

World Journal of *Gastroenterology*

World J Gastroenterol 2021 April 14; 27(14): 1362-1523



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Editorial Board Member of *World Journal of Gastroenterology*, Takuya Watanabe, MD, PhD, Director, Department of Internal Medicine and Gastroenterology, Watanabe Internal Medicine Aoyama Clinic, Aoyama 1-2-21, Nishi-ku, Niigata 950-2002, Japan, nabetaku@dia-net.ne.jp

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INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Lin; Production Department Director: Yun-Xiaoqian Wu; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

April 14, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/gerinfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

COVID-19 and the gastrointestinal tract: Source of infection or merely a target of the inflammatory process following SARS-CoV-2 infection?

Jacopo Troisi, Giorgia Venutolo, Meritxell Pujolassos Tanyà, Matteo Delli Carri, Annamaria Landolfi, Alessio Fasano

ORCID number: Jacopo Troisi 0000-0003-2962-7379; Giorgia Venutolo 0000-0001-8396-9412; Meritxell Pujolassos Tanyà 0000-0003-0313-3506; Matteo Delli Carri 0000-0002-1921-1516; Annamaria Landolfi 0000-0002-4975-4722; Alessio Fasano 0000-0002-2134-0261.

Author contributions: Troisi J, Venutolo G and Landolfi A collected and analyzed the data; Troisi J, Venutolo G, Pujolassos Tanyà M, Delli Carri M and Fasano A wrote the manuscript; Fasano A and Landolfi A edited the manuscript; All the authors approved the final version.

Conflict-of-interest statement:

Authors declare that there are no conflicts of interest.

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Jacopo Troisi, Meritxell Pujolassos Tanyà, Matteo Delli Carri, Metabolomics Section, Theoreo srl - Spin-off Company of the University of Salerno, Montecorvino Pugliano 84090, SA, Italy

Jacopo Troisi, Matteo Delli Carri, Department of Chemistry and Biology "A. Zambelli", University of Salerno, Fisciano 84084, SA, Italy

Jacopo Troisi, Giorgia Venutolo, Alessio Fasano, European Biomedical Research Institute of Salerno, Salerno 84125, SA, Italy

Annamaria Landolfi, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi 84081, SA, Italy

Alessio Fasano, Mucosal Immunology and Biology Research Center and Center for Celiac Research, Harvard Medical School, Massachusetts Gen Hosp Children, Mucosal Immunology and Biology Research Center, Boston, MA 02114, United States

Corresponding author: Jacopo Troisi, MBBS, MSc, Professor, Metabolomics Section, Theoreo srl - Spin-off Company of the University of Salerno, Via degli Ulivi, 3, Montecorvino Pugliano 84090, SA, Italy. troisi@theoreosrl.com

Abstract

Gastrointestinal (GI) symptoms have been described in a conspicuous percentage of coronavirus disease 2019 (COVID-19) patients. This clinical evidence is supported by the detection of viral RNA in stool, which also supports the hypothesis of a possible fecal-oral transmission route. The involvement of GI tract in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is corroborated by the theoretical assumption that angiotensin converting enzyme 2, which is a SARS-CoV-2 target receptor, is present along the GI tract. Studies have pointed out that gut dysbiosis may occur in COVID-19 patients, with a possible correlation with disease severity and with complications such as multisystem inflammatory syndrome in children. However, the question to be addressed is whether dysbiosis is a consequence or a contributing cause of SARS-CoV-2 infection. In such a scenario, pharmacological therapies aimed at decreasing GI permeability may be beneficial for COVID-19 patients. Considering the possibility of a fecal-oral transmission route, water and environmental sanitation play a

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 1, 2021

Peer-review started: February 1, 2021

First decision: February 27, 2021

Revised: March 13, 2021

Accepted: March 19, 2021

Article in press: March 19, 2021

Published online: April 14, 2021

P-Reviewer: Merrett ND

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Wang LL



crucial role for COVID-19 containment, especially in developing countries.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal symptoms; Gut microbiome; Dysbiosis; Zonulin; Fecal-oral transmission

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Core Tip: Coronavirus disease 2019 (COVID-19) patients may suffer from gastrointestinal symptoms that are associated with gastrointestinal dysbiosis. Even though the exact role of gut microbiome perturbation as either a cause or a consequence of the disease is still to be elucidated, pharmacological interventions aimed at containing intestinal permeability may be of support in COVID-19 patients.

Citation: Troisi J, Venutolo G, Pujolassos Tanyà M, Delli Carri M, Landolfi A, Fasano A. COVID-19 and the gastrointestinal tract: Source of infection or merely a target of the inflammatory process following SARS-CoV-2 infection? *World J Gastroenterol* 2021; 27(14): 1406-1418

URL: <https://www.wjnet.com/1007-9327/full/v27/i14/1406.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i14.1406>

INTRODUCTION

In December 2019, in Wuhan, one of the largest cities in the Chinese province of Hubei, a new coronavirus appeared that was responsible for a pneumonia epidemic that was named by the World Health Organization (WHO) on February 11, 2020 as coronavirus disease 2019 (COVID-19), and declared as a dangerous threat to public health and an international health emergency^[1,2]. Indeed, COVID-19 infections rapidly spread and was declared a pandemic by the WHO one month later on March 11, 2020. In a short time, the pandemic involved all continents, and at the time of writing this review, accounts for more than 100 million confirmed cases worldwide, also becoming a serious threat to the global economy^[3,4].

At the beginning of January 2020, the new coronavirus responsible for this pandemic was named "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" by the International Committee on Taxonomy of Viruses^[5]. It is a single-stranded RNA virus with positive polarity and is closely related to the B-line of beta-coronaviruses, which are typically responsible for severe and lethal respiratory syndromes^[2,6]. Phylogenetic analysis showed that the viral sequence of this new coronavirus has a strong similarity (89%) with two other coronaviruses similar to SARS and deriving from bats, namely bat-SL-CoVZC45 (GenBank access n. MG772933.1) and bat-SL-CoVZXC21 (GenBank access n. MG772934.1). Similarities were also found with SARS-CoV, the virus that caused the SARS pandemic in 2002/2003, and the Middle East Respiratory Syndrome (MERS-CoV) pandemic of 2012, with which SARS-CoV-2, shares sequence homologies (79% with SARS-CoV and 50% with MERS-CoV)^[7-9] as well as zoonotic transmission and several clinical features.

MECHANISM OF INFECTION

Studies carried out so far suggest that the human angiotensin converting enzyme 2 (ACE2) is the main target receptor for the virus to gain access into human host cells. Binding occurs between the ACE2 binding domain located at the C-terminal end of the viral spike protein and the ACE2 target receptor located on the surface of the host cell membrane^[10]. After binding to ACE2 receptors on human cells^[11], the SARS-CoV-2 spike protein is cleaved by two mucosa-specific serine proteases, namely TMPRSS2 and TMPRSS4, to facilitate viral cellular infection^[12].

Tissues with the highest expression of ACE2, and therefore a high sensitivity to infection are present in both the respiratory and the gastrointestinal (GI) tracts. The receptor is present in the pulmonary epithelium, in type 2 pneumocytes that are present in the alveoli where the exchange between oxygen and carbon dioxide takes

place, in the nose, mouth, stratified epithelial cells in the upper esophagus, and absorbent enterocytes of the ileum and colon. Other receptors that are known to allow entry of SARS-CoV-2 are DC-SIGN (CD209), CD147 and L-SIGN (CD209L)^[13-15]. Transmission of the virus can take place through direct contact with respiratory droplets from infected subjects or indirectly from contaminated objects and surfaces^[16].

CLINICAL SYMPTOMS

Clinical manifestations associated with COVID-19 infection range from complete absence of symptoms (asymptomatic subjects) to serious and even fatal infections. In most cases, the disease is mild to moderate, so that symptoms can be managed safely at home without the need for hospitalization. The main target of the infection is the respiratory tract, and therefore, the clinical manifestations associated with the disease are mostly respiratory. The most common symptoms are similar to those of seasonal flu and include fever, dry cough, dyspnea, sore throat, headache, muscle aches, and asthenia. Severe respiratory distress, chest pain, pneumonia, and pulmonary insufficiency can also be found in severe cases^[17-19]. In SARS-CoV-2 pneumonia, lung computed tomography scans shows bilateral, subpleural ground-glass opacity lesions^[20-22]. In addition to pulmonary clinical manifestations, heart damage can also occur in infected patients. Shi *et al*^[23] in a study conducted in Wuhan on 400 patients, found that about one-fifth experienced heart disease as a risk factor for worse outcome. Heart damage essentially consists of sudden and severe myocardial inflammation leading to heart failure and arrhythmias^[24]. For this reason, hypertensive patients, and in general all individuals with a positive history of cardiovascular disease, are more at risk of experiencing a poor prognosis than other patients^[25]. SARS-CoV-2 can also damage the central nervous system, with symptoms that range from mild (anosmia, dysgeusia) to severe (viral encephalitis). Moreover, COVID-19 infection, like other pulmonary infectious diseases, may represent a risk factor for acute cerebrovascular events. The observed D-dimer elevation in COVID-19 patients may indicate additional risk of cerebrovascular events^[26]. Kidney and liver damage have also been reported. Proteinuria, hematuria, increased aspartate transaminase (AST, also known as aspartate aminotransferase or glutamic oxaloacetic transaminase), alanine aminotransferase (ALT, also known as alanine transaminase or glutamic-pyruvic transaminase), and bilirubin have been found in about half of infected patients^[27,28].

The virulence of microorganisms determines the damage to host cells before the microorganisms are cleared by host immunity^[29]. Yet, the virulence of the infective microorganism does not fully account for the virulence of the disease, the majority of which results from inflammation produced by the immune response^[29]. That has been demonstrated for many infective diseases and is particularly true for SARS-CoV-2. Most viral and bacterial infections in humans are self-limiting^[29,30], and infecting microorganisms become commensal if they can coexist with the human host. The SARS-CoV-2 virus infection is no different^[31], and that could explain why most COVID-19 cases are asymptomatic or mild.

COVID-19 AND THE GI TRACT

Although, as reported, SARS-CoV-2 infection mainly affects the respiratory system^[32], leading to breathing difficulties, dry cough, and nasal congestion to respiratory failure, this novel coronavirus can be found in the GI tract as well^[33]. Furthermore, SARS-CoV-2 RNA has been isolated from stools. Viral nucleocapsid protein can be observed in duodenal and rectal glandular epithelial cells by laser scanning confocal microscopy. The available results provide evidence of the activity of this virus in the GI tract^[34].

GI SYMPTOMATOLOGY

GI symptoms are present in approximately 50% of COVID-19 patients, consisting mainly of diarrhea, nausea, vomiting, and abdominal discomfort^[35]. Moreover, several studies have shown that SARS-CoV-2 is able to interact with ACE2 receptors on ileal enterocytes and colon epithelial cells, so that a tropism for the GI tract has been hypothesized as well^[27,36]. Further evidence supporting the possibility that both the

small and large intestines may be susceptible to SARS-CoV-2 infection, was the isolation of viral RNA from the GI epithelium and staining of the viral nucleocapsid protein in these cells^[34]. In addition, viral RNA was also isolated in stool samples from COVID-19 patients, and it was presumed that the viral components originated from infected enterocytes^[34,36]. Considering the overall evidence, several reports have expressed concerns of possible fecal-oral transmission of SARS-CoV-2^[37,38]. Nevertheless, the findings were not unexpected as other well-known coronaviruses, including those causing the MERS and SARS epidemics, have shown to infect enterocytes, leading to several GI symptoms^[39].

Several reports have focused on the GI symptomatology in COVID-19 patients, underlining clinical outcomes that varied widely in terms of frequency. Nine of those studies that included a total of 4177 patients found that the incidence of GI symptoms varied from 4.9% to 61.3%. The most frequent symptoms were diarrhea (8.4%) and lack of appetite (7.4%); 4.1% of patients complained about nausea-related disorders, while vomiting was reported in 2.4% and abdominal pain in 1.7% of the cases^[40-48]. Interestingly, the frequency of diarrhea, nausea, and abdominal pain in COVID-19 patients was shown to be higher among women than men^[49]. Finally, Yang *et al*^[50] examined 50 COVID-19 patients by dividing them in two groups by the presence of either initial pulmonary or initial GI symptoms. They found that patients with GI manifestations as initial symptoms had more severe clinical outcomes, leading to longer hospitalization.

As stated above, and similar to SARS-CoV-1, SARS-CoV-2 infection is mediated by ACE2, which allows the virus to enter the cells and replicate by taking advantage of the host synthesis apparatus^[51]. A recent study has shown that the binding affinity of the spike protein of SARS-CoV-2 is about 10-20 times higher than that of SARS-CoV-1^[52]. ACE2 receptors are widely expressed in the epithelia of both the respiratory and GI tracts. A recent multiomic *in vitro* study has shown that expression of these membrane enzymes is higher in intestinal cell lines than lung cell lines^[53].

The pathophysiology of GI symptoms is not entirely clear, but it seems that they originate as a result of several phenomena. ACE2 performs an essential function in the intestine by regulating amino acid homeostasis and microbiome balance^[53]. It is possible that the binding of SARS-CoV-2 to these membrane receptors reduces their availability, giving rise to an alteration of physiological function that induces a dysbiosis that leads to diarrhea, one of the most frequent symptoms reported during SARS-CoV2 infection^[54]. The development of a cytokine storm could be indeed the cause of damage to the GI tract. Autopsies of SARS patients found increased expression of proinflammatory cytokines in ACE2-expressing cells compared with those that do not express this enzyme on their membranes^[55]. It is fair to think that this happens following SARS-CoV-2 infection. Inflammation could also stimulate the gut microbiota to release molecules that increase the inflammatory state of the intestine and subsequently spread from the intestine into the circulatory system to cause systemic damage with more severe consequences than the viral infection itself^[56]. In addition to locally occurring phenomena, the gut-lung axis seems to have a pivotal role in the development of GI symptoms as well. This axis represents a link between two organs that share a common mucous immune system^[57]. Its influence has been hypothesized as a result of studies that have described COVID-19 patients with GI symptoms but without SARS-CoV-2 RNA-positive stool samples^[54].

The impact of GI comorbidities on the development of symptoms in COVID-19 patients is yet to be defined. While the relationship between disorders such as diabetes, cardiovascular diseases, and hypertension and COVID-19-related severity was proven by several studies^[58]. There are not yet sufficient studies to demonstrate a causal link between the presence of previous GI conditions and the onset of COVID-19-related symptomatology.

Indeed, existing studies do not provide indisputable results. A study carried out in China found that pre-existing GI disorders represent a third comorbidity in COVID-19 patients^[59]. Another study carried out in Wuhan reported a relatively high percentage of COVID-19 patients with GI disorders^[60]. Conversely, other studies carried out in the United States^[61] and in Italy^[62] have not found a significant correlation between SARS-CoV-2 infection and the presence of inflammatory bowel disease. On the contrary, Papa *et al*^[63] observed a better clinical outcome in patients presenting with digestive comorbidities, as presumably they do not hinder the immune response against SARS-CoV-2. However, the authors point out that the number of cases observed was small^[63].

FECAL-ORAL TRANSMISSION OF SARS-COV-2

A potential fecal-oral transmission route of SARS-CoV-2, in addition to respiratory droplets, person-to-person contact, or indirect infection following contact with contaminated surfaces, has been proposed by several authors^[37,38,64,65]. The presence of common GI symptoms in the COVID-19 patients mentioned above is evidence that the GI tract is involved in SARS-CoV-2 infection.

Viral RNA has been detected in esophagus, stomach, duodenum, and rectum tissue from patients with severe SARS-CoV-2 infections^[66]. Notably, the first COVID-19 patient in the United States tested positive for SARS-CoV-2 in loose stool specimens by real-time reverse transcription polymerase chain reaction^[67]. Several studies report detection of viral RNA in stool samples in adults^[34,68-72] and children^[73-75] diagnosed with COVID-19. Interestingly, two studies confirmed that SARS-CoV-2 was detectable in fecal samples even after negative testing of respiratory swabs^[70,72], and in patients who did not present GI symptoms^[66,69,71]. In addition to SARS-CoV-2 RNA detection in stool samples, positive staining of viral nucleocapsid protein in gastric, duodenal, and rectal epithelia might demonstrate the infection of GI glandular epithelial cells^[34]. Wang *et al*^[68] found a high content of viral RNA in fecal specimens from COVID-19 patients, and electron microscopy confirmed the presence of living viral particles in those samples. Wölfel *et al*^[69] could not isolate living SARS-CoV-2 from stool samples despite the presence of high concentrations of viral RNA, but did detect cells in a few stools that contained subgenomic mRNA, which suggests active replication of the virus in the intestinal tract. The presence of viral subgenomic mRNA indicates actively infected cells because such mRNA is transcribed only in infected cells and is not found packaged into virions^[69]. As in adults, SARS-CoV-2 in children might persist in the GI tract longer than in the respiratory system. Actually, a high percentage of children diagnosed of COVID-19 tested positive on rectal or anal swabs, and some were positive after nasopharyngeal or throat swabs became negative^[73-75].

Other evidence that supports an alternative fecal-oral transmission of COVID-19 is the expression of SARS-CoV-2 entry-genes in the cells of intestinal tissues. Mucosal cells of the lower intestine can be infected by other coronaviruses, resulting in diarrhea and other enteric symptoms. In this case, SARS-CoV-2 could be carried by saliva and secretions into the digestive tract, where it would infect the ACE2-expressing enterocytes. It has been confirmed that SARS-CoV-2 can infect enterocytes present in human small intestine organoid models, which supports virus replication and a GI route of infection^[76]. However, another study demonstrated that human GI secretions were able to inactivate SARS-CoV-2, which suggests that although virus infection and pathogenesis is enhanced in the intestine, it is not clear if it would be a primary site of infection and possible route of transmission^[77]. An alternative route of transmission that acts together with the respiratory route might explain the rapid spread of disease.

GUT MICROBIOME ROLE IN COVID-19 SEVERITY

COVID-19 symptomatology is strictly related to both a physiological and an aberrant activation of immune system, leading in very severe cases to a cytokine storm^[78]. Based on this premise, it is not surprising that the gut microbiome, which is closely linked to the immune status of the host, may play a role in COVID-19 severity. A gut microbiome imbalance has been associated in COVID-19 patients with elevated concentrations of inflammatory cytokines, and blood markers, including C-reactive protein (CRP), lactate dehydrogenase, and aspartate aminotransferase^[79]. Yeoh *et al*^[79] examined blood and fecal samples from 100 young (mean age of about 36 years) confirmed positive COVID-19 patients in two Hong Kong hospitals. They also analyzed samples from patients for up to 30 days after clearance of SARS-CoV-2. All patients had slight or moderate symptomatology, with only 5% with severe and 3% with critical conditions. Compared with a group of healthy adult controls, COVID-19 patients had higher fecal populations of *Ruminococcus gnavus*, *Ruminococcus torques*, and *Bacteroides dorei* species. This imbalance seemed not to depend on the pharmacological therapy administered. The same investigators reported a stratification of gut microbiota composition associated with disease severity in hospitalized COVID-19 patients. Cytokine (IL-10 and tumor necrosis factor- γ), enzyme (AST, -glutamyl transferase, lactate dehydrogenase), CRP, N-terminal proB-type natriuretic peptide levels, and erythrocyte sedimentation rate were previously reported as associated with increased COVID-19-related symptomatology^[80-82]. Those parameters were also significantly associated with microbiota composition in COVID-19 patients.

Remarkably, the levels of those molecules increased in parallel with changes in the microbiota composition, representing more severe disease states^[79]. Overall, the results suggest that the gut microbiota composition might be linked to the extent of the immune response to COVID-19 and subsequent tissue damage, thus playing a role in regulating disease severity. The persistence of gut microbiota dysbiosis even 30 days after clearance of SARS-CoV-2 might also be linked to the persistence of COVID-19 related symptoms, such as fatigue, dyspnea, and joint pain.

Moreover, Yu^[83] suggested that nutritional disorders impair immunity, causing hyperinflammation and leading to an overload of cytokines in COVID-19 patients. Autophagy induced by restrictive eating could be an efficient strategy to prevent COVID-19-related symptomatology. Indeed, it inhibits overgrowth of the microbiota and partially reduces excessive nutrition for replication. Autophagy also attenuates inflammation. On that basis, Yu^[83] recommended restoration of good nutritional status together with restriction of food intake, especially in older subjects, to reduce the risk of developing severe symptomatology if infected by COVID-19.

On the other hand, as inflammation can be considered as a physiological response of the immune system to damaged tissues^[84], it is a protective reaction to remove the injurious stimuli and to initiate the healing of damaged tissues^[84]. Nutrition excess slows tissue healing, indeed nutrition derived from the degradation of the damaged tissue coupled with excess nutrition intake will be mostly turned into lipid intermediates and deposited in nonadipose tissue, lipotoxicity and further tissue damage. Thus, in a state of overnutrition, inflammation can become chronic. In this regard, undernutrition might be beneficial in fighting viral infection, as anorexia nervosa patients seem to be free of common viral infections^[85,86].

ROLE OF THE GI TRACT IN COVID-19 COMPLICATIONS

Multisystem inflammatory syndrome in children (MIS-C) is defined by the Centers for Disease Control and Prevention^[87] as a severe illness requiring hospitalization that occurs in individuals < 21 years of age with evidence of current or recent SARS-CoV-2 infection, or recent exposure to an individual with COVID-19. Children with MIS-C have fever, laboratory evidence of inflammation, and multiorgan involvement without an alternative plausible diagnosis. Ninety-two percent of children with MIS-C report GI symptoms^[88] and 80% develop cardiac pathology. MIS-C is characterized by a superantigen-mediated hyperinflammatory response with a unique T-cell profile and multiple autoantigens^[89,91]. It has been recently shown that the spike protein of SARS-CoV-2 contains sequence and structural motifs similar to a *Staphylococcal Enterotoxin B* superantigen^[92], and superantigen-induced skewing of the T-cell repertoire in MIS-C patients with expansion of the T-cell receptor beta variable gene correlates with the cytokine storm and hyperinflammation seen in MIS-C^[91]. Inflamed expansion of antibodies for multiple non-COVID-19 pathogens, including common coronaviruses, influenza and respiratory syncytial virus^[93] plus numerous self-antigens^[89,90] also correlates with the severe cardiac complications of MIS-C. Immune complexes stimulate monocytes/macrophages, eliciting phagocytosis, macrophage activation and cytokine storm^[94,95] (Figure 1). The instigating factor for MIS-C has not been elucidated, but prominent GI symptoms suggest an intestinal source. The upper or lower respiratory tract are unlikely sources of antigens triggering this hyperinflammatory response, given the relative lack of respiratory symptoms in MIS-C, low/undetectable viral load in respiratory secretions^[93], and the 2-4 wk delay between initial infection/exposure and development of MIS-C. Rather, ongoing antigen exposure is much more likely to be from the GI tract as has been shown in Kawasaki disease (KD), a similar illness with a hyperinflammatory profile leading to fever, rash, elevated inflammatory markers resulting in vasculitis, coronary aneurysms, and cardiac pathology. In KD, increased intestinal permeability secondary to upregulation of zonulin, a molecule that regulates paracellular molecule trafficking, has been associated with increased circulating immunoglobulin A and cardiac complications in children with KD^[96].

PHARMACOLOGICAL IMPLICATIONS OF FECAL-ORAL TRANSMISSION

A study by Yeoh *et al*^[79] was not designed to determine whether dysbiosis is the consequence of patient immune response rather than a contributing cause in disease onset and severity. Nevertheless, the reported association seems to be sufficiently

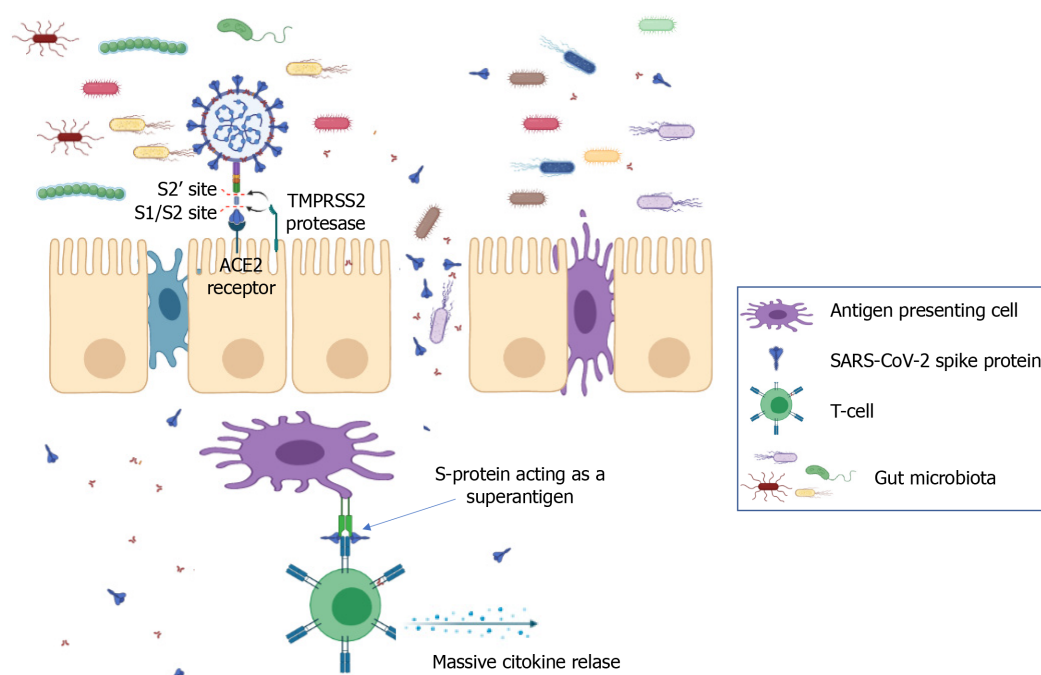


Figure 1 Gut dysbiosis induced by the immune response to severe acute respiratory syndrome coronavirus 2 in the gastrointestinal tract increases gut permeability, which in turn increases spike protein trafficking. Spike protein was reported to act as a superantigen that links the T-cell receptor and major histocompatibility complex II on antigen-presenting cells. ACE2: Angiotensin converting enzyme 2; S-protein: Spike protein; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

robust to support the benefit of pharmacological intervention aimed at decreasing gut permeability for COVID-19 GI symptoms management, and potentially to reduce the risk of its complications, including MIS-C. Such a strategy could both reduce GI tract inflammation and help accelerate naturally occurring dysbiosis correction. Larazotide acetate, a synthetic octapeptide designed as a specific zonulin receptor antagonist, was successfully and safely used to modulate gut permeability and the related inflammation^[97,98]. Di Micco *et al*^[99] recently proposed an additional role for larazotide in COVID-19 patients. Based on an in-silico evaluation, they reported the ability of larazotide to inhibit the N3 protease of SARS-CoV-2. As larazotide was specifically designed as an oral drug able to reach the lower GI tract, it might be useful both for its direct anti-SARS-CoV-2 effect and to prevent antigen trafficking of SARS-CoV-2-derived molecules, including spike protein from the gut lumen to the bloodstream, which could trigger a cytokine storm leading to MIS-C.

CONCLUSION

In summary, whether digestive symptoms are a direct response to SARS-CoV-2 infection of the GI tract, or a secondary outcome of COVID-19, is still to be completely understood. The presence of viral RNA in the GI tract might partially explain GI symptoms even if it does not mean that there is infection in the intestine. In either case, robust evidence supports GI tract involvement in COVID-19 as well as a potential fecal-oral transmission route. The GI seems to be not only a reservoir of SARS-CoV-2, but also an active battlefield in which virus, innate and adaptive immune system responses, epithelial cells, and gut microbiota play critical roles. The interventions for managing GI-related issues should be twofold. From a patient perspective, pharmacological treatment to reduce the severity of GI symptoms and support a quick re-establishment of eubiosis should be evaluated. Moreover, interventions to ensure water sanitation should be added to the current policies for COVID-19 pandemic control. Considering that many people worldwide lack access to clean drinking water and good sanitation, the possible containment of COVID-19 through water treatment should be carefully taken into account to reduce the actual and future magnitude of the pandemic.

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