Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Reply. We are extremely grateful for the interest of Prof Ponzetto in our article and would like to take the opportunity to answer his very interesting comments.

The possible association of *Helicobacter pylori* with intestinal ischemic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sounds really intriguing. Unfortunately, because all of the analysis was performed during an important sanitary emergency in Lombardy,[1] none of the patients was tested for possible coinfections.

We would also like to emphasize that the strong tropism of SARS-CoV-2 for the gastrointestinal tract may probably be mediated by the abundance of angiotensin-converting enzyme 2 receptors in the intestinal mucosa.[2] A possible explanation for the virus-induced endothelial damage in the gastrointestinal tract could lie in the lectin pathway, which is speculated to be responsible for SARS-CoV-2–mediated thrombotic microangiopathy in lung tissues.[3] The central role of lectin and mannan-binding lectin-associated serine protease-2 in the gastrointestinal ischemic reperfusion damage has already been described in murine model in the pre–COVID-19 era.[4,5] These findings, if confirmed, could open new interesting therapeutic fields of research for SARS-CoV-2 ischemic manifestations.

In conclusion, we would like to thank Prof Ponzetto for the agreeable contributions, and we are pleased to see that our findings are considered valuable and could open new field of research for the scientific community toward an appropriate definition of, and treatment for, SARS-CoV-2.

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Conflicts of interest
The author discloses no conflicts.

Most current article

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The New Foe and Old Friends: Are We Ready for Microbiota-Based Therapeutics in Treating COVID-19 Patients?

Dear Editors:

We read with interest the work by Zuo et al[1] reporting altered gut microbiota in patients with coronavirus disease 2019 (COVID-19) during hospitalization. The authors reported that certain beneficial commensals of the patients are in inverse correlation with fecal load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and/or clinical severity. Although this pioneer study attempts to highlight the potential value of the gut microbiota as a therapeutic target, we believe that extra mechanistic links merit discussion and functional analysis of the readily available metagenomic data would provide further mechanistic insights.

Based on the finding of negative association between the abundances of 4 *Bacteroides* species and the fecal viral load, the authors anticipated that these bacteria may down-regulate angiotensin-converting enzyme 2 (ACE2), the entry point of SARS-CoV-2 into host cells. This justification was based on a previous report in which mice monocolonized with *Bacteroides* species.[2] Most members of *Bacteroides* are able to produce sphingolipids, which play an important role in host–microbial interactions by elevating exogenous sphingolipid (eg, ceramide) levels, while inhibiting de novo synthesis of sphingolipids in both human cells and mice models.[3,4] The benefits of elevated exogenous sphingolipid levels and consequently inhibited de novo synthesis of sphingolipids would be multifaceted. For one thing, increased exogenous sphingolipid levels could suppress the replication of coronaviruses by enhancing the differentiation of regulatory T cells,[5] and stimulating dendritic cell maturation that promotes T cell responses to viral infections.[6] For another, reduced de novo synthesis of sphingolipids in host enterocytes may suppress ACE2 expression and synthesis of human cell surface gangliosides, in which sphingolipids are an integral part. Given that the spike protein of SARS-CoV-2 is known to use the ACE2 receptor and could also use sialic acids linked to host cell surface gangliosides for entry,[7] reduced de novo synthesis of sphingolipids will consequently minimize viral entry. In addition, due to structural differences from host-derived sphingolipids,[4] *Bacteroides*-derived sphingolipids may lower the binding affinity of SARS-CoV-2 spike protein with ACE2 and human cell surface gangliosides and thus reduce viral entry. Given these potential roles of *Bacteroides*-derived sphingolipids, analysis on functional potentials of the microbiome from the readily available metagenomes in this study could somehow reveal possible mechanistic links between gut microbiota–derived sphingolipids and host defense against SARS-CoV-2, although other omics data and experimental studies are needed for verification. It is worth

investigating the therapeutic potentials of exogenous bacterial-derived sphingolipid and/or sphingolipid-producing *Bacteroides* in patients with COVID-19 while no effective treatment is currently available. Despite having the potential functions mentioned above, none of the 4 *Bacteroides* species were increased in healthy controls than COVID-19 patients. This is also supported by another study by Gu et al[8] in a population with similar genetic background. The preventive potential of these bacteria in healthy individuals from the viral infection is still questionable.

In addition, Gu et al[8] also reported a decreased microbial diversity, which is a general marker for gut dysbiosis, in patients with COVID-19 compared with healthy controls, but no significant difference between general and severe COVID-19 patients.[8] Because the study by Zuo et al[1] did not measure microbial diversity indices, it remains unknown whether these findings are generalizable. Given that viral loads were determined in this study, it is feasible and will be thought-provoking to explore the relationship between viral loads and microbial diversity.

The authors suggested enhancing intestinal butyrate production by dietary changes for promoting a healthy microbiome in general. One relevant explanation should link to the finding that negative correlations of 2 beneficial commensals, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, with viral load and disease severity, respectively. *Faecalibacterium* was also underrepresented in antibiotic-exposed COVID-19 patients in the study[1] and in COVID-19 patients compared with healthy controls, according to Gu et al.[8] These commensals and *Bacteroides* species are well-known producers of short-chain fatty acids, which play a pivotal role in modulating host immune homeostasis. Perhaps in patients with COVID-19, short-chain fatty acids produced by gut commensals prevent proinflammatory conditions. However, more functional studies are needed to confirm the role of butyrate producers or butyrate itself in preventing viral infection.

Despite that the mechanistic links discussed above somehow support the important role of the gut microbiota in the pathogenicity of SARS-CoV-2 infection, the association of fecal microbial alteration with COVID-19 does not establish causality. This important distinction needs to be made before considering microbiota-based therapy for COVID-19.

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Conflict of interest
The authors disclose no conflicts.

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Reply. We would like to thank Ye Peng and colleagues[1] for their interest in our article and for highlighting the need for further mechanistic studies to shed light on the potential therapeutic values of the gut microbiome in coronavirus disease 2019 (COVID-19).

We reported that multiple *Bacteroides* species inversely correlated with the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in feces in patients with COVID-19.[2] Based on this correlation, Peng et al[1] raised the hypothesis that sphingolipids produced by *Bacteroides* species might play a role in combatting SARS-CoV-2 by both enhancing the function of regulatory T cells and dendritic cells and lowering the binding affinity of SARS-CoV-2 spike protein to human angiotensin-converting enzyme 2,[1] a receptor for viral entry. We have therefore performed additional analysis on our metagenomic dataset to probe bacterial metabolic abundance of sphingolipid synthesis pathway (metacyc pathway: SPHINGOLIPID-SYN-PWY) via *HUMAnN2*.[3] We did not find significant differences in fecal DNA abundance of sphingolipid synthesis pathway between patients with COVID-19 and healthy controls, or any correlation with SARS-CoV-2 viral loads in feces.

Beyond sphingolipids, the function of *Bacteroides* on host immunity is manifold. *Bacteroides* species have high levels of surface component diversity, exemplified by its surface polysaccharides. It is widely reported that capsular polysaccharide A (PSA) produced by commensal *Bacteroides* has beneficial effects on the immune system.[4] PSA is capable