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Normal human microbiota and dysbiosis - implications for health and disease

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Abstract

The normal human microbiota, formerly called the "*microbial flora*," consists of bacteria, fungi, viruses, and parasites that colonise the skin and mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts. The number and diversity of microorganisms varies between different body niches and is greatest in the intestinal tract. The microbiota contributes to the homeostasis of the human organism by preventing colonisation by pathogenic microorganisms, participating in digestive processes and metabolism, and regulating immune functions.

Various environmental and genetic factors can lead to an imbalance in the human microbiota, called *dysbiosis*, which can affect human health. Dysbiosis is usually the result of decreased microbial diversity and a lower number of saprophytic microorganisms, followed by an overgrowth of opportunistic species. The most common diseases directly related to intestinal dysbiosis are antibiotic-associated diarrhoea and pseudomembranous colitis, both of which are associated with the excessive growth of harmful bacteria and *Clostridioides difficile* following broad-spectrum antibiotic therapy.

Dysbiosis is associated with various health conditions or diseases such as acne, psoriasis, eczema, chronic obstructive pulmonary disease, inflammatory bowel disease, obesity, metabolic syndrome, type 2 diabetes, autoimmune diseases and allergies, neurological diseases such as Parkinson's disease, Alzheimer's disease, epilepsy and stroke, depression, anxiety, infertility, preterm birth, and malignancies.

Key words: human microbiota, dysbiosis, commensal bacteria, dysbiosis-associated diseases

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Introduction

The normal human microbiota consists of bacteria, archea, fungi, viruses and parasites that colonise the skin and mucous membranes of humans without causing disease when the host is immunocompetent and in good general health. The human microbiota used to be referred to as the *"physiological microbial flora"*, or "*microflora*", but in the last decade the term "*human microbiota"* has gained acceptance and is widely used amongst healthcare professionals and the scientific community. Bacteria are the most numerous members of the human microbiota. It used to be assumed that their number was ten times higher (1×10^{14}) than that of our own tissue cells (1×10^{13}). According to new findings, however, this ratio is closer to 1:1 (3.8×10^{13} to 3×10^{13}), as red blood cells have been included in the total number of cells in the human body (1). There are an estimated 500–1000 bacterial species that exist in the human body, although the number of subspecies could be orders of magnitude higher (2, 3). Most species of these bacteria colonise the gastrointestinal tract, and nowadays many scientific studies aim to elucidate the role of the gut microbiota in health and disease (4).

The microorganisms that populate the human body interact with it in various ways, and the result of these interactions can be neutral, beneficial, or harmful to the host. Most members of the human microbiota enter into neutral or beneficial interactions with our organism, which can be characterised as saprophytic (neutral), commensal or mutualistic (5, 6, 7). *Saprophytism* (neutralism) is defined as an interaction between microorganisms and the human body in which both organisms coexist without affecting each other. In contrast, *commensalism* is beneficial to the microorganism (referred to as commensal) and neutral to the human organism, and most members of the human microbiota belong to the commensal bacteria (6). An interaction that is beneficial to both the microorganism and the human body is *mutualism*. The bacteria in the microbiota of the gastrointestinal tract were originally commensals, but evolved into mutualists when they began to produce vitamin K, which the human body cannot synthesize on its own (7). A harmful interaction between microorganisms and the human body manifests as *parasitism*, which benefits the microorganism and harms the human. In this type of relationship, the parasite uses the human body to maintain its biological cycle, or it feeds on human cells and thus damages the human organism. This damage is usually gradual, allowing the parasite to coexist in the host's body for a long period of time, which in rare cases can lead to death. Although many species of yeasts, moulds and parasites coexist in the human body, they are not considered strict parasites and thus harmful, as they are part of the normal human microbiota (5).

The microbiota that is always present in the human organism is called the resident microbiota. It consists of microorganisms that have a fixed body niche in one part of the body where they remain indefinitely. The transient microbiota is able to colonise the human organism for a short period of time, as it is quickly suppressed by the resident microbiota or the activity of the immune response. Strictly pathogenic bacteria can also colonise the skin or mucous membranes of the host and form a neutral relationship with it, which is referred to as asymptomatic carriage. The causative agents of pneumonia

and/or meningitis, *Haemophilus influenzae* and *Neisseria meningitidis*, can be isolated from throat swabs in 5% to 40% of healthy people (8, 9).

The colonisation by microorganisms that constitute the human microbiota and the composition of the microbiota depend on numerous exogenous and endogenous factors. It used to be assumed that the uterus is a primarily sterile organ, and that the fetus is sterile until the rupture of the fetal membranes during birth. Recent studies using molecular techniques point to bacterial colonisation of the uterus, placenta, and amniotic fluid that appears to impact fertility and pregnancy (10, 11, 12, 13). Intrauterine colonisation of the fetus by members of the microbiota has also been demonstrated by isolating bacteria from meconium (i.e., the first fetal stool) (10, 13). Mass colonisation of the baby's skin and mucous membranes occurs during birth and continues in the first days after birth, primarily by the mother's microbiota, but also by other microorganisms from the environment. The composition of the microbiota is influenced by the mode of delivery, so that babies born vaginally are dominated by bacteria of the genus *Lactobacillus*, which are found in the microbiota of the maternal vaginal mucosa, while babies born by caesarean section are dominated by bacteria of the genus *Staphylococcus*, which represent the skin microbiota of the mother (14, 15).

In the first days of an infant's life, the composition of the microbiota depends on random exposure to microorganisms that colonise specific sites of the infant's body without competition. Later, the microorganisms that are best adapted to colonise a particular site (called the body niche) prevail and become the dominant species. In the first years of life, the composition of the microbiota is influenced by the type of diet, so that in breastfed infants it is significantly more diverse and dominated by bifidobacteria, while in formula-fed infants it is less diverse, and lactobacilli predominate (15). The composition of the microbiota changes significantly after the transition to solid food, so that around the age of three years a permanent microbiota is formed which is unique to each individual and remains stable in adulthood (16).

Throughout life, human microbiota is influenced by a number of endogenous factors such as gender, age, hormonal status, and general health of the organism, as well as exogenous factors such as personal hygiene (use of soap, deodorant, mouthwash, skin peeling, vaginal rinsing, etc.), diet, intake of certain medications (especially broad-spectrum antibiotics), quality of drinking water, environmental changes, and exposure to toxins or chemical compounds from the environment (2, 17, 18).

Physiological role of microbiota in human organism and dysbiosis

The normal human microbiota has numerous beneficial effects on the human body, although in some cases its presence can be harmful. The positive effects of the microbiota are reflected in the prevention of colonisation by pathogenic microorganisms, participation in digestive processes, and influence on the metabolism and immunity of the host (19).

The prevention of colonisation by pathogenic microorganisms is largely a consequence of the preponderance of members of the human microbiota, resulting in

competition for nutrients and receptors on the surface of epithelial cells to which pathogenic microorganisms would bind. Members of the microbiota also produce small antibacterial molecules called bacteriocins, such as colicin, microcin, nisin, enterocin, lugdunin, lantibiotics and cutimycin, which inhibit growth and colonisation by pathogenic species (20). The skin microbiota produces fatty acids, and the lactobacilli of the vaginal microbiota produce lactic acid, which creates an acidic pH on the mucosa that inhibits the growth of pathogenic microorganisms (21, 22).

In addition to digesting common nutrients such as proteins, lipids and carbohydrates, intestinal bacteria are also involved in the digestion and metabolism of complex carbohydrates that the human body cannot utilise. The gut microbiota has numerous enzymes for the utilisation of dietary fibres such as cellulose, pectin, xylan, lignin, non-starch polysaccharides, starch, and oligosaccharides (fructo-oligosaccharides and galacto-oligosaccharides) that are resistant to host digestive enzymes (23). Fermentation of dietary fibres releases a variety of secondary products, such as gases (hydrogen, carbon dioxide and methane), short-chain fatty acids (acetate, propionate, butyrate, valerate, isovalerate, formate and hexanoate), organic acids (lactate and succinate) and alcohols (ethanol and methanol), which have antibacterial activity or are used by human cells as an energy source (19, 23). Short-chain fatty acids or their deficiency may influence the development of a variety of diseases, from allergies and asthma to cancer, autoimmune diseases, metabolic diseases, glucose homeostasis, including insulin secretion and insulin sensitivity, obesity, and neurological diseases such as multiple sclerosis (24). The intestinal microbiota is also capable of synthesising vitamin K, and B group vitamins thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folates, nicotinic acid, and cobalamin (25).

The human microbiota influences the state of the immune system by constantly providing non-specific antigenic stimuli to immune system cells and stimulating secretory IgA production on mucosal surfaces (4). The importance of this role is reflected in the higher incidence of immunopathological diseases (e.g., asthma) in children exposed to a less diverse microbiota during growth (26).

The negative effects of the human microbiota are reflected in the development of opportunistic infections and the production of carcinogenic and toxic products that can lead to disease, malignancies, and an impaired response to cancer immunotherapy (27). Members of the microbiota may also be involved in mechanisms of antimicrobial resistance, facilitated by horizontal transfer of resistance genes between bacteria or production of enzymes that degrade antibiotics (28).

A balanced microbial ecosystem in the host is called *eubiosis* and ensures normal and healthy functioning of the human body. In contrast to eubiosis, an imbalance in the composition and diversity of the host-associated microbiota, known as *dysbiosis*, is associated with many human diseases. These terms are often used in the context of the intestinal microbiota, as the microorganisms of the gut are the most numerous populations (4). Most health conditions caused by dysbiosis are the result

of the elimination of beneficial microorganisms and/or excessive growth and proliferation of opportunistic pathogens or pathogenic microorganisms that cause a state of acute or chronic inflammation. The use of broad-spectrum antibiotics such as cephalosporins leads to a reduction in the intestinal microbiota and excessive proliferation of the anaerobic bacterium *Clostridium difficile*, which causes a diarrhoea syndrome or pseudomembranous colitis. An imbalance in the oral or vaginal microbiota can also lead to the occurrence of fungal infections caused by *Candida* species (29).

Dysbiosis can be caused by a variety of factors, including poor nutrition, antibiotic use, concomitant infections, stress, and other environmental factors. Restoring a balanced gut microbiota often requires dietary changes, the use of prebiotics and probiotics, and other lifestyle changes aimed at promoting the growth of beneficial bacteria and suppressing harmful ones.

Composition of microbiota in health and dysbiosis-related diseases

With regard to the presence of members of the human microbiota, regions of the human organism are divided into primarily sterile regions, where no microorganisms are present, and colonised regions, which are inhabited by members of the human microbiota. Primary sterile regions include blood, cerebrospinal fluid, pleural, pericardial, and peritoneal fluids, urine from the upper parts of the urinary tract, and all tissues and internal organs. Under normal circumstances, microorganisms are not present in these regions, but they may be present temporarily if the epithelial barrier is breached after trauma or during delivery, and they are removed by the cells of the reticuloendothelial system. Transient bacteraemia lasts for minutes or a few hours and most commonly occurs after manipulation of non-sterile body sites, such as dental procedures, gastrointestinal biopsies, percutaneous catheterization of the vascular system, bladder or common bile duct, and surgical debridement or drainage, i.e., after procedures involving contaminated or colonised skin and/or mucous membranes, and at the onset of acute bacterial infection (30). However, in medical microbiology, transient bacteraemia has no clinical significance as it is usually asymptomatic and cleared by the immune system response and is not an indication for microbiologic diagnosis by means of haemoculture.

The colonised areas of the human organism are the skin and mucous membranes which are in contact with the external environment. The number of microorganisms present in these areas and the diversity of species vary from region to region and depend on the nutritional needs of the microorganisms and the conditions in which their growth is possible. Some microorganisms that are strict aerobes grow on the surface of the skin, whereas facultative and strict anaerobes are most abundant in the gut microbiota. Table I provides an overview of the most common species found in the resident microbiota of colonised parts of the body, and species with pathogenic potential found in carriers (31, 32, 33, 34).

Table I Microbiota of the colonised regions of the human body and potentially pathogenic bacteria

Tabela I Mikrobiota kolonizovanih regija ljudskog organizma i potencijalno patogene bakterije

Colonised part of the human organism	**Resident microbiota (low virulence potential)**	**Major potential pathogens in carriers**
Skin	*Cutibacterium* spp. (formerly *Propionibacterium* spp.*)* *Corynebacterium* spp. Coagulase negative staphylococci	*Staphylococcus aureus*
Oral cavity	*Neisseria* spp. Viridans streptococci *Moraxella* spp. *Peptostreptococcus* spp.	*Streptococcus pyogenes* *Candida albicans*
Nasopharynx	*Neisseria* spp. Viridans streptococci *Moraxella* spp. *Peptostreptococcus* spp.	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* Goup A streptococci *Staphylococcus aureus* (anterior nares)
Stomach and small intestine	*Streptococcus* spp. *Peptostreptococcus* spp. (oral)	/
Colon	*Eubacterium* spp. *Lactobacillus* spp. *Bacteroides* spp. *Fusobacterium* spp. *Enterobacteriaceae* *Enterococcus* spp. *Clostridium* spp.	Enterotoxigenic *Bacteroides fragilis* Enteropathogenic *E. coli* *Pseudomonas* spp. *Candida* spp. *Clostridium* spp. (*C. perfringens, C. difficile*)
Vagina **Prepuberty/menopause**	*Corynebacterium* spp. Staphylococci *Enterobacteriaceae*	*C. albicans*
Reproductive age	*Lactobacillus* spp. Streptococci	Group B streptococci *C. albicans*

Since most colonised regions harbour at least two different bacterial species, normal microbiological findings show a polymicrobial saprophytic microbiota in low numbers, indicating a state of health and no need for antibiotic therapy. However, in the state of dysbiosis, one bacterial species supresses the others and predominates, resulting in the isolation of a monomicrobial pure culture in high numbers, without the presence of a saprophytic microbiota. This microbiological finding indicates a state of infection and should be interpreted carefully along with other clinical signs and symptoms.

The most significant health conditions and diseases related to dysbiosis are presented in Figure 1.

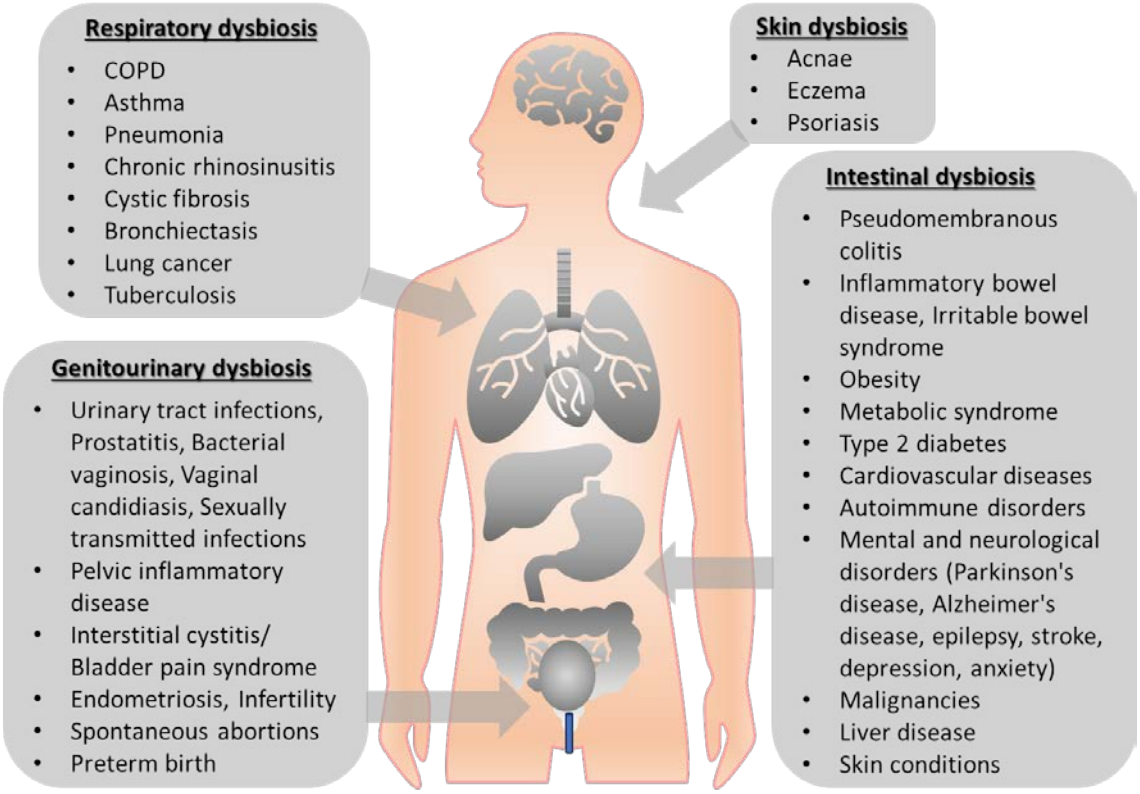

Figure 1. Dysbiosis-related diseases of the skin, respiratory tract, intestinal tract, and genitourinary tract

Slika 1. Bolesti kože, respiratornog, gastrointestinalnog i urogenitalnog trakta koje su povezane sa disbiozom

Gastrointestinal tract

The intestinal microbiota has the greatest diversity and abundance in terms of the number of microorganisms or species in the gastrointestinal tract. The total number of microorganisms per millilitre of intestinal contents increases along the gastrointestinal tract from $10^1 – 10^3$/ml in the oesophagus and stomach, to $10^8 – 10^9$/gramme of contents

in the lower part of the small intestine. The largest number of microorganisms, 10^{12} – 10^{14}/gramme of faeces, is found in the colon and rectum (35). The predominant microbial phyla in the gut are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia, with the most important genera being *Lactobacillus, Bacillus, Clostridium, Enterococcus, Ruminicoccus, Bacteroides, Prevotella.* and *Bifidobacterium* (36).

The oropharynx is colonised by streptococci, diphtheria, oral *Neisseria, Moraxella* spp. and *Actinomyces* spp., and a small number of *Candida* spp. Anaerobes and microaerophilic microorganisms colonise the deeper areas of the gingival crevices and tonsillar crypts. Saliva normally contains a mixed microbiota of about 10^8 microorganisms per millilitre. In the small intestine the resident microbiota is sparse, with the exception of the lower ileum, where a microbiota similar to that of the colon is found. The colon has the most numerous and diverse microbiota in the body. More than 90% of bacteria are anaerobes, mainly members of the genera *Bacteroides, Fusobacterium, Eubacterium,* and *Clostridium,* and the remaining 10% belong to the *Enterobacteriaceae* family (*E. coli, Klebsiella* spp., *Enterobacter* spp.) (19, 35).

The innate and adaptive immune response have the ability to discriminate between commensal and pathogenic bacteria through the activity of pattern-recognition receptors, such as Toll-like receptors, and a fine balance between regulatory T cells and $CD4^+$ effector T cells in the intestinal mucosa. An imbalance in the composition and diversity of the intestinal microbiota due to environmental and genetic factors increases the risk of infection with pathogens and promotes their excessive growth. Overuse and misuse of broad-spectrum antibiotics such as cephalosporins or fluoroquinolones often leads to antibiotic-associated diarrhoea or life-threatening pseudomembranous colitis caused by *C. difficile,* with toxic megacolon, perforation of the colon, and sepsis (37). Microbial dysbiosis can induce chronic inflammation of the intestinal mucosa, mediated by Th_1, Th_2 and Th_{17} cells and cytokines IL-4, IL-5, IFN-γ, IL-13, IL-17, IL-6, IL-8 and IL-22, leading to the development of numerous pathologic conditions of noninfectious aetiology, e.g. gastrointestinal disorders, metabolic disorders (obesity, metabolic syndrome, and type 2 diabetes), immune system disorders, autoimmune diseases and allergies, mental and neurological disorders, skin diseases, and malignancies (18, 19).

Gastrointestinal diseases associated with intestinal dysbiosis include inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). The two most important and common IBDs characterised by chronic inflammation of the gastrointestinal tract, biochemical changes in mucins in the colon, and decreased production of defensins are Crohn's disease and ulcerative colitis. In addition to genetic risk factors for the development of the disease, a reduction in microbial diversity and a decrease in the number of *Faecalibacterium prausnitzii* and *Roseburia hominis* have been demonstrated in patients with Crohn's disease (35). Gut dysbiosis may also contribute to the exacerbation of these diseases (33, 38, 39, 40). A study by Raftery et al. reviewed the association between IBD and chronic obstructive pulmonary disease, and suggested that the gut microbiota may also have an impact on respiratory health (41). However, gut

dysbiosis in COPD has not yet been described, although this would be expected given that environmental and genetic factors leading to microbial dysbiosis and chronic inflammation are present in both the intestinal tract and lungs (41). Irritable bowel syndrome is a functional gastrointestinal disorder characterised by abdominal pain, bloating, and changes in bowel motility. Alterations in the gut microbiota at the level of genera, such as *Coprococcus* spp., *Collinsella* spp., and *Coprobacillus* spp., have been associated with IBS symptoms (42, 43).

Several research papers suggested that altered gut microbiota composition may play a role in obesity by affecting metabolism, inflammation, and dietary energy production (44, 45, 46, 47). A high-fat, high-carbohydrate diet causes *Firmicutes* (*Clostridium* spp.), *Prevotella* spp., and *Methanobrevibacter* spp. to predominate, and beneficial genera and species such as *Bacteroides* spp., *Bifidobacterium* spp., *Lactobacillus* spp., and *Akkermansia* spp. to significantly decrease. Dysbiosis also alters the integrity of the intestinal epithelial barrier, translocation of bacteria and inflammation, expression of starvation hormones, induces dyslipidemia and low-grade chronic inflammation caused by metabolic endotoxemia, leading to obesity and its concomitant diseases (46, 47). Metabolic syndrome includes a number of risk factors such as obesity, hypertension, insulin resistance, and abnormal lipid levels that may eventually lead to the onset of cardiovascular and cerebrovascular diseases and type 2 diabetes (48, 49).

The gut microbiota plays an important role in the gut-brain axis and its bidirectional neurocrine, endocrine, and immune-mediated signalling pathways (50, 51, 52). Gut dysbiosis has been associated with various **neurological diseases** such as Parkinson's disease, Alzheimer's disease, epilepsy, stroke and vascular cognitive impairment, amyotrophic lateral sclerosis (ALS), and even mood disorders such as depression and anxiety (53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68). The composition of the gut microbiota also mediates the anti-seizure effects of the ketogenic diet in patients with severe epilepsy (69).

Among other health conditions, intestinal dysbiosis has been linked to the development of allergies such as asthma and atopic dermatitis, as well as autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis due to its potential influence on immune responses, inflammation and immune system regulation, increased risk of colorectal cancer due to the production of certain metabolites that trigger genotoxic stress and promote genetic/epigenetic alterations (*Fusobacterium nucleatum* has been associated with cancer, and *Ruminococcus bromii* with a favorable outcome), liver diseases such as nonalcoholic fatty liver disease and alcoholic liver disease, and skin diseases such as acne, eczema, and psoriasis (4, 16, 19, 35).

Skin

As the largest human organ, the skin has multiple functions and serves as the first line of defence against microorganisms and various environmental factors. The skin provides a dry, slightly acidic, and aerobic environment and is colonised by approximately 10^4 to 10^5 microorganisms per cm^2. The composition and number of

microorganisms in the skin's microbiota are determined by the activity of the sebaceous and sweat glands, so moist areas (armpits, perineum, and interdigital spaces) have a richer microbiota than other areas of the skin. The skin microbiota is most numerous in the hair follicles and sebaceous gland excretory ducts, and is easily recovered from these niches after the application of antiseptics or disinfectants. The most common species are staphylococci (*S. aureus* and coagulase-negative staphylococci *S. epidermidis* and *S. warneri*) and *Cutibacterium* spp. (formerly known as *Propionibacterium* spp.), which are scattered over the entire skin surface, whereas diphtheria bacilli of the genus *Corynebacterium* are more common in moist skin folds. *Cutibacterium* spp. grow in sebum and break down skin lipids to fatty acids, which inhibit or kill other bacteria that may colonise the skin. Other microorganisms, such as *Streptococcus* spp. and *Micrococcus* spp., apathogenic bacteria and anaerobes *Clostridium* spp. and *Peptostreptococcus* spp., and fungi *Candida* spp. and *Malassezia* spp., are present to a lesser extent (31, 70).

The conjunctiva of the eye has a strong mechanism against pathogenic bacteria and therefore a very sparse microbiota, mainly derived from the skin. The presence of antimicrobial compounds (lysozyme, defensins, and lactoferrin) and secretory IgA in lacrimal secretions, as well as the action of blinking and rinsing the eye with tears, ensure that the number of bacteria remains low (71).

Various factors can damage the skin barrier and lead to dysbiosis. These factors include varying hygiene practices (excessive use of harsh soaps, antibacterial products, and frequent washing), use of topical or oral antibiotics, certain skin diseases and underlying health conditions, diet and lifestyle, and environmental factors (exposure to pollutants, UV radiation, and other environmental stressors). Dysbiosis of the skin microbiota can manifest itself in various skin conditions such as irritation, itchiness, dryness, redness, inflammation, and susceptibility to infection, and has a strong impact on barrier function and a role in inflammatory skin diseases such as acne, psoriasis, and atopic dermatitis. In psoriasis, *Firmicutes*, and the genera *Corynebacterium* spp., *Cutibacterium* spp., *Staphylococcus* spp., and *Streptococcus* spp., are the most common bacterial strains in the skin microbiota, while *Actinobacteria* are relatively rare. Atopic dermatitis is characterised by a lower diversity of the skin microbiota and a greater number of *Staphylococcus* spp., especially *S. aureus*, and lower numbers of *Cutibacterium* spp., *Corynebacterium* spp., *Streptococcus* spp., *Acinetobacter* spp. and *Prevotella* spp. (72).

Respiratory tract

The upper respiratory tract, the nose and nasopharynx, are colonised with different bacterial species that form the microbiota. The microbiota of the nasopharynx is similar to the microbiota of the skin (*S. epidermidis* and diphtheria bacilli), and 25% to 30% of healthy people carry pathogenic *S. aureus* as a resident or transient microbiota. This microbiota is also similar to the oral microbiota, but potentially pathogenic

microorganisms such as *Haemophilus* spp., *Streptococcus pneumoniae, Neisseria* spp., and *Moraxella* spp. are frequently transmitted here (32).

The lower respiratory tract below the larynx is protected by the action of the ciliary epithelium and the movement of mucus, which expels microorganisms that reach the mucosa of the trachea or large bronchi. The sterile areas of the respiratory tract are the bronchioles and alveoli, which are sterile due to the presence of alveolar macrophages, as well as the paranasal sinuses and middle ear.

Respiratory dysbiosis, bacterial overgrowth, and alterations in the number and function of $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and regulatory T cells populations can promote inflammatory responses in the airways and lungs, leading to acute and chronic respiratory diseases. Bacterial overgrowth of the resident microbiota plays an important role in common lung infections like bronchitis, pneumonia associated with risk factors (community-acquired pneumonia, immunodeficiency-related pneumonia, ventilator-associated pneumonia, SARS-CoV-2-associated pneumonia), acute respiratory distress syndrome, and chronic obstructive pulmonary disease (COPD) (73).

Chronic obstructive pulmonary disease is a group of progressive lung diseases, including emphysema and chronic bronchitis, characterised by breathing difficulty and decreased airflow. Recent studies point to the role of the gut-lung axis in COPD, as dysbiosis of the gut and airway microbiota may contribute to inflammation and exacerbations in COPD patients (74, 75, 76). The most common bacterial isolates from the sputum of COPD patients during exacerbations are phyla *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*, and *Fusobacteria*, and the genera *Streptococcus*, which is the most abundant, *Neisseria, Porphyromonas, Haemophilus, Veillonella, Prevotella, Rothia, Pseudomonas, Staphylococcus, Proteus*, and *Moraxella*. Numerous studies indicate that lower microbial diversity is associated with acute COPD exacerbation (76, 77, 78, 79). COPD patients with declining respiratory function have a greater abundance of the *Firmicutes* in the gut microbiota than other patients in whom the phylum *Bacteroidetes* and the genus *Alloprevotella* predominate (75).

Asthma is a chronic inflammatory disease of the respiratory tract that affects 300 million children and adults worldwide. The development of asthma is strongly influenced by environmental and other exogenous factors (allergens, air pollutants), as well as genetic predispositions, which shape the respiratory microbiota, particularly during birth and early childhood (26). Alterations in the respiratory microbiota with an abundance of proteobacteria with genera *Haemophilus* and *Moraxella* in children and adult asthmatics influence airway inflammation and contribute to bronchoconstriction and bronchial hyperreactivity, leading to exacerbation of asthma symptoms (80, 81, 82).

The importance of the respiratory and intestinal microbiota in modulating immune responses also plays a role in other respiratory diseases, including common respiratory infections such as viral infections and pneumonia, chronic rhinosinusitis, cystic fibrosis, bronchiectasis, lung cancer, and tuberculosis (83). An imbalance in the respiratory

microbiota affects susceptibility to viral infections, such as influenza and the common cold, and increases susceptibility to pneumonia-causing pathogens. Chronic rhinosinusitis (CRS) is a persistent inflammation and infection of the nasal passages and sinuses. Dysbiosis in the microbiota of the nose and sinuses is thought to contribute to the development and persistence of CRS (84).

Cystic Fibrosis (CF) is a genetic disorder that results in thick, hyper-viscous mucus production that harbours bacteria and can lead to chronic respiratory infections. The core microbiota of CF patients' lungs shows an overexpression of *Proteobacteria* and *Actinobacteria*, and includes genera *Streptococcus, Prevotella, Rothia, Veillonella, Actinomyces, Fusobacterium, Gemella, Granulicatella, Neisseria, Atopobium*, and *Porphyromonas*. Disorders in the respiratory microbiota may play a role in the progression of respiratory infections in individuals with CF (85).

Among other respiratory diseases, intestinal and respiratory dysbiosis may contribute to recurrent respiratory infections in individuals with bronchiectasis, and the immunomodulatory role of the gastrointestinal microbiota significantly influences the immune response to tuberculosis infection, susceptibility to tuberculosis, and its progression (86, 87). Although the direct relationship with lung carcinogenicity is not fully understood, some studies have investigated the possible role of respiratory dysbiosis in the development and progression of lung cancer (86).

Genitourinary tract

The kidneys, renal pelvis, ureters, and urinary bladder are among the primary sterile regions, while the lower part of the urethra contains 10^3 - 10^4 microorganisms transferred from the perineal skin. The urinary tract microbiome (i.e., urobiome) consists of coagulase-negative staphylococci (*S. epidermidis*), diphtheroids, *Enterococcus* spp, *Streptococcus* spp, and the anaerobes *Bacteroides* spp, *Fusobacterium* spp, and *Peptostreptococcus* spp. (88, 89).

The vaginal microbiota plays an important role in the resistance to colonisation by invading pathogens, which is critical for the prevention of sexually transmitted infections, urinary tract infections, and vulvovaginal candidiasis. The vaginal microbiota varies with age and hormonal status (34, 90). Before puberty and after menopause, it is mixed, nonspecific, and relatively sparse, containing microorganisms belonging to the microbiota of the skin and colon. In the reproductive period, it consists mainly of anaerobic and microaerophilic bacteria. The most abundant bacteria in the vaginal microbiota of reproductive age women are *Lactobacillus* spp. and anaerobic bacteria, including *Gardnerella vaginalis*, *Prevotella* spp., *Mobiluncus* spp., *Ureaplasma urealyticum*, and *Mycoplasma hominis* (91, 92). The vaginal microbiota has been grouped into five types known as community state types I–V, and all five types are dominated by *Lactobacillus* spp. (*L. crispatus, L. gasseri, L. iners, L. jensenii*), polymicrobial microbiota including *Lactobacillus* and bacterial vaginosis-associated bacteria. Types I, III and IV are commonly found in women, while the other two types are rare (93).

The *Lactobacillus* genus bacteria break down glycogen deposited in the epithelial cells of the vagina under the influence of estrogen hormones and metabolize it to lactic acid, which provides the acidic pH of the vaginal secretion (pH 3.5-4.5). This has an inhibitory effect on most microorganisms, with the exception of gram-positive cocci and yeasts, which can survive in an acidic environment (22). *Gardnerella vaginalis, Prevotella* spp. (*Prevotella bivia, Prevotella disiens*), *Porphyromonas* spp., *Peptostreptococcus* spp. and *Mobiluncus* spp. may also be present in small numbers on the vaginal mucosa. These bacteria are the causative agents of bacterial vaginosis, which occurs when the normal vaginal microbiota is disturbed due to a decrease in lactobacilli (94).

Genitourinary microbiota is distinct from other microbial communities in the body and can be influenced by various factors, including sexual activity, hygiene practices, and hormonal changes. An imbalance in the urogenital microbiota contributes to an increased risk of urogenital infections, urinary tract dysfunction, infertility, endometritis, and preterm birth, and may play a role in the development of cervical cancer, among other factors.

Urinary Tract Infections (UTIs) occur when bacteria, often from the gut, enter and multiply in the urinary tract. Changes in the urobiome and vaginal microbiota might impact the susceptibility to UTIs, benign prostatic hyperplasia, urinary incontinence and overactive bladder syndrome, interstitial cystitis/bladder pain syndrome, bladder cancer, and urinary tract infections (88, 89, 95, 96, 97).

Alterations in the urinary and genital microbiota can contribute to the development or exacerbation of prostatitis, as they induce prostate inflammation, which leads to benign prostatic conditions such as prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. The whole human microbiota is capable of influencing systemic hormone levels and may play an important role in the development of prostate cancer that is dually affected by estrogen and androgen levels (98, 99).

Bacterial Vaginosis (BV) is an anaerobic polymicrobial disease characterised by subclinical inflammation of the vaginal mucosa. This can lead to itching, discharge, and an increased risk of other infections. Women with BV have reduced lactobacillus abundance and species diversity, with *L. iners*, *L. rhamnosus*, *L. salivarius*, and *L. reuteri* predominating, and other beneficial species such as *L. crispatus, L. fermentum, L. acidophilu*s, and *L. delbruckii* absent (100, 101).

An imbalance in the vaginal microbiota, especially after broad-spectrum antibiotic therapy, also contributes to vaginal candidiasis caused by *Candida albicans* and other non-albicans species (102). Alterations in the number and distribution of lactobacilli species may also lead to an overgrowth of *Candida* species and cause asymptomatic vulvovaginal candidiasis (101).

The genital microbiota may influence the susceptibility to sexually transmitted infections (STIs) such as chlamydia, gonorrhoea, trichomoniasis, and HPV, and lead to the development of pelvic inflammatory disease (103, 104, 105). Alterations in the

vaginal microbiota and increased incidence of HPV infection have been associated with cervical intraepithelial neoplasia (CIN) and cervical cancer (106, 107). Patients with HPV infection and CIN or cervical cancer were found to be depleted of *Lactobacillus crispatus* and to have an increased diversity of anaerobic microorganisms *Atopobium vaginae, Dialister invisus, Finegoldia magna, Gardnerella vaginalis, Prevotella buccalis,* and *Prevotella timonensis* (108, 109). Studies on HIV virus transmission suggest that lactic acid produced by a *Lactobacillus*-rich microbiota likely inhibits HIV transmission, whereas polymicrobial microbiota (type IV of vaginal secretions) and STIs likely increase HIV transmission (110).

In addition to gynaecological health, the vaginal microbiota has a strong influence on the reproductive health of females (111, 112). The type of predominant species in the vaginal microbiota may have role in endometriosis, fertility and infertility, and outcome of assisted reproduction technologies (113, 114, 115). Altered microbiota could also determine pregnancy outcomes (116, 117). Recurrent spontaneous abortions in the first trimester of pregnancy have been associated with a high prevalence of *Leptotrichia amnionii, Atopobium vaginae* and *Sneathia sanguinegens* (118, 119, 120). Several studies have suggested a possible association between an imbalance in the vaginal microbiota and an increased risk of preterm birth (121, 122, 123). The risk of preterm birth was greater in women with high concentrations of *Atopobium vaginae, Gardnerella vaginalis*, or ureaplasma. An increased risk was associated with the predominance of *Lactobacillus iners, Streptococcus* and *Bifidobacterium* in the vaginal microbiota, compared with the protective effect of *Lactobacillus crispatus* found in women with term births (122, 123).

Conclusion

The human microbiota is an essential and complex ecosystem that profoundly influences various aspects of human health. This complex community of microorganisms which colonise various niches of the human body plays a multifaceted and pivotal role in maintaining health and well-being. Moreover, an imbalanced microbiota is associated with a variety of health conditions and diseases, emphasizing the importance of maintaining and preserving its diversity and balance. Therapeutic approaches to dysbiosis focus on supplementing the normal microbiota with probiotic microorganisms in probiotics, prebiotics, postbiotics, and synbiotics, or on regenerating the intestinal microbiota with fecal transplants. Research in this area continues to advance, promising innovative treatments and interventions that harness the power of the microbiota to improve human health.

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Normalna ljudska mikrobiota i disbioza - implikacije po zdravlje i bolest

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Kratak sadržaj

Normalna ljudska mikrobiota, koja se ranije nazivala „*mikroflora*“, sastoji se od bakterija, gljivica, virusa i parazita koji kolonizuju kožu i sluzokožu respiratornog, gastrointestinalnog i genitourinarnog trakta. Broj i raznovrsnost mikroorganizama variraju između različitih telesnih niša i najveći su u crevnom traktu. Mikrobiota doprinosi homeostazi ljudskog organizma tako što sprečava kolonizaciju patogenim mikroorganizmima, učestvuje u procesima varenja i metabolizma i reguliše imunološke funkcije.

Disbioza je stanje u kome dolazi do neravnoteže sastava mikrobiote usled uticaja različitih egzogenih ili endogenih faktora, što može uticati na ljudsko zdravlje. Ona je najčešće rezultat smanjene raznovrsnosti mikroorganizama i manjeg broja saprofitnih bakterija, što je praćeno prekomernim rastom potencijalno štetnih vrsta. Najčešće bolesti koje su direktno povezane sa crevnom disbiozom su dijareja povezana sa primenom antibiotika i pseudomembranozni kolitis, a obe nastaju kao posledica prekomernog rasta štetnih bakterija i *Clostridioides difficile* nakon terapije antibioticima širokog spektra.

Disbioza je povezana sa različitim zdravstvenim stanjima ili bolestima kao što su akne, psorijaza, ekcem, hronična opstruktivna bolest pluća, inflamatorna bolest creva, gojaznost, metabolički sindrom, dijabetes tipa 2, autoimunske bolesti i alergije, neurološke bolesti kao što su Parkinsonova bolest, Alchajmerova demencija, epilepsija i moždani udar, depresija, anksioznost, neplodnost, prevremeni porođaj i maligni tumori.

Ključne reči: humana mikrobiota, disbioza, komensalne bakterije, bolesti povezane sa disbiozom