Symptomatology and microbiology of the gastrointestinal tract in post-COVID conditions

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Introduction

Severe acute respiratory conditions coronavirus 2 (SARS-CoV-2) caused the coronavirus disease 2019 (COVID-19) that has spread swiftly since its first description in December 2019, resulting in over 6 million deaths worldwide.¹ SARS-CoV-2, in contrast to popular opinion, impacts multiple organs, namely the brain, liver, heart, kidneys, and gastrointestinal (GI) tract. In this regard, an unspecified number of COVID-19 survivors continue to experience certain symptoms for prolonged periods of time, including extreme fatigue or muscle weakness, joint pain, anxiety, short-term memory loss, sleep disturbances, sadness, brain fog, and light and sound sensitivity.² ³ These persistent chronic symptoms suggest the increased likelihood of multiple-organ impairment in the post-COVID era. Several investigations have shown patients with COVID-19, in addition to respiratory manifestations, have at least one organ impairment even if the symptoms are minor.⁴

In the aftermath of COVID-19, numerous infected individuals have been reported to develop new, recurrent, and/or chronic clinical presentations.⁵ As a result, studies have been conducted worldwide to evaluate risk factors, epidemiological data, and pathology behind prolonged organ involvement to elucidate post-COVID conditions or post-acute sequelae of SARS-CoV-2 (PASC), assisting health care providers and the infected general public. The present review article seeks to concisely address the post-COVID GI manifestations, provide a summary of putative pathophysiological mechanisms underlying GI involvement, and recite relevant evidence regarding the occurrence of persistent gut microbiome dysbiosis in COVID-19 survivors.

Epidemiological evidence of post-COVID GI sequelae

Based on the timeline and framework proposed by Datta et al., SARS-CoV-2 infection can be classified into three phases: (i) the first 2 weeks after the onset of symptoms (acute infection), (ii) 2–4 weeks after the onset of symptoms (post-acute inflammatory phase), and (iii) beyond 4 weeks after the onset of symptoms (late sequelae).⁶ According to the National Institute for Health and Care Excellence (NICE) guidelines, there is a significant temporal difference between post-COVID conditions and long COVID, as the term “long COVID” refers to COVID19-related symptoms and signs that manifest 4 weeks after being infected with SARS-CoV-2, while post-COVID...
conditions are characterized by manifestations lasting longer than 12 weeks.\textsuperscript{7} The Centers for Disease Control and Prevention (CDC), on the other hand, describes post-COVID conditions as a plethora of recurrent, new, or chronic health disorders or disturbances occurring within 4 weeks or more from SARS-CoV-2 infection.\textsuperscript{8}

It is difficult to predict the exact proportion of patients who might develop long COVID, due to differences in reporting mortality and incidence rates of COVID-19 between countries. Likewise, the currently available epidemiological data on long COVID is rather complicated. The number of studies reporting patients with long COVID is increasing steadily, resulting in a better insight into its epidemiology. Various investigations have been conducted on sizeable populations of COVID-19 patients with a wide range of ongoing gastrointestinal symptoms (Table 1). While diarrhea and anorexia have been frequently cited as the most commonly occurring GI symptoms in post-COVID conditions, a number of investigations have also highlighted the rather high prevalence of abdominal pain,\textsuperscript{20,26} gastrointestinal reflux disorder (GERD)\textsuperscript{22} and nausea\textsuperscript{24} in patients with post-COVID conditions.

COVID-19 patients have a greater risk of mortality and are more likely to seek medical assistance for gastrointestinal issues such as dysphagia, GERD, abdominal pain, and other gastrointestinal complaints.\textsuperscript{16} Furthermore, it seems possible that new gastrointestinal symptoms may emerge in the aftermath of COVID-19.\textsuperscript{29} Collectively, clinical manifestations of GI involvement in post-COVID conditions are not uncommon. As a result, health care practitioners should consider SARS-CoV-2 as a possible etiology of gastrointestinal symptoms in the post-COVID era.

**Putative pathophysiology of GI injury in COVID-19 and PASC patients**

**Intestinal ACE2 receptor in SARS-CoV-2 infection.**

Whilst the respiratory tract is primarily targeted by SARS-CoV-2 the GI tract is the largest immunological organ, and the resident gut microbiota can modulate both systemic and local immune responses in the body. In addition, the gut microbiota has been proposed as a mediator of host inflammatory and immunological responses during SARS-CoV-2 infection, possibly contributing to the severe systemic inflammation reported in patients requiring hospitalization.\textsuperscript{34,35}

Previous investigations indicated that binding of SARS-CoV-2 spike protein to Angiotensin-Converting Enzyme II (ACE2) mediates virus entry into various host cells.\textsuperscript{30} Interestingly, ACE2 receptors are highly expressed in intestinal enterocytes, colonocytes,\textsuperscript{37} and gastric glandular cells, except for esophageal epithelial cells.\textsuperscript{38} This could be due to the histologic structure of the esophagus, which is only slightly made of glandular cells. The prolonged GI symptoms in post-COVID conditions might be related to the viral entry via the ACE2 receptor, resulting in considerable cellular and molecular damage. Furthermore, ACE2 expression in the gut might establish an additional means of SARS-CoV-2 transmission through the oral-fecal route.\textsuperscript{39}

ACE2 also has a renin-angiotensin system-independent function, as it plays a major role in the intestinal amino acid homeostasis, a mechanism associated with the expression of antimicrobial peptides, suggesting its role in intestinal barrier integrity and the maintenance of gut microbiota.\textsuperscript{40} Reduced production of antimicrobial peptides, increased susceptibility to experimentally induced colitis and altered gut microbiome have been shown in ACE2-mutant mice, which is restored by the dietary tryptophan.\textsuperscript{41} Similarly, during SARS-CoV-2 infection, the ACE2-mediated amino acid transport is suggested to contribute to gut microbial ecology.\textsuperscript{42} In 2020, Yang et al. demonstrated that reduced colonic expression of ACE2 was associated with impaired gut microbiota colonization in gnotobiotic (germ-free) rats, contributing to SARS-CoV-2 pathogenesis.\textsuperscript{43} In another murine study, ACE2 deficiency was linked with high susceptibility to intestinal inflammation secondary to epithelial damage.\textsuperscript{41} Moreover, ACE2 depletion in tissues results in enhanced viral pathogenicity and replication.\textsuperscript{44} SARS-CoV-2 may also disrupt ACE2 function, resulting in diarrhea.\textsuperscript{45} In addition to this, a high level of calprotectin in stool specimens, a marker of GI tract inflammation, was observed in COVID-19 patients with diarrhea, as well.\textsuperscript{46} Collectively, the GI tract may serve as an extrapulmonary reservoir for SARS-CoV-2 infection, particularly in COVID-19 patients with GI manifestations like diarrhea. In this regard, a study confirmed that SARS-CoV-2 readily infects and replicates in human small intestine enterocytes, leading to the release of a large number of viral particles into the intestinal lumen.\textsuperscript{47}

**Prolonged fecal shedding of SARS-CoV-2 in patients with COVID-19.**

With regards to SARS-CoV-2 RNA detection in fecal samples,\textsuperscript{48} fecal viral shedding was reported in patients with COVID-19 following a mean period of 11.2 days after respiratory clearance of SARS-CoV-2.\textsuperscript{49} In another investigation, even in the absence of gastrointestinal symptoms and convalescent phase of SARS-CoV-2 respiratory infection (up to 6 days after a negative RT-qPCR result), evidence of active and extended quiescent GI infection was found, albeit, with reduced viral infectivity and transcriptional activity.\textsuperscript{50}

Interestingly, patients with no or mild symptomatic COVID-19 and also persistent respiratory virus shedding exhibited shedding of SARS-CoV-2 in feces up to 50 days after diagnosis, highlighting an association between viral levels in stool and respiratory samples.\textsuperscript{22} Therefore, the gastrointestinal tract can be a route of SARS-CoV-2 transmission just as well as the respiratory tract. In 2021, Gaebler et al. collected biopsies of intestinal enterocytes from 14 asymptomatic patients within 5.7 months after they were diagnosed with COVID-19, only to observe that SARS-CoV-2 proteins and nucleic acids were still present in half of the specimens. Notably, at the time of biopsy, all 14 participants had negative RT-qPCR tests.\textsuperscript{51} These findings together imply that even after the virus has been cleared from the respiratory tract, SARS-CoV-2 may actively continue to replicate in the GI tract, suggesting long-term gut infection and also a potential transmission of SARS-CoV-2 via the fecal-oral route.

**Persistent gut dysbiosis in COVID-19 and PASC patients.**

To date, a plethora of scientific evidence has added to our understanding of gut dynamics, pointing out the role of gut microorganisms in a variety of infectious and degenerative disorders.\textsuperscript{52} The gut microbiota of patients with COVID-19 was significantly altered up to 30 days after viral clearance from
| Study                  | Country   | Population size | Anorexia | Diarrhea | Abdominal pain | Nausea | Vomiting | Others       | Duration | From       | References |
|-----------------------|-----------|-----------------|----------|----------|----------------|--------|----------|--------------|----------|------------|------------|
| Romero-Duarte A       | Spain     | 797             | 8 (1%)   | 82 (10.3%) | 43 (5.4%)      | 16 (2%) | —        | Constipation | 180      | Discharge  | 9          |
| Osikomaiya B          | Nigeria   | 274             | 24 (8.8%)| 11 (4%)   | 17 (6.2%)      | 6 (2.2%) | 2 (0.73%)| —            | 15       | Discharge  | 10         |
| Bellan M              | Italy     | 238             | 3 (1.3%) | 3 (1.3%)  | —              | —      | —        | —            | 120      | Discharge  | 11         |
| Huang C               | China     | 1655            | 138 (8%) | 80 (5%)   | —              | —      | 80 (5%) | —            | 186      | Onset      | 2          |
| Haran JP              | USA       | 27              | 4 (14.8%)| —        | —              | —      | —        | —            | 45.8     | Onset      | 12         |
| Carfi A               | Italy     | 143             | 1 (8%)   | 1 (8%)    | —              | —      | —        | —            | 60.3     | Onset      | 13         |
| Landi F               | Italy     | 131             | 13 (9.9%)| 5 (3.8%)  | —              | —      | —        | —            | 55.8     | Onset      | 14         |
| Liang L               | China     | 76              | —        | —        | —              | —      | —        | —            | 90       | Discharge  | 15         |
| Tomasoni D            | Italy     | 105             | 1 (1%)   | —        | —              | —      | —        | —            | 30–90    | Onset      | 16         |
| Moreno- Pérez O       | Spain     | 277             | —        | —        | —              | —      | —        | —            | 70–98    | Discharge  | 17         |
| Al-Aly Z              | USA       | 73 435          | —        | —        | (5.73%)        | —      | —        | —            | 30       | Diagnosis  | 18         |
| Petersen MS           | Faroe Islands | 190             | —        | <5%      | —              | <5%    | —        | —            | 99.4–124.6 | Onset      | 19         |
| Tenforde MW           | USA       | 274             | —        | —        | (1.4%)         | —      | (1.8%)  | (13%)        | 14–21    | Onset      | 20         |
| Dennis A              | UK        | 201             | —        | 119 (59.2%)| 108 (53.7%)   | —      | —        | —            | 140      | Onset      | 21         |
| Park SK               | South Korea| 46              | —        | 1 (2.1%) | 2 (4.3%)      | 1 (2.1%)| —        | Dyspepsia 2 (4.3%)| 30       | Diagnosis  | 22         |
| Zhao YM               | China     | 55 (30.91%)     | —        | 1 (2.1%) | 2 (4.3%)      | 1 (2.1%)| —        | —            | 64–93    | Onset      | 23         |
| Goertz YMJ            | Netherlands| 2113            | —        | (10%)    | —              | (12%)  | (1%)     | —            | 79       | Onset      | 24         |
| Daher A              | Germany   | 33              | —        | 3 (9%)   | 1 (3%)        | 2 (6%) | —        | —            | 42       | Discharge  | 25         |
| Eiros R               | Spain     | 139             | —        | —        | 6 (4%)        | —      | —        | —            | 72.8     | Onset      | 26         |
| Galvan-Tejada CE      | Mexico    | 141             | —        | —        | —              | 22 (15.6%)| —        | —            | 36       | Onset      | 27         |
| Jacobs LG             | USA       | 183             | —        | 7 (3.8%) | —              | —      | —        | —            | 30–40    | Discharge  | 28         |
| Blackett JW           | USA       | 749             | —        | 72 (9.6%)| 70 (9.4%)     | 53 (7.1%)| —        | GERD 122 (16.3%)| 180      | Diagnosis  | 29         |
| Weng J                | China     | 117 (24%)       | 17 (15%) | 8 (7%)   | 21 (18%)      | 11 (9%)| —        | Constipation 83 (11.1%)| 90       | Discharge  | 30         |
| Taquet M              | UK        | 273 618         | —        | 22 683 (8.29%)| —      | —        | —            | 90–180   | Diagnosis  | 31         |
| Wang X                | China     | 131             | 3 (2.29%)| 2 (1.53%)| 1 (0.76%)     | 1 (0.76%)| —        | GERD 21 (18%)| 14       | Onset      | 32         |
| Carvalho-Schneider C  | France    | 150             | —        | 15 (10%)| —              | —      | —        | Bloody stool 2 (2%)| 60       | Onset      | 33         |
nasopharyngeal swabs, regardless of whether they had received antibiotics or another medicine. The gut microbiome composition of patients with COVID-19 in the convalescent phase was enriched in *Bifidobacterium dentium* and *Lactobacillus ruminis*, while being deficient in *Eubacterium rectale*, *Ruminococcus bromii*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii*. *F. prausnitzii* and *E. rectale* are known to have vital immunomodulatory functions in the human gut and can contribute to its defense. *F. prausnitzii* has also been found to have anti-inflammatory properties, as it has the capability of inhibiting interleukin-8 (IL-8) synthesis and release, repressing the NF-κB pathway, while inducing human colonic type 1 regulatory T cells that produce IL-10, which is known to be an anti-inflammatory cytokine. On the other hand, comparatively high populations of *E. rectale* residing in the GI tract have been correlated with lower inflammation in Alzheimer’s disease. Furthermore, similar to the plasma levels of inflammatory cytokines and blood markers like lactate dehydrogenase (LDH) and C-reactive protein (CRP), the gut microbiome composition correlated with COVID-19 severity during the acute phase of the disease.

In 2021, Zuo et al. found SARS-CoV-2 RNA in stool specimens of 15 patients with COVID-19 upon hospitalization and examined the SARS-CoV-2 transcriptional activity to establish the range of infectivity linked to the gut microbiota. Stool specimens were divided into two categories based on the signatures of SARS-CoV-2 infectivity; (i) stool specimens with a high SARS CoV-2 infectivity signature had a greater abundance of opportunistic bacteria such as *Morganella morgani*, *Streptococcus infantis*, *Collinsella tanakaei*, and *Collinsella aerofaciens*, with enhanced capacity for carbohydrate, amino acid, and nucleotide biosynthesis. While on the contrary, stool specimens with low to no SARS-CoV-2 infectivity signature had a greater abundance of short-chain fatty acids (SCFA)-generating bacterial species such as *Alistipes onderdonkii*, *Bacteroides terrorism*, *Lachnospiraceae bacterium* and *Parabacteroides merdae*. Additionally, alterations in the fecal fungal microbiome (mycobiome) of COVID-19 patients were observed during hospitalization, as they exhibited enrichment of fungal pathogens from the genera Aspergillus and Candida in their mycobiome, which was deemed a concordant event correlated with disease severity, persisting up to 12 days after nasopharyngeal swab specimens returned negative results for RT-qPCR.

A recent investigation using shotgun metagenomic sequencing revealed that gut microbiome composition in patients with PASC, compared with uninfected individuals, was enriched in bacteria species *Bacteroides vulgatus* and *Ruminococcus gnavus* while being depleted of *E. rectale*, *Blautia obeum*, *C. aerofaciens* and *F. prausnitzii* 6 months after being admitted to the hospital. *F. prausnitzii* and *Bifidobacterium pseudocatenulatum*, as butyrate-producing bacteria, had the strongest inverse relationships with PASC (see Fig. 1). These beneficial gut bacteria such as *F. prausnitzii*, *B. pseudocatenulatum*, and *E. rectale* produce anti-inflammatory metabolic sub-products from SCFAs, including propionate, acetate, and butyrate through fermentation. Butyrate exerts regional immunomodulatory effects on the gut epithelium, and it is crucial for intestinal barrier integrity as the major energy source for enterocytes. SCFAs attach to immune cell receptors, promoting the production of anti-inflammatory cytokines like antioxidant enzymes and IL-10, while inhibiting the synthesis of pro-inflammatory cytokines. Besides, SCFAs increase CD8+ effector T cell activity by promoting cellular metabolism. *B. obeum*, a member of the *Blautia* genus, possesses anti-inflammatory properties. In comparison to *B. vulgatus*, which is implicated in diverse inflammatory gut disorders, including ulcerative colitis and irritable bowel disease. Likewise, *R. gnavus* in the gut has been known to associate with inflammatory bowel disease (IBD). Importantly, changes in the intestinal population of commensal bacteria are linked to GI symptoms. Despite gut dysbiosis, the presence of SARS-CoV-2 in the respiratory or GI tract did not correlate to PASC within 6 months after the onset of COVID-19 symptoms. Nor was there any substantial variation in intestinal microbiota composition between patients with non-PASC COVID-19 and otherwise healthy individuals.

In a most recently published follow-up of gut microbiota, fecal microbiota was monitored in COVID-19 patients for 6 months after they were discharged from the hospital. The study concluded that the composition of gut microbiota did not recover to normal levels. Patients with decreased post-convalescence richness also showed increased severity of COVID-19 (the requirement for ICU admission), as well as a high level of CRP during the initial phase, and reduced pulmonary function in the post-convalescence phase (after 6 months of recovery).

**GI injury via gut-lung axis in COVID-19.** The lungs and gut are both derived from the same primordial foregut during embryonic development. After birth, both organs serve as a mucosal barrier to prevent the entrance of extrinsic stimuli, while maintaining the homeostasis of their local microbial to enable the exchange of gas (the lungs) and nutrients (the gut). In a newborn, almost immediately after being delivered, both the gut and lungs are colonized by an early microbiome that is similar to each other in their composition with regard to dominant bacterial phyla. From a certain age forward, the lungs, similar to the gut, develop a particular microbiome rich in Firmicutes and Bacteroidetes as dominant bacterial phyla. However, the dominant species and genera in these organs may differ. In comparison to the lungs, the gut harbors at least a million more bacteria per gram of tissue. These organs communicate with their local microbiome, since the way through which the lung and gut respond to invading pathogens, and the mechanisms underlying this human-microbe interaction, are surprisingly similar. Circulating lymphocytes patrol both the airway and intestinal mucosaes, acting as a direct immunological link between the two organs. The gut-lung axis is the principal circuit responsible for crosstalk between these two organs that allows them to communicate with one another. Table 2 summarizes several important studies within the last decade that have delivered evidence on bidirectional interactions between the lungs and the gut.

The bloodstream is the primary means of communication between the gut and lungs. SCFAs generated in the gut are transported to the lungs by the bloodstream, where they can boost pulmonary epithelial cell health in the same way they do in the GI tract. Pathogens can infect both the lungs and the gut, and an illness in one may influence the health of the other. Therefore, as a result of pulmonary disease, the microbial populations in the GI tract might become subject to alterations, which may render the lungs susceptible to infection. In terms of the gut-lung axis, SARS-CoV-2 infection can cause diarrhea and damage to the gut immune system by inducing CD4+ effector T lymphocytes to
enter the small intestine by interacting with the C-C chemokine receptor type 9 (CCR9). In this regard, the lung microbiome in critically ill COVID-19 patients, in contrast to individuals with pneumonia, shows a decreased microbial diversity with a considerably greater relative abundance of the genus Pseudomonas.

**Role of NLRP3 inflammasome in SARS-CoV-2 pathogenesis**

Pyrin domain-containing protein 3 (NLRP3) inflammasome is the most extensively discussed inflammatory complex that is linked to aseptic inflammation and multiple organs’ immune responses, including the lungs and gut. Structurally, NLRP3 is a cytosolic protein complex consisting of three fundamental subunits: (i) the sensor protein, NLRP3 protein (ii) the adaptor protein known as apoptosis-associated speck-like protein containing a CARD (ASC), and (iii) the effector cysteine aspartase Caspase-1. Pattern recognition receptor (PRR) is an intracellular sensor for signals that interact with pathogen-associated molecular pattern (PAMP). This interaction induces a cell signaling cascade at the very early stages. Consequently, inflammasomes activate inflammatory substances particularly Caspase-1 a major inflammatory substance in response to a large number of virus infections. Upon a specific viral invasion, PRR/PAMP interactions prime NLRP3 to oligomerize, which is followed by K+ efflux. The NLRP3 inflammasome was then assembled as a result of downstream the ASC and the effector pro-Caspase-1 recruitment through interactions between the Caspase-1 recruitment domain (CARD/CARD) and the pyrin domain (PYD/PYD). The pro-CASP1 zymogen is subsequently recruited by the PYCARD through its CARD domain to create an NLRP3-PYCARD-Caspase-1 complex, which causes Caspase-1 to become activated. The activated Caspase-1 as the core of NLRP3-dependent inflammation cleaves its substrates, the pore-forming protein named gasdermin D (GSDMD), pro-IL-18, and pro-IL-1β. On the other hand, activated GSDMD induces pore formations in the cell membrane structure which permits the secretion of active IL-18, IL-6, IL-1β, and other inflammatory cytokines that cause a broad range of inflammatory responses and subsequent cell death (pyroptosis).

Inflammation, particularly the NLRP3 inflammasome, is essential for host protection during the early phases of an infection’s inflammatory response because it promotes immune cell recruitment, differentiation, and proliferation. If early inflammation is stopped, pathogens might disperse. According to van der Berg and coworker, various intrinsic immunological capabilities can dictate the level of NLRP3 inflammasome priming and activation, these diverse responses may be a factor in the range of clinical scenarios observed in COVID-19. Generally, the formation of mitochondrial reactive oxygen species (mitROS), an
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increase in cytosolic Ca2, and intracellular K+ efflux are the major triggers of NLRP3 inflammasome activation.88 There have been several studies on the mechanisms by which SARS-COV-2 stimulates the NLRP3 inflammasome activation, directly and indirectly, the proteins involved in this activation, and the subsequent events. In a mouse model, Nlrp3 impairment decreased SARS-Cov-2-induced lung damage by suppressing the pro-inflammatory response. Inflammasome activity specifically inhibited by a potent molecule MCC950 reduced COVID-19-like symptoms in vitro with fecal contents of SPF mice but not GF, IL-1β was produced. Moreover, following DSS-induced colitis, GF mice’s colonic lamina propria cells were isolated, although they failed to generate IL-1β ex vivo. These findings demonstrate that inflammasome activation is decreased in mice cells lacking bacteria.99 Antibiotics have also been used to study how variations in the microbiome construction impact downstream reactions, such as inflammasome activation. In this regard, mice who received a broad-spectrum antibiotic mixture had dysbiosis and higher levels of Nlrp3, IL-1β, Caspase-1, ASC, and cleaved IL-1β in their ileal ileum.100 Similarly, oral treatment of an antibiotic mixture lowered the number of bacteria in the body, which was followed by a rise in brain cortical expression of ASC and Nlrp3, serum IL-1β, cortical and small intestinal expression of IL-18 and IL-1β.101 Hemolysin (hpmA) from Proteus mirabilis, as a commensal bacterial species, activated BMDMs to generate IL-1β in an Nlrp3-dependent pathway.99 Likewise, BMDMs activated by Escherichia coli and Citrobacter rodentium, two Gram-negative bacteria, generated IL-18 and IL-1β in an Nlrp3-dependent pathway.100 These indicate that commensal gut bacteria play a significant role in the NLRP3 inflammasome activation, which is a vital mediator of gut IL-1β responses induced by the microbiome. As stated above, gut dysbiosis has been displayed in COVID-19 and PASC subjects which may trigger adverse outcomes, especially in lung and other organs.101

Studies using GF mice have underscored the pivotal capacity of the microbiome in modulating the NLRP3 and its activity, as well as the subsequent production of IL-18 and IL-1β. As bone marrow-derived macrophages (BMDMs) were stimulated in vitro with fecal contents of SPF mice but not GF, IL-1β was produced. Moreover, following DSS-induced colitis, GF mice’s colonic lamina propria cells were isolated, although they failed to generate IL-1β ex vivo. These findings demonstrate that inflammasome activation is decreased in mice cells lacking bacteria.99 Antibiotics have also been used to study how variations in the microbiome construction impact downstream reactions, such as inflammasome activation. In this regard, mice who received a broad-spectrum antibiotic mixture had dysbiosis and higher levels of Nlrp3, IL-1β, Caspase-1, ASC, and cleaved IL-1β in their ileal ileum.100 Similarly, oral treatment of an antibiotic mixture lowered the number of bacteria in the body, which was followed by a rise in brain cortical expression of ASC and Nlrp3, serum IL-1β, cortical and small intestinal expression of IL-18 and IL-1β.101 Hemolysin (hpmA) from Proteus mirabilis, as a commensal bacterial species, activated BMDMs to generate IL-1β in an Nlrp3-dependent pathway.99 Likewise, BMDMs activated by Escherichia coli and Citrobacter rodentium, two Gram-negative bacteria, generated IL-18 and IL-1β in an Nlrp3-dependent pathway.100 These indicate that commensal gut bacteria play a significant role in the NLRP3 inflammasome activation, which is a vital mediator of gut IL-1β responses induced by the microbiome. As stated above, gut dysbiosis has been displayed in COVID-19 and PASC subjects which may trigger adverse outcomes, especially in lung and other organs.101

### Table 2: Studies exploring the gut-lung crosstalk

| Axis | Effects | References |
|------|---------|------------|
| Gut-lung | Segment filamentous bacteria colonization in the gut protects the lungs against Staphylococcus aureus and stimulates T helper 17 response in the lungs | 70 |
| | Gut microbiome alleviates pulmonary inflammation and viral load in respiratory syncytial virus (RSV)-infected mice by producing short-chain fatty acids acetate | 71 |
| | Enrichment of Bifidobacterium pseudolongum and Bifidobacterium animalis following influenza virus infection confers resistance to infection in antibiotic-treated mice | 72 |
| | Clostridium orbiscindens generates desaminotyrosine, a microbial metabolite that counteracts inflammation in influenza virus-infected mice via modulation of type I IFN response | 73 |
| | Antibiotic-treated mice with depletion of certain commensal bacteria in their gut exhibit higher levels of influenza virus in their lungs and a profound impairment in the immune response | 74 |
| Lung-gut | Respiratory influenza infection alters the gut microbiota composition, which is mediated by Th17 cells, causing intestinal immune injury in mice | 75 |
| | Dysbiosis of the lung microbiome after lipopolysaccharide instillation in mice leads to alterations in gut flora which can be modulated using antibiotics | 76 |
NLRP3 to stabilize a chronic inflammatory condition. Collectively, there is a mounting body of evidence supporting the idea that focusing on inflammatory cytokine cascade and the molecular signaling relating to NLRP3 inflammasome may deliver a newer avenue for a therapeutic approach in COVID-19 and/or PASC patients.

For reasons that are yet to be explained, a considerable number of COVID-19 patients develop GI manifestations, while others recover completely. Long COVID is correlated with disease severity (demand for hospitalization, ventilation support, or intensive care unit) in the acute phase, age, female sex, and comorbidities, for example, underlying respiratory diseases or asthma, increased body mass index, and obesity. Though, a substantial fraction of patients with PASC come from the population of COVID-19 patients with mild or moderate disease during the acute phase of the illness, indicating that other risk factors might be involved as well. Another question to be answered is how the host immune system, as well as the virus itself, might contribute to the persistence of symptoms. Therefore, prolonged detection of SARS-CoV-2 in the GI tract might implicate the GI symptoms of post-COVID conditions, implying physicians and gastroenterologists should keep this in mind and not dismiss SARS-CoV-2 as a potential pathogen.

Patients with an altered gut microbiota composition at admission are more likely to develop PASC within 6 months from the onset of COVID-19. Remarkably, in post-COVID conditions, patients who had received antibiotics during the acute phase exhibited certain overlaps in their gut microbiota, compared with those who had not received antibiotics. Most importantly, bacterial diversity and richness were dramatically reduced in PASC patients than in uninfected controls and patients without PASC. Depletion of commensal gut bacteria including E. rectale, B. obeum, and F. prausnitzii has been linked with decreased host inflammatory response in various inflammatory-related disorders. These findings hint at a putative favorable function for gut beneficial commensals in human defense against SARS-CoV-2 infection, and also a putative adverse function for opportunistic pathogens. However, it is unclear whether or not these species can be recruited for therapeutic reasons.

Thus, the emergence of COVID-19–induced gastrointestinal symptoms may be related to lung infection with SARS-CoV-2 regardless of the virus’s presence in the GI tract. The use of specific probiotics and prebiotics in COVID-19 clinical treatment may balance patients’ gut and lung microbial ecology and boost their immune responses against the virus. Further study and clinical trials are required to fully investigate this issue and reach the most trustworthy results.

Conclusions

SARS-CoV-2 can induce various gastrointestinal manifestations in acute, post-acute, and late phases of illness. However, it is undetermined in which phase of the disease the GI tract is more involved and damaged by the virus. In the same way, the mechanisms of developing GI symptoms in COVID-19 and PASC are rather less well understood. Though certain factors are known to be heavily implicated in this process, namely, (i) high expression of ACE2 in the gut as a gate for virus entry, (ii) role of ACE2 in the intestinal homeostasis via transport of amino acids, and (iii) ACE2 deficiency resulting in intestinal inflammation and diarrhea. In addition to these, (i) persistent fecal shedding of SARS-CoV-2, (ii) prolonged presence of the virus in the GI tract, and (iii) persistent infectivity of SARS-CoV-2 in the gut, even after the clearance of the virions from the respiratory tract stand among other important factors that might contribute to post-COVID GI sequelae. Last, but not least, we have the gut dysbiosis-related events, including; (i) prolonged dysbiosis of gut microbiota, (ii) gut dysbiosis associated with acute-phase severity, and (iii) gut dysbiosis linked to decreased pulmonary function in the aftermath of COVID-19. Last, but not least, the NLRP3-mediated inflammation in COVID-19 appears to.

Figure 2  An schematic illustration of the NLRP3-mediated inflammatory pathway in COVID-19.
comprise Caspase-1, IL-1β, and GSDMD production downstream of NLPR3 activation induced by the SARS-COV-2 ORF3a, N, and/or E proteins. Further studies are warranted to determine the underlying pathophysiology of GI involvement in post-COVID conditions and related risk factors to provide treatment and diagnostic options.

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