Gut Dysbiosis Correlates with COVID-19 Severity

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For
Senior Thesis
Fall 2023
December 4th, 2023
Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) impacts not only respiratory but also gut and oral microbiomes, influencing the manifestations of COVID-19. Each person’s unique microbiome consists of microorganisms such as bacteria, fungi, and viruses, some of which are symbiotic and others potentially harmful. Alterations in the gut microbiome, specifically, can affect the severity and symptoms of COVID-19. A review of studies indicate a pattern of gut dysbiosis in COVID-19 patients characterized by a decrease in beneficial microbiota and/or an increase in opportunistic pathogens. This gut imbalance correlates with disease severity, suggesting that the gut microbiome plays a significant role in the body's response to SARS-CoV-2 infection. The potential bidirectional relationship between COVID-19 and gut dysbiosis warrants research on possible therapeutics that could rebalance the gut microbiome both pre- and post SARS-CoV-2 infection. Though COVID-19’s manifestations are multifaceted, research focused on the depletion of butyrate-producing bacteria could prove to be fruitful in developing effective treatments.
Introduction

The virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes the disease named coronavirus 19 (COVID-19). The COVID-19 pandemic ensued soon after the disease’s discovery in December of 2019, with almost 800 million confirmed cases worldwide as of November 23, 2023. Although initially thought to be a respiratory disease, we now know it can affect the gastrointestinal (GI) tract, heart, brain, and many more organs (Figure 1). Additionally, the impact of COVID-19 varies greatly from mild-flu like symptoms to severe, life-threatening manifestations. In an attempt to uncover the reason for this symptom discrepancy between individuals, the amount of COVID-19 research has exploded. This review will focus primarily on any potential relationship between COVID-19 and the gut microbiome as microbial alterations could explain why SARS-CoV-2 affects people in dramatically different ways.

Figure 1. Multi-Organ Dysfunction with COVID-19. COVID-19 can be manifested in various body parts and systems, such as the brain, circulatory system, digestive system, sinus, and colon. Potential symptoms are stated for each organ. Adapted from Narayanan et al., 2023.
SARS-CoV-2 contains a spike protein on its surface that facilitates the spread of COVID-19 (Jackson et al., 2020). Once the spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on host cells, it has its outer portion (S1 domain) stripped from it, allowing the inner core (S2 domain) to be cut by a protein called TMPRSS2 (Figure 2; Jackson et al., 2020). After being freed from its S1 and S2 domains, the spike protein is able to unfold and anchor itself onto the host cell where it can release its RNA via endocytosis (Jackson et al., 2020). ACE2 receptors have been found to be highly expressed in the stomach and intestines, making the GI tract a potential route of infection (Figure 3; Oudit et al., 2023).

Figure 2. SARS-CoV-2 structure. The SARS-CoV-2 spike (S) protein consists of S1 and S2 domains that are then cleaved by furin before anchoring itself onto the host cell. Adapted from Jackson et al., 2020.
Figure 3. ACE2 Expression on the Human Body. scRNA-Seq was used to measure the density of ACE2 receptors. ACE2 receptors are predominantly expressed in the small intestines, shown by the bright red coloring in the abdominal region. Adapted from Oudit et al., 2023.

The Gut Microbiome

The human gut microbiome houses well over a trillion microorganisms of thousands of different species, with the largest amount being in the small and large intestines (Ursell et al., 2012). These microorganisms consist of bacteria, fungi, parasites, and viruses, some participating in a symbiotic relationship with humans and others being deleterious to human health (Ursell et al., 2012). Each person has a unique composition of microbiota originally determined by their DNA, making research all the more complicated (Ursell et al., 2012). The microorganisms in the gut are especially of interest due to their possible effects on the immune and digestive system.
Due to microbes' role in digesting otherwise indigestible complex substances, any interruption could lead to irritations in the gastrointestinal tract (Jovel et al., 2018). Additionally, studies suggest that the gut microbiome plays a vital role in the formation of mucosal immunity, thus maintaining a healthy microbiome can establish a strong immune system (Shi et al., 2017).

Factors such as antibiotics and the COVID-19 pandemic could contribute to an imbalanced gut microbiome and disrupt gut immunity. Though meant to target specific, pathogenic bacteria, antibiotics can also eradicate beneficial bacteria that play key roles in maintaining microbial diversity and richness (Patangia et al., 2022). Losing beneficial bacteria has led to consequences as extreme as death, proving the misuse of antibiotics to be of high importance (Patangia et al., 2022). Overusing or misusing antibiotics can also lead to antibiotic resistant bacteria, resulting in increased risk for microbial imbalances, named dysbiosis, and possibly worsened COVID-19 manifestations (Patangia et al., 2022). When the COVID-19 pandemic ensued, scientists were already investigating the hygiene hypothesis. The most updated version of the hygiene hypothesis states that some factors such as increased urbanization, hygienic practices, and overuse of antibiotics have contributed to decreased microbial diversity (Finlay et al., 2021). The pandemic amplified hygienic practices with measures such as being six feet away from others at all times, the use of a mask, constant washing of hands, and increased use of sanitizers (Finlay et al., 2021). Though key in preventing the spread of SARS-CoV-2, these hygienic measures could also lead to loss of microbial diversity (Finlay et al., 2021). In the process of trying to eradicate COVID-19, we may have made it harder for those with weakened gut microbiomes to recover from the infection. However, antibiotics and the pandemic aren’t the only factors that could exacerbate COVID-19 as dysbiosis has been observed in the oral and respiratory tract microbiomes of COVID-19 patients (Belizário et al., 2018). Though the gut
microbiome is of special interest, it is possible that dysbiosis in other microbiomes also contributes to COVID-19 severity.

**Potential Respiratory Tract Dysbiosis May Correlate with COVID-19 Severity**

SARS-CoV-2 was once thought to be solely a respiratory disease as it caused symptoms such as coughs and difficulty breathing, with many needing to be hospitalized and placed on a ventilator. Considering the impact SARS-CoV-2 has on the respiratory system, the respiratory tract microbiome may play a large role in COVID-19 severity. In a cross-sectional study, the bacterial profiles of 69 COVID-19 inpatients were analyzed (Chen et al., 2020). Eight potential biomarkers were identified to distinguish between severe and mild patients, including *Treponema, Leptotrichia, Lachnoanaerobaculum, Parvimonas, Alloprevoteva, Porphyromonas, Gemella, and Streptococcus* (Chen et al., 2020). Additionally, microbial diversity and richness were significantly lower in severe cases of COVID-19 when compared to mild cases (Chen et al., 2020). When comparing the microbiomes of the upper respiratory tract to that of the lower respiratory tract, findings varied (Figure 4). One review found no significant differences in the nasopharyngeal microbiome, part of the upper respiratory tract, of COVID-19 patients when compared to that of control patients who tested negative for SARS-CoV-2 (Yamamoto et al., 2021). On the other hand, the lung microbiomes, part of the lower respiratory tract, of patients with COVID-19 were significantly different from that of healthy controls (Yamamoto et al., 2021).

Further research is still required to confirm dysbiosis in the respiratory tract and if it develops pre- or post- SARS-CoV-2 infection. Dysbiosis in the respiratory tract microbiome could explain why some patients need additional interventions like ventilation and others don’t.
Identifying potential biomarkers could also help identify if a patient is prone to a severe reaction or not, allowing for the early intervention of medical professionals.

![Conducting Passages Diagram]

Figure 4. Anatomy of the upper and lower respiratory tract. The nasopharynx is where the nasal cavity and pharynx meet. Adapted from NIH, 2019.

**How SARS-CoV-2 and the Oral Microbiome Correlate**

Considering that the mouth can be an initial point of contact with SARS-CoV-2, it is important to understand the correlational relationship between oral dysbiosis and COVID-19 severity. Patients experiencing severe COVID-19 were found to have more local inflammation than patients experiencing less severe symptoms (Soffritti et al., 2021). This inflammation also correlated with decreased alpha diversity and species richness (Soffritti et al., 2021). Local inflammation could allow SARS-CoV-2 to more easily infect, possibly increasing COVID-19 severity (Soffritti et al., 2021). Specifically, microbiota including the genera *Prevotella* and *Veillonella*, which are known to be pro-inflammatory, were in abundance in patients with
COVID-19 (Table 1; Soffritti et al., 2021; Haran et al., 2021). Many species within the Prevotella, Leptotrichia, and Fusobacterium genera were also found to be associated with longer lasting symptoms in COVID-19 patients (Table 1; Haran et al., 2021).

Though still yet to be confirmed, increased inflammation and/or pro-inflammatory genera could help explain why some people suffer more severe COVID-19 symptoms and others do not. One possibility could be that large amounts of pro-inflammatory microbiota in the oral microbiome prior to infection allow SARS-CoV-2 to better establish itself and may worsen symptoms. On the other hand, SARS-CoV-2 could alter the oral microbiome such that pro-inflammatory microbiota increase in abundance, weakening the immune system further. The relationship between dysbiosis in the oral microbiome and COVID-19 still needs to be established. If there is a clear relationship, understanding the role of pro-inflammatory microbiota genera on COVID-19 severity may explain symptom discrepancies between individuals.

Table 1. Oral Bacteria and Their Characteristics

<table>
<thead>
<tr>
<th>Genera</th>
<th>Characteristics</th>
<th>Implications on COVID-19</th>
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<tbody>
<tr>
<td><em>Prevotella</em></td>
<td>- Pathogenic (Soffritti et al., 2021)</td>
<td>- In patients with longer lasting symptoms (Haran et al., 2021)</td>
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<tr>
<td></td>
<td>- Virulence mechanisms: attachment to mucosa, immune system invasion, increased production of virulence factors, and can disable and kill neutrophils (Murray et al., 2016)</td>
<td>- Pro-inflammatory, which could make it easier for SARS-CoV-2 to establish itself (Soffritti et al., 2021; Haran et al., 2021)</td>
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<td></td>
<td>- About 20 species have been linked to causing human diseases (Garrett et al., 2015)</td>
<td>- Potential biomarkers (Lu et al., 2023)</td>
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<td>- Promotes viral infections (Khan, 2020)</td>
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**Veillonella**
- Of limited pathogenicity, considered harmless or even beneficial (Actor, J.K, 2012)
- Considered normal flora in the mouth, gastrointestinal tract, and sometimes the vagina (Actor, J.K, 2012)
- Often associated with oral and soft tissue infections (Actor, J.K, 2012)
- Implicated as pathogens in infections of the sinuses, heart, lungs, bone, and central nervous system (Actor, J.K, 2012)
- Enriched in gastric cancer patients (Bartelli *et al.*, 2019)
- Pro-inflammatory, which could make it easier for SARS-CoV-2 to establish itself (Soffritti *et al.*, 2021; Haran *et al.*, 2021)
- Most prominent biomarker in patients compared to healthy controls or flu patients (Ma *et al.*, 2021)

**Leptotrichia**
- May be pathogenic (Chapter 3 - Supragingival Microbes, 2015)
- Found in oral and vaginal cavities (Gupta & McGrath, 2008)
- Enriched in gastric cancer patients (Bartelli *et al.*, 2019)
- Could be used to treat respiratory diseases such as COVID-19 (Deol *et al.*, 2022)
- Found in patients with longer lasting symptoms (Haran *et al.*, 2021)
- Could contribute to inflammation (Gupta & McGrath, 2008)

**Fusobacterium**
- Opportunistic pathogen (Booth, 2007)
- Normal flora of mouth, gastrointestinal tract, and female genital tract (Brook, 2008)
- Can produce a lipopolysaccharide that is responsible for the production of cytokines and other inflammatory mediators (Cobo, 2022)
- Found in patients with longer lasting symptoms (Haran *et al.*, 2021)
- Have been present in the bloodstream, possibly increasing COVID-19 severity (Wolff *et al.*, 2021)

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**Gut Dysbiosis Correlates with COVID-19**

Significant dysbiosis in the gastrointestinal tract of COVID-19 patients is characterized by decreased beneficial microbiota and increased opportunistic pathogens. In some patients, SARS-CoV-2 can cause gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and
vomiting, all of which could be exacerbated by gut dysbiosis (Groff et al., 2021). COVID-19 patients tended to have increased abundances of Acidaminococcaceae, Erysipelatoclostridiaceae, and Erysipelotrichaceae families when compared to healthy controls (Table 2; De Nies et al., 2023). Acidaminococcaceae, Erysipelatoclostridiaceae, and Erysipelotrichaceae families are of special interest as they were associated with increased abundance and expression of virulence factors (VFs), factors that contribute to the success of some pathogens by allowing them to colonize host niches and establish infections (De Nies et al., 2023). Antimicrobial resistance genes (ARGs), encoded and expressed by members of the Acidaminococcaceae and Erysipelatoclostridiaceae family, were also found to be in abundance in COVID-19 patients, showing a possible link between VFs and ARGs (De Nies et al., 2023). This association between COVID-19 and ARGs could prove to be dangerous as co-infections would be increasingly difficult to treat if antibiotics are inefficient and VFs, in higher abundance, are aiding pathogens.

Associations between some bacteria and COVID-19 severity were identified. Members of the Bacteroidaceae family, which downregulate expression of ACE2 receptors in murine gut, were inversely correlated with SARS-CoV-2, potentially worsening COVID-19 symptoms (Table 2; Zuo et al., 2021). An inverse correlation between Faecalibacterium prausnitzii, which produces butyrate and bioactive anti-inflammatory molecules, and COVID-19 severity was observed as well (Parsaei et al., 2021; Zuo et al., 2021). COVID-19 patients with severe symptoms also had greater abundances of Coprobacillus, Clostridium ramosum and Clostridium hathewayi, all of which could exacerbate COVID-19 (Table 3). Coprobacillus has been shown to upregulate colonic ACE2 expression in the murine gut, which could make it easier for SARS-CoV-2 to successfully invade (Zuo et al., 2021). Additionally, C. ramosum and C.
* hathewayi * have been associated with infection and bacteremia, the presence of bacteria in the blood (Zuo *et al*., 2021).

Table 2. Gut Bacterial Families and Their Characteristics

<table>
<thead>
<tr>
<th>Family</th>
<th>Characteristics</th>
<th>Implications on COVID-19</th>
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<tbody>
<tr>
<td>Acidaminococcaceae</td>
<td>- Produces butyrate (Duttaroy, 2021)</td>
<td>- Encode antibiotic resistant genes (De Nies <em>et al</em>., 2023)</td>
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<td>- Show some antibiotic resistance (Chen &amp; Liu, 2022)</td>
<td>- Association with increased expression of virulence factors (De Nies <em>et al</em>., 2023)</td>
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<tr>
<td></td>
<td>- Association to obesity (Salsinha &amp; Pintado, 2023)</td>
<td>- Contains pathogenic microbes, such as Phascolarctobacterium, that are enriched in COVID-19 patients (Wang <em>et al</em>., 2023)</td>
</tr>
<tr>
<td>Erysipelatoclostridiaceae</td>
<td>- Typical in normal gut flora (de Nies <em>et al</em>., 2023)</td>
<td>- Specific species, such Erysipelatoclostrium ramosum, have been associated with systemic infection and inflammatory response syndrome (de Nies <em>et al</em>., 2023)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Encode antibiotic resistant genes (De Nies <em>et al</em>., 2023)</td>
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<tr>
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<td></td>
<td>- Association with increased expression of virulence factors (De Nies <em>et al</em>., 2023)</td>
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**Erysipelotrichaceae**
- Short-chain fatty acid producer (Waluga, 2020)
- Specific taxa within may be correlated with inflammation (Kaakoush, 2015)
- Positively correlated with COVID-19 severity, possibly playing a role in augmenting SARS-CoV-2 infection in the gut (Zuo et al., 2020)

**Bacteroidaceae**
- Fermentative abilities (Berman, 2019)
- Associated with cirrhosis (Punzalan & Qamar, 2017)
- Common in healthy gut flora (Yin et al., 2022)
- Downregulate ACE2 receptors and found to have an inverse correlation with SARS-CoV-2 (Zuo et al., 2021)

Several bacteria that are known to maintain intestinal health are depleted in COVID-19 patients. For example, *Bifidobacteria, Eubacterium rectale*, and *F. prausnitzii* have been shown to be diminished in COVID-19 patients (Table 3; Rossini et al., 2022). This depletion could be detrimental to gut health as they all, directly and indirectly, contribute to butyrate production. *Bifidobacteria* produce acetate, the consumption of which is a major driver of butyrate production by *F. prausnitzii* and *E. rectale* (Table 3; Lebas et al., 2020; Lordan et al., 2019; O’Callaghan et al., 2016). Butyrate, a short-chain amino acid, typically benefits human health by maintaining intestinal barrier function and participating in immune-regulation (Canani et al., 2011). Butyrate may also play a role in reinforcing the colonic defense barrier by stimulating MUC2 mucin production, which in turn protects the gastrointestinal mucosa (Canani et al., 2011). This decreased butyrate production in COVID-19 patients may lead to a weakened gastrointestinal barrier, characterized by low mucus levels. A weakened barrier means pathogens are more likely to successfully invade, increasing the risk of gastrointestinal symptom severity.
and complete invasion of SARS-CoV-2 (Wang et al., 2022). However, individuals with severe gastrointestinal symptoms may have already had relatively low butyrate levels prior to SARS-CoV-2 infection. The relationship between butyrate and COVID-19 has yet to be defined.

Table 3. Characteristics of Bacterial Species and Genera

<table>
<thead>
<tr>
<th>Species/Genera</th>
<th>Characteristics</th>
<th>Implications on COVID-19</th>
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<tbody>
<tr>
<td>Clostridium hathewayi</td>
<td>- Newly described species (Elsayed &amp; Zhang, 2004)</td>
<td>- Linked to fatal infection cases like sepsis, possibly increasing COVID-19 severity (Rossini et al., 2022)</td>
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<td></td>
<td>- Opportunistic pathogen (Zuo et al., 2021)</td>
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<tr>
<td>Clostridium ramosum</td>
<td>- Opportunistic pathogen (Zuo et al., 2021)</td>
<td>- Associated with infection, increasing chances of co-infection (Zuo et al., 2021)</td>
</tr>
<tr>
<td></td>
<td>- Immune-regulatory characteristics (Zuo et al., 2021)</td>
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</tr>
<tr>
<td>Faecalibacterium praunitzii</td>
<td>- Beneficial (Zuo et al., 2021)</td>
<td>- Inverse relationship with COVID-19 severity (Zuo et al., 2021)</td>
</tr>
<tr>
<td></td>
<td>- Butyrate-producing (Zuo et al., 2021)</td>
<td>- Decreased butyrate in the gut (Rossini et al., 2022)</td>
</tr>
<tr>
<td></td>
<td>- Anti-inflammatory (Zuo et al., 2021; Parsaei et al., 2021; Fitzgerald et al., 2018)</td>
<td></td>
</tr>
<tr>
<td>Eubacterium rectale</td>
<td>- Beneficial (Zuo et al., 2021)</td>
<td>- Decreased butyrate in the gut (Rossini et al., 2022)</td>
</tr>
<tr>
<td></td>
<td>- Butyrate-producing (Zuo et al., 2021)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Beneficial for colon health (Wang et al., 2021)</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>- Beneficial (O’Callaghan &amp; van Sinderen, 2016)</td>
<td>- Decreased butyrate in the gut (Rossini et al., 2022)</td>
</tr>
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<td></td>
<td>- Among the first to colonize the gastrointestinal tract (O’Callaghan &amp; van Sinderen, 2016)</td>
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<tr>
<td></td>
<td>- Could act as a probiotic (O’Callaghan &amp; van Sinderen, 2016)</td>
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</table>
- Produces acetate, acting as a driver for butyrate production by *F. prausnitzii* (Lebas et al., 2020)

**Coprobacillus**
- Opportunistic pathogen (Zuo *et al.*, 2021)
- Obesity-associated (Bermano *et al.*, 2020)
- Upregulates colonic ACE2 expression in the murine gut (Zuo *et al.*, 2021)

These bacterial depletions in COVID-19 patients have been correlated with an increase in production of pro-inflammatory cytokines and chemokines (Rossini *et al.*, 2022). Following the infection of SARS-CoV-2 on various tissues of the gastrointestinal tract, immune cells release cytokines (Rossini *et al.*, 2022). High levels of cytokine storms, also referred to as cytokine release syndrome (CRS), were also associated with COVID-19 severity (Cleveland Clinic, 2022; Villapol, 2020). This is logical as cytokines are chemical messengers that attract immune cells to the area of the body in need of repair (Cleveland Clinic, 2023). However, this hyperactivity of the immune system can be harmful as inflammation increases significantly and CRS is characterized by multi-organ dysfunction, a severe symptom of COVID-19 (Montahersaze *et al.*, 2022). Thus, if bacterial depletions correlate with CRS, there is a possibility that gut dysbiosis contributes to the symptom severity range we see in COVID-19 cases.

**Fungal Dysbiosis Correlates with COVID-19 Severity**

Fungal dysbiosis in COVID-19 patients, characterized by increased opportunistic fungal pathogens, could explain severity discrepancies. The fungi *Candida albicans*, *Candida auris*, *Aspergillus flavus*, and *Aspergillus niger* were of note as they could both be correlated to COVID-19 severity (Zuo *et al.*, 2020; Zuo *et al.*, 2021). COVID-19 patients with candidemia, a blood infection of *C. albicans*, tended to need mechanical ventilation (Roudbary *et al.*, 2021). Candidemia also has a high mortality rate, with reports as high as 50%, possibly contributing to
the high COVID-19 mortality rates (Mora Carpio & Calimaco, 2023). A. flavus and A. niger are known to cause pulmonary aspergillosis and coughs (Zuo et al., 2020). A. flavus was present in 6/30 patients with mild COVID-19 with an abundance of up to 2.28%, while A. niger was present in 4/30 patients with a lower abundance of <1%, with both appearing at various times after their nasopharyngeal swab yielded a negative result (Zuo et al., 2020). The presence of Aspergillus in patients with mild cases of COVID-19 uncovers the possibility that fungi can also serve as potential biomarkers for severity (Zuo et al., 2020). Thus, further research should be conducted on the relationship between Candida fungi and severe COVID-19 cases and Aspergillus fungi and mild COVID-19 patients.

**Potential Therapeutics to Maintain and/or Improve Gut Health**

Therapeutic approaches may restore or strengthen the gut microbiome, possibly preventing and/or helping people recover from severe COVID-19 symptoms. One possible intervention is a fecal microbiota transplantation (FMT), where the feces of a healthy donor is transplanted to a patient in need by colonoscopy, a capsule, an enema, or, less commonly, a tube that travels down the duodenum (Johns Hopkins Medicine, 2022). FMT has had great success in the treatment of Clostridium difficile infection and is being considered for the treatment of other gastrointestinal disorders (Gupta et al., 2015; Patangia et al., 2022). Studies are already beginning to emerge on this topic with one reporting that 5 out of 11 COVID-19 patients had improved gastrointestinal symptoms and increases in Bifidobacterium and Faecalibacterium (Wang et al., 2021). FMT could assist the colonization of bacteria such as Bifidobacterium, F. Prausnitzii and E. Rectale, increasing butyrate production and in turn strengthening the gastrointestinal barriers. Additionally, if these bacterium revert back to their respective abundances, the risk of cytokine storms could reduce, hopefully decreasing hyperinflammation.
and the risk of multi-organ failure. Overall, FMT is an appealing option for those with microbial dysbiosis before or after COVID-19.

A new butyrate releaser N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA) could be is a promising strategy against COVID-19 with it reducing cell mediators of SARS-CoV-2 and pro-inflammatory cytokines (Paparo et al., 2022). A study tested FBA’s protective action against SARS-CoV-2 after reports of microbial dysbiosis in COVID-19 patients were found to lead to decreases in butyrate production (Paparo et al., 2022). After incubating healthy human small intestine samples with FBA, they found that ACE2, TMPRSS2, and NRP1 expression decreased in comparison to the medium alone (Paparo et al., 2022). They found the same results with the human enterocytes cell line (Paparo et al., 2022). They also found that Nf-kB, a nuclear factor that activates cytokine storms, had reduced activity in the presence of FBA (Paparo et al., 2022). This study’s findings suggest that FBA could be administered orally to limit COVID-19, but many more clinical trials would need to be conducted to confirm FBA is both effective and safe for human use. Moving forward, FBA should be tested on mild and severe cases COVID-19, as well as on people who had prolonged symptoms of COVID-19 despite testing negative, to see if it can be used once SARS-CoV-2 has infected the body.

Pre- and probiotics are another encouraging approach for restoring the gut microflora balance. Prebiotics are foods high in fiber that act as food for human microflora, while probiotics are foods or supplements with live organisms (Mayo Clinic, 2022). Probiotics work to maintain or restore the gut microbiome by promoting antimicrobial peptide production, producing bacterial inhibitors, enhancing barrier function, modulating immunity, and suppressing the growth of non-commensals (Patangia et al., 2022). Probiotics could carry specific bacteria seen to be depleted in COVID-19 patients, such as Bifidobacterium (Olaimat et al., 2020). They could
also inhibit ACE enzymes by blocking the active sites with the production of bioactive peptides and/or by acting as debris once dead (Olaimat et al., 2020). Prebiotics could support a healthy microbiome by promoting the metabolism and proliferation of beneficial bacteria. In doing so, they indirectly contribute to the blocking of ACE enzymes (Olaimat et al., 2020). Though the potential of probiotics and prebiotics as a therapeutic approaches is exciting, there are no conclusive statements yet made.

**Conclusion**

Due to its multi-organ effects and wide-range of symptoms, COVID-19 has proven difficult to understand. One of the organs COVID-19 affects is the gastrointestinal tract, causing scientists to draw their attention to alterations in the gut microbiome and what role they can play in COVID-19 severity. Gut dysbiosis has been found COVID-19 patients, characterized by a depletion in beneficial, symbiotic bacteria and increase in bacterial and fungal opportunistic pathogens. Beneficial bacterium such as *Bifidobacteria*, *F. prausnitzii*, and *E. rectale*, all key in maintaining a healthy gut, are depleted in COVID-19 patients. The lack of butyrate could compromise the immune system by weakening the intestinal barrier, making it easier for SARS-CoV-2 to infect an individual. Additionally, these depletions are correlated with cytokine storms, which exacerbate COVID-19 through hyperinflammation. Members within the *Acidaminococcaceae*, *Erysipelatoclostriidae*, and *Erysipelotrichaceae* families were associated with increased virulence factors (VFs) and antibiotic resistant genes (ARGs) in COVID-19 patients. VFs and ARGs could make SARS-CoV-2’s infection more successful and severe, especially in those with weakened immune systems.

The relationship between gut dysbiosis and COVID-19, however, is far from being determined as it is very complex and could be bidirectional. While it may be that COVID-19
causes alterations in the gut microbiome, pre-existing microbial imbalances could predispose people to more severe manifestations. It is also important to note that dysbiosis in the oral and respiratory tract microbiomes could contribute to COVID-19 severity. Therapeutics such as probiotics, prebiotics, FMT, or a new butyrate releaser could help restore the gut microbiome to a healthy state, possibly mitigating the symptom severity discrepancy found person to person.

Research on the depletion of bacteria that produce butyrate could prove to be beneficial as butyrate plays a vital role in maintaining a healthy intestinal barrier. If the gastrointestinal lining is fortified, perhaps SARS-CoV-2, along with other opportunistic pathogens, would not infect as successfully. Moreover, a better understanding of the relationship between COVID-19 and gut dysbiosis could help prevent severe symptoms from manifesting, decreasing hospitalizations and even fatalities related to COVID-19.
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