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Coronavirus infection and gut microbiota

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Abstract

At present time, a number of questions regarding the pathophysiological characteristics and therapeutic approaches to the treatment of the new coronavirus infection COVID-19 remain unresolved. In some cases, patients with COVID-19 may experience symptoms of gastrointestinal tract disorder. According to the literature, the new SARS-CoV-2 coronavirus can replicate in the gastrointestinal tract and may affect the gut microbiota. The article aims to review studies about the possible relationship between the gut microbiota condition and the course of COVID-19 infection, as well as to consider the gut microbiota as a potential therapeutic target and probiotic drugs as possible therapeutic agents in the treatment of viral infections, including COVID-19 infection. It is known that gut microbiota condition is one of the factors determining the susceptibility and features of the body's response to various infectious agents, possibly including the COVID-19 infection. Currently published studies demonstrate a possible relationship between the gut microbiota condition and the course of COVID-19 infection, however, to confirm this hypothesis, additional studies are required, which will allow to make more unambiguous conclusions with subsequent development of new approaches to the prevention and treatment of infection. Potentially a lot of hope in this direction is inspired by the results of probiotics studies, which showed that their use may reduce the frequency and severity of viral infections of the upper respiratory tract. However, currently, there is insufficient data to extrapolate the results of these studies to COVID-19 patients.

Keywords: gut microbiota, COVID-19, novel coronavirus infection, probiotics.

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Introduction. Coronavirus disease-2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which occur in a wide variety of clinical variants, ranging from asymptomatic forms to most severe, complicated by acute respiratory distress syndrome and respiratory failure with a high risk of death [1]. Therefore, the new COVID-19 is included in the list of dangerous diseases [2], and the World Health Organization recognized the epidemic caused by the SARS-CoV-2 virus as a pandemic [1].

Given the unique new nature of the infectious process caused by SARS-CoV-2 and the lack of long-term experience in the management of patients with COVID-19 infection, many pathophysiological and clinical disease aspects remain poorly understood. Moreover, current specific etiotropic infection therapy is unavailable.

The initial stage of infection is now established as SARS-CoV-2 viral penetration into the target cells by attaching to the type II angiotensin-converting enzyme (ACE2) receptors in epithelial cells of the upper respiratory tract [1, 3]. ACE2 receptors are also abundant in the renal tissue and enterocytes [4–6]. The upper esophagus, epithelial cells of the stomach, duodenum, ileum, and colon also contain a large amount of ACE2 receptors, which indicate the possibility of SARS-CoV-2 affecting the gastrointestinal tract (GIT) cells. The biopsy samples of the small and large intestines, obtained during colonoscopy/autopsy, detected the virus, which was present in stool samples for >70 days after the onset of the first disease symptoms [7–9].

Moreover, evidence in some patients detected a ribonucleic acid (RNA) of the SARS-CoV-2 in respiratory tract secretions and stool samples for >1 month after the disease onset, whereas viruses are not cultured after 3 weeks [10]. According to other data, the viral excretion in the stool lasts longer than that in the respiratory tract [11].

Currently, information on SARS-CoV-2 replicative activity in the GIT cells is contradictory [12].

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Some studies confirm that SARS-CoV-2 RNA is found in stool samples from some patients with COVID-19 for a long time even after disease symptom disappearance, which, according to the authors, indicates the ability of the virus to replicate in the GIT cells [13, 14]. Moreover, R. Woelfel et al. (2020) detected that patients infected with SARS-CoV-2 have high concentrations of viral RNA and single targeting RNA molecules in the fecal samples, which indicate the presence of replicative viral activity in the GIT [8, 15].

T. Zuo et al. (2020) performed a genome-wide sequencing of the virus RNA in fecal samples using the example of 15 patients hospitalized for COVID-19 and studied the fecal microbiota composition and its functional potential. Viral RNA was detected in 7 patients, both during the period of illness, including in the absence of clinical manifestations in the GIT and after clinical recovery, as well as the transcriptional and replicative activity of the virus. The authors concluded that their study results confirm the replicative activity of SARS-CoV-2 in the intestines of patients hospitalized for COVID-19 [16].

The incidence of gastrointestinal symptoms of COVID-19 varies widely, ranging, according to various authors, from 2%–10% to 20% [17]. According to other scientists, approximately 3.34%–11.4% of patients with COVID-19 have symptoms of GIT lesions [18, 19]. Patients with diarrhea due to COVID-19 have an increased level of fecal calprotectin, which confirms the presence of intestinal inflammatory changes in presence of infection [20].

Currently, the intestinal microbiota performs essential functions in the human body, such as protection, digestion, metabolism, and immunomodulation. The intestinal microbiota is involved in the formation of colonization resistance to potential pathogenic bacteria through the bacteriostatic and antimicrobial metabolite secretion, as well as in bacterial toxins degradation and bile acid deconjugation, thus maintaining the state of intestinal microbial homeostasis [21].

The immunomodulatory role of the microbiota consists the nonspecific defense factor formation and adaptive immune response regulation. The intestinal microbiota is involved in the nonspecific humoral defense factor synthesis (lysozyme, properdin, and complement), phagocytosis, and matured intestinal lymphoid apparatus stimulation, as well as immunoglobulin A, cytokines, and interferon synthesis [21, 22].

A healthy intestinal microbiome is of great importance in maintaining optimal immunity, in which a hyperreactive or a reduced immune response is unnoted when faced with an infectious agent. Adequate body protection against various infections in this state, including the new coronavirus infection, is possible.

The intestinal microbiota is involved in short-chain fatty acid secretion, such as acetic, propionic, and butyric acids, as well as secondary bile acids secreted by the microbiota commensals. Microbiota metabolites, in turn, regulate immune cell functions, such as dendritic cells and macrophages [23].

Intestinal microbiota composition disorders are possible in many diseases of both the GIT and other organs and systems (e.g., obesity and diabetes mellitus, as well as cardiovascular, autoimmune, mental illnesses, etc.) [24].

The available literature reported that the intestinal microbiota affects the respiratory system functions through organ interaction within the gut-lung axis. This interaction occurs both in the forward and reverses directions, that is, endotoxins and microbial metabolites present in the lung tissues also affect the intestinal microbiota composition [25].

Thus, given the relationship between the intestinal microbiota and the respiratory system, the novel SARS-CoV-2 coronavirus poses an impact on the intestinal microbiota. This fact was presented in some study results, which demonstrated that intestinal microbiota composition disorders occur in infectious respiratory system diseases [26].

The literature revealed that the risk of viral infections increases with intestinal microbiota composition disorders, whereas some studies demonstrate that viral infections themselves, such as influenza and respiratory syncytial virus, lead to changes in the fecal microbiota composition [17].

Particularly, H.S. Gill et al. (2001) demonstrated that the use of probiotics based on the bacteria *Bifidobacterium lactis* in healthy elderly volunteers increased the mononuclear leukocytes and NK cell activity in the blood serum proportion [27].

Some researchers believe that the intestinal microbiome underlies the predisposition of healthy people to COVID-19. Moreover, the proteomic analysis of blood samples from patients with COVID-19 identified 20 proteomic biomarkers that are associated with the infection course severity, based on the proteomic risk scale for COVID-19 [19].

The above facts and individual study results suggest that the intestinal microbiota plays a significant role in immunity formation, which in turn determines the risk of disease and characteristics of the infectious process caused by SARS-CoV-2. However, most aspects of the relationship between intestinal microbiota and COVID-19 disease remain open at this time, as well as many other issues regarding the new coronavirus infection.

The intestinal microbiota of the elderly is characterized by low diversity and a lower beneficial bacteria representation, such as bifidobacteria and some others [28]. The experience with COVID-19 showed that elderly patients and patients with compromised immunity, as well as patients with concomitant diseases, such as arterial hypertension, diabetes mellitus, obesity, etc., have an increased risk of severe COVID-19 and high mortality rates. This suggests an indirect relationship between the intestinal microbiota status and COVID-19 severity [17].

The literature provides limited information on the effect of coronavirus infection in its natural course on the intestinal microbiota, since in any disease forms, from the mildest to the most severe, therapeutic measures are used.

Some studies showed that the intestinal microbiota composition in patients with COVID-19 is characterized by a lower abundance of "beneficial" bacteria, such as *Bifidobacterium, Lactobacillus*, and *Eubacterium*, and a higher abundance of opportunistic bacteria, such as *Corynebacterium (Actinobacteria*) and *Ruthenibacterium (Firmicutes)* [19].

T. Zuo et al. (2020) analyzed the intestinal microbiota composition in patients hospitalized for COVID-19 infection. A total of 15 patients with COVID-19 were enrolled in the study (7 patients without antibiotics and 8 patients taking antibiotics until hospitalization) and the control group consisted of 15 participants. All patients had respiratory symptoms, only 1 complained of diarrhea upon admission; none developed other GIT symptoms during hospitalization.

The intestinal microbiota composition was studied by metagenomic shotgun sequencing of stool samples (Illumina NextSeq 550).

Patients were divided according to the clinical variants of the infection course, namely, mild (without radiographic signs of pneumonia), moderate (with signs of pulmonary involvement), severe (respiratory rate of ≥30 cycles/min or oxygen saturation of ≤93%), or extremely severe (respiratory failure, artificial pulmonary ventilation necessity, etc.). The authors compared the initial intestinal microbiota composition of the groups, adjusted for age, gender, antibiotic use, and concomitant diseases [17].

Results revealed that the intestinal microbiota of patients with COVID-19, who did not take any antibacterial drugs until hospitalization, had a higher prevalence of pathogenic and opportunistic bacteria, such as *Clostridium hathewayi, Bacteroides nordii, and Actinomyces viscosus*. The intestinal microbiota of patients with severe COVID-19 had an initially higher prevalence of *Clostridium hathewayi*. The researchers noted that most of the above-mentioned bacteria caused bacterial infections, which also serve as an indicator of a severe disease course, including the risk of secondary bacterial complications.

The group who received antibiotic therapy during hospital admission and hospitalization period recorded a further decreased number of potentially beneficial bacteria, such as *Fecalibacterium prausnitzii, Lachnospiraceae bacterium 5_1_63FAA, Eubacterium rectale, Ruminococcus obeum, and Dorea formicigenerans* in the intestinal microbiota compared to the group without antibacterial drugs.

In addition, the researchers found abundant bacteria in the phylum *Firmicutes*, namely *Clostridium ramosum* and *Clostridium hathewayi*, which correlated with COVID-19 infection severity. Contrarily, the abundance of bacteria *Alistipes onderdonkii* and *Faecalibacterium prausnitzii* was inversely correlated with COVID-19 infection severity. According to various data, the genus *Alistipes* bacteria are involved in tryptophan metabolism and intestinal microbiota homeostasis maintenance [29, 30], whereas the bacterium *Faecalibacterium prausnitzii* is well known for its anti-inflammatory properties [31].

The presence of certain bacteria in the intestinal microbiota, such as *Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis,* and *Bacteroides ovatus*, inversely correlated with SARS-CoV-2 viral load determined in the intestinal microbiota. The researchers noted that all four bacteria are associated with decreased ACE2 receptor expression in the colon of mice. Thus, according to the authors, bacteria of the genus *Bacteroides* are potentially protective against SARS-CoV-2.

A positive correlation was established between the presence of the bacterium *Erysipelotrichaceae bacterium 2_2_44A* and the level of SARS-CoV-2 viral load in the fecal microbiota. Separate study results showed that bacteria of the genus *Erysipelotrichaceae* are involved in inflammatory bowel disease development [32].

In general, the intestinal microbiota composition in patients with COVID-19 significantly differed from that of the control group in the form of a higher representation of opportunistic bacteria and a lower relative representation of beneficial commensals, both at baseline and during the hospital stay. Concurrently, even after clinical improvement and respiratory system complaint disappearance, these patients retained a lower representation of beneficial bacteria in the intestinal microbiota.

The authors concluded that the intestinal microbiota of patients with COVID-19 infection is characterized by longer preservation of changes in its composition compared to healthy people. Concurrently, changes in severity was associated with the intestinal viral load degree and disease course severity. According to the authors, therapeutic measures aimed at correcting the intestinal microbiota composition became an additional aspect in COVID-19 treatment [17].

Y.K. Yeoh et al. (2020) studied the effect of microbiota composition on the immune response and COVID-19 severity. The authors conducted a cohort study that included 100 patients with laboratory-confirmed infection caused by SARS-CoV-2 (positive nasopharyngeal swab test result). Fecal and blood samples were taken from the patients. The microbiota composition was studied by genome-wide sequencing (Illumina NovaSeq 6000) of total bacterial deoxyribonucleic acid isolated from the fecal samples, and the immune response was analyzed by determining the blood level of inflammatory biomarkers and cytokines.

The intestinal microbiome composition in patients with COVID-19 significantly differed from that of the control group of healthy individuals, whether they received antibiotic therapy or not. Concurrently, the microbiota composition of patients during the period of illness and within 30 days after clinical recovery was distinguished by a lower representation of intestinal microbiota commensals with immunomodulatory potentials, such as bifidobacteria, *Faecalibacterium prausnitzii*, and *Eubacterium rectale.*

The authors revealed a negative correlation between the presence of the bacteria *Faecalibacterium prausnitzii* and *Bifidobacterium bifidum* and disease severity (after adjusting the use of antibiotics and age of patients; $p < 0.05$). In addition, a more severe disease course was characterized by a higher blood level of inflammatory cytokines and biomarkers (C-reactive protein, lactate dehydrogenase, aspartate aminotransferase, and γ-glutamyl transferase) [33].

The work described previously revealed that the composition of the intestinal microbiota of patients with signs of a higher SARS-CoV-2 infectious activity was characterized by a higher representation of opportunistic bacteria, such as *Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis, and Morganella morganii*, and a lower representation of "beneficial" microorganisms. Concurrently, the intestinal microbiota composition of patients with signs of low viral infectious activity was characterized by a higher abundance of bacteria producing short-chain fatty acids, such as *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii, and Lachnospiraceae bacterium 1_1_57FAA* [16].

Another study aimed to determine the differences in the intestinal microbiota composition of patients with COVID-19, influenza (H1N1), and healthy volunteers [18]. The study included 30 patients with COVID-19, 24 with influenza A (H1N1), and 30 healthy volunteers in the control group, who were comparable in age, gender, and body mass index with the patient groups. Patients who received antibacterial drugs and/or probiotics within 4 weeks before enrollment were excluded from this study. A real-time polymerase chain reaction was used to confirm viral infections. The intestinal microbiota composition was studied by sequencing the V3–V4 regions of the 16S ribosomal RNA gene.

The authors revealed that the intestinal microbiota in patients with COVID-19 was characterized by low diversity, a high opportunistic bacterial representation, a low beneficial microbiota representation, and bacterial dominance of the genera *Streptococcus, Rothia, Veillonella, Erysipelatoclostridium,* and *Actinomyces* compared with the microbiota of healthy volunteers. Concurrently, patients with COVID-19 had a significantly less bacterial representation of the *Lachnospiraceae* families (*Fusicatenibacter, Anaerostipes, Agathobacter, Lachnospiraceae*, and *Eubacterium hallii* group) than in the group of patients with influenza.

Microbial diversity indices were significantly reduced in patients with COVID-19 and H1N1 compared with healthy volunteers, in line with the literature on other respiratory viral infections that presented similar changes in the microbiota composition. The authors noted that the structure of the intestinal microbiome and its diversity is not statistically significantly different between patients with different degrees of infection severity.

The study also examined the correlations between various laboratory markers of inflammation and the state of intestinal microbiota. Thus, it was established that bacteria representation of *Agathobacter, Fusicatenibacter, Roseburia,* and *Ruminococcaceae UCG-013*, which was reduced in patients with COVID-19 compared with healthy volunteers, inversely correlated with the level of laboratory markers of inflammation, namely C-reactive protein, D-dimer, and procalcitonin. The levels of C-reactive protein and D-dimer directly correlated with the presence of *Streptococcus, Rothia, Veillonella,* and *Actinomyces* bacteria in the intestinal microbiota. These bacteria were more abundant in the fecal microbiota of patients with COVID-19. Bacteria of the genus *Rothia* had an etiopathogenetic link in pneumonia development,

especially in immunocompromised people [34]; and the role of *Streptococcus* and *Rothia* bacteria in the occurrence of secondary bacterial infections in patients with the H7N9 virus is also discussed [35].

According to the authors, the intestinal microbiota serves as both a potential biomarker of COVID-19 severity and a potential therapeutic target in infection treatment; however, further research is required in this field [18].

COVID-19 and probiotic drugs. Questions of possible therapeutic methods for influencing the intestinal microbiota remain unresolved. Probiotic drug intake should be recognized as one of the most promising fields in this area. However, can probiotic drugs have a positive effect on the course of respiratory viral infections, including COVID-19 infection?

Probiotics, strains of lactic acid bacteria have a modulating effect on the intestinal microbiota, mainly by growth suppression of opportunistic bacteria [36]. Moreover, evidence actively discussed the positive effect of probiotics on the immune system functions and reduced allergic reaction severity, as well as the antitumor properties of certain bacterial strains [18, 23].

Some researchers believe that prebiotics and/or probiotics are potentially used as adjunctive therapy for COVID-19 to maintain an intestinal microbiota balance and minimize the risk of secondary infection in these patients [37].

A similar opinion is shared by L. Di Renzo et al. (2020), who reported that probiotics based on *Lactobacillus rhamnosus* and *Bifidumbacterium lactis HN019* have anti-inflammatory and immunomodulatory properties and are used in COVID-19 to maintain an intestinal microbiota balance and prevent secondary bacterial complications in this group of patients [38].

The development of antibiotic-associated diarrhea was previously reported in approximately 2%–36% of patients with COVID-19 in China with ongoing antibiotic therapy, thus the use of probiotics in these patients was advised to minimize the risk of secondary infections [37, 39].

Some studies showed evidence that probiotics have potential anti-inflammatory and antiviral properties. Moreover, their suppression ability in proinflammatory cytokine synthesis is implemented both directly at the level of the intestinal mucosa and the systemic level. Some clinical studies showed that probiotics are successfully used in immune-mediated disease treatment, such as atopic dermatitis, rheumatoid arthritis, and upper respiratory tract allergic and infectious diseases [37].

The possibility of using probiotics in viral disease treatment is widely discussed. Y. Wang et al. (2016) revealed that the use of probiotics reduced the severity of the infectious process in the upper respiratory tract viral diseases, as well as the disease duration [40].

Other studies noted that certain strains of lactic acid bacteria are used as prophylaxis and various viral infection therapies, particularly, a decreased Ebola virus and cytomegalovirus titers, a decreased symptom severity, and the duration of the upper respiratory tract, and GIT infectious diseases [41].

Probiotic drugs, based on the bacteria *Lactobacillus gasseri*, showed effective prevention of respiratory syncytial virus infection in mouse models [42]. During therapy, a decreased viral load and expression of pro-inflammatory cytokines were recorded. Concurrently, the genes involved in the interferon production were in an activated state after the therapy.

Results of a randomized, double-blind, placebo-controlled clinical trial revealed that the use of prebiotics and probiotics in premature infants at an early age significantly reduced the incidence of respiratory viral infections, mostly caused by rhinovirus [43].

Experimental studies demonstrated that preparations based on bacteria of the *Lactobacillus mucosae* and *Lactobacillus fermentum* strains have anti-inflammatory properties, leading to an increased gene expression and anti-inflammatory cytokine level (interleukin-10), as well as a decreased gene expression and pro-inflammatory cytokine level (interleukin-6 and necrosis factor tumor α) in the model of paw edema in rats [44].

Clinical studies also confirm the anti-inflammatory properties of probiotic drugs. Study results revealed that probiotic therapy reduced the level of interleukin-6 and C-reactive protein, as well as an increased level of interleukin-10 in the serum of patients with multiple sclerosis, and decreased the level of systemic proinflammatory biomarkers and cytokines in the blood plasma of patients with ulcerative colitis, psoriasis, and chronic fatigue syndrome after 6–8 weeks of usage [45, 46].

To date, interleukins-6 and -10 and tumor necrosis factor α levels significantly increased in the blood of patients with COVID-19, and patients requiring hospitalization have significantly higher levels of these cytokines [1].

Some randomized controlled clinical trials demonstrated that patients with severe respiratory diseases, who received artificial pulmonary ventilation and using probiotics based on strains of bacteria *Lactobacillus rhamnosus GG, Bacillus subtilis, and Enterococcus faecalis*, developed much less common pneumonia associated with artificial pulmonary ventilation compared with the placebo group [47, 48].

Concurrently, experimental work on animal models showed that the use of probiotics based on *Lactobacillus acidophilus* and *Bacillus clausii* did not reduce ACE2 receptor expression in the small intestine of mice compared to the control group and the group of animals with a post-salmonella infection in mice [49].

Currently, no clinical studies in the literature assess probiotic efficiency as adjunctive therapy for COVID-19 infection; therefore, asserting unequivocally the potential efficiency of probiotic drugs in this group of patients is impossible.

However, according to several researchers, oral probiotic strains demonstrated strong evidence to reduce the frequency and course severity of viral upper respiratory infections. Probiotics are a potentially additional tool in the pandemic to reduce the viral load and infection severity [50].

Conclusion. Therefore, an increasing number of studies demonstrate the relationship between the intestinal microbiota state and the COVID-19 infection course. Preliminary grounds suggested a link between the intestinal microbiota state, level of inflammation laboratory markers, presence of certain types of bacteria, and COVID-19 infection course severity. Correction of the intestinal microbiota composition is considered as a potential therapeutic target in the complex coronavirus infection treatment.

The study results on probiotic drugs offer a potentially greater hope in this field; however, currently, evidence is insufficient to extrapolate them to COVID-19 patients. Additional research is necessary to draw more unambiguous conclusions regarding probiotic drug efficiency in the complex therapy of patients with COVID-19 infection.

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