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.

LETTERS TO THE EDITOR

Readers are encouraged to write letters to the editor concerning articles that have been published in Clinical Gastroenterology and Hepatology. Short, general comments are also considered, but use of the Letters to the Editor section for publication of original data in preliminary form is not encouraged. Letters should be typewritten and submitted electronically to http://www.editorialmanager.com/cgh.

Putative Mechanisms of Diarrhea in COVID-19

Dear Editor:

We read with much interest the article "Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention and Management" published by D'Amico et al[1] in *Clinical Gastroenterology and Hepatology*. The article highlights the importance of gastrointestinal symptoms in coronavirus disease 2019 (COVID-19), which are increasingly being recognized. In this article, the authors report that the frequency of diarrhea in COVID-19 could be as high as 50%. They also elaborated on the role of angiotensin-converting enzyme 2 (ACE-2) receptors in severe acute respiratory syndrome–associated coronavirus 2 (SARS-CoV-2)–induced diarrhea.

We would like to discuss other putative mechanisms that could be involved in the etiopathogenesis of diarrhea in COVID-19. First, we would like to stress the importance of having a strict definition of diarrhea in COVID-19 patients, mainly because diarrhea can develop with any kind of viral illness, and it is usually short-lived (<48 hours). Hence, the term *persistent diarrhea* defined by at least 3 bowel movements for >48 hours might be more appropriate in this setting.[2] The presence of viral RNA in stool samples has been noted in up to 53.4% of cases of diarrhea in COVID-19, but it is unclear whether the presence of RNA correlates with diarrheal symptoms.[1] It is yet to be determined whether the presence of the virus in the stool sample is just a bystander/fecal shedding or due to its cytopathic effects. If the diarrhea is due to the direct cytopathic effects, then stool viral RNA is expected to be positive in significantly higher numbers in COVID-19 as compared with non-cytopathic causes. Nevertheless, the other following mechanisms could also play a role.

Severe COVID-19 is known to cause a cytokine storm with an increase in cytokine levels such as interleukins (ILs) (IL2, IL6, IL7, etc), tumor necrosis factor, and granulocyte monocyte colony-stimulating factor.[3] These proinflammatory cytokines can alter the gut-brain axis by getting their access via the vascular/lymphatic systems.[3] Studies showing significant gut inflammation in COVID-19 patients are limited. However, fecal calprotectin is elevated in COVID-19 patients with persistent diarrhea, which is consistent with increased gut inflammation. Interestingly, fecal calprotectin correlated with levels of IL6 but not with C-reactive protein or ferritin.[2]

The COVID-19 patients are known to have altered gut flora,[4] which could be due to the use of antimicrobials, concomitant infections, and the severe illness itself. The composition of gut flora could also be altered by an increase in proinflammatory mediators because of viral-induced inflammation. The use of antibiotics can have a profound effect on the gut microbiota, immune system, and antibody production, which can delay the clearance of SARS-CoV-2 from the gut.[5] ACE-2 receptor binding has shown to have aberrant mammalian target of rapamycin activity with a decrease in antimicrobial peptides that could alter the gut flora.[6] In addition, enteral nutrition with tube feeds is known to alter gut flora and can contribute to increased bowel output in patients with vent-dependent respiratory failure.

The COVID-19 patients are commonly treated with antibiotics because of suspicion for secondary bacterial infections.[7] These microbial agents (such as fluoroquinolones and cephalosporins) can cause antibiotic-associated diarrhea as an adverse effect. Furthermore, antiviral agents such as ritonavir-lopinavir, hydroxychloroquine, and remdesivir are increasingly used among these patients, and diarrhea is a common side effect of these drugs. These medications are commonly being used in COVID-19 patients during the course of the disease. It remains unclear whether they play any role in the fecal clearance of SARS-CoV-2.

The diarrheal symptoms in the patients with preexisting gastrointestinal diseases such as irritable bowel syndrome, inflammatory bowel disease (IBD), and malabsorption syndromes can potentially worsen with any viral infections. The ACE-2 receptors are overexpressed in the inflamed tissue in IBD, which can theoretically increase the risk of diarrhea in IBD patients with COVID-19.[8]

It is unclear whether the factors mentioned above play a role alone or in combination in causing diarrhea in COVID-19 patients. However, these mechanisms can, at least in part, explain the reason for negative stool RNA testing in cases of diarrhea. Future studies are needed with a strict definition of diarrhea in COVID-19 to understand its pathogenesis and role in the feco-oral transmission.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We appreciate the thoughtful comments of Perisetti and colleagues. In line with our article they support our hypothesis that diarrhea in patients with coronavirus disease 2019 (COVID-19) may be related not only to the activity of the new coronavirus but also to the drugs used for its treatment as antibiotics and antivirals. Interestingly, they add that even the cytokine storm generated by COVID-19 may play a role in diarrhea etiopathogenesis by influencing the gut-brain axis and causing increased intestinal permeability.[1] If this theory is confirmed, the use of biological drugs such as tumor necrosis factor inhibitors, which selectively block a proinflammatory cytokine and small molecules such as JAK inhibitors, that target entire inflammatory pathways could represent a possible therapeutic option. Two case reports have previously described cases of COVID-19 patients with inflammatory bowel diseases successfully treated with anti–tumor necrosis factor drug[2] or JAK inhibitor,[3] but the impact of these therapies on diarrhea has not yet been investigated.

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Conflicts of interest
These authors disclose the following: S. Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor. L. Peyrin-Biroulet has served as a speaker, consultant, and advisory board member for Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, and Theravance. The remaining author discloses no conflicts.

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Clinical Outcomes of COVID-19 Patients With Chronic Hepatitis B Virus Infection Still Need To Be Explored

Dear Editor:

We read with great interest the study by Zou et al.[1] Their results are interesting and important, but we do have some concerns about them.

In this study, the authors found that liver injury in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and chronic hepatitis B virus (HBV) coinfection was associated with severe illness and an overall poor prognosis. However, these results are built on a single cohort, meaning that coronavirus disease 2019 (COVID-19) patients with HBV coinfection have not