
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.

Furthermore, with the growing spread of COVID-19 infection, concerns should raise on how to guarantee safety for Endoscopy operators. Undetected cases (asymptomatic patients or during the latency period) could undergo endoscopy for many indications. Currently, local authorities from a high-incidence area in Italy recommend the use of extraordinary personal protective equipment only for microaerosol-generating procedures, including esophagogastroduodenoscopy. However, unrecognized exposure to potentially infectious biologic samples during endoscopy is well-documented;[5,6] thus, the presence of SARS-CoV-2 RNA in stools, as found in the present study, could lead to a not negligible risk of transmission also for colonoscopy in endemic areas, especially in absence of additional protection measures. Dedicated personal protective equipment should be provided to all clinical staff.

In conclusion, evidence on fecal–oral contagion by SARS-COV-2 is growing. Stepping up infection control measures both among the general population to avoid fecal–oral transmission, and the health care workers operating in the endoscopy room, would be highly desirable.

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# Why Does SARS-CoV-2 Invade the Gastrointestinal Epithelium?

Dear Editors:

In patients with coronavirus disease-29 (COVID-19), stool samples may persistently test positive, even when the respiratory sample is negative for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. This phenomenon cannot be explained by the temporary gastrointestinal transit of swallowed saliva that contains the virus. Clues to solving this enigma were evident in a study performed by Xiao et al.[1] Gastrointestinal endoscopy was performed on patients who were diagnosed as positive for SARS-CoV-2 in stool samples, and biopsy samples were taken from the esophagus, gastric tissue, duodenum, and colon for histopathologic and immunofluorescent staining. The mucous epithelium of the esophagus, stomach, duodenum, and rectum showed no significant damage with hematoxylin and eosin staining; however, viral host receptor angiotensin-converting enzyme-2 and viral nucleocapsid protein–stained positive, mainly in the cytoplasm of gastrointestinal epithelial cells in the stomach, duodenum, and rectum. These results suggest that the SARS-CoV-2 virus may invade the mucosal cells of the stomach and the small and large intestines, multiply, and produce infectious virions.

There are 2 key findings in this study. The first is the surprising fact that coronaviruses are present in the highly acidic gastric epithelium—the spike protein of SARS-CoV-19 can mediate fusion with the host cell at a neutral pH. SARS-CoV-19 is completely inactivated by highly acidic conditions (pH 1–3) at 37°C, but moderate variations of pH conditions from 5 to 9 had little effect on virus titer, regardless of the temperature (from 4°C to 37°C).[2] In other words, for the SARS-CoV-2 virus to invade epithelial cells without being inactivated in the stomach, the gastric pH must be neutral.

The second important finding is that patients who tested positive on respiratory specimens but tested negative on the stool were, on average, 36 years old [(43 years × 73 cases – 49 years × 39 cases)/(73 – 39 cases) = 36 years]. The average age of the virus-positive population in stool samples was 49 years, suggesting that aging is involved in the ease of virus invasion. Age-related increases in gastric pH can be explained by atrophic gastritis (AG) and gastric intestinal metaplasia owing to *Helicobacter pylori* infection. In China and many other countries, the likelihood of having AG and intestinal metaplasia increases with age.[3] In the stomachs of patients with intestinal metaplasia and/or AG, the pH of the surface of the gastric mucosa increase to $\geq$3,[4] and for elderly AG, the pH found is 5–7.[5] Based on these data, in the stomachs of elderly people with advanced chronic gastritis, it is presumed that the SARS-CoV-2 virus is not inactivated by stomach acid, but instead enters the epithelial cells of the stomach, and further invades the epithelial cells of the small and large intestines.

If this hypothesis is correct, an individual with a history of *H pylori* infection may be susceptible to fecal–oral infection. In the report from China, blood group A had a significantly higher risk for COVID-19 compared with non-A blood groups, whereas blood group O had a significantly lower risk for the infectious disease compared with non-O blood groups.[6] According to >2000 case-control studies in Japan, blood group A is susceptible to *H pylori* infection and AG.[7] Similarly, in Chinese case-control studies, the proportion of *H pylori* infection in blood group A individuals was significantly higher than that of non-A blood groups.[8] These findings indicate that, for individuals with blood group A, the route of viral transmission is likely to include the risk of gastrointestinal infections, in addition to those of the respiratory tract. There are also concerns that users of

drugs such as proton pump inhibitors or potassium-competitive acid blockers for treating gastroesophageal reflux disease—regardless of whether they have blood type A, chronic gastritis, or *H pylori* infection—may be similarly at risk.

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# Gastrointestinal ACE2, COVID-19 and IBD: Opportunity in the Face of Tragedy?

Dear Editors:

We read with interest the articles by Xiao et al[1] and Du et al[2] regarding severe acute respiratory syndrome coronavirus-2 (SARS Co-V 2) shedding in feces, staining of viral nucleocapsid protein in the cytoplasm of gastrointestinal epithelial cells, and the characterization of angiotensin-converting enzyme 2 (ACE2) receptors across tissues in the human body. The relationship between coronavirus disease 2019 (COVID-19), intestinal ACE2 expression, and gastrointestinal symptoms is worth exploring further, and may offer unique clues to the pathogenesis of intestinal inflammation.

We have previously characterized multiple components of the renin–angiotensin system (RAS) in the terminal ileum and colon in patients with and without inflammatory bowel disease (IBD).[3] Notably, all of the components of the classical and alternative RAS were expressed in the mucosa, demonstrating the presence of a locally active intestinal RAS. In particular, ACE2 was localized by immunohistochemistry to the brush border and epithelium, and ACE2 messenger RNA expression was 10-fold higher, and ACE2 activity 7- to 10-fold higher, in terminal ileal biopsies when compared to colonic biopsies in patients without IBD.[3] ACE2 activity was lower in inflamed colonic biopsies than non-inflamed biopsies from patients with IBD, and angiotensin (Ang) 1–7 immunohistochemical staining intensity was lower in colonic biopsies from patients with IBD when compared with healthy controls. Ang 1–7 has been shown to exert anti-inflammatory, antifibrotic, and antiproliferative actions in various tissues, and decreased myofibroblast proliferation and collagen secretion in cultured colonic myofibroblasts.[3] ACE2 knockout mice had increased susceptibility to colitis and an altered microbiota profile, which was associated with higher colonic Ang II levels, the putative peptide of the classical RAS pathway that exerts proinflammatory and profibrotic effects.[4] Plasma ACE2 activity was higher in patients with IBD, especially Crohn's disease, than non-IBD controls, perhaps representing a compensatory mechanism.[5]

Intestinal ACE2 is also required for absorption of tryptophan, an essential amino acid required for niacin production. Pellagra, caused by the deficiency of niacin (vitamin $B_3$), is characterized by intestinal inflammation and protein malnutrition.[4] Serum tryptophan levels were lower in patients with IBD, especially Crohn's disease, than controls without IBD.[6]

SARS-CoV-2, which, like the original SARS-CoV of earlier this century, infects humans via its spike proteins binding to ACE2 on mucosal membranes.[7] Multiple mucosal surfaces express ACE2, including alveoli, esophagus, stomach, small bowel, and colon. The original transmission of COVID-19 from an animal reservoir to human, initially described in Wuhan, China, likely occurred by the oral route, perhaps mediated via intestinal ACE2.[1,7] SARS-CoV was shown to induce shedding of the ACE2 ectodomain following cellular entry, dependent on tumor necrosis factor (TNF)-$\alpha$ converting enzyme production.[8] This was also associated with increased TNF-$\alpha$ production and tissue damage.[8]

Conceivably, if SARS-CoV2 also induces reduction of mucosal ACE2 after entry, intestinal inflammation may result via multiple mechanisms: elevated Ang II, reduced Ang 1–7 levels, increased TNF-$\alpha$, and tryptophan deficiency. Gastrointestinal symptoms, including diarrhea, occur in approximately 4%–20% of patients with COVID-19, and severe colitis has recently been described. Hence, multiple potential targets for therapy for COVID-19, and intestinal inflammation in IBD, may result from further investigation of these pathways.

In our studies, we have additionally analyzed whether conventional therapies for IBD were associated with altered intestinal mucosal ACE2 expression. No association between steroids, mesalamine, thiopurines, or anti–TNF-$\alpha$ medication use and terminal ileal or colonic ACE2 messenger RNA expression, ACE2 activity, or ACE2 immunohistochemical staining intensity was noted (Supplementary Figure 1). Furthermore, no effect of these drugs on plasma ACE2 activity was noted (Supplementary Figure 2). Whether the use of these drugs alters the risk of acquiring COVID-19, or developing gastrointestinal symptoms or other complications, remains to be elicited, as data are acquired in an international registry.