism is often accompanied by intestinal dysfunction"(Page 10); in page 9 the word about autoimmune diseases, we have changed them to " The incidence of autoimmune diseases is dramatically increased, but the causes of these conditions are remained poorly understood. Idiopathic thrombocytopenic purpura (ITP) is caused by production of autobodies against platelet surface antigens. In a patient with ITP who was treated with FMT for UC, prolonged reversal of ITP was reported, as a normalization of platelet levels achieved"(Page11); page #11 the complicated flora (*Streptococcus bovis*, *Helicobacter hepaticus*) have been added in detail(Page 13). Changes in the revised manuscript are highlighted in blue font.

(5)" I was wondering as well if another alternative to promote success of FMT could be that they carry/produce specific adhesin molecules that facilitate the colonization of the new bacteria infused."

Response: Thanks for pointing out this important issue and we totally held a favorable view of the Reviewer. FMT not only introduces the new flora to the patient's intestinal tract but also defense against invading pathogens. This occurs through a series of substances (adhesin, immunomodulatory molecules, bacteriocin, etc.) produced by them. The adhesin molecules can compete for adhesion sites with pathogens, which are prevented from colonization (Gastroenterol Clin N Am. 2012; 41:781-803). Polysaccharide A (PSA), a symbiosis factor and immunomodulatory molecule of *B. fragilis*. A prior study has displayed *B. fragilis*△PSA (*B. fragilis* defected with PSA) reduced numbers of of tissue-associated bacteria when compared to animals colonized with wild-type *B. Fragilis* (Science. 2011; 332:974-977). Hence, in the process of commensal colonization, immune system can facilitate specific bacteria colonization through recognition of symbiotic bacterial molecules (Page 5 and 6). Changes in the revised manuscript are highlighted in blue font.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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