

CHANGES IN INTESTINAL MICROBIOCENOSIS IN PATIENTS WITH COVID-19

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ИЗМЕНЕНИЕ МИКРОБИОЦЕНОЗА КИШЕЧНИКА У БОЛЬНЫХ С COVID-19

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Annotation. Coronavirus infection remains a pressing problem of modern healthcare. Despite the end of the pandemic stage, its spread, the likelihood of mutation and the emergence of new genetic lines of SARS-CoV-2, capable of causing significant epidemic increases in morbidity, predetermine the continuation of scientific research in the field of pathogenesis, a personalized approach to the treatment and rehabilitation of patients.

Key words: intestinal microbiocenosis, COVID-19, laboratory diagnostics.

Аннотация. Коронавирусная инфекция остается актуальной проблемой современного здравоохранения. Несмотря на завершение пандемического этапа ее распространение, вероятность мутации и появление новых генетических линий SARS-CoV-2, способных вызывать значимые эпидемические подъемы заболеваемости, предопределяет продолжение научных исследований в области патогенеза, персонифицированного подхода к лечению и реабилитации больных.

Ключевые слова: микробиоценоз кишечника, COVID-19, лабораторная диагностика.

Introduction. The pathogenesis of the new coronavirus infection is influenced by many factors, one of which is the state of the microbiome of the macroorganism. Without a doubt, the microbiocenosis of various organs plays a key role in maintaining human health. It is no coincidence that many scientists have drawn attention to the potential relationship between the state of intestinal microbiocenosis and the severity of COVID-19 during the pandemic. In patients with COVID-19, an imbalance of bacterial diversity was revealed: a decrease in the number of bacteria of the Firmicutes type producing short-chain fatty acids (SCFAs), an increase in opportunistic pathogens of the Proteobacteria type [1, 14].

In the structure of bacteria inhabiting the intestines of an adult, Firmicutes and Bacteroidetes account for 90%, Actinobacteria, Proteobacteria, Verrucomicrobia and Fusobacteria, yeast-like fungi, phages and protozoa account for 10% [3, 16]. Microorganisms in the large intestine ferment complex carbohydrates, the main metabolites of which are SCFAs: acetate, propionate and butyrate. Butyrate increases mucin production by goblet cells and activates regulatory T cells, which play a vital role in attenuating cytokine production by minimizing T cell activation [2, 11]. As the level of butyrate in the intestine decreases, the likelihood of SARS-CoV-2 fusion with angiotensin-converting enzyme 2 (ACE2) with subsequent activation of the renin-angiotensin system (RAS) increases. This leads to systemic vasoconstriction and the development of systemic inflammatory response syndrome (SIRS) [2, 15, 17]. Gut microbiota influences the expression of interferon receptors (IFN) type 1 in respiratory epithelial cells, which quickly respond to viral infections by secreting IFN-alpha and IFN-beta, limiting viral replication [2, 5, 12].

Purpose of the study: to quantitatively assess the state of the colon microbiocenosis in patients with moderate COVID-19.

Material and methods. 64 patients with moderate COVID-19 who were hospitalized in an infectious diseases hospital were under observation. Inclusion criteria: age 18–75 years, laboratory confirmed COVID-19, availability of informed consent to the processing of personal data. The work is a simple descriptive study based

on the analysis of clinical and laboratory parameters of patients, data from standard laboratory and instrumental examination methods in a hospital setting. The diagnosis of a new coronavirus infection was established based on the detection of SARS-CoV-2 RNA by polymerase chain reaction (PCR) in smears from the nasopharynx and oropharynx (100%). Laboratory analysis, in addition to standard studies, included an assessment of the quantitative composition of the microbiocenosis of the large intestine using the PCR method with fluorescent detection of amplification results in real time.

Results. We observed 64 patients who met the inclusion criteria and were diagnosed with moderate COVID-19. The study group consisted of 27 (42%) women and 37 (58%) men, median age – 59 [18; 75] years. The age of the majority of patients (n = 33) was from 57 to 75 years.

On average, patients were admitted to hospital for treatment 6.6 ± 5.5 days from the onset of the first symptoms of the disease. During days 1–3 and 4–7, the same number of patients were hospitalized – 36% each. More than seven days after the onset of the disease, 28% of patients were admitted to the infectious diseases hospital.

The average length of hospitalization was 6.6 ± 3.8 days (range, two to 24 days). At the outpatient stage, 15.6 and 20.3% of patients, respectively, received antiviral and antibacterial therapy; in the hospital, 59.3% of hospitalized patients were prescribed antibiotics, and 100% - antiviral. In the hospital, 20.3% of patients took probiotics. Upon admission to the hospital, the most common complaints were fever (87.5%), cough (50%), asthenic syndrome (43.7%), pain and sore throat (23.4%), shortness of breath (21.8%), dyspepsia (14%), rhinitis (12.5%).

In 25 (39%) patients, according to computed tomography (CT) of the chest, pneumonia was diagnosed at the time of hospitalization. However, SpO₂ levels below 94% were observed in only 5 (7.8%) patients.

In a clinical blood test, 39% of patients had leukocytosis with a neutrophilic shift and monocytosis, and 34% had lymphopenia. Analysis of biochemical parameters demonstrated an excess of reference values: C-reactive protein - 85.9% of cases, lactate dehydrogenase (LDH) - 34.4%, ferritin - 20.3% of cases. The coagulogram showed an increase in D-dimer (46.9%) and fibrinogen (43.6%). A study of the bacterial composition of the large intestine was carried out. Analysis of the results obtained revealed changes in the quantitative parameters of the main representatives of the intestinal microbiocenosis of patients in the study group. Dysbiotic disorders of the large intestine were registered in 95.4% of patients during hospitalization and in 100% upon discharge. Shannon and Simpson indices were used to assess alpha diversity of the gut microbiota. In the acute phase and convalescence period of COVID-19, the average values of the Shannon diversity index were 0.54 ± 0.36 and 0.52 ± 0.33 , the Shannon evenness index was 0.31 ± 0.18 and 0.29 ± 0.16 , Simpson index – $0.73 \pm$

0.21 and 0.71 ± 0.23 , respectively. Thus, the results indicate serious disturbances of the microbiome.

In the acute period of the disease upon admission to the hospital, a decrease in the number of symbiotic taxa of the intestinal microbiocenosis was revealed: the proportion of patients with a reduced number of bacteria of the genera *Bifidobacterium* spp., *Bacteroides* spp., *Faecalibacterium prausnitzii* was 50, 4.6 and 28%, respectively. At the same time, there was an increase in the proportion of patients with opportunistic (*Klebsiella* sp., *Citrobacter* spp. and *Enterobacter* spp.) and pathogenic bacteria (*Escherichia coli* enteropathogenic, *Candida* spp., *Staphylococcus aureus*, *Clostridium* spp., *F. nucleatum*) were above the norm by 1.5 and 11.7%, respectively.

During the period of convalescence upon discharge from hospital, there was an increase in the proportion of patients with a reduced number of bacteria *Bifidobacterium* spp., *Bacteroides* spp., *F. Prausnitzii* compared with the acute period of the disease - up to 2.26 times, depending on the taxon. In addition, a decrease in the proportion of patients with a reduced amount of *E. coli* was recorded - from 6.25% upon admission to 4% upon discharge. Upon discharge from the hospital, elimination of enteropathogenic *E. coli*, *S. Aureus* and *Clostridium perfringens* was noted. The proportion of patients with *Klebsiella oxytoca*, *Candida* spp., *Enterobacter* spp. also decreased. and *F. Nucleatum* exceeded the norm - up to 2.3 times, depending on the taxon. However, despite the elimination and/or decrease in the intestinal microbiocenosis of opportunistic and pathogenic bacteria during the period of convalescence of COVID-19, there was an increase in the proportion of patients with higher than normal levels of *Enterococcus* spp., *K. pneumoniae*, *C. difficile*, *Proteus vulgaris/mirabilis*, *Citrobacter* spp. – up to 4.1 times depending on the taxon.

Thus, in the examined patients, dysbiotic disorders of the large intestine were established: colonization by opportunistic and pathogenic microflora against the background of a decrease in symbiotic flora. In addition, a connection has been established between microbiocenosis disturbances and laboratory parameters and clinical manifestations of COVID-19.

Discussion. In recent years, many studies have been carried out on the intestinal microbiocenosis of patients with COVID-19 during different periods of the disease (acute stage, convalescence period, post-Covid period - long COVID-19). According to the literature, at all stages of COVID-19 there are significant dysbiotic disorders of the large intestine [2, 13].

The results of our studies partially coincide with the data of Chinese authors [1, 8, 10]. A study of the microbiocenosis of patients with COVID-19 in the acute period showed a decrease in bacterial diversity and depletion of representatives of the normal intestinal microflora *Bifidobacterium* spp., *Bacteroides* spp. and *F. prausnitzii*, as well as an increase in the content of opportunistic microorganisms *Klebsiella* sp.,

Citrobacter spp. and Enterobacter spp. However, the number of Lactobacillus spp. remained within normal limits. Information on the quantitative content of lactobacilli in the stool of patients with COVID-19 is contradictory. Some authors point to a reduced content of lactobacilli, others to an increased one [2, 11, 18].

As in a number of other studies, in our study, in patients after elimination of SARS-CoV-2, the levels of Bifidobacterium spp., Bacteroides spp. and F. Prausnitzii remained reduced, the content of opportunistic bacteria increased [3, 6]. Our study recorded an increase in the number of Enterococcus spp., Proteus vulgaris/mirabilis, Citrobacter spp. in the period of convalescence compared to the acute period. This is probably due to post-Covid syndrome. Regardless of the use of antibacterial drugs, patients showed an imbalance of bacterial diversity, most likely associated with the indirect influence of the SARS-CoV-2 virus through the lung-gut axis [2, 12].

A relationship has been established between low levels of Bifidobacterium spp. and the presence of rhinitis in patients with COVID-19. Previously, a connection has been noted between the composition of the intestinal microbiota and immune changes involved in the development of allergic rhinitis [1, 4]. The positive correlation between asthenia and the Shannon diversity index is likely due to the effects of SARS-CoV-2 on the gut-brain axis [14]. For the first time, a connection between opportunistic fungal microorganisms Candida spp. With D-dimer, LDH and Shannon Diversity Index levels. The work of Y. Zhou (2021) shows that in patients with COVID-19, against the background of high body temperature, the level of Enterococcus faecalis positively correlates with the levels of LDH and D-dimer [2, 7, 8].

Thus, an imbalance of bacterial diversity in patients with COVID-19 affects the clinical course of the disease and may also contribute to the development of post-Covid syndrome.

Conclusions. COVID-19 infection of moderate severity is accompanied by a dysbiotic disorder of the large intestine - a decrease in the number of representatives of the normal intestinal microflora Bifidobacterium spp., Bacteroides spp. And F. prausnitzii, as well as an increase in opportunistic microorganisms Klebsiella sp., Citrobacter spp., Enterobacter spp., Proteus vulgaris/mirabilis and pathogenic bacteria E. coli enteropathogenic, Candida spp., S. aureus, Clostridium sp., Fusobacterium nucleatum. The average values of the Shannon and Simpson indices both in the acute phase of the disease and at the stage of convalescence are approximately the same and indicate a decrease in intestinal diversity. There is a relationship between the composition of the intestinal microbiota and the clinical course of COVID-19.

Thus, the results of the study indicate serious disturbances in microbiocenosis in patients with COVID-19. These data can be used to improve approaches to the treatment of new coronavirus infection, as well as for the rehabilitation of patients with post-Covid syndrome.

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