

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 76320

**Title:** Immunological mechanisms of fecal microbiota transplantation in recurrent *Clostridioides difficile* infection

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02462498

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Doctor, Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2022-03-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-03-12 02:37

**Reviewer performed review:** 2022-03-13 07:28

**Review time:** 1 Day and 4 Hours

Scientific quality	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
Language quality	<input checked="" type="radio"/> Grade A: Priority publishing <input type="radio"/> Grade B: Minor language polishing <input type="radio"/> Grade C: A great deal of language polishing <input type="radio"/> Grade D: Rejection
Conclusion	<input type="radio"/> Accept (High priority) <input type="radio"/> Accept (General priority) <input checked="" type="radio"/> Minor revision <input type="radio"/> Major revision <input type="radio"/> Rejection
Re-review	<input checked="" type="radio"/> Yes <input type="radio"/> No

<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Comments: This is an updated mini-review focusing on FMT immune mechanism. It is integrative and helpful for understanding this topic. The structure and the language are good.

1. Main comment: There is one important point on the core difference of the methods of FMT (using bacteria or filtered matters) which essentially affects the immune pathways. This should be discussed clearly in the manuscript. The origins of the both reports were shown as below: Using filtrated matters: Ott SJ, et al. Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With Clostridium difficile Infection. Gastroenterology. 2017 Mar;152(4):799-811.e7. Using purified bacteria Zhang T, et al. Washed microbiota transplantation vs. manual fecal microbiota transplantation: clinical findings, animal studies and in vitro screening. Protein Cell. 2020 Apr;11(4):251-266. This method as medical therapy has been used as expert recommended practice: Nanjing consensus on methodology of washed microbiota transplantation. Chin Med J (Engl). 2020 Oct 5;133(19):2330-2332. doi: 10.1097/CM9.0000000000000954. Feuerstadt P, et al. SER-109, an Oral Microbiome Therapy for Recurrent Clostridioides difficile Infection. N Engl J Med. 2022 Jan 20;386(3):220-229. This method as IND has been used in clinical trial with success.

2. Minor comment: In page 7: "The first attempts to gain knowledge to elucidate the immunological events elicited by FMT to successfully treat rCDI in 2017". This is an old question, though it is not enough clear. Therefore, it is impossible that this topic was studied in 2017. Researchers in the world have studied this for many years.

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**Reviewer's code:** 06149824

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Assistant Professor, Chief Physician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2022-03-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-03-14 12:00

**Reviewer performed review:** 2022-03-15 14:17

**Review time:** 1 Day and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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#### **SPECIFIC COMMENTS TO AUTHORS**

Soveral et al. minireviewed immunological mechanisms of FMT in rCDI. The title, "Immunological Mechanisms of Fecal Microbiota Transplantation in Recurrent Clostridioides Difficile Infection", may be more appropriate. The history and pathophysiology of CDI, in paragraph "CLOSTRIDIROIDES DIFFICILE INFECTION AND INTESTINAL DYSBIOSIS CORRECTION WITH FMT", may be needless in this minireview. They are beside the question. Besides, I think, if possible, the relationship between immunological molecules and microbial metabolites should also be illustrated. Microbes and their metabolites are both significant in FMT. The language is idiomatic and I recommend the paper to need major revision.

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**Peer-review model:** Single blind

**Reviewer's code:** 06271739

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Romania

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2022-03-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-03-12 09:27

**Reviewer performed review:** 2022-03-24 06:47

**Review time:** 11 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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## **SPECIFIC COMMENTS TO AUTHORS**

The authors performed an uptodate mini-review focusing on the immune mechanisms involved in the host's response to FMT when treating rCDI. The paper brings insights into the new immunological pathways contributing to restoration of the host's mucosal barrier after the acute inflammation caused by C. difficile colitis. The paper is well structured, easy to read and concise. I identified two minor issues related to citing of information (page 4, paragraph regarding the secondary dysbiosis lacks citation), as well as a phrase that I would recommend to be reformulated (page 5, last paragraph, there is also a citation lacking, as well as the information that states C. difficile antibiotic resistance as the main cause for recurrent CDI?).

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 06149824

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**Academic degree:** PhD

**Professional title:** Assistant Professor, Chief Physician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2022-03-12

**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-06-05 08:14

**Reviewer performed review:** 2022-06-05 10:00

**Review time:** 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

**statements**

Conflicts-of-Interest: [ ] Yes [Y] No

**SPECIFIC COMMENTS TO AUTHORS**

This minireview is supposed to summarize studies on the immune response to the treatment of FMT in rCDI. Although the content is novel and interesting, the present manuscript has some questions as followed: 1. In abstract, the background of FMT is introduced, while the relationship with rCDI or immunity is not fully elucidated. The applications of FMT in other diseases do not match with the title. 2. The introduction that describes the functions of human microbiota and the questions of dysbiosis is off the point. 3. Though manuscript lists many examples of trials to describe the immunoreactions, few of the internal points have been summarized. The manuscript is indeed interesting and promising, but there is not enough scientific construction and orderliness to publish in the WJG.