

Managing the Inevitable Surge of Post-COVID-19 Functional Gastrointestinal Disorders

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GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH COVID-19

The most common clinical manifestations of coronavirus disease 2019 (COVID-19) include fever, cough, dyspnea, sore throat, muscle or bone aches, chills, and headache. However, as the pandemic evolved, gastrointestinal (GI) symptoms emerged as important clinical manifestations, and several reviews addressed this issue (1,2). For example, a review of data of 2023 patients found a GI-symptom incidence ranging from 3.0% to 79% (1). Symptoms included anorexia, mean: 46.5% (range: 39.9%–50.2%), vomiting: 44% (3.6%–66.7%), nausea: 21.3% (1.0%–29.4%), diarrhea: 12.9% (2.0%–49.5%), GI bleeding: 9.6% (4.0%–13.7%), and abdominal pain: 6.0% (2.2%–6.0%) (1). Another review of 15 studies of 2,800 patients found a pooled frequency of GI symptoms ranging from 3.0% to 39.6%, these included diarrhea: 7.5%, nausea: 4.5%, anorexia: 4.4%, vomiting: 1.3%, and abdominal pain and belching/reflux: $\leq 0.5\%$ (2). Interestingly, GI symptoms may be the first manifestation of COVID-19—even before fever, or respiratory symptoms occur or surge—during the clinical course of the illness (2). Albeit the high prevalence of GI symptoms in the published COVID-19 series, confounding factors may have influenced the results because these studies were not controlled and were often conducted on hospitalized patients, who most probably received antibiotics and other treatments, which may well induce GI side effects. Despite these limitations, the Centers for Disease Control and Prevention currently recommends looking out for symptoms such as nausea, vomiting, or diarrhea in patients with COVID-19.

UNDERLYING MECHANISMS FOR GI SYMPTOMS IN COVID-19

The pathophysiology of GI symptoms in COVID-19 is not well understood; however, evidence points to a role of angiotensin-converting enzyme 2 (ACE2) cell-surface receptors and to a severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2)–induced inflammatory process in the digestive tract (3). A vital structural protein of the SARS-CoV-2 is the spike glycoprotein (S). It consists of 2 functional units, S1 and S2, that binds to the host cell-

ACE2 receptor by membrane fusion, replicates it through replication-transcription complexes, and promotes proliferation by interfering with and suppressing the host's immune response (4). SARS-CoV-2 is abundantly contained in air droplets exhaled by infected subjects and inhalation of these particles by a noninfected individual, which may lead to viral access to the recipient's respiratory tract where it binds to ACE2 receptors, making the airways one of the main sites of viral entry. However, the ACE2 receptors are also localized in the myocardium, proximal kidney tubule, and urothelial bladder cells. Notwithstanding, ACE2 receptors are abundantly expressed in the digestive tract, including, the mucosal surface of the oral cavity and tongue, esophagus, and absorptive enterocytes of the ileum and colon, making the digestive tract a potential route of SARS-CoV-2 infection (5). Evidence of fecal shedding of viral RNA further supports viral replication in the digestive tract and potentially a fecal-oral transmission (6).

In COVID-19 patients with diarrhea without inflammatory bowel disease (IBD), high fecal calprotectin was found when diarrhea ceased and was even higher in those with persistent diarrhea as compared to patients without diarrhea, suggesting that the infection evokes an intestinal inflammatory process (3). Furthermore, fecal calprotectin levels significantly correlated with the proinflammatory interleukin (IL)-6 serum concentrations (3).

Gut dysbiosis has also been reported in patients with COVID-19 with enrichment of opportunistic pathogens and depletion of beneficial commensals (7). An inverse correlation between the abundance of *Faecalibacterium prausnitzii* and disease severity was also observed (7). *F. prausnitzii* has anti-inflammatory properties, and its depletion has been related to irritable bowel syndrome (IBS) and IBD (8,9). In addition, bacterial groups belonging to the genus *Bacteroides*, known to downregulate the ACE2 expression in the murine colon, inversely correlated with fecal SARS-CoV-2 nucleic acid loads (7).

POSTVIRAL-FUNCTIONAL GI DISORDERS

Initially, postinfection (PI)-IBS was reported after acute bacterial gastroenteritis (8) (e.g., *Shigella*, *Salmonella*, and *Campylobacter*); however, later studies reported that protozoa (e.g., *Giardia lamblia*), as well as viruses (e.g., Norwalk-like viruses, Rotavirus, and

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Table 1. Studies on postinfection irritable bowel syndrome (IBS) after viral gastroenteritis

Study	Country	Pathogens	IBS among cases	IBS among controls	P Values
Marshall et al., (11)	Canada	Norwalk-like virus	21/89 (23.6%)	1/29 (3.4%)	0.03
Zanini et al., (12)	Italy	Norovirus	40/186 (21.5%)	3/198 (1.5%)	<0.00001
Saps et al., (13) ^a	USA, Italy	Rotavirus	7/44 (16%)	3/44 (7%)	0.3

^aStudy in pediatric population.

Norovirus), were also associated with PI-IBS (10) (Table 1). Although most viruses are considered noninvasive pathogens, recent studies showed that other noninvasive pathogens such as *Vibrio cholerae* might cause PI-IBS (14).

PROPOSED BIOLOGICAL MECHANISMS FOR POSTINFECTION GI DYSFUNCTION

Evidence supports the development of functional gastrointestinal disorders (FGIDs)/disorders of the gut-brain interaction (DGBI) after a bout of viral, bacterial, or protozoal gastroenteritis (8) or after resolution of an acute flare of IBD (9). Individual susceptibility to these so-called PI and postinflammatory FGIDs/DGBI involves genetic predisposition and the presence of pre-existing psychologic disturbances such as anxiety and/or depression (8). PI-FGIDs/DGBI have also been associated with dysregulation of gut motility, visceral hypersensitivity, dysbiosis, increased intestinal permeability, bile acid malabsorption, and modifications of enteroendocrine cell and serotonin metabolism (8). Current data suggest that the resolution of SARS-CoV-2 infection may lead to persistent GI dysfunction resembling certain aspects of PI/postinflammatory FGIDs/DGBI. Transient nonspecific gut inflammation is the common trigger for long-lasting symptoms of FGIDs/DGBI, regardless of the initiating event (i.e., viral, parasitic, bacterial, after resolution of IBD flares, celiac disease, or acute diverticulitis).

Similarly, SARS-CoV-2 infection of GI epithelial cells has been associated with (i) lamina propria infiltration of plasma cells and lymphocytes, and edema in the stomach, duodenum, and rectum (15); (ii) increased levels of fecal calprotectin (3); (iii) higher fecal levels of IL-8 and lower levels of the anti-inflammatory IL-10, compared with uninfected controls (Britton GJ, Chen-Liaw A, Cossarini F, et al. SARS-CoV-2-specific IgA and limited inflammatory cytokines are present in the stool of select patients with acute COVID-19. medRxiv 2020 PREPRINT. 10.1101/2020.09.03.20183947); and (iv) intestinal dysbiosis (7). Interestingly, gut dysbiosis persisted after the resolution of SARS-CoV-2 infection, suggesting that microbiota perturbation may contribute to the persistence of gut dysfunction and symptom generation after the infection has subsided (7). Indeed, the persistent dysbiosis may contribute to maintaining a chronic state of low-grade intestinal inflammation, increased permeability, and bile acid malabsorption, which have all been previously associated with gut dysmotility, increased sensory perception, and symptom generation in patients with FGIDs/DGBI (16).

POST-TRAUMATIC STRESS AND PSYCHOLOGICAL FACTORS

Psychological factors act as triggers of GI symptoms but also represent the consequence of bowel disturbance, creating a self-maintaining vicious circle. Given the ability of SARS-CoV-2 to

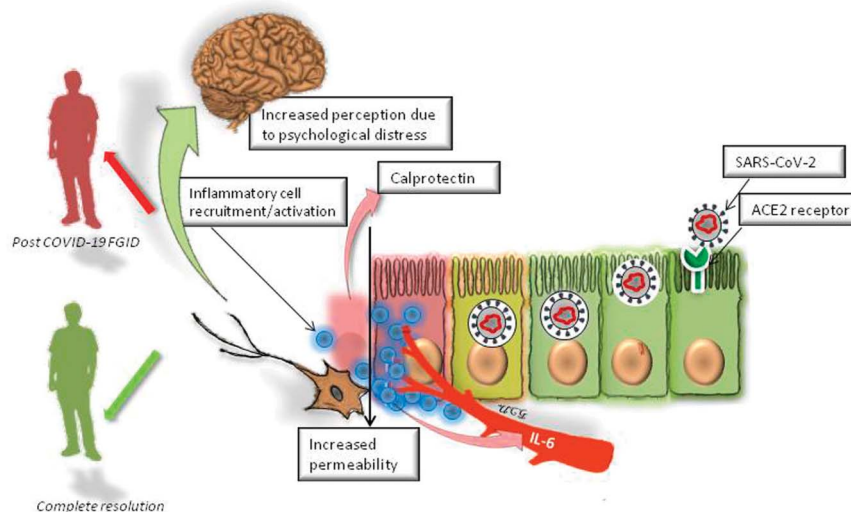


Figure 1. Proposed pathogenesis of post-COVID-19 FGIDs/DGBI. Severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) enters the gastrointestinal epithelial cells after binding to the angiotensin converting enzyme-2 (ACE-2) receptors. As a consequence, there is an inflammatory response that increases intestinal permeability, cytokine liberation into the blood stream (e.g., interleukin [IL]-6), and increase in fecal inflammatory markers (e.g., calprotectin). Increased visceral sensitivity at the level of the digestive tract organs and in the central nervous system (the latter being exaggerated by psychological stress) is expected to contribute to the development and severity of symptoms of post-COVID-19 FGIDs/DGBI. COVID-19, coronavirus disease 2019; DGBI, disorders of gut-brain interaction; FGID, functional gastrointestinal disorder.

Table 2. Proposed diagnostic criteria for post-COVID-19 FGIDs/DGBI

Fulfilling Rome IV criteria for any FGID/DGBI in the past 3 mo, with symptom onset at least 6 mo before diagnosis associated with:

Previous COVID-19 infection confirmed by SARS-CoV-2 real-time PCR performed at regional reference laboratories

Symptom development immediately after resolution of acute COVID-19 infection

Should not meet criteria for FGIDs before onset of acute illness

COVID-19, coronavirus disease 2019; DGBI, disorders of gut-brain interaction; FGID, functional gastrointestinal disorder; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

affect the GI tract, leading to symptom development, and based on the high prevalence of psychological impairment during COVID-19, it seems reasonable to speculate that this combination would lead to a wave of post-COVID-19 FGIDs/DGBI. These long-term effects may include the development of post-traumatic stress disorders (e.g., flashbacks, nightmares, increased arousal, and reduced social life) associated with persistent PI-IBS, which were well described in veterans who experienced acute infectious gastroenteritis during the Persian Gulf War (17).

HYPOTHESIS: POST-COVID-19 FGID/DGBIs IN THE LONGER RUN

The complex interaction between the previously listed biological abnormalities and environmental and psychological factors may contribute to the development and persistence of post-COVID-19 FGID/DGBIs (Figure 1). The SARS-CoV-2 human infection has only emerged in the past 6 months; hence, there is no study in this direction, yet. In addition, the most current Rome IV criteria for DGBIs require that symptoms must be present during the previous 3 months with onset 6 months before. Hence, the time period since the onset of the pandemic may be yet too short for diagnosing PI-FGIDs/DGBI after COVID-19. Therefore, as gastroenterologists, we need to be aware of the possibility of PI-FGIDs/DGBI in patients who suffered from COVID-19, especially among those who had GI symptoms (Table 2). Moreover, the authors of the current study have already started to consult patients likely to have symptoms of post-COVID-19 FGIDs/DGBI. Furthermore, although there are no available treatment trials for these patients, it is likely that they will be treated based on their predominant symptoms.

CONCLUSIONS

A proportion of patients affected by COVID-19 and GI symptoms may develop PI-FGIDs/DGBI based on the relationship of low-grade intestinal inflammation, increased permeability, and dysbiosis, together with environmental and psychological distress. Clinicians must be aware of this new clinical scenario, and studies will be needed to characterize this condition further. In the meantime, we are proposing diagnostic criteria for these disorders, and treatment should be directed at the predominant symptoms, similar to what is performed for DGBI in general.

CONFLICTS OF INTEREST

Guarantor of the article: Max Schmulson, MD, RFF.

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Ethical responsibilities: This is a brief review of the literature, and authors own opinions; therefore, for patients who were not studied, no informed consent was needed. Based on the above, no Ethic Committee authorization was required. In addition, no specific cases are discussed; thus, no patient identification is possible.

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