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Revised manuscript #63526, "COVID-19-associated diarrhea"

March 19, 2021

Dear Editors-in-Chief,

We are grateful for your letter and for the Reviewer's comments, which proved most helpful in our revision of the manuscript. All of the suggested revisions have been accepted and all of the questions raised by the Reviewer have been covered on a point-by-point basis. The modifications have been identified by page or figure number and indicated by underlining in the manuscript. We enclose the revised manuscript and our replies to the comments of the Reviewer.

We hope that our manuscript in this revised form will now prove fully acceptable for publication.

Sincerely yours,

Klára Megyeri M.D., Ph.D.

Reply to Reviewer #1

We are grateful to Referee #1 for the reviewing work.

"It would be better if the potential therapy (especially drugs) could be described carefully."

We fully agree and are grateful to the Reviewer for the suggestion to describe the main drugs used to treat COVID-19. We have included this information in the revised form of our manuscript, as requested by the Reviewer. Accordingly, we have included a new section, and modified the text and the References (see pp 12, 14, and 15).

"Second, several factors could be responsible for the prevalence of diarrhea in COVID-19 patients. If diarrhea is not present at the admission, it becomes challenging to ascertain the cause of diarrhea. Several confounding variables, such as the use of enteral feeding (tube feeds), antiviral and antibiotics, altered gut flora, hyperinflammatory response, secondary bacterial infections, use of proton pump inhibitors (PPI) can potentially cause diarrhea in hospitalized COVID-19 patients. It would be better if you can emphasis this point."

We again agree with the Reviewer on the necessity to provide more information about the diarrhea-inducing effects of various SARS-CoV-2-independent causes of COVID-19-associated diarrhea.

We have now included the information relevant to COVID-19 on enteral feeding and we have modified the text of a newly included section entitled "Virus-independent causes of COVID-19-associated diarrhea" (see p. 14). We have also amended the References by including additional publications (pp 32 and 33).

We have also included a summary on the diarrhea-inducing effects of antiviral agents and antibiotics and modified the text on p. 14, as requested by the Reviewer. We have also amended the References by including additional publications (pp 32).

We thank the Reviewer for drawing our attention to the importance of *altered gut flora* and *hyperinflammatory response* in COVID-19-associated diarrhea. As requested by the Referee, we have added two new paragraphs to the manuscript. We have modified the text on pp 12-14 and Figure 1. We have also amended the References by including additional publications (see pp. 31 and 32).

The diarrhea-provoking effect of PPI has now been summarized on pp 14 and 15. We have also amended the References by including additional publications (p. 33).

We are extremely grateful to the Referee, as we consider that these modifications do improve the manuscript.