

The Role of Gut Microbiota Dysbiosis as a Potential Factor in Early Diagnosis, Prognosis, and Therapeutic Strategy of COVID-19 Patients

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ABSTRACT

The global pandemic triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the most extensive public health crisis since the influenza pandemic of 1918. Beyond targeting the respiratory system, SARS-CoV-2 can also affect multiple organs, leading to a range of clinical manifestations from asymptomatic cases to severe multiorgan dysfunctions. However, the impact of the coronavirus disease 2019 (COVID-19) is devastating and has become the current world major public health issue. It is typically associated with a set of comorbidities such as hypertension, diabetes, obesity, and advanced age, which significantly exacerbates the consequences of infection. During the early stages of COVID-19, SARS-CoV-2 can cause gastrointestinal symptoms such as vomiting, diarrhea, or abdominal pain. Intestinal dysfunction alters intestinal microbes and increases inflammatory cytokines. Subsequently, it is important to identify these symptoms before respiratory issues become crucial for timely diagnosis and treatment. Discovering the composition of the microbiota and the metabolic products in the context of COVID-19 can aid in the identification of novel disease biomarkers and therapeutic targets. Further investigation is needed to elucidate changes to the microbiome as reliable biomarkers in the context of COVID-19.

Keywords: correlation, COVID-19, diagnosis, microbiota, prognosis, therapeutic

ABSTRAK

Virus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) telah menyebabkan pandemi secara global dan lebih luas dibandingkan dengan pandemi influenza pada tahun 1918. Konsekuensi dari penyakit yang diakibatkan oleh virus Coronavirus-19 (COVID-19) adalah menjadi masalah kesehatan masyarakat utama di dunia saat ini. SARS-CoV-2 tidak hanya menyerang sistem pernapasan, tetapi juga dapat menyerang banyak organ dalam tubuh. Manifestasi klinis yang ditimbulkan bersifat bervariasi dari disfungsi multiorgan tanpa gejala hingga gejala yang parah. COVID-19 biasanya dikaitkan dengan serangkaian penyakit penyerta seperti hipertensi, diabetes, obesitas, dan/atau usia lanjut, yang secara signifikan memperburuk konsekuensi infeksi. Pada tahap awal penyakit, SARS-CoV-2 juga dapat menyebabkan gejala gastrointestinal seperti muntah, diare, atau sakit perut. Disfungsi usus mengubah mikroba pada usus dan meningkatkan sitokin inflamasi. Oleh karena itu, diagnosis gejala gastrointestinal yang memicu masalah pernapasan selama infeksi COVID-19 mungkin

diperlukan untuk diagnosis dan pengobatan dini yang lebih baik. Menemukan komposisi mikrobiota dan produk metabolismenya dalam konteks penyakit COVID-19 dapat membantu mengidentifikasi biomarker dan target terapi. Penjelasan perubahan pada mikrobiota sebagai potensi biomarker merupakan bagian dari teka-teki penyakit yang perlu diselidiki lebih lanjut.

Kata kunci: Covid-19, diagnosis, korelasi, mikrobiota, prognosis, terapi

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global disaster resulting in more than 100 million infections and 2 million deaths. Although patients typically experience mild respiratory symptoms, such as the common cold, severe cases are usually associated with a cytokine storm that can lead to multi-organ dysfunction.¹ COVID-19 infection can affect many organs, including the lungs, kidneys, heart, liver, central nervous system, and gastrointestinal (GI) tract. Recent research suggests that the resident microbial communities can act as local and systemic inflammatory modulators, showing the presence of a communication axis between gut microbiota and several organs in the human body.²

Considering its importance, gut microbiota has been referred to as "the second brain." The recent SARS-CoV-2 pandemic has underscored the role of gut microbiota in influencing disease progression and clinical outcomes. Symptoms propose that the microbiota of infected patients may undergo substantial dysbiosis, specifically in individuals exhibiting symptoms of long COVID-19 (post-associated COVID-19 sequelae).³ In this context, GI symptoms and the diagnosis of gut dysbiosis have been observed in SARS-CoV-2 patients, particularly prevalent in those experiencing prolonged symptoms. Furthermore, preliminary investigation found that this fecal microbiota was significantly altered compared to healthy subjects, with an enrichment of opportunistic pathogens and a depletion of beneficial bacteria.^{3,4} The presence of GI symptoms significantly increased the deterioration of clinical symptoms in COVID-19 patients. Therefore, this research aims to examine the current understanding of dysbiosis during SARS-CoV-2 infection and the role in early diagnosis, predicting disease severity, and as a potential target for new treatment in COVID-19 infection.

COVID-19 INFECTION AND GASTROINTESTINAL TRACT

SARS-CoV-2 virus infection not only causes respiratory symptoms but also contributes to an exacerbation of diverse GI manifestations. The development of GI abnormalities, both short-term and long-term, due to coronavirus infection is not fully understood, this is likely due to multifactorial mechanisms within the intestine. These mechanisms involve direct viral cytotoxicity mediated by angiotensin-converting enzyme-2 (ACE-2) on the intestinal mucosa, inflammation triggered by increased levels of inflammatory cytokines, disruption of the intestinal microbial ecosystem, and vascular abnormalities.^{5,6}

The precise underlying mechanisms causing the exacerbation of GI abnormalities are still unknown. However, the presence of viral ribonucleic acid (RNA) genome detected in stool samples from 86-100% of patients more than 30 days after infection, as well as positive staining of the viral nucleocapsid protein in the cytoplasm of gastric, duodenal, and rectal epithelium in endoscopic samples, suggests a reasonable infectious capacity and pathogenic effect of the virus at the enteric level.⁷

There is a close correlation between the composition of gut and lung microbiota, suggesting a comprehensive wide network in the human body established since birth. The long-reaching immune impact of gut microbiota is now being recognized, specifically on the pulmonary immune system. The mesenteric lymphatic system serves as an important bridge between intestine and lung, through which intact bacteria, their fragments, or metabolites (e.g. short-chain fatty acid/SCFA) may translocate across the intestinal barrier, accessing the systemic circulation, and modulate the lung immune response.⁸

Gut microorganisms also contribute both local and systemic inflammatory activity, with investigation revealing that respiratory infections are associated to compositional and functional changes in gut microbiota. This occurs through vital crosstalk known as the 'gut-lung axis' between gut microorganisms and

the pulmonary system. The bi-directional interactions between gut microbiota and the lungs have been associated with host immune responses to SARS-CoV-2.⁹ In human examination, microbiome alterations and gut barrier dysfunction are associated with COVID-19, which could increase the translocation of bacterial products and toxins into the circulatory system and increase the systemic inflammatory response.² Disruption of gut microbiota could negatively influence the recruitment of immune cells to the lung and increase susceptibility to developing respiratory tract infections. Furthermore, gut microorganisms could lead to a decreased expression of ACE-2, a key regulator of innate immunity and microbial ecology, thereby influencing viral invasion and replication. In general, state-of-the-art microbiome analyses have significantly advanced the understanding of the role gut microorganisms play in SARS-CoV-2 pathogenesis, COVID-19 severity, and prognosis.¹⁰

Another etiopathogenic hypothesis for GI changes in COVID-19 patients could be the ACE-2 receptor, which is abundant in intestinal epithelial cells. ACE-2 plays a role in regulating Na⁺ and the neutral amino acid co-transporter B⁰AT1, as well as maintaining intestinal microbial homeostasis, innate immunity, intestinal inflammation, and colitis susceptibility. Research showed that the absence of the B⁰AT1 transporter on the apical surfaces of enterocytes in ACE-2 mutant mice increased susceptibility to epithelial inflammation and immunity through attenuation of the mTOR pathway and altered expression of antimicrobial peptides (AMPs) by Paneth cells, in addition to causing a drastic reduction in Na⁺ and amino acid uptake.^{2,5,6} The mTOR-autophagy molecular crosstalk sheds light on how SARS-CoV-2 adhesion to the ACE-2/B⁰AT1 complex may result in altered enterocyte viability, epithelial barrier dysfunction, and chronic GI dysfunction. The dysfunction of tryptophan, phenylalanine, glutamine, and leucine absorptive mechanisms can cause an ionic imbalance in the intestinal lumen, resulting in persistent diarrhea and inflammation and altering the ecology of the bacterial flora.¹¹

GUT MICROBIOTA DYSBIOSIS OF COVID-19 PATIENTS

Numerous research reported a correlation between COVID-19 and gut microbiota dysbiosis. Acute COVID-19 infection is associated with consistent changes in gut microbiota composition impaired SCFA biosynthesis and disrupted tryptophan metabolism.

Disrupted SCFA and tryptophan metabolism causes alteration of gut microbiota characterized by increased of *Enterococcus*, *Rothia*, and *Lactobacillus*, and also depletion of *Faecalibacterium*, *Eubacterium*, *Coprococcus*, *Ruminococcus*, *Lachnospira*, and *Roseburia*. In the post-acute COVID-19 phase, gut microbiota remain persistently disrupted, characterized by persistent depletion of SCFA-producing bacteria such as *Faecalibacterium*, *Eubacterium*, and *Roseburia*.¹⁰

The bacterial composition of COVID-19 patients shows a significant depletion of *Ruminococcus*, *Alistipes*, *Eubacterium*, *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, *Fusicathenibacter*, and *Blautia* and enrichment of *Eggerthella*, *Bacteroides*, *Actinomyces*, *Clostridium*, *Streptococcus*, *Rotia*, and *Collinsella* was the most significant change in the bacterial composition of COVID-19 patients.^{11,12} Regarding *Candida* spp., there was an increase in *Candida albicans* and a decrease in *Candida glabrata* and *Candida parapsilosis*. There was an enrichment of *Aspergillus flavus* and *Aspergillus niger* and a depletion of *Aspergillus rugulosus*, *Aspergillus tritici*, and *Aspergillus penicillioides* in the *Aspergillus* spp. In addition, one investigation found a decrease in seven unclassified species from the order Helotiales, Pleosporales, and Sordariales, the family Exidiaceae, and the genera *Microscypha* and *Emericellopsis* in COVID-19 patients.¹³ Patients had lower levels of the phyla Firmicutes and Bacteroidetes and higher levels of the phylum Actinobacteria.

According to Zuo et al, most alterations in gut microbiota composition persist even after viral clearance, suggesting that the infection and hospitalization may be associated with a long-term adverse effect on the composition of the intestinal microflora community and subsequent recovery delays.¹⁴ Subsequently, a correlation between COVID-19 severity grade and the basal fecal microbiota has been established. In this research, 23 bacterial taxa showed a significant positive correlation with disease severity, using the main bacteria presenting a positive association with COVID-19 severity belonging to the filo Firmicutes and the genus *Coprobacillus*, as well as the *Clostridium ramosum* and *Clostridium hathewayi* species.¹⁴

Alteration in gut microbiota causes significant inflammation and immune dysregulation, which results in GI symptoms.¹⁵ Therefore, the presence of GI symptoms may correlate with COVID-19 infection and its detection may have a beneficial role in early diagnosis. This hypothesis was supported by the

research conducted by Lin et al, which reported that 11% of patients infected with COVID-19 present with GI symptoms at admission, and earlier data suggested that 3% of patients could present with GI symptoms.¹⁵ There have been cases of diarrhea, nausea, vomiting, and abdominal pain or discomfort described before the beginning of an illness or even before respiratory symptoms. GI symptoms, which on average appeared 4.9 days before admission but might have appeared up to 20 days earlier, can signal COVID-19. The data confirm the significance of incorporating GI symptoms into the spectrum of COVID-19 features. This inclusion enables early diagnosis and appropriate treatment, particularly in patients who may not exhibit respiratory symptoms. This could be of particular importance considering the rapid human-to-human transmission among close contacts, which could be related to GI viral infection and potential oral-fecal transmission, possibly persisting even after viral clearance from the respiratory tract. GI manifestations of COVID-19 are early, and possibly isolated, signs of the disease. Therefore, the presence of GI symptoms during COVID-19 should always be considered as an infection.¹⁵ In healthy individuals, gut microbiota may offer a better understanding of individuals' susceptibility to COVID-19.¹⁶ Changes in the standard composition and function of intestinal microbiota may predispose healthy individuals to an atypical inflammatory response, such as the one seen in COVID-19 cases.¹⁷

BIOCHEMICAL AND IMMUNOLOGIC MODIFICATIONS CONCERNING GUT MICROBIOTA ALTERATIONS OF COVID-19 PATIENTS

The promotion of immunomodulation as a therapeutic approach acknowledges the challenges in preventing viral spread and the absence of a definitively effective treatment against viruses.¹⁸ Given the increased generation of proinflammatory cytokines, which is known to be essential to the pathophysiologic process of severe COVID-19, this method is specifically important. In these circumstances, the absence of negative feedback immune system leads to excessive synthesis of inflammatory cytokines, with harmful effects and a poor prognosis. Subsequently, severe COVID-19 has been associated with interleukin-1 (IL-1), interferon-gamma (IFN-gamma), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1 (MIP-1alpha/

CCL3), and monocyte chemoattractant protein-1 (MCP-1/CCL2).¹⁹

Serum C-reactive protein (CRP) has been identified as a crucial measure that undergoes significant alteration in severe COVID-19 patients.²⁰ CRP rises quickly within 6 to 8 hours and reaches the greatest peak 48 hours after the commencement of the disease. The concentration drops when the inflammatory stages are over and patients are recuperating. Subsequently, phosphocholine, which is heavily expressed on the surface of injured cells, is where CRP prefers to bind. This binding activates the traditional complement of the immune system pathway and modifies phagocytic activity to eliminate pathogens.^{18,20} Small mononuclear cells known as lymphocytes without specialized granules are migratory cells that move to inflammation-affected regions both early and later on in the process. These cells are crucial in immunologic reactions because they are the source of cellular immune response and serum immunoglobulins.²¹

COVID-19 patients had significantly higher levels of interleukin (IL-2, IL-4, IL-6, IL-10), tumor necrosis factor (TNF), C-reactive protein (CRP), and lower lymphocyte counts in most research when compared to healthy controls.²² A positive correlation was found between *Bifidobacterium* spp. and prothrombin time (PT) and lactate dehydrogenase (LDH) in one investigation. In critical COVID-19 patients, there was also a negative correlation between *Atopobium* spp. and D-dimer, *Bacteroides* spp. and LDH and creatine kinase (CK) level, *Clostridium butyricum* and CRP and neutrophil count, and *Faecalibacterium prausnitzii* and CRP.²³ One research discovered a correlation between a specific genus of gut microbiota and immunological and biochemical changes in critical and severe COVID-19 patients. *Faecalibacterium prausnitzii* and *Clostridium leptum* had a positive correlation with neutrophil count in severe patients, as did *Eubacterium rectale* with IL-6 and *Enterobacteriaceae* with aspartate aminotransferase (AST).^{14,16,17} *Bacteroides ovatus*, *Lachnospiraceae* bacterium, and *Eubacterium ventriosum* had a positive correlation with CD4 and CD8 lymphocytes and other T-cells. Meanwhile, *Faecalibacterium prausnitzii* had a positive correlation with natural killer (NK) cells and a negative correlation with *Coprobacillus* spp., *Clostridium ramosum*, and *Clostridium symbiosum*.^{23,24}

COMORBIDITIES AS COVID-19 RISK FACTORS CORRELATED WITH MICROBIAL DIVERSITY LOSS

SARS-CoV-2 can infect people of all ages, but older adults and those with preexisting medical conditions are more likely to have severe manifestations. One contributing factor could be the age-related loss of microbial diversity, leading to heightened susceptibility to inflammation.^{24,25} Subsequently, comorbidities such as asthma, hypertension, smoking, male gender, Alzheimer disease, or dementia are recognized as COVID-19 risk factors, associated to alterations in gut microbiota and immune systems, thereby increasing vulnerability to severe complications.²⁶

Gut microbiota undergoes dynamic changes in life. The infant microbiota has low diversity and will be unstable for the first few years of life until it matures into an adult-like microbiota. During adulthood, gut microbiota is generally considered stable. However, in the elderly, diversity decreases, and dysbiosis rises, with a reduced Firmicutes to Bacteroidetes ratio.^{25,27,28} All of this correlated to cognitive deficits, depression, and a pronounced inflammatory state. Therefore, COVID-19 appears more dangerous in the elderly, men, and those with comorbidities.²⁷

Obesity is a risk factor for severe COVID-19 infection and is also correlated to changes in intestinal flora. Furthermore, it is present in at least 25% of COVID-19 patients who die in the United States, compared to the reported rates of cardiovascular disease in the same high-risk group (21%).²⁹ Adipose tissue can act as a reservoir for SARS-CoV-2 transmission, virus clearance, and systemic immune activation. Obese patients adipocytes express higher levels of ACE-2 and reduce or eliminate inflamed adipose tissue, which can reduce systemic viral spread, viral entry, and viral prolongation.³⁰

Diabetes mellitus is another disease correlated to increased COVID-19 symptoms and complications, which can be attributed to systemic inflammation and gut-metabolite dysfunction. Subsequently, cardiovascular diseases were associated with a disruption in gut microbiota and reduced microbiota diversity. Individuals with cardiovascular disease who become infected with SARS-CoV-2 are more likely to develop a worse prognosis of COVID-19 and cardiovascular complications such as myocardial infarction, arrhythmias, stroke, or heart features or myocardial suppression.³¹ Factors such as diet, lifestyle, and the microbiome likely impact hypertension, with increased SCFA correlating with lower blood pressure and improved arterial compliance.³²

THE CORRELATION BETWEEN GUT MICROBIOTA AND SEVERITY OF COVID-19 INFECTION

Gut microbiota is critical to the development and function of the immune system. Numerous research found significant changes in COVID-19 innate and adaptive immune systems. The cytokine storm, in particular, appears to result from an uncontrolled dysregulation of the host immune function. Several pieces of evidence point to the presence of lymphocytopenia in SARS-CoV-2 patients.³³

Research showed that gut microbiota might contribute to COVID-19 severity. *Bacteroides* spp., *Parabacteroides* spp., *Clostridium* spp., *Bifidobacterium* spp., *Ruminococcus* spp., *Campylobacter* spp., *Rothia* spp., *Corynebacterium* spp., *Megasphaera* spp., *Enterococcus* spp., and *Aspergillus* spp. were elevated in severe infection of COVID-19 patients. The enrichment of *Eubacterium* spp. was found to be significant in patients with mild disease.^{34,35}

Two research mentioned changes in gut virome composition in severe COVID-19 cases.^{29,33,36} In severe cases, 14 Microviridae phages, 1 Inoviridae phage, 1 Podoviridae phage, and 1 unclassified virus were increased, while plant-derived RNA virus, pepper chlorotic spot virus (PCSV), *Myxococcus* phage, *Rheinheimera* phage, *Microcystis* virus, *Bacteroides* phage, *Murmansk* poxvirus, *Saudi moumouvirus*, *Sphaerotil* were significantly decreased in COVID-19 patients with severe infection.^{36,37}

Published research has identified a correlation between gut microbiota disturbance and SARS-CoV-2 viral loads. Notably, *Prevotella copri* and *Eubacterium dolichum* were found to be positively correlated in this context. Meanwhile, *Streptococcus anginosus*, *Dialister* spp., *Alistipes* spp., *Ruminococcus* spp., *Clostridium citroniae*, *Bifidobacterium* spp., *Haemophilus* spp., had been negatively correlated with SARS-CoV-2 viral load.^{34,36}

Analysis of transcriptomes from CD4+ T lymphocytes in bronchoalveolar lavage fluid (BALF) of moderate and severe COVID-19 patients revealed that SARS-CoV-2 induces activation and differentiation processes, accelerating both activation and death of these cells. In critically ill patients, there is a proposed hypothesis that abnormally activated CD4+ T cells might promote viral entry through Furin production. When compared to moderately ill patients, CD4+ T cells from severe patients express more *fos*, *fosb*, and *jun* genes, as well as increase activation marker *MKI67*, Th2-related genes *maf* and *il4r*, chemokines *CCL2*, *CCL3*, *CCL4*, *CCL7*, *CCL8*, and *CXCL8*.^{29,33,34,35,38}

DIETARY CHANGES IN GUT MICROBIOTA COMPOSITION TO TREAT COVID-19 INFECTION

The effect of dietary patterns on susceptibility and severity of SARS-CoV-2 infection is largely unnoticed. The commensal microbiome, while susceptible to alteration and dysbiosis during viral infection, can be positively influenced by dietary components and probiotic treatments.^{36,37,39} Numerous research reported that an optimal immune response to SARS-CoV-2 infection depends on proper diet and nutrition. In general, malnutrition can impair the immune response, making the response to COVID-19 more vulnerable. Consideration of dietary and nutritional factors during viral infection can reduce inflammation and oxidative stress as well as strengthen the immune system to prevent infection.^{35,36}

A lack of vitamin A or zinc has also been correlated to an increased risk of infection. Branched-chain amino acids can improve the intestinal barrier by increasing intestinal immunoglobulin levels and keeping its hairiness.^{35,36,39} High-quality proteins are integral to an anti-inflammatory diet, with sufficient protein intake playing a crucial role in antibody production. Nutritional dietary components such as omega-3 fatty acids, vitamin C, vitamin E, and phytochemicals found in plant-based foods such as carotenoids and polyphenols can interact with anti-inflammatory and antioxidant cellular signaling components. Of all these components, omega-3 fatty acid is known to have the most potent anti-inflammatory effect. Vitamin D deficiency is also associated with severe manifestation and the supplementation can strengthen the immune system.^{29,35,38}

Prebiotic effects of plant-based fiber include promoting the growth of good bacteria such as *Bifidobacterium* and *Lactobacillus* spp. as well as reducing potential pathogens such as *Clostridium* spp. Adequate fiber intake has been correlated to a 20-40% reduction in the relative risk of mortality from infectious and respiratory diseases and a lower risk of chronic obstructive pulmonary disease. Whole grain consumption is also associated with more favorable intestinal microbiome composition, reducing intestinal and systemic inflammation, and correlated to a decrease in CRP, IL-6, and tumor necrosis factor-alpha (TNF- α). Fiber found in fruits, vegetables, and legumes has been correlated to anti-inflammatory properties via fermentation by gut microbiota.^{34,35}

APPROACHES BASED ON GUT MICROBIOTA TO ALLEVIATE THE SYMPTOMS OF COVID-19

Bifidobacterium spp., *Faecalibacterium* spp., *Ruminococcus* spp., and *Prevotella* spp. are abundant in healthy gut microbiota and correlated to low systemic inflammation. Probiotics are live microorganisms used to improve health by modulating the composition and function of the intestinal microbiota.^{33,34} The use of prebiotics and probiotics to balance intestinal flora could prove effective in reducing the risk of bacterial and viral infections. Exploring the impact of high-fiber diets and/or probiotics on SARS-CoV-2 infection outcomes is an intriguing avenue. From this perspective, administering both probiotics and prebiotics or nutrients could be beneficial in replacing missing bacteria and preventing systemic infection. As previously stated, COVID-19 patients with intestinal microbial dysbiosis were identified in research in Zhejiang (China), implying that these patients should receive supportive nutritional therapy.^{39,40} The National Health Commission of China recommended using probiotics to treat patients with severe COVID-19 to maintain intestinal balance and prevent secondary bacterial infections.

Investigating the role of probiotics in COVID-19 is crucial, given the potential to interact with the intestinal microbiota and modulate the immune system. It remains to be seen whether the detected changes in the bacterial flora indicate increased susceptibility to more severe progression or if the infection can be reversed. Gut microbiota may represent a new therapeutic target and probiotics may play a role in COVID-19 patient management.^{29,33}

Although there is currently no evidence to correlate the efficacy of probiotics in reducing symptoms, the inflammatory response and severity of infection could be significantly reduced by an appropriate probiotic combination. Individual responses to probiotics can vary, and examining the interaction of administered bacterial microbes with the host resistance is crucial to ensure a balanced and effective outcome.^{29,38} It is hard to determine if the intestinal flora has changed as a result of infection, however, there is a need to consider switching to an anti-inflammatory diet as a precaution. Subsequently, therapeutics based on well-defined microbes will provide greater confidence in the efficacy of treatments, as well as risk mitigation for better patients.

Despite the limited number of available published research, an omics-based investigation reported an association between Consuming fermented foods

can contribute to variations in beneficial microbiota. These foods and drinks, being rich in live bacteria and prebiotic fibers, play a role in fostering a healthy gut microbiome. The fermentation of dairy products yields kefir, yogurt, and cottage cheese. The cell line research reported the effects of kefir on reducing T-cell proliferation and cytopathic effects of Zika virus exposure. Novel kefir that contains *Lactobacillus* acts as a natural adjuvant of dendritic cells to improve the secretion of several cytokines, augmenting the activities of cytotoxic T-cells and acting against the viral infection.³⁹

Numerous research reported that intestinal microbiota, among other host-predisposing factors, influence food sensitivities through the mechanisms of food antigen degradation, gut barrier integrity, and anti-inflammatory regulatory T-cell promotion. With these pieces of evidence, an individual with known food sensitivities, allergies, or risk for autoimmune conditions, may consider a restricted diet to promote host tolerance during the outbreak of COVID-19.⁴¹

Fecal microbiota transplantation (FMT) aims to restore microbial dysbiosis by transferring a healthy microbiome to an individual with a disease. Two case reports have shown the use of FMT in COVID-19.^{42,43} Improved GI symptoms were reported in 5 of 11 with COVID-19 patients,⁴² and favorable improvement was observed in blood immunity markers and gut microbiota composition with increased abundance of *Bifidobacterium* and *Faecalibacterium*. In two patients with COVID-19 and concurrent recurrent *Clostridioides difficile* infection, FMT treatment seemed safe, and COVID-19-related respiratory symptoms rapidly resolved in 1 month after FMT.^{42,43} Many initial conclusions about FMT and probiotics rely on associative and retrospective analyses. Further research is needed to unravel the mechanistic underlining the therapeutic effects of these microbiota-based interventions.

CONCLUSION

In conclusion, gut microbiome dysbiosis represented a new paradigm in understanding the contribution of specific microorganisms to host susceptibility and immune response to SARS-CoV-2 infection. Some published research found that COVID-19 patients had a significantly different gut microbiome composition compared to healthy individuals. Dysbiosis could contribute to increased susceptibility to SARS-CoV-2 infection, increased COVID-19 severity, and

worsened clinical outcomes. Preliminary clinical investigations showed potential modulatory effects of probiotic bacteria and microbiota-based interventions in SARS-CoV-2 infection. Because of the magnitude of the impact, gut microbiota has been proposed as a potential diagnosis, prognosis, and therapeutic strategy for COVID-19.

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