Progress on Gastrointestinal Symptoms, Treatment and Protection in COVID-19 Patients

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Abstract

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induced a worldwide pandemic. The main clinical manifestations of COVID-19 patients have been fever, cough, dyspnea, and other respiratory symptoms. However, some patients’ initial symptoms have been nausea, vomiting, diarrhea and other gastrointestinal symptoms, and SARS-CoV-2 RNA could be found in their stool samples. Studies have shown that the gastrointestinal tract highly-expressed angiotensin-converting enzyme 2 is used by SARS-CoV-2 to enter cells. Therefore, exploring the damage caused by SARS-CoV-2 to the gastrointestinal tract and whether it could replicate in the gastrointestinal tract and transmit through fecal-oral route has significance for the diagnosis, treatment and prevention of COVID-19. We combined the current clinical data about COVID-19 patients with gastrointestinal symptoms as well as its pathogenic mechanism and prevention methods herein to review the relationship between the disease and gastrointestinal symptoms.

Introduction

As of 20 April 2020, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected more than 22,256,220 people worldwide and killed more than 782,456. The disease caused by SARS-CoV-2 was named coronavirus disease 2019 (COVID-19) by the World Health Organization.1 Scientists have divided the coronaviruses into four groups, namely alpha, beta, gamma, and delta.2 SARS-CoV-2 and Middle East respiratory syndrome coronavirus (MERS-CoV) are beta-coronaviruses. SARS-CoV-2 spreads the fastest among them, and its reproduction number (R0) was estimated at 3.7,3 which meant that with no external intervention and immunity, an average of 5.71 humans would become infected by SARS-CoV-2. The up-to-date guideline noted the infection source of COVID-19 to be mainly patients infected by SARS-CoV-2 and having asymptomatic infections; in addition to the common respiratory droplets and close contact transmission routes, we should pay attention to the fact that SARS-CoV-2 can be detected in feces and urine, and environmental pollution caused by human excrement can result in the spread of this virus and disease.4 The World Health Organization proclaimed that COVID-19 was a Public Health Emergency of International Concern,5 and it became recognized as a major threat to public health around the world.

SARS-CoV-2 infects organs by combining with the angiotensin-converting enzyme 2 (ACE2) receptor on a cell expressing its ligand. SARS-CoV-V2 has the same cell entry receptor ACE2 as SARS-CoV-6 Li et al.7 analyzed the expression of ACE2 using datasets from the Genotype-Tissue Expression (GTEx) project and showed that ACE2 was expressed highest in the small intestine, testis, kidneys and heart, lowest in the blood, spleen, bone marrow, brain, blood vessels and muscle, and medium in the lungs, colon, liver and bladder (Fig. 1). Thus, COVID-19 patients’ clinical manifestations can vary from asymptomatic to multiorgan and systemic dysfunctions. The overall damage mechanism can be summarized as direct damage caused by the virus and a variety of indirect damage mechanisms, including immune-mediated damage, hypoxia, in-
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Inflammatory factor storm, abnormal blood coagulation, and so on.9-11

The main clinical manifestations of COVID-19 patients have been fever, cough, dyspnea, and other respiratory symptoms. However, a study pointed out many patients presenting with nausea, vomiting, diarrhea and other gastrointestinal symptoms as the initial symptoms.12 Viral protein has been detected in the gastrointestinal epithelium,13 and SARS-CoV-2 RNA has been detected in stool samples of infected patients.14,15 These results suggested gastrointestinal cells as potential targets of SARS-CoV-2 and the potential for virus replication in such.

Although SARS-CoV-2 can cause damage to multiple organs, given the existence of a majority of patients with atypical gastrointestinal symptoms and the possibility of a fecal-oral transmission route, our study reviewed the clinical manifestations in the gastrointestinal tract, mechanisms and treatment of gastrointestinal tract injury, and protection measures based on the studies of COVID-19 to date.

Gastrointestinal symptoms

Gastrointestinal symptoms might be the single manifestation of COVID-19 patients, and a majority of patients infected by SARS-CoV-2 have been admitted to the gastroenterology department.16 If physicians do not pay enough attention to these patients, it might lead to delayed diagnosis and inadequate management of infected patients. About 10% of patients develop diarrhea and nausea 1–2 days before the onset of fever and respiratory symptoms.17 A study by Wang et al.17 supported the possibility that diarrhea might be an earlier clinical symptom of the COVID-19 patient, possibly prior to fever or respiratory symptoms. What is more, with the progression of the disease, the gastrointestinal symptoms’ occurrence rate also increases.18 The definition of diarrhea was 3 or more loose/liquid stools per day or an increase in the number of evacuations compared with the usual.19 The incidence rate of gastrointestinal symptoms in COVID-19 patients has varied in different studies, which reflects that clinical workers paid different degree of attention to COVID-19 patients’ gastrointestinal symptoms. A study including 140 COVID-19 patients in Wuhan showed that gastrointestinal symptoms were found in up to 39.6% of these patients, nausea in 24 (17.3%), diarrhea in 18 (12.9%), and vomiting in 7 (5.0%).20 Among 74 COVID-19 patients with gastrointestinal symptoms in the Zhejiang province, 53 (71.6%) had the symptom of diarrhea only, 11 (14.9%) only had vomiting and 10 (13.5%) only had nausea.21 Our previous meta-analysis collected 10 articles and included 1994 COVID-19 patients, and showed that 95 (4.8%) and 78 (3.9%) patients had diarrhea or nausea and vomiting, respectively.22 A study that collected data of 1,099 patients reported nausea or vomiting in 55 (5.0%) and diarrhea in 42 (3.8%).23 A meta-analysis comprising 13,251 patients showed that the most common gastrointestinal symptoms were anorexia (10.2%), diarrhea (8.4%), and nausea (5.7%).24 Another meta-analysis containing 4,243 patients from China, Singapore, South Korea, United Kingdom, and United States also showed that 17.6% had gastrointestinal symptoms, anorexia in 26.8%, diarrhea in 12.5%, nausea and vomiting in 10.2%, and abdominal pain or discomfort in 9.2%.25 The frequencies of diarrhea have varied from 2.0% to 10.1% and nausea and/or vomiting varied from 1.0% to 10.1% in different studies.8,26-28

Fecal-oral transmission

Wang et al.29 found infectious virions of SARS-CoV-2 in feces, and Amirian et al.30 detected the viral RNA in feces and sewage. During the 2003 outbreak, the Xiao Tang Shan Hospital and 309th Hospital of PLA first reported SARS-CoV RNA in wastewater.31 The first confirmed COVID-19 patient in the United States was on January 20, 2020, and had nausea and vomiting, with stool and respiratory specimens being positive for SARS-CoV-2 by real-time reverse transcriptase polymerase chain reaction.15 Hospitals in China also reported a number of COVID-19 patients positive for SARS-CoV-2 in fecal virus tests.32-34 At the same time, studies showed that COVID-19 patients could remain positive (via fecal virus test) after respiratory symptoms disappeared and negative throat swab test was obtained.14 The study of Öng et al.35 showed that samples from a COVID-19 patient with confirmed fecal positivity and no diarrhea, taken from the surface of the toilet bowl, inside bowl...
of the sink and the door handle, were positive for SARS-CoV-2, while post-cleaning samples were negative. Cheung et al. proved that viable virus existed for at least 3 hours in aerosols after their formation, and for up to 2 or 3 days on plastic and stainless steel surfaces. Based on the high viral infectivity of SARS-CoV-2, one study found that exposure to a fecal–polluted environment might cause “fecal-aerosol-respiratory transmission”. All of these facts suggest that, apart from the classic respiratory droplets and close contact transmission of the virus, we should not ignore the “fecaloral” and “fecal-aerosol-respiratory” transmission routes. Preventing the spread of diseases, we should cut off such.

Possible mechanisms of gastrointestinal injury

ACE2 is the receptor used by SARS-CoV to enter host cells. Genome sequencing test indicated that SARS-CoV-2 shared 79.6% sequence identity to SARS-CoV; moreover, the sequences encode and express the spike glycoproteins which can combine with the entry receptor ACE2 to help these viruses enter human cells. The spike protein is a ligand on the SARS-CoV-2 surface that can combine with ACE-2. Many research studies have provided evidence to support that ACE2 is the same cell entry receptor for the spike protein of SARS-CoV-2 and SARS-CoV and its mRNA and protein are highly expressed in lung and the small intestinal enterocytes but not in the goblet cells or intestinal immune cells. Gut cells in contact with food and foreign pathogens directly highly express ACE2 on the surface in the digestive tract, which might lead to inflammation susceptibility and gastrointestinal symptoms. ACE2 expression on the surface cells of the small intestine might mediate the invasion of the virus and amplification of the activation of gastrointestinal inflammation, which might be a possible mechanism of digestive symptoms in COVID-19 patients and explain the presence of the virus in patients’ stool samples.

A study showed that ACE2 played a significant role in amino acid homeostasis and in maintaining the intestinal microbiota. The ACE2 knockout mouse model showed a decline in the uptake of tryptophan, which resulted in decreasing the expression of antimicrobial peptides from small intestinal Paneth cells, changes in the intestinal microbiota, and ultimately in a high sensitivity to colitis, but all of those disturbances were restored by tryptophan supplementation. This might further explain the diarrhea observed in COVID-19 patients.

Another possible explanation for diarrhea in COVID-19 patients is an intestinal flora disturbance. A prospective, randomized, controlled study investigated changes in the fecal microbiota in COVID-19 patients. The authors compared microbiome data between 15 COVID-19 patients, 6 subjects with community-acquired pneumonia, and 15 healthy individuals (controls). At the time of hospitalization and at all timepoints during hospitalization, patients with COVID-19 had significant alterations in fecal microbiomes compared with controls, and characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals. Depleted symbionts and gut dysbiosis persisted even after clearance of SARS-CoV-2 (throat swab-negative) and resolution of respiratory symptoms.

Treatment and protection

There has been no exact evidence on the efficacy of drugs in the therapy of gastrointestinal symptoms that caused by SARS-CoV-2. Reviewing relative studies, we have summarized here potential therapies, for which safety and efficiency need more clinical study to confirm.

Studies have suggested that the use of ACE2 inhibitors might reduce direct damage to the gastrointestinal tract caused by coronavirus. Hashimoto et al. reported that ACE2 inhibitors could reduce the inflammatory state of mouse intestinal tract, and ACE2 might be a key target for the treatment of COVID-19. In the diagnosis and treatment scheme of COVID-19, chloroquine was included in the therapeutic drug category. Similar to chloroquine, azathioprine was an immunosuppressant and could inhibit vaccinia virus in vitro. Screening by bioinformatics suggested that azathioprine might be a potential ACE2 inhibitor. Directly binding to ACE2 or the coronavirus’ spike glycoproteins could directly prevent invasion of the virus. Clinical trials of recombinant human ACE2 inhibitors are currently underway and have shown efficacy in animal studies.

ACE inhibitor/angiotensin receptor blocker (ACEI/ARB) is an antagonist of the renin-angiotensin-aldosterone system. Compared with non-ACEI/ARB patients, patients who were in the ACEI/ARB group had a significantly lower risk of gastrointestinal symptoms and abnormal liver function throughout the disease course.

Zhang et al. reported that ACEI/ARB could upregulate ACE2 expression, which might increase the entry of SARS-CoV-2. Thus, more clinical data are needed to confirm the efficacy of ACEI/ARB in COVID-19 patients.

Direct viral injury or drug use could cause intestinal flora disorders, which could also result in gastrointestinal symptoms. Gut dysbiosis can interfere with distant disorders as well as with gut–lung axis; lung inflammation can also affect the gut microbiota. Zuo et al. demonstrated that Bacteroides species might have a potential protective role in combating SARS-CoV-2 infection by hampering host entry through ACE2 but that Erysipelotrichaceae might augment SARS-CoV-2 infection in the host gut. Therefore, probiotics might be another good option for the treatment of COVID-19.

Patients with inflammatory bowel disease and other autoimmune diseases are considered a high-risk group for COVID-19, as they are more likely to make immune-suppressive or immune-modulatory treatment. For these patients, the use of biologicals have been suggested to modulate the immune system, such as Bactyctinib, a JAK inhibitor, which can reduce the viral passage into the host cell and reduce inflammatory.

Zhou et al. reported that, in symptomatic and asymptomatic patients, nasal swabs yielded higher viral loads than throat swabs. Campione et al. reported that lactoferrin could reduce infection and inflammation, acting as the barrier of both respiratory and intestinal mucosa or reverting the iron disorders caused by the viral colonization, which could be used in asymptomatic or mildly symptomatic patients.

We believe that more attention should be paid to the gastrointestinal symptoms of COVID-19 patients. Ignoring the atypical clinical manifestations of COVID-19 patients might lead to more infection of people and exacerbate the epidemic. Patients with diarrhea were usually treated in the gastroenterology department. If the outpatient physicians were not sufficiently vigilant about the gastrointestinal symptoms of COVID-19 patients, especially before the onset of fever and respiratory symptoms, it will inevitably increase the infection rate among medical workers. On the other hand, gastroenterology endoscopy staff should pay more attention to such patients, for they are more likely to make physical contact with infected patients’ gastric or intestinal fluids and feces during care, such as surgery. Therefore, clinicians and not only doctors working in fever and respiratory clinics should raise their awareness of protecting themselves, treat all suspected patients as confirmed cases, and take strict protective measures. Clinicians should wear standard protective clothing, investigate all patients’ and their relatives’ epidemiological history, collect their body fluid samples.
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(nasopharyngeal swabs, feces, blood, etc.) for etiological testing by means that will minimize their own risk of infection, and wash hands or change clothes after each physician examination. After endoscopic surgery, all used endoscopes and the endoscopy room itself must undergo standardized disinfection. For patients who were cured and returned home, some of them could still test positive for SARS-CoV-2 RNA in feces, although their nucleic acid tests are negative by throat swab. We believe that feces might be a potential route to transmit SARS-CoV-2. Therefore, we recommended that patients discharged from the hospital who met the clinical cure standard should still pay strict attention to hand hygiene, disinfecting public toilets and sinks thoroughly, and avoiding sharing toilets with others. If permitting, we recommend fecal nucleic acid detection before discharge of any COVID-19 patient.

Future directions

COVID-19 is a common enemy to all mankind in the 21st century. Further research studies are needed to reveal the specific mechanism of gastrointestinal injury and the effective and safe treatment measures. In order to effectively prevent and treat the disease, find the source of infection early, and cut off the possible transmission routes, it is important to pay attention to the gastrointestinal manifestations and fecal-oral transmission of SARS-CoV-2. Physicians, especially gastroenterologists, should be highly vigilant, make definitive diagnosis as soon as possible, and take care of themselves. In terms of disease treatment, further clinical studies are needed to clarify the efficacy and safety of ACEI/ARB. It is necessary to further research other receptors by which viruses can invade host cells, in order to guide clinical targeted therapy. In addition, the intestinal flora is the second genome of the human body and participates in immune regulation. It is necessary to clarify the efficacy and safety of probiotic therapy for the treatment of COVID-19 patients.

Conclusions

Although we do not know the exact source of the virus in the digestive system yet, we believe that fecal-oral transmission is possible. In clinical work, we should pay attention to atypical gastrointestinal symptoms and treat these patients actively and effectively. We should also adapt to research ACE2 inhibitors and probiotics for the treatment of COVID-19. In addition, we recommend taking early measures to prevent the spread of COVID-19 in hospitals and communities.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

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