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## The role of microbiota in pathogenesis and development of viral infections

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### Abstract

#### Introduction and purpose

The microbiota plays an important role in human metabolism, immune system, and development of many chronic diseases, cancers, and infectious diseases. The aim of the study is to present the role of gut microbiota in viral infections, including HBV, Herpesviridae, HIV, and SARS-CoV-2. The newest publications from the last 5 years available on the PubMed database were taken into account.

#### A brief description of the state of knowledge

The mechanism by which bacteria have an impact on viral infection is based on a synthesis of specific short-chain fatty acids (SCFAs) and modulation of cytokine release and immune system function by bacteria. Domination of *Gardnerella vaginalis* and lack of *Lactobacillus* in the vaginal microbiome increased the risk of HSV-2 infection in women. Inflammation of the genital tract can influence susceptibility to HIV infection, but probiotics via enhancement of the gut barrier integrity, change TH17/Treg ratio, can restore microbiome composition. LPS - component of the structure of Gram-negative bacteria can be a marker of

HBV infection. In the airway microbiome of patients with COVID-19 opportunistic microorganisms were identified.

### **Conclusions**

Diet, intake of probiotics, fecal microbiota transplantation (FMT) are interventions that might be efficient methods in prophylaxis and treatment of viral diseases. Further studies are needed to evaluate the mechanism of action of microbiome in pathogenesis of infectious diseases.

**Key words:** microbiota, dysbiosis, virus infection, HIV, SARS-CoV-2

### **Introduction and purpose**

Microbiota consists of bacteria, viruses, fungi, and symbiotic protozoa which have an impact on metabolism and host immune system [1]. Nowadays, due to widespread different environmental factors, inadequate foods, use of antimicrobial drugs influencing the microbiome, the bacterial community can be disrupted [2, 3]. Human microbiota colonizing the oral mucosa, intestinal tract, genital tract, and airways plays an important role in the human body and influences the development of chronic diseases such as alcoholic liver disease, autoimmune liver disease, or cancers [2, 4, 5]. It has been evidenced that the intestinal microbiome can be involved in inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), type 2 diabetes (D2M), and colorectal cancer [2, 6]. One of the most interesting subjects in medicine is the interaction between the microbiome and brain called the gut-brain axis. According to studies, dysbiosis can contribute to autism spectrum disorder, so fecal microbiota transplantation (FMT) is considered as conjunctive therapy in improving the behavior of patients with autism [2, 6]. Another potential indication for use of FMT is recurrent *Clostridioides difficile* infection, IBD, or IBS [6]. Human microbiota has an important role in noninfectious diseases as infectious diseases [3, 7]. Moreover, administration of probiotics described as microorganisms with beneficial properties for metabolism and immunity of the host is known as an efficient treatment strategy in IBD, diarrhea, allergies, and the prevention of upper respiratory tract infections [3]. Bacterias on the mucosal surface or adhered to the mucosal surface are involved in the immune system [3]. Moreover, dendritic cells from the mucosal immune system represent responders to pathogens [8]. According to studies, the microbiome plays an important role in the prevention of infections - bacterial or viral. The diversity of the microbiome depends on genes, diet, drugs, environmental factors, therefore these factors can affect the development of chronic and infectious diseases. It is noticed that the administration of probiotics by stimulating response to viruses, increasing the level of regulatory T cells, and reducing levels of cytokines involved in inflammation, can enhance the intestinal barrier.

The aim of the study is to present the role of microbiota in viral infections, including HBV, Herpesviridae, HIV, and SARS-CoV-2. The newest publications from the last 5 years available on the PubMed database were taken into account.

## The state of knowledge

### Herpesviridae (HSV)

Herpes simplex virus type-1 (HSV-1) is a virus transferred usually by oral-to-oral contact, while HSV-2 is transferred mainly sexually. In the study of Lee, chemotherapy was associated with reduced diversity of oral bacterial microbiota and increased occurrence of HSV-1 infection in patients undergoing auto-HSCT [4]. Interestingly, HSV-1 infection reduced microbial diversity after treatment with chemotherapy. Furthermore, a combination of chemotherapy, dysbiosis in oral mucosal bacteriota exaggerate symptoms of OM - oral mucositis in patients undergoing auto-HSCT - autologous hematopoietic stem cell transplantation).

Herpes simplex virus type-2 (HSV-2) infection is noted more frequently in African, Caribbean, and other black (ACB) women [9]. Despite the evidenced relationship between bacterial vaginosis (BV) and HSV-2 infection, Shannon et al. did not note the connection between vaginal CST (community state type) and HSV-2 infection [9]. However, another study revealed an increased risk of HSV-2 infection in women with the domination of *Gardnerella vaginalis* and lack of *Lactobacillus* in the vaginal microbiome [10]. In the study performed by Mehta et al., the vaginal and penile microbiome was in association with HSV-2 in women and their male sex partners [11].

### HIV

HIV - Human Immunodeficiency Virus is extensively widespread in the world, but only less than 1 in 1000 vaginal exposures to HIV results in transmission [9]. Therefore, it is important to describe factors contributing to symptomatic infection or severe course HIV infection. Due to many ways of transmission of HIV, microbiomes from different locations in the body are engaged in the development of the disease. It has been evidenced that gut microbiota and cervicovaginal microbiota play important roles in the pathogenesis of HIV infection. According to studies, dysbiosis in the cervix and vagina increased the risk of HIV infection [12]. Some anaerobic bacteria species such as *Prevotella* and *Sneathia* via exacerbation inflammation in the genital system caused an increased risk of HIV infection, which confirmed that. Interestingly, bacterial sexually transmitted infections (STIs) increase proinflammatory cytokine levels and the risk of HIV infection by 3-5 fold. Asymptomatic HSV-2 infection increases the risk of HIV infection by 3 fold [9]. On the other hand, domination of *Lactobacillus* in cervicovaginal microbiota reduced the risk of HIV infection. It is noticed that domination of *Lactobacillus* and lin vagina commensal microbial community can inhibit the development of disease. It has been evidenced that this infection with low levels of *Lactobacillus crispatus* increased the risk of disease. Moreover, inflammation of the genital tract promoted by bacterias contributes to injury of the genital epithelial barrier, which increases susceptibility to HIV infection [ 9]. In addition, bacterial infection induces activation of CD4+ T cells, which leads to increased expression of target action of the virus - coreceptor chemokine receptor 5 (CCR5) [9]. The mechanism by which bacterias have an impact on viral infection is based on a synthesis of specific short-chain fatty acids (SCFAs) by intestinal bacterias [12]. SCFAs are involved in maintaining the intestinal barrier. Therefore, dysbiosis of the microbiome might be a cause of dysfunction of the intestines. HIV replicates mainly in the gastrointestinal tract and contributes to mucosal barrier injury, translocation of microorganisms, and changes gut microbiota composition - elevation of the level of *Pseudomonas aeruginosa* and *Candida albicans* and decrease in *Bifidobacteria* levels and *Lactobacillus* species [3]. Microbial translocation can result in

systemic immune activation and promoting inflammation [3]. HIV-positive patients had increased levels of LPS and bacterial ribosomal DNA, compared with healthy people.

HIV infection is associated with depletion of immune cells and disruption of the bacterial community involved in the immune response. As described, immunity of the intestines can be disrupted despite antiretroviral therapy in HIV-positive patients and exaggerate infection [3]. Therefore, other forms of treatment are needed. Due to the potential role of the microbiome in inhibition of progress of HIV infection, supplementation of probiotics is supposed to restore intestinal microbiome and improve CD4+ T cells number, reducing risk of immunosuppressive infections. Probiotics affect gut microbiome composition, leading to enhancement of the gut barrier integrity, reduction of microbial translocation, and decrease risk of systemic inflammation. Moreover, probiotics promote gut reconditioning by TH17/Treg ratio. As described, HIV infection can be related to injury of the mucosal barriers in the oral cavity and genital tract, coexist with bacterial vaginosis and periodontal disease. Thus, the use of specific probiotics in case of these comorbidities in patients with HIV infection is worth considering.

## **HBV**

Chronic hepatitis B virus is one of the most noted infections worldwide [13]. Despite the high efficacy of the hepatitis B vaccine and progress in pharmacology associated with the treatment of chronic HBV infection, this disease is still a huge economical and medical problem [2]. Due to the same embryonic origin of the gut and the liver, it is supposed that the gut microbiota has the potential to affect the severity of hepatitis induced by HBV [2]. Moreover, chronic HBV infection is usually noted in children and infants because of their undeveloped immune system, which is associated with microbiota. *Faecalibacterium prausnitzii*, *Enterococcus faecalis*, and Enterobacteriaceae were bacterial species observed at higher levels in patients with chronic hepatitis B or patients with decompensated HBV cirrhosis, compared with asymptomatic carriage group and healthy controls [13]. Concentrations of *Bifidobacteria* and bacteria producing lactic acid were reduced both in the asymptomatic carriage of HBV and chronic hepatitis B, decompensated HBV cirrhosis. As described, limiting oxygenation of the liver reduces the number of intestinal *Bifidobacteria* and *Lactobacillus* which are beneficial bacterias for metabolism, immune system, or nutrition. Furthermore, metabolic products from the intestinal flora exacerbate liver diseases [2]. Pathogen-associated molecular patterns (PAMPs) are recognized by TLRs - toll-like receptors which identify molecules from microorganisms and are involved in the immune response. Then, it induces cytokine (IL, TNF, and IFN) release and injury of hepatocytes. To confirm the role of bacterias in the development of liver disease, a high level of LPS - component of the structure of Gram-negative bacteria was noted in patients with liver failure caused by chronic HBV. Binding LPS with TLR induces the release of cytokines such as IL-10 - with immunosuppressive properties, which limits immune response against HBV [14]. Additionally, chronic HBV infection was associated with decreased levels of unmethylated CpG DNA participating in immune response which leads to reduced synthesis of protective cytokines such as interferon (IFN). It is supposed that application of synthetic unmethylated CpG DNA might be a treatment therapy for infectious diseases. Another promising efficient strategy, besides antiviral drugs or IFN, is the use of FMT and compound probiotics due to their potential benefits in chronic liver diseases [2, 13].

## **SARS-CoV-2**

Since the Coronavirus pandemic outbreak, we know more and more information about its pathogenesis, symptoms, and complications. Coronavirus disease 2019 (COVID-19)

induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manifests as pneumonia, kidney failure, neurological symptoms - anosmia, encephalitis, or gastrointestinal symptoms - diarrhea, vomiting, nausea, or abdominal pain [15]. Although the virus is transmitted mainly via respiratory droplets and mostly affects the respiratory tract, it was identified in the feces of patients infected with SARS-CoV-2 [16]. Angiotensin-Converting Enzyme 2 (ACE2) is a receptor for SARS-CoV-2, by which the virus invades a cell. Interestingly, ACE2 is expressed by epithelial cells of the lung, kidney, and gastrointestinal cells [8]. Gut dysbiosis can be the result of respiratory infection while a change of the microbiome can affect lung function. Therefore, the relationship between the microbiome from the intestines and the lungs is bidirectional and is called the gut–lung microbiota axis [5]. As the studies reported, intestinal dysbiosis is an important factor influencing the severity of COVID-19 [5, 17]. In the study of Tang et al., they reported an increased level of opportunistic pathogens *Enterococcus* and Enterobacteriaceae and decreased level of beneficial bacteria including probiotic bacteria (*Lactobacillus* and *Bifidobacterium*) and anti-inflammatory bacteria (*F. prausnitzii*, *C. butyricum*, *C. leptum*, and *E. rectale*) in hospitalized patients with COVID-19 [18]. The next study showed domination of *Proteobacteria* and decrease of *Spirochaetes* and *Fusobacteria* in patients with COVID-19. Another study revealed a high level of CRP - inflammatory marker in patients with the lowest diversity of the gut microbiota. These results from studies suggest that composition and diversity of the microbiome are potential markers of the severity of COVID-19. As described, during the course of COVID-19 bacterias synthesizing butyrate - SCFAs were at lower concentration while reduced level of SCFAs promoting depletion of ACE2, is suspected to have proinflammatory activity [5].

To date, there is limited data on effects of using FMT in the prevention and treatment COVID-19. Lie et al. found beneficial effects in the immune system after FMT use in COVID-19 patients [19]. They observed elevated levels of memory B cells and non-switched B cells with reduced levels of the naive B cells. Furthermore, the efficacy of FMT in post-COVID19 patients was confirmed by reduced gastrointestinal symptoms [5].

It is supposed that not only gut microbiota but also the airway microbiome is involved in the pathogenesis of COVID-19. Rueca et al. assessed nasal/oropharyngeal microbial community of COVID-19 patients and healthy people. They identified opportunistic microorganisms in COVID-19 patients admitted to the intensive care unit (ICU) [20]. In another study conducted by Nardelli et al., the negative association between *Fusobacterium periodonticum* (FP) and severity of the infectious disease was reported [21]. Compared with healthy individuals, the airway microbiome in COVID-19 patients was characterized by less diversity, which can be related to a lower lymphocyte to neutrophil ratio [22]. Among COVID19 patients, opportunistic pathogens such as *Salmonella*, *Pseudomonadaceae*, *Bacteroidetes*, *Streptococcus*, *Staphylococcus*, *Haemophilus*, *parainfluenzae*, *Neisseria*, *Human influenza virus*, *Respiratory syncytial viruses* were detected in the airway while *Bacteroides* and *Bifidobacterium* were at lower concentrations in the airway [23].

## Summary

According to studies, microbiome from the oral cavity, intestines, airway, genital tract, are involved in immune response, also against viruses. However, further studies are needed to assess the effect of the use of different drugs combined on microbiota and their influence on microbiota and the role of microbiota in pathogenesis and progress of infectious diseases. Diet, intake of probiotics, FMT are interventions that might be efficient methods in prophylaxis and treatment of infectious diseases, including diseases caused by viruses.

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