

Name of journal: World Journal of Gastroenterology

ESPS Manuscript NO: 16810

We would like to thank our reviewers for their thoughtful comments. We have addressed each point and changed the manuscript accordingly. We consider the manuscript to be improved by your feedback.

Reviewer #1:

Review of the ms “The Microbiome as Mediator: Do Systemic Infections Start in the Gut?” by Latorre M, et al. This paper summarizes the relevant literature data on the role of the intestinal microbiome in the development and treatment of C. difficile infection and in the development of other, systemic disease states and non-gastrointestinal infections. The authors consider a number of important questions raised about the therapies of the syndrome (i.e. fecal transplantation or short-chain fatty acids) and provided a very reader-friendly discussion. The paper is well organized and well cited. Beyond this, I have 2 noted comments. 1. The Gram staining method differentiates bacterial species into Gram-positive or Gram-negative groups. The name of the Gram staining method comes from its inventor, Hans Christian Gram. This is one of the most important discoveries in microbiology - Mr Gram deserves a capital G. 2. A scheme (figure) of SCFAs in microbial changes leading to increased survival after CLP-induced sepsis is needed -it would increase the quality of the paper significantly.

We thank you for identifying this error. The manuscript has been corrected accordingly and all references to Gram have been capitalized.

Reviewer #2:

The authors presented the importance of microbiome as a crucial mediator of critical illness and infection. The topic is very interesting, but the contents are too brief and not well-organized. The authors tried to explain the relationship between gut flora and systemic or other infections. They mentioned some aspects of their relationship like migration, however, did not in-depth details like influence of systemic immune system, et al.

We thank you for your careful reading of our editorial. We agree with a need for further discussion regarding immunology and have included additional text in the editorial.

Reviewer #3:

The manuscript makes a broad critical discussion on the role of microbial flora as a trigger for systemic infections initiated in the intestine. However, it fails to discuss the role of the immune system as a mediator, for example, in cases of transplanted in immunodeficient patients. Nonetheless, the manuscript deserves to be published as it contributes to a systemic view of the role of microbiota. In addition, the manuscript is very well designed written.

We thank you for your thoughtful commentary. We agree with a need for further discussion regarding immunology and have included additional text in the editorial.

Reviewer #4:

The intestinal microbiome is emerging as a crucial mediator between external insults and systemic infections. The manuscript reviewed the role of the intestinal microbiome in the pathogenesis and treatment of C. difficile infection. And then, the author discussed the novel research about the microbiome in periods of critical illness and non-gastrointestinal infectious disease. Finally, they look at current treatments for intestinal dysbiosis such as probiotics and the future microbiome-based therapies in the treatment of systemic disease. The manuscript is logical and well written. Only a little issue should be considered. This review is written in the first person. It is suggested that use the third person.

We appreciate your careful evaluation of our editorial and have adjusted the manuscript accordingly to the third person.

Reviewer #5:

The authors of the review manuscript titled “The Microbiome as Mediator: Do Systemic Infections Start in the Gut?” intended to summarize the current evidences supporting the existence of a strong link between gut flora and systemic infections. This article has structural flaws which are mainly related to citations. Starting from the first reference, many statements are not centrally related to the citations given. Moreover, many sentences were left unreferenced although they needed at least one. I did not go into detail more because such structural and conceptual issues are outside the referees’ duty.

We thank your for your commentary regarding citations and have corrected them accordingly.