

# THE MUTUAL RELATIONSHIP BETWEEN COVID-19 AND GUT MICROBIOTA

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**Abstract** – There is increasing evidence that the gut microbiota can have a mutual relationship with Coronavirus Disease-19 (COVID-19). COVID-19 can influence our gut microbiota, not only through direct action of the SARS-CoV-2 virus, but also due to environmental and iatrogenic factors, including antibiotics or hospitalization. On the other hand, the gut microbiota may have an important influence on the host response to SARS-CoV-2 infection, and its composition may be a marker of disease course, associated with disease severity, paving the way to new potential therapeutic strategies, such as probiotic supplementation or fecal microbiota transplantation, to manage the infection. In this review, we will summarize the latest evidence of the complex relationship between human gut microbiota and COVID-19.

**Keywords:** COVID19, Gut microbiota, Microbiota, Intestinal homeostasis, Fecal microbiota transplantation.

## INTRODUCTION

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), responsible for coronavirus Disease 2019 (COVID-19), emerged in late 2019 causing a global health pandemic. According to the Johns Hopkins coronavirus resource center (coronavirus.jhu.edu), as of April 2021, 133 million cases worldwide have been confirmed.

COVID-19 has a wide clinical presentation, ranging from asymptomatic or a mild disease, whose most frequent symptoms are fever, dry cough and fatigue, to severe respiratory disease requiring hospitalization and also death<sup>1-3</sup>. Although COVID-19 predominantly affects the respiratory system, evidence<sup>2</sup> suggests that nearly 20% of patients present with gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and abdominal pain.

Beyond associative data, there are several mechanistic findings which support the fact that SARS-CoV-2 affects the gastrointestinal tract. SARS-CoV-2 has been found in stool samples and anal swabs in almost 50% of COVID-19 cases, and its active replication in intestinal cells has been clearly shown<sup>4,5</sup>, indicating that the gastrointestinal tract could be an important site for viral colonization<sup>6</sup>. Moreover, the presence of increased fecal calprotectin levels in diarrhetic COVID-19 patients suggests that a gastrointestinal inflammatory response is part of the SARS-CoV-2 pathogenesis<sup>7</sup>.

A healthy gut microbiota may play a critical role in the different stages of SARS-CoV-2 infection, from the early phase of viral invasion and replication to the later phase characterized by clinical complications and hyperinflammation<sup>9</sup>. COVID-19, as well as other infections, can damage the gut microbiota homeostasis and eventually drive to dysbiosis. The ACE2 (angiotensin-converting enzyme 2) receptor is highly expressed in the gastrointestinal and respiratory system and is used by SARS-CoV-2 to enter human cells<sup>8</sup>. This receptor has also an important role in controlling gut microbiota and intestinal inflammation<sup>9</sup>.



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In this review we discuss the most recent evidence on the relationship between COVID-19 and the intestinal microbiota, outlining its impact on the host physiology and disease response and painting the landscape of potential therapeutic implications.

## IMPACT OF COVID-19 ON INTESTINAL HOMEOSTASIS AND GUT MICROBIOTA

SARS-CoV-2 can exert its effect on gut microbiota through different pathways, influencing not only on bacterial communities but also on other factors that are in close connection with gut microbiota, including the gut barrier, the immune system, and the ACE2 receptor.

### Gut Barrier

The intestinal barrier has an important role in the regulation of gut microbiota, and SARS-CoV-2 could impair this complex structure<sup>10</sup>. In 39 hospitalized patients with COVID-19, the LPS binding protein (LBP), a marker of gut permeability, was found to be higher than in controls, suggesting an impairment in gut barrier function<sup>11</sup>. In another study, increased serum levels of zonulin, a protein involved in the regulation of the tight junctions of the gastrointestinal tract, were found in patients with severe COVID-19. The elevated levels of zonulin correlated with higher levels of several markers of systemic inflammation, including IL-6, and with higher mortality, outlining the relationship between the severity of the disease and the intestinal barrier function<sup>12</sup>. These initial but insightful data suggest that SARS-CoV-2 infection can cause translocation of bacteria, metabolites and endotoxins, through the alteration of the intestinal mucosal barrier, leading to a state of systemic hyper-inflammation may contribute to the development of severe clinical presentations<sup>12</sup>.

### Immune System

The immune system is a critical regulator of the homeostasis between the host and the gut microbiota. Considerable dysregulation of the immune response has been observed in COVID-19 patients, with a decrease of all T-cell subtypes, especially regulatory and memory T cells<sup>13</sup>. There is also a correlation between levels of inflammatory biomarkers (with a marked increase of IL-1, IL-2, IL-6, IL-8, IL-13, IL-17, TNF) and disease severity, potentially leading to a systemic hyperinflammatory state<sup>2,13</sup>.

### ACE2 Receptor

The ACE2 receptor is highly expressed through the GI tract and is involved in the uptake of dietary amino acids, but also in microbial and immune homeostasis<sup>14</sup>. ACE2 acts a chaperone, on amino acid transporters on the enterocyte cell membrane, called B0AT1<sup>15</sup>, that contributes to the absorption of dietary tryptophan on the luminal surface of the small intestinal epithelium<sup>16,17</sup>. The activation of the mammalian target of rapamycin (mTOR) occurs through nutrient sensing and/or through the tryptophan-nicotinamide pathway, regulating the expression of antimicrobial peptides which ultimately affects the composition of the gut microbiota<sup>18,19</sup>. SARS-Cov-2 infection leads to a downregulation of ACE2 expression<sup>20</sup>, therefore, it is possible to hypothesize that during COVID-19, expression of antimicrobial peptides is decreased which could contribute, at least in part, to dysbiosis<sup>21,22</sup>.

### Gut Microbiota

There is increasing evidence of gut microbiota dysbiosis in patients with COVID-19 compared with healthy controls<sup>23</sup>. In fecal samples from 30 COVID-19 patients, there was a dramatic reduction in bacterial diversity and an increase in the number of opportunistic pathogens,

including *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* compared with healthy controls. Additionally, COVID-19 patients treated with antibiotics experienced a reduction in favorable species, such as *Eubacterium rectale*, *Lachnospiraceae*, *Ruminococcus obeum*, *Dorea formicigenerans*, *Faecalibacterium prausnitzii*, compared with antibiotics naive patients<sup>23,24</sup>. Evidence<sup>9</sup> suggests that this imbalance does not return easily to the steady-state: after recovery from COVID-19, despite infectious agent clearance, with the post COVID-19 gut microbiome seeming to stay stably different from healthy controls.

Some microbial features appear to be associated with clinical manifestations of COVID-19. In a pilot study of 15 hospitalized COVID-19 patients, an increase in *Ruminococcus gnavus*, and a decrease in Clostridia respectively correlated positively and negatively with inflammatory indexes<sup>25</sup>. Moreover, COVID-19 severity was associated with increase in *Coprococcus*, *Clostridium ramnosus* and *Clostridium hathewayi*, and a decrease in *F. prausnitzii* (known to have anti-inflammatory properties)<sup>25</sup>. In addition, the clinical setting of patients with COVID-19 may influence gut microbiota profiles, and hospitalization in wards or intensive care units appears to be associated with an increase in potentially pathogenic bacteria (e.g., *Peptostreptococcaceae*, *Enterobacteriaceae*, or *Staphylococcaceae*) compared with controls<sup>26</sup>.

Additionally, the presence of SARS-CoV-2 in human stools may influence the composition of the intestinal microbiota with levels of short-chain fatty acid producing bacteria, including *Parabacteroides merdae*, *Bacteroides stercoris*, *Lachnospiraceae bacterium 1\_1\_57FAA* and *Alistipes onderdonkii* being negatively correlated with the concentration of SARS-Cov-2 in feces<sup>27</sup>.

The profile of fecal metabolome appears to be significantly different between healthy controls and Covid-19 patients. Recently, stool samples from COVID-19 patients were found to be enriched with adsorbable nutrients, e.g., sucrose and 2-palmitoyl-glycerol, and with harmful metabolites, such as oxalate, while microbial-derived products, e.g., 2,4-di-tert-butylphenol, were reduced potentially reflecting the presence of dysbiosis and malnutrition in this setting<sup>28</sup>.

Although the gut bacteriome has been the most extensively investigated microbiome compartment, there is also some evidence of alterations in the gut mycobiome in COVID-19 patients. The intestinal fungal microbiome is composed of a large community of species that have a complex interaction with the bacteriome and is equally as capable of regulating the host immune system<sup>29</sup>. Hospitalized patients with COVID-19 have a more heterogeneous fecal mycobiome, enriched with opportunistic pathogens, such as *Candida* and *Aspergillus*, than healthy controls, but less diverse than those with bacterial pneumonia<sup>30</sup>.

Antibiotics, mainly moxifloxacin, ceftriaxone and azithromycin, are also commonly used to prevent secondary infections and complications of COVID-19<sup>31,32</sup>, as antibiotics are known to alter gut microbiota<sup>33</sup>, this overall amount of evidence pinpoints the use of antibiotic therapies in patients with COVID-19 as another potential driver of gut dysbiosis, beyond the presence of SARS-CoV2 itself.

## INFLUENCE OF GUT MICROBIOTA ON COVID-19

The human microbiota has an important influence on the host response to the infection, not only in the GI tract but also in the respiratory mucosa<sup>34,35</sup>, and dysbiosis could worsen the clinical picture. Other viral infections, such as influenza, have been studied in animal models, showing that the depletion of gut microbes through antibiotic exposure facilitates viral replication<sup>36</sup>. On the other hand, short-chain fatty acids (SCFAs) can reduce tissue damage caused by influenza infection as well as stimulate adaptive antiviral immunity, thus restoring a balanced immune system<sup>37</sup>. Another aspect of the influenza infection is that it can predispose to a successive bacterial superinfection, contributing to the morbidity and mortality in these patients. In murine models, a fecal transfer of gut microbes; conditioned by influenza A infection, was able to impair lung defenses against pneumococcal infection, through the reduction of SCFAs production<sup>33,38</sup>. In clinical studies, gut microbiota composition can not only differentiate between COVID-19 patients and controls, but can also be a marker of disease course, as it is associated with disease severity. In particular, there is a negative correlation between beneficial bacteria, such as *F. prausnitzii* or *Bifidobacterium bifidum*, and disease

severity<sup>39</sup>. The study also found that microbiota composition is significantly associated with plasma levels of cytokines and markers such as TNF- $\alpha$ , CRP, IL-10, CXCL10, LDH, GGT, AST, and NT-proBNP. These markers are typically increased in severe COVID-19, suggesting that gut microbiota may play a role in controlling the host's inflammatory response and the following outcomes of the disease<sup>39</sup>.

### Potential Therapeutic Approaches: Probiotics & Fecal Microbiota Transplantation

Probiotics can play an important role in modulating immune responses, and many studies have reported a favorable effect of different bacteria such as *Lactobacillus casei*, *Lactobacillus plantarum*, *Bifidobacterium bifidum*, and *Bacillus subtilis* in experimental animal models of respiratory tract viral infection<sup>40</sup>. Several studies of probiotics on COVID-19 outcomes and related gastrointestinal symptoms are ongoing. Current findings<sup>41</sup> to date have shown that probiotic therapies have led to improved survival rates in animals, attenuating clinical symptoms and lowering viral load in the lungs.

Fecal microbiota transplantation (FMT) may become an interesting possibility in the context of COVID-19 treatment. FMT is the transfer of a donor's feces in the intestine of a patient, in order to treat conditions associated with gut microbiota alterations. This procedure is recognized as life-saving therapy for recurrent *Clostridium difficile* infection but has also encouraging perspectives for the treatment of other pathologies<sup>42,43</sup>. Concerns about the risk of transmission of COVID-19 through the FMT have been raised, leading to specific updates of the protocols that minimize the risk of infection<sup>44-47</sup>. It has been hypothesized that FMT could be a possible treatment for COVID-19, through the regulation of the human immunity mediated by the gut microbiota, but the only data currently available are limited to COVID-19 patients who received FMT for an associated *C. difficile* infection. No studies have specifically studied FMT's potential therapeutic role in COVID-19 infection<sup>48</sup>. However, in a pilot study<sup>49</sup>, FMT has been used to treat residual gastrointestinal and psychological symptoms in a cohort of COVID-19 patients after discharge, suggesting its potential during post-infection recovery. Further studies are warranted to assess the real role and optimal protocol for FMT in patients with COVID-19.

### CONCLUSIONS

COVID-19, as other infectious diseases with gastrointestinal involvement can induce deep alterations of intestinal homeostasis, leading to a wide range of clinical manifestations. Gut microbiota may not only play a role in the pathogenesis of the COVID-19-related gastrointestinal disease, but also as a potential therapeutic tool. Further evidence is needed to clarify the relationship between SARS-CoV-2 and gut microbiota, and the potential consequences in clinical practice.

### Conflict of Interest

The authors declare no conflict of interest.

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