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Microbiocenosis Of Open Cavities Of The Body

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ABSTRACT

The article is devoted to a review of the topical problem of our time “Microbiocenosis of open cavities of the body and its role in the occurrence of many diseases of the human body ”. It has now been proven that the normal microflora of the human body plays a huge role in the normal course of life processes. The slightest violation of the composition of microorganisms leads to various irreversible defects in the normal course of human life, which are associated with the functions of the microbiocenosis and which no medicine can replace. The concept of microbiocenosis appeared in the 70s of the last century, although the first stone in this direction was put by Louis Pasteur, who proved the role of a microorganism in the process of fermentation and digestion. Many scientists contributed to the leap forward development of this science, which was forced due to errors in the use of antibiotics and chemotherapeutic drugs. Yes, indeed, the path of development of the science of biocenoses is closely related to the misuse of drugs, which often leads to dysbiosis. In addition, environmental pollution due to the uncontrollable development of urbanization plays a huge role in the development of dysbiotic processes.Therefore, with the aim of acquainting readers with the concept of biocenoses, certain pathways of pathogenetic links in the development of various diseases in violation of the composition of the normal microflora of the human body, we set ourselves the task of conducting a partial review of the achievement of the science of biocenoses of open cavities of the body.

KEYWORDS

Microbiocenosis, population, community of microorganisms, constancy of microbial species.

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INTRODUCTION

Man and the environment is a single ecological system in a state of biological balance between macro - and microorganisms. The normal microflora of a person is the basis of his microecology and has a direct impact on the vital activity and state of the macroorganism, this determines the relationship between man and the environment; it is a single ecological system that is in a state of biological balance between macro- and microorganisms. Human microflora is an additional organ, weighing 2.5-3 kg. The skin and mucous membranes of the respiratory tract, digestive tract, organs of vision and genitourinary system are inhabited by a huge number of bacteria in the amount exceeding the number of cells of the entire human macroorganism (1014 versus 1013). The main advantage that microorganisms coexisting with multicellular organisms receive is the stability of the environment in terms of temperature, ionic composition, and the presence of nutrients. Microbial populations of the skin, mucous membranes, and intestines normally act as symbionts or saprophytes, being in ecological balance with the human body [14].The coexistence of bacteria and humans is absolutely equal and the same [44]; it is called microbiocenosis. Recent studies have convincingly shown that the microbiocenosis of humans and animals is an integral part of the host organism and is a sensor for metabolites, mitigates the shifts induced by infections or the host due to their conservative metabolism, and stabilizes the human and animal population on Earth. Human microbiocenosis is determined by periods of ontogenetic development, sexual characteristics, ecological living conditions, stressful situations. Their condition is affected by competition, accommodation, and a possible (temporary) change in the prebiotic microbiocenosis of a person who has temporarily left for another geographic zone and consumes local food products (including together with local prebiotic strains). The ecological system, the components of which is a macroorganism, its microflora and environment, are characterized by unity and the ability to self-regulation. Normal microflora (autoflora) is a set of associations of microorganisms typical for a particular biological type, the natural activity of which occurs in those organs and tissues of the macroorganism that communicate with the external environment (represented by bifidobacteria, lactobacilli, enterobacteria and Escherichia coli). Normal microflora is an evolutionarily developed ecosystem (called enoecology) of various symbiotic microorganisms that inhabit the open cavities of the human body and maintain biochemical, metabolic and immunological equilibrium necessary for maintaining human health and is an integral part of human microbiocenosis. Microbiocenosis is a kind of dynamic microecological system that contributes to the creation of more or less homogeneous conditions for the normal life of the autoflora and performs or regulates numerous functions of the macroorganism, depending on the external conditions among. When characterizing the microflora of a particular biotope, the terms are often used: population, community, microbial succession. A population is a collection of individuals of the same species occupying a specific biotope and having a common gene pool. Community - an accumulation of several populations of different types of microorganisms. Communities of microorganisms form the biocenosis of a particular biotope and, together with the host organism, form permanent or temporary ecosystems. Within ecosystems, populations and communities of

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microorganisms occupy their ecological niches. Biotopes of mucous membranes of human open cavities are of particular interest. Microbial ecosystems of the mucous membranes of open cavities and human skin are formed gradually, starting from the moment a child is born, and change in the process of its growth and development.A sequential change in a certain area of the habitat of some communities of microorganisms by others is called a succession, which ends with the formation of a relatively stable microbiocenosis.

All normal human microflora is subdivided into resident microflora (it is obligate, autochthonous or indigenous), optional (it is additional or allochthonous) and transient (it is also random). The index of constancy of the microbial species C (%) is determined by the formula [35,36,65,66]:

p

C = - x 100%, where -

P {{1 }}

p - the number of samples containing the studied species,

P - the total number of samples.

Depending on the value of the constancy index of the microbial species C (%) microorganisms are divided into permanent (autochthonous), found in the biotope under consideration in more than 50% of cases, additional (allochthonous), found in 25% - 50% of cases, and random (transient), occurring in less than 25% of cases. .

In the formed microbiocenosis, 90% are resident, less than 9.5% are optional, and up to 0.5% are random microorganisms. In the human body, normal (symbiotic, indigenous, resident, or autochthonous) microflora is constantly present and spreads unevenly: 77.5% of it is present in the gastrointestinal tract; 12% is located on the surface of the skin and in deeper layers; 5% in the upper respiratory tract (trachea, bronchi and alveoli are usually sterile); 5% in the genitourinary system: on the external genitals, urethral mucosa, in the vagina (kidneys, uterus, ureters, bladder are usually sterile) and 0.5% on the conjunctiva of the eyes.Transient (non-permanent, or allochthonous) microflora is not capable of long-term existence, its retention in the human body can cause various inflammatory processes and lead to serious diseases.

About 20% of the normal flora live in the oral cavity (more than 200 species), 40% - in various parts of the gastrointestinal tract, 18-20% - on the skin, 15-16% - on the oropharynx, 2-4% - on the urogenital tract of men, about 10% - on the vaginal biotope in women. Microorganisms are distributed in the human body both vertically - from the oral cavity to the lower (distal) parts of the colon, and horizontally - from the lumen to various layers of the mucous membrane. Distinguish between mucous or parietal microflora and luminal microflora [36,65].

Colonization resistance (CR).

The skin, respiratory, urogenital and gastrointestinal tract, conjunctiva, oral mucosa, constantly exposed to a variety of foreign substances and microorganisms, perform their own barrier function. The barrier function of these areas is determined by the state of CR, which means the ability of microflora and a macroorganism in

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cooperation to protect the ecosystem of mucous membranes from pathogenic microorganisms. The mucous membranes of the open cavities of the macroorganism represent a single system [10,37,38,45,50,72].

Colonization resistance (CR) is a physiological phenomenon aimed at maintaining microecological homeostasis and is provided by numerous inherited mechanisms. It is a manifestation of nonspecific antimicrobial resistance of a macroorganism - one of the manifestations of the general physiological reactivity of a macroorganism, its reaction to a kind of stimulus - a microbial agent. Antimicrobial resistance is purely individual, its level is determined by the genotype of the organism, age, living and working conditions, etc. The state of dynamic balance between the host's organism, its microorganisms inhabiting it and the environment is usually called "eubiosis", in which human health is at an optimal level. CR includes a complex of local factors, which include inhibitors of microbial adhesion, biocidal and biostatic products of secretions, normal microflora, mechanical factors (ciliated epithelium, the integrity of the skin and mucous membranes), AT [2,32,40,71,97,106,129,133,138,160].The mechanisms of the CR phenomenon include skin and mucous membranes (they form a physical and ecological barrier for the penetration of pathological agents into the body), movement of mucociliary epithelium, intestinal motility, desquamation of mucosal cells, antimicrobial effect of secretions of saliva, bile, gastric and intestinal contents, composition and amount of mucin , oxygen tension across biofilm thickness, pH of the medium, rate of renewing mucosal epithelium, local immunological defense mechanisms [35].

Molecular evolution of mucosal epithelium took place under selection pressure, which contributed to a decrease in the body's response to commensal bacteria, while maintaining the ability response to pathogenic microorganisms. In other words, the relationship between normal microflora and mucous membranes can be explained as a result of the convergent evolution of TL receptors and surface molecules of microorganisms and epithelial cells. Obviously, in the course of evolution, microorganisms have developed a system that allows them to avoid the directed antimicrobial action of the protective forces of the human body. This, to a certain extent, explains the ability of the indigenous microflora to avoid the controlling mechanism of mucosal CR and to be weakly immunogenic for the host. The expression of these receptors can be increased in response to inflammatory mediators [96]. The indigenous microflora plays an important role in the provision of CR for biotopes.Its protective functions consist in shielding receptors from adhesins of foreign microorganisms, competing with the latter for food substrates, stimulating the mobility of the mucosal epithelium and the processes of its renewal, producing biologically active compounds, including antibiotic-like substances, detoxifying xenobiotics (including those of microbial origin) due to their absorption or biotransformation, induction of an immune response that has a cross-reaction against pathogenic microorganisms, production of nonspecific immunogenesis stimulants and activators of phagocytic and enzymatic activity. Maintaining the CD of the macroorganism by the normal microflora is a multifactorial process. An important factor in maintaining a balance in the microflora-macroorganism ecosystem is adhesion,

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through which the organism controls the number of bacteria [44,56]. At present, cytadhesion is considered not only as the initial stage in the pathogenesis of the infectious process in response to most pathogenic and opportunistic microorganisms (OCP), but also as a general biological property by which microorganisms colonize mucous membranes. All microorganisms have a pronounced ability to attach to organic and inorganic surfaces. The natural way of life of most microorganisms is associated with their fixation on any substrates. Among the many factors that bring obvious benefits of attachment, stand out [24]: attachment to the substrate, as a rule, providing more favorable conditions for access to nutrients; attached bacteria are much easier than free-swimming bacteria to form cooperative structures with other species; the attachment and subsequent multiplication of microorganisms with the formation of microcolonies and / or a film provides them with more favorable conditions of existence, associated, in particular, with resistance to the mechanical removal of bacteria from the macroorganism; in attached bacterial communities, there are more opportunities for the exchange of genetic material (plasmids), the pathway along which information about the determinants of resistance spreads. The attachment of bacterial cells to the surface is a process associated with both physicochemical interactions and biological activity. There are two groups of adhesion mechanisms - nonspecific and specific. Nonspecific adhesion is usually reversible [18,19]. The term “docking” is sometimes used to describe this type of adhesion in the English literature. To describe a specific adhesion (interaction involving special adhesin molecules), which is considered irreversible, the term "anchoring" is used. To establish an adhesive contact, the bacterial cell and the target cell must overcome electrostatic repulsion, since their surface molecules normally carry a negative charge.

Hydrophobic adhesive contacts between bacteria and mucosal epithelial cells are also possible.The adhesion of microorganisms to the surface of the mucosal epithelium can also be carried out using fimbriae, ordered filamentous outgrowths on the surface of bacterial cells. However, the most important role is played by interactions between adhesins and receptors of mucosal epithelial cells, some of which are species-specific. The establishment of the interaction between the pathogen and the target cell as a result of bacterial adhesion is the defining link in the course of the infectious process. The molecular mechanism of bacterial adhesion is universal for pathogenic and commensal forms [170]. It has been proven that the adhesiveness of microorganisms often correlates with their pathogenicity and virulence [64,103,181]. In vivo, the adhesion process is significantly influenced by the dissolved components of biological fluids and secretions, with which pathogens are more likely to meet before contact with target cells and which are chemically similar to cell receptors. E. coli adhere to salivary mucin earlier than to the epithelium of the oral cavity [183]. Pathological changes in the tissues of the macroorganism create additional conditions that promote the adhesion of microorganisms [26]. It has been shown that normal aerobic intestinal microflora reduces the recession of enterobacteriaceae (pathogenic and non-pathogenic strains of Escherichia coli, Shigella spp.), Reducing the number of receptor sites for representatives of transient (optional) microflora. The role of representatives of the

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commensal microflora in the regulatory function of natural microbiocenosis at the adhesion stage is also shown on the model of buccal epithelial cells of healthy people.Thus, the relative resistance of epithelial cells to adhesion of grams of negative bacilli against the background of natural colonization of epithelial cells by streptococci has been established. The antagonistic activity of representatives of the indigenous human microflora is a fundamental factor determining CR and the body's natural resistance to pathogenic microbes [44,56,85,180]. The normal resident microflora, through low molecular weight metabolites, as well as special antimicrobial substances, suppresses the vital activity of a number of pathogenic microorganisms. This is intermicrobial antagonism - the production of organic acids, hydrogen peroxide, muramidase, bacteriocins, microcins and other antagonistically active substances. Activation of the immune system - activation of phagocytosis, induction of the synthesis of immunoglobulins, lysozyme, interferon, cytokines. One of the main protective mechanisms of the mucous membrane is moistening its surface with mucus, which is produced either by individual cells or by specialized multicellular glands. Mucus plays an important role in preventing pathogens from entering the body by forming a viscous layer that binds pathogens. The active movement of mucus along the surface of the mucous membrane contributes to the further removal of microorganisms. For example, in the respiratory tract, mucus moves due to the activity of the cilia of the multi-row epithelium, and in the intestine due to the peristaltic activity of the latter. In some places, in the conjunctivitis, oral and nasal cavities, the urogenital tract, microbes are removed from the surface of the mucous membranes by flushing with appropriate secretions. The mucous membrane of the nasal cavity produces about half a liter of fluid during the day. The ureoplasm is washed with urine, and the mucus secreted from the vagina helps to remove microorganisms. In mucus, both nonspecific protective factors (pH, redox potential, viscosity, low molecular weight metabolites of microflora) and specific ones - sIgA, phagocytes and immune cells act. The sIgA in mucus acts as the first line of mucosal immune defense to neutralize pathogens. Studies have shown that the presence of sIgA correlates with resistance to infection by various pathogens of bacterial, viral and fungal origin. Confirmation of the role of IgA in preventing the colonization of mucous membranes by foreign microorganisms is the fact that 99% of anaerobic representatives of the indigenous microflora are not covered with secretory Ig, while aerobic bacteria (enteric bacteria, enterococci, etc.) are completely covered with sIgA.At the same time, it is well known that microorganisms that constantly inhabit the skin and mucous membranes are predominantly obligate anaerobes, the number of which is tens of times greater than the number of aerobes. In animals receiving bifidobacteria per os, the production of IgA, antibodies in blood serum and bile increased and cellular immunity increased. Another important component of the immune defense of the mucous membranes is T-lymphocytes. T cells from one of the populations come into contact with epithelial cells and have a protective effect, killing infected cells and recruiting other immune cells to fight the pathogen. Interestingly, the source of these lymphocytes in mice are the clusters of cells located directly under the epithelial lining of the intestine. T cells are able to move in mucosal tissues thanks to special receptors on

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their membranes. If the immune response develops in the gastrointestinal mucosa, T cells can move to other mucous membranes, such as the lungs or nasal cavity, providing the body's protection at the systemic level [12,13,15,16,93].

CR can be considered as integrating component of local immunity. Initially, local immunity meant a complex of cellular and secretory nonspecific and specific reactions, including the barrier functions of skin cells and mucous membranes, phagocytic activity of neutrophils and macrophages, T-cell immunity, antibodies, antimicrobial proteins of external secretions, enzyme inhibitors.Local immunity was not identified with secretory immunity, but the B-cell response of the lymphoid tissue of the mucous membranes with the participation of the glandular epithelium, which supplies the secretory component, was considered as its central link. Later, the concept of local immunity expanded and now includes the totality of responses of all cells of the lymphoid series that populate the mucous membranes, in cooperation with macrophages, neutrophilic and eosinophilic granulocytes, mast cells and other cells of connective tissue and epithelium [9,27,137,163,167,182,185].

Indicators of the state of microbiocenoses - indicators of reactivity of a macroorganism

Reactivity of an organism - the ability of an organism to respond to the effects of the external environment by changing its vital activity, which ensures its adaptation to various living conditions. Resistance is closely related to the reactivity of the organism, representing one of its main consequences and expressions. The realization of the mechanisms of resistance of the organism is provided, as a rule, not by any one organ or system, but by the interaction of a complex of various organs and physiological systems, including all links of regulatory processes. The body's resistance can be determined by the relatively stable properties of various organs, tissues and physiological systems, during which they are not associated with active reactions to this effect. Significant fluctuations in individual resistance can be associated with the characteristics of the reactivity of the organism during its interaction with the damaging agent. Resistance can decrease with a lack, excess or qualitative inadequacy of biologically significant factors (nutrition, physical activity, labor activity, information load and stressful situations, various intoxications, environmental factors, etc.). In the formation of resistance, active protective-adaptive reactions are of decisive importance, aimed at maintaining homeostasis in the event of potentially harmful effects of environmental factors or unfavorable shifts in the internal environment of the body.The effectiveness of such reactions and, consequently, the degree of resistance to various factors depends on the congenital and acquired individual characteristics of the organism. Resistance changes in the process of ontogenesis, and its age dynamics in relation to various influences is not the same, however, in general, it turns out to be highest in adulthood and decreases with aging of the organism. Distinguish between nonspecific and specific resistance. Non-specific resistance is understood as the ability of the body to withstand the effects of various factors in nature. Specific resistance characterizes a high degree of resistance of the body to the effects of certain factors or their close groups, resistance against various disease-causing effects [2,32,40,83,84]. Currently, a large amount of factual material

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has been accumulated on the role of microflora in human life and in the formation of its reactivity and anti-infectious resistance. Normal microflora helps to maintain the necessary barrier level of mucous membranes, skin and forms the first line of defense against infections, and also performs a number of other important functions in the body.

Microorganisms in certain situations form biofilms which are associated with the communicative manifestation of the "quorum sense" (QS) of microorganisms in communities characterized by a high population density and high physiological activity of its constituent individuals. This feature is of great biological importance for the survival of the microorganism in an unfavorable environment.Microbial PD are communities formed by related and unrelated microorganisms, whose cells have specialization and contact with each other (including contacts in the form of adhesion). Intercellular contacts are carried out by some molecules without their release into the external environment and, among other factors, form a single cooperative cellular system. They consist of three components: microorganisms, extracellular matrix, surface envelope. The matrix holds a large amount of water, contains neutral or polyanionic polysaccharides (gram-negative bacteria), cationic polysaccharides and teichoic acids (gram-positive bacteria), proteins, lipids, extracellular DNA and RNA, enzymes and toxins produced by the cells of the community themselves; contains from 50% to 90% organic carbon of biofilm. It is a barrier between microbial cells and the external environment, protects them from immunity factors and antibiotics, redistributes flows of organic and inorganic molecules in the biofilm. Bacteria called "persisters" exhibit maximum resistance to external factors (due to differentiation, they are temporarily in a state of complete resistance to almost all drugs). Quorum sensing reactions (closely related to an increase in the resistance of biofilm bacteria to antibiotics, the production of toxins, gene transfer, the formation of spores, etc.) in gram-positive bacteria are provided by oligopeptide signaling molecules and low-molecular substances containing a lactone group; in gram-negative bacteria - homoserine lactones. The extracellular DNA matrix is also involved in the self-regulation of PD properties (it is necessary for normal PD formation). Destruction of the extracellular DNA matrix of bacterial PD leads to a change in their properties and contributes to an increase in the effectiveness of antibiotic therapy. BP is ideal for the exchange of genetic information between microorganisms.The surface envelope, which on electron diffraction patterns resembles a plasma membrane, is represented by lipids, identical to those in the bacterial membrane and differing in the number of individual components. Resettlement of PD occurs due to the separation of its part or individual cells, some of which differentiate into special cells [46,60,78,92,110,122,151,178,184]. In comparison with simple colonies, BP has a higher pathogenic potential and, at the same time, greater resistance to the action of unfavorable factors. The constancy of the composition of biofilms is an important characteristic of this type of communities and the process of their formation does not depend on the presence or absence of pathology and proceeds according to the known laws of surface colonization. Plaque is one of the types of BP. Oral streptococci possessing high adhesiveness to the tissues of

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the oral cavity, due to co-adhesion, create conditions for the attachment of microorganisms that are unable to linger on the surface of the teeth on their own [101, 375, 388, 507].

The hierarchically highest level of virulence regulation is the phenomenon of cooperative sensitivity, which controls the formation of PD, the synthesis of almost all extracellular enzymes exhibiting toxic properties. In its most general form, this phenomenon can be regarded as an example of the social behavior of bacteria, since its meaning lies in the modification of the physiological functions of bacteria in response to a change in their numbers. With the help of BP, bacteria colonize a variety of hard surfaces, medical catheters, implants and body tissues, oral mucosa, skin, and blood vessels. In PD, microbial cells are better protected both from the action of bactericidal immunity factors and antibacterial drugs. Dense fixation of biofilms to the urothelium can lead to a decrease in the number of bacteria in the secretion of the prostate, and as a result, an erroneous interpretation of the etiological role of the secreted pathogen is possible. Moreover, the tight adhesion of bacterial cells in the PD leads to the formation of large conglomerates, which, when inoculated on solid nutrient media, are regarded as the growth of a single colony. This fact can lead to an incorrect assessment of the quantitative results of sowing. The development of the inflammatory process caused by UPM is closely related to the formation of PD, which further determines the development of infection from the formed "springboard" of grouped pathogens attacking the body. In the area of PD fixation, epithelial cells are activated and begin to produce defensins and other substances that are directed to the suppression of foreign microorganisms; factors that activate the migration of neutrophils through the layer of epithelial cells; chemokines that attract neutrophils, eosinophils, basophils, mast cells, monocytes, dendritic cells to this site. These cells are activated by antigens of microorganisms and release various proinflammatory cytokines into the environment, as a result of which a focus of inflammation is formed [23,75,118,119].

PD with microorganisms included in it can be considered as a target that is the first to be involved in recognition processes, adsorption and translocation, metabolism of both useful and potentially harmful agents. It is a mucopolysaccharide “glove” covering the entire skin and all mucous membranes without exception. It prevents the penetration of exogenous microorganisms into its lower layers, coming with water, food, etc., and for endogenous microorganisms it is an obstacle to adhesion and colonization of areas that are not characteristic of them.In addition to exopolysaccharides of microbial origin, PD of human mucous membranes consists of microcolonies of autochthonous microflora and mucin secreted by goblet cells. PD disorders occur: against the background of the death of autochthonous microorganisms that provide CR; in violation of the synthesis of microbial polysaccharides, thinning of the biofilm and access of potential pathogens to the receptors of epithelial cells in these areas; when thinning and replacing the old biofilm with a new one formed by opportunistic pathogens of exo- and endogenous origin. Consequently, BP is a product of joint activity of the organism and microflora. Possessing numerous factors of specific and nonspecific protection, it cooperatively interacts with the

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intraluminal and parietal microflora and macroorganism, protecting the ecosystem from pathogenic microflora [18,19,20,22,67].

Currently, the proportion of infectious diseases, the etiological agents of which are the UPM of the normal microflora of the human body, such as staphylococci, streptococci, escherichia, serrata, klebsiella, enterobacteria, proteus. Their acquisition of pathogenic properties is, to a certain extent, due to the appearance of pathogenicity islands (OP) in them. Under OP it is customary to understand DNA fragments ranging in size from 1 to 10 kb ("islets") or from 10-20 to 200 kb ("islands"), including discrete virulence genes and found only in pathogenic microorganisms.These DNA fragments differ from the "core genome" in the content of% G + C, as a rule, they are flanked by small direct nucleotide repeats (DR-directly repead) and are often associated with the 3 'region of loci of various transport RNAs (tRNAs). The determinants of OP are able to spread among related bacterial species during conjugation, transduction, or transformation. This mobility of OP is associated with the fact that they can be part of bacteriophages, transposons, or plasmids. It is the integration, stabilization and expression of virulence genes that make up the OP that underlies the formation of new properties, including virulent ones, in related non-pathogenic bacterial species of various taxonomic groups [20,137]. Registration and increase in UPM infection in dysbacteriosis are objective criteria for their severity [44]. Consequently, dysbacteriosis is any qualitative and quantitative changes in the microflora of humans and animals typical for a given biotope, arising as a result of exposure of a macro- and microorganism to various factors of an exogenous and endogenous nature, entailing clinical manifestations on the part of the macroorganism or resulting from any pathological processes in organism. Dysbiosis is a microbiological imbalance in the body, which over time manifests itself as local symptoms, and then general disorders that aggravate the course of various diseases. Dysbacteriosis of various localization, as a rule, is caused by microecological and immunological disorders that contribute to the development of infectious processes. Any infectious process in the mucous membrane, regardless of etiology, develops according to the same scenario. The first stage is the adhesion of microbes in parietal mucin or epithelial cells, which is provided by special structures of the pathogen. Once established, microorganisms begin to multiply, which leads to pathological colonization of the mucous membrane - this is the second stage of the infectious process (dysbiosis). The next, third stage of the infectious process is the invasion of microorganisms, when they overcome the protective barrier of the mucous membrane and penetrate into the epithelial cells or underlying tissue, while causing a local immune response (colitis, vaginitis, pharyngitis, etc.). When overcoming the local protective barrier, generalization of the infection is possible. The pathogenicity of certain bacteria species depends on the presence or absence of representatives of other species [21, 44, 172]. Therefore, when assessing mucosal microbiocenoses, it is necessary to take into account the number and species composition of both microorganisms that are freely located in the lumen and adhered to epithelial surfaces (parietal region) [20].

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Skin microbiocenosis

From the moment a person is born, billions of microorganisms begin to populate human skin with an area of about 20,000 cm2 and mucous membranes, creating a complex bioecosystem, the balance of which can be disturbed under the influence of various factors. The outer layer of the skin is represented by a strong stratified keratinizing epithelium, the epidermis. On the surface of the skin, as a rule, there is little moisture, and the secretions of the skin glands prevent the reproduction of microorganisms. Due to constant contact with the external environment, the skin most often becomes a habitat for transient microorganisms (Streptococcus spp., Peptococcus spp., Bacillus subtilis, Escherichia coli, Enterobacter spp., Acinetobacter spp., Lactobacillisspp., Candida albicans and others). The normal flora of the skin is represented by a biological film of microbial cells, microbial exopolysaccharide glycocalyx and secretions of integumentary tissues. Nevertheless, there is a stable and well-studied permanent microflora, the composition of which is different in different anatomical zones, depending on the oxygen content in the environment of the bacteria (aerobes - anaerobes) and proximity to the mucous membranes (mouth, nose, perianal region), secretion characteristics, and even the clothes of a person. The most populated with microorganisms are places protected from light and drying. The most constant composition of microflora in the area of the mouths of the sebaceous hair follicles. More often, Staphylococcus epidermidis and S. saprophyticus, fungi of the genus Candida, are detected, less often diphtheroids and micrococci. The main representatives of the skin microflora are diphtheroids (corynebacteria, propionic bacteria), mold fungi, yeast, spore aerobic bacilli (bacilli), staphylococci (S. epidermidis predominates, but S. aureus is also present in small amounts on healthy skin). Usually, there are 103-104 microorganisms on human skin per 1 cm2, 10b microorganisms per 1 cm2 are in the axillary and groin areas. The resident skin microflora includes Staphylococcus epidermidis, Staphylococcus aureus, Sarcina spp., Coryneform bacteria, Propionibacterium spp. Normal skin microflora includes: coagulase-negative staphylococci, Corynebacterium spp., Various types of propionbacteria and some others, mainly gram-positive cocci. S. aureus can colonize the skin on which it comes from the nasal cavity (when colonizing the nasal passages with this pathogen). 25% of the healthy human population is colonized by Staphylococcus aureus. The skin is closely related to the immune, nervous and endocrine systems. CR of the skin is provided by the epidermis (impermeable to the vagina, counteracts the damaging effect of mechanical factors and prevents the penetration of bacteria into the body, together with Corynebacterium spp., Microorganisms are also removed from the body surface), normal flora, bactericidal factors of the sebaceous and sweat glands, acidic reaction of the surface environment, skin lysozyme, antimicrobial peptides, IgG, IgA, transferrin, organic acids, low pH levels.The innate and acquired immunity of the skin involves keratinocytes, dendritic cells, T-helper cells, YST and NKT lymphocytes, macrophages and mast cells. Neither profuse sweating, nor washing or bathing can remove the normal permanent microflora or significantly affect its composition, since the microflora is quickly restored due to the release of microorganisms from the sebaceous and sweat glands, even in cases where contact with other areas of the

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skin or with the external the environment is completely terminated. Thorough hand washing reduces germs on the skin by 90%, but it returns to baseline after 8 hours. Therefore, an increase in the contamination of a particular area of the skin as a result of a decrease in the bactericidal properties of the skin can serve as an indicator of a decrease in the immunological reactivity of a macroorganism. At the same time, the number of Staphylococcus aureus and gram-negative bacteria on the skin increases, herpes simplex viruses and human papilloma viruses multiply [46,47,48].

Microbiocenosis of the oropharynx

The microbiocenosis of this area is second only to the large intestine and oral cavity in terms of diversity of species. Since the microflora of the gastrointestinal tract and the airways are mixed here, commensals and pathogens belonging to both systems are secreted on the mucous membrane of the posterior pharyngeal wall. Much attention has been paid to the study of the microbial ecology of the respiratory tract in recent years. Specific anatomical and physiological features of a particular area of the respiratory tract determine both the qualitative and quantitative composition of the microorganisms present in them.

The microflora of the nasal passages of healthy people is represented mainly by staphylococci and micrococci. In the nasal passages there are diphtheroids, primarily Corynebacterium spp., Persistent staphylococci (resident S. epidermitis), neisseria, hemophilic bacteria, streptococci (alpha-hemolytic), propionibacteria. In the nasopharynx - corynebacteria, streptococci (S. mitis, S. salivarius, etc.), staphylococci, neisseoi, vylonella, hemophilic bacteria, enterobacteria, bacteroids, fungi, enterococci, lactobacilli, pseudomonas aeruginosa are found more transiently. subtilis, Branchamela.

The most abundant and diverse microflora of the orotogolot, especially the surface of the tonsils. Significant amounts of both aerobic and anaerobic microorganisms are found here. The indigenous group includes streptococci (S. salivarius, S. mitis, S. mutans, S. sanguis, S. anginosus, S. pneumonia, S. bovis, S. uberis, Streptococcus spp. Groups C and G) and non-pathogenic Neisseria (N. subflava, S. perflava, N. flava, N.flavescens, N. sicca, N. mucosa). These microorganisms are found in 90-100% of the examined in the amount of 4-6 lg CFU / g. Additional micro flora of the oropharynx: staphylococci, Corynebacterium spp. and Haemophilus influenzae are found in 25-50% of healthy people in an amount not exceeding 3-4 lg CFU / g. The transient group of bacteria in the oropharyngeal region is represented by a wide range of aerobic and anaerobic microorganisms, including enterobacteria, gramoritic non-fermenting bacteria, candida, peptostreptococci, veilonella, fusobacteria, bacteriodes, actinomycetes, etc. 3 lg CFU / g (Table 1). Table # 1

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Characteristics of microbiocenosis Characteristics	***Microflora colonizing the mucous membrane of the oropharynx***		
	Indigenic (constant)	***Additional***	***T ranked (random)***
Microorganism's	***Streptococcus Neisseria Lactobacillus Bifidobacterium***	***Staphylococcus Corynebacterium Haemophilus***	***Bacillus Candida Micrococcus Escherichia Klebsiella Pseudomonas***
Detection frequency, %	***76,9% - 90,4%***	***26,9% - 46,2%***	***1,9% - 25,0%***
The nature of colonization	Associations of 2-3 or more types: ***Streptococcus:*** *S. salivarius* *S. pneumoniae* *S. mitis* *S. anginosus* *S. sanguis* *S. uberis* *S. mutans*	1-2 or more types: ***Staphylococcus:*** *S. aureus* *S. epidermidis* *S. saprophyticus* ***Corinebacterium:*** *C. pseudodiphteriticum* *C. xerosis* *C. ulcerans* *Corinebacterium spp.* ***Haemophilus:*** *H. influenza*	Monotype (one of the types): ***Bacillus spp.*** ***Candida:*** *C. albicans* *C. zylonoides* *C. bumptii* *C. krusei* *C. utilis* *Candida spp.* ***Micrococcus spp.*** ***E. coli*** ***K. pneumonia***

The mucous membrane of the larynx, trachea, bronchi and all underlying sections remains sterile due to the activity of their epithelium, macrophages, and sIgA production.

When conducting a microbiological study, a quantitative method of accounting for isolated microorganisms is used to separate etiologically significant microflora from contaminating microbes. The causative agent, as a rule, is found in the material in a significantly larger amount than human symbiont microbes.

The activity of antibodies of external secretions is mainly determined by locally produced secretory sIgA and sIgM, but the secretions also contain significant amounts of IgG-Ab due to their "leakage" through the surface of the epithelium.

The secretory component of immunity is central to emergency protection of the mucous membrane of the upper respiratory tract. Polymeric IgA is able to more effectively neutralize viruses, bacterial toxins, enzymes and agglutinate bacteria in comparison with the monomeric form of IgA. Secretory immunity is stimulated mainly by live microbial and corpuscular antigens (lipopolysaccharides, polyglucans). Soluble protein antigens and haptens mainly cause suppression of the local (local) humoral immune response (IgG-Ab and

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IgE-Ab), as well as delayed-type hypersensitivity mediated by activated T-helper cells (CD4 +) of the 1st order [26]. sIgA blocks the adhesion of a wide range of microorganisms to epithelial cells of the mucosal surface [30, 435] due to carbohydrate-specific interactions independent of the specificity of the IgA molecule.The effect of sIgA largely depends on the state of the normal microflora colonizing the mucosal surface [30,87,137,144,145,146,163,177,179]. sIgA is involved in the regulation of the immune response, enhancing the antibacterial activity of phagocytes [15,26,27,119,111].

Intestinal microbiocenosis

The intestinal microbiocenosis is a very important system of the body that performs or regulates its numerous functions to maintain homeostasis. The number of bacteria inhabiting the human body is several orders of magnitude higher than the number of cells in the human body. Their role in human life is enormous. In fact, it is a kind of additional body that performs many functions. The intestinal microbiocenosis is a dynamic ecological system that contributes to the creation of uniform conditions for the normal life of the autoflora and regulates the numerous functions of the macroorganism. A deficiency or excess of one or another substrate or metabolite is a signal to enhance the growth or death of the corresponding link in the ecosystem. In the process of evolution, specialization of the functions of the permanent representatives of the normal microflora took place. The mucous membrane of the small intestine has a surface area of 75000-100000 cm2, and that of the large intestine is 2500 cm2. The presence of folds, villi and microvilli on the intestinal mucosa increases its surface 20 times, which can reach 150-200 m2. Sterile at birth, the gastrointestinal tract is colonized by microorganisms in a specific sequence.In the first 24 hours of life, the intestine is colonized by bifidobacteria and lactobacilli, then, during the next week, by anaerobic cocci. The composition of the intestinal flora of a child after 2 years practically does not differ from that of an adult. The microflora of the gastrointestinal tract is the most important barrier for pathogenic bacteria and has more than 500 species of microorganisms, the content of which in its various departments ranges from 103 to 1012 CFU / ml. The density of bacteria in the stomach, jejunum, ileum and colon, respectively, is 1000, 10,000, 100,000 and 1,000,000,000 in 1 ml of intestinal contents. The composition of the microflora of each biotope of the digestive tract is different, but remains constant, which is associated with the ability of bacteria to fixate to strictly defined receptors of the epithelial cells of the mucous membrane. In the mucous membrane of the small intestine, there are receptors for the adhesion of predominantly aerobic flora, while receptors for the fixation of anaerobic strains predominate in the large intestine [34,35,83,93, 131]. The population of microorganisms in the gastrointestinal tract varies in composition and number, depending on the section of the tract. The acidic environment of the stomach limits the multiplication of bacteria, however, here, under normal conditions, you can find lactobacilli and streptococci, which transit through the stomach. Lactobacilli, enterococci, yeast, bifidobacteria, E. coli are more often found in the stomach with an acidic reaction of the environment and the upper parts of the small intestine. In the intestine, streptococci, lactobacilli are detected, and gram-negative bacilli may also be present. In the duodenum, jejunum and the initial parts of the ileum, the

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total number of bacteria is 103-104 CFU / g of contents. It is important to note that in this biotope there are practically no obligate anaerobic bacteria, as well as representatives of the enterobacteriaceae family and, first of all, Escherichia coli.In the small intestine, microorganisms are localized mainly parietally. In the distal parts of the small intestine, the concentration of microorganisms increases and is 105-109 CFU / g of intestinal contents, and obligate anaerobic bacteria (bacteroids, bifidobacteria, etc.) join the inhabitants described above. In the proximal areas of the small intestine, there are fewer types of microflora than in the large intestine. These are lactobacilli, enterococci, sardines, mushrooms, in the lower parts of the growing number of bifidobacteria, Escherichia coli. Quantitatively, this microflora may differ in different individuals. Possible minimum degree of contamination (10'-103 CFU / g content), and significant - 103-104 CFU / g. In the colon, bacteria make up about 55% of the solids. Bacteria of 40 species are constantly present here, although representatives of at least 400 species can be identified. The large intestine is the main habitat for normal intestinal flora (Tables 2, 3). The total biomass of colon microbial cells is about 1.5 kg, which corresponds to 10n-1012 CFU / g of intestinal contents and approximately 1/3 of the dry weight of feces. The microflora of the large intestine is the most stable and diverse. More than 250 species have been found. In 1 gram of intestinal contents there are 250 billion different representatives of microflora. A person releases over 17 trillion microbes per day. To date, more than 400 microorganisms have been isolated from the colon biotope - representatives of 17 families, 45 genera. The dominant group is normally spore-free anaerobic bacteria (bifidobacteria and bacteroids) - up to 99%. [131]. It is the large intestine (tab.2 and 3), due to such a high microbial contamination, it carries the greatest functional load in comparison with other biotopes [25, 62].

The composition of the anaerobic and aerobic microflora of the large intestine of a healthy person.

The composition of the microflora of the colon includes: 1- obligate (basic, resident, main, obligatory, indigenous, autochthonous) is subdivided into main (strict anaerobes - bifidobacteria and bacteroids -108 - K) "CFU / cm2 or 90-99%) and accompanying microflora or aerobes (Escherichia coli - 0.5%, lactobacilli, enterococci - 1-9%, propionic acid bacteria). The sum of all microorganisms of this group is at least 90% from the total number of microbes contained in the feces; 2 - facultative (unstable, accompanying) microflora (its composition varies, not more than 1% of the total microflora): - saprophytes (bacterioids, peptococci, staphylococci, streptococci, bacilli, yeast fungi), aerobic and anaerobic bacilli; - opportunistic (Klebsiella, Proteus, Citrobacter, Enterobacter) The microflora of the large intestine includes: 1 - Obligate (main, resident, main, mandatory, indigenous, autochthonous) is divided into main (strict anaerobes - bifidobacteria and bacteroids -108 - K) "CFU / cm2 or 90-99%) and accompanying microflora or aerobes (E. coli - 0.5%, lactobacilli, enterococci - 1-9%, propionic acid bacteria).

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Table 2

Composition of anaerobic and aerobic microflora of the large intestine of a healthy person

Anaerobic microflora	Aerobic microflora
Bifidobacteria Bacteroids Lactobacilli (optional) Fusobacteria Anaerobic cocci Veilonella Clostridia,	E. coli Streptococci (enterococcus, hemolyzing streptococcus) Staphylococci Klebsiella Proteus Yeast Campylobacter

Composition of the main colon microflora of healthy people

The colon microflora includes: 1- obligate (main, resident, main, obligatory, indigenous, autochthonous) subdivided into main (strict anaerobes - bifidobacteria and bacteroids -108 - K) "CFU / cm2 or 90-99%) and accompanying microflora or aerobes (E. coli - 0.5%, lactobacilli, enterococci - 1-9%, propionic acid bacteria The sum of all microorganisms of this group is at least 90% of the total number of microbes contained in the feces; 2 - facultative (unstable, accompanying) microflora (its composition varies, no more than 1% of the total microflora): - saprophytes (bacterioids, peptococci, staphylococci, streptococci, bacilli, yeast fungi), aerobic and anaerobic bacilli; - opportunistic (Klebsiella, Proteus, citrobacter, enterobacter). Their specific weight is no more than 10% of the total number of microorganisms - transient , about residual, allochthonous) microflora: Escherichia coli (0.5%), lactobacilli, enterococci - 1-9%. Allocate microflora: - protective (bifidobacteria, lactobacilli, full-fledged Escherichia); - saprophytic (yeast, saprophytic and epidermal staphylococcus); - UPM (proteus, candida, coagulase-positive staphylococcus, hemolytic streptococcus, spore-bearing anaerobes); - pathogenic (Salmonella, Shigella, enteropathogenic Escherichia, Yersinia, Clostridia, Helicobacter) [82]. The normal intestinal microflora is 92-95% composed of strictly anaerobic bacteria species (bifidobacteria and bacteroids). Aerobes and facultative anaerobes make up 2-5%.The number of anaerobic microorganisms in the large intestine exceeds aerobes by 100-1000 times. The composition of the intestinal microflora is quite individual, but the quantitative relationships between different microbial populations are characterized by a certain stability. Changes in the living conditions of the host organism can lead to

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changes in the composition and number of intestinal microflora, which is not always indifferent for macroorganism. The most complex biotope of microbiocenosis is intestinal cooperation, represented by various populations of microorganisms [51,52,79,83,88,89,93, 131].

In the microflora of the gastrointestinal tract, parietal (mucous) and luminal flora are distinguished. Microorganisms belonging to the normal intestinal microflora colonize both the lumen of the intestinal tract and the surface of the intestinal mucosa, forming the parietal or mucous microflora (M-microflora) and cavity microflora (P-microflora) [20,83,93]. Their composition is different. Although feces and parietal mucin have a similar species composition of microorganisms, there are a number of significant differences in their frequency of occurrence. When comparing the microbial composition of the parietal mucin of the large intestine and feces, it was found that bifidobacteria are more often present in parietal mucin (by 33%, p <0.001). At the same time, lactobacilli (by 14%, p <0.05), enterococci (by 20%, p <0.001) and candida (by 3.64 times, p <0.001) are sown from feces a little more often. Staphylococci and Clostridia from both biotopes are sown at the same frequency. The microbial landscape of feces is represented in 80% of cases by 5-6-component associations formed by Enterococcus spp. (103'8 CFU / g) with a predominance of E. faecalis (80%), bifidobacteria and lactobacilli (10x210 CFU / g), E. coli (10x69 CFU / g), K. pneumoniae (10x25 CFU / g), yeast-like fungi (10x24 CFU / g) [41]. At the same time, a correlation analysis admissible in this situation did not reveal significant relationships between the number of microorganisms in feces and the colon, that is, the concentration of microbes in feces practically does not depend on their number in parietal mucin [18]. There are certain connections between the luminal and parietal microflora.This is confirmed by the similar species composition of the isolated microorganisms. A certain relationship between the two biotopes is due to their direct contact during the passage of the chyme along the intestinal tube. Meanwhile, the adhesive ability of microbes [18], the quantitative composition and principles of the organization of microbial associations in the biotopes under consideration have individual characteristics, which suggests their certain isolation. In addition, the vector of mutual influence of the two biotopes is not completely clear. The biotope of parietal mucin of the small intestine in its quantitative and qualitative microbial composition differs significantly from that of the large intestine. In the small intestine, the studied microbes are found much less frequently than in the large intestine. In particular, bifidobacteria from the parietal mucin of the small intestine are released 1.5 times less often (p <0.05), lactobacilli - 2.9 times (p <0.001), clostridia - 4.5 times (p <0.01) , and enterococci - by 37%. E. coli, staphylococci and candida were not inoculated from the parietal mucin of the small intestine at all. The specific content of microorganisms in the parietal region of the small intestine is 4-4.5 lg CFU / g of tissue and, in comparison with the large intestine, is lower on average by 1.4-3.2 lg. In particular, the specific content of bifidobacteria in the parietal mucin of the small intestine is lower by 3.17 lg (p <0.001), lactobacilli by 1.38 lg (p <0.01), enterococci - by 1.25 lg (p <0.01). The specific content of clostridia in the small intestine does not significantly differ from that in the large intestine [18]. The parietal mucin of the colon region from the ascending colon to the

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sigmoid, with some exceptions, has a similar microbial composition.At the same time, the rectum is significantly different from other parts of the large intestine. A comparative analysis of the frequency of occurrence of microorganisms in the parietal mucin of various parts of the colon revealed significant differences between the individual levels of this biotope. Thus, the frequency of isolation of clostridia from the ascending colon is 8.7-12 times lower ($p < 0.01$), and enterococci are less frequently sown from the transverse colon (1.6-2.1 times, $p < 0.05$) and candida (1.5-3.7 times, $p < 0.05$) than from other parts of the colon. The rectal mucosa was the most scarce in terms of contamination. From this section, bifidobacteria were sown 2 times less frequently ($p < 0.01$), and staphylococci were not sown at all. The specific content of microorganisms in the parietal mucin of different parts of the colon does not differ significantly. Nevertheless, in the ascending and transverse colon, in comparison with other parts of the colon, the specific content of Clostridia and Candida is lower by 1–2 lg CFU / g of tissue, and in the rectum there are bifidobacteria and Escherichia [18]. The settlement of the parietal mucin of the human intestine significantly depends on the morphofunctional state of the intestinal wall, as well as on the general physiological processes occurring in the human body. The luminal flora, along with bifidobacteria and lactobacilli, includes other permanent inhabitants of the intestine. The function of the microbial ecological system of the gastrointestinal tract can be likened to the work of a large biochemical laboratory carrying out hundreds of biochemical processes [82].

By the nature of metabolism, the intestinal microflora is divided into two groups: proteolytic and amylolytic bacteria. Proteolytic strains (bacteroids, proteus, Escherichia, Clostridia, etc.) use the products of protein hydrolysis as a nutrient substrate and form toxic substances (ammonia, aromatic amino acids, endogenous carcinogens, sulfides, etc.) as the final metabolites of their vital activity, cause putrefactive processes , contributing to the development of inflammation, diarrhea, neoplasia. Most proteolytic microorganisms are UPM. Amylolytic bacteria (bifidobacteria, lactobacilli, etc.), which make up the bulk of the microbial cells of the colon, use food carbohydrate substrates and polysaccharides of intestinal mucus in their life.The metabolic functions performed by amylolytic microbes are beneficial to the host; they maintain homeostasis and neutralize the negative effects of proteolytic microflora. Currently, 4 types of intestinal microflora are known, each of which is characterized by a predominance: 1-Bacteroids, 2-Bifidobacteria, Z-Eubacterium, 4-Mixed microflora. One of the most important functions of normal microflora is to provide CR. The living conditions of intestinal microorganisms are mainly strictly anaerobic, and the presence of oxygen and the redox potential of the mucous membrane limits their reproduction. The intestinal microflora is located on the mucous membrane in layers. The first layer of bacteria is located directly on the cells of the epithelium (mucosal microflora), the subsequent layers are located one above the other (luminal microflora) and immersed in the mucous substance, which is the intestinal mucosa or the bacteria themselves. Microorganism colonization by microorganisms is a normal process, commensal relationships are beneficial for the macroorganism and bacterial microflora. From modern positions, the normal intestinal microflora can be considered as a set of

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indigenous microorganisms that constantly populate the digestive tract and represent a nonspecific barrier of protection against pathogenic bacteria and other exogenous factors of aggression. It has a bactericidal and bacteriostatic effect on pathogenic microflora, provides anti-infectious protection and immunoregulatory function, takes part in the synthesis of IgA, natural antibodies, in the morphogenesis of the immune system [83,88,89,93,131]. The leading role of normal intestinal bacteria is to protect the body from colonization by UPM and pathogenic bacteria and to prevent bacterial overgrowth in the intestine. M-microflora, inhabiting the intestinal mucosa and forming a dense bacterial "sod", providing the CR of the intestinal wall and the normal course of metabolic processes in its epithelial cells. The associative connections between enterocytes and microbial colonies of natural autoflora lead to the formation of a protective biolayer on the surface of the intestinal mucous membranes, "sealing" the intestinal wall and preventing the penetration of pathogenic toxins into the bloodstream. Normal intestinal bacteria do not penetrate into the internal environment of the body due to the existence of a barrier function of the mucous membranes of the gastrointestinal tract.Microbiological barrier provides resistance to colonization; competition with pathogens for nutrients, vitamins, minerals and metabolites; promotes acidification of the environment due to the activation of the metabolism of lactic, acetic and other fatty acids; production of bactericidal substances (bacteriocins, short-chain fatty acids) that inhibit the reproduction of pathogenic strains and their adhesion to the receptors of the mucous membranes and prevent external invasion [16.83.93]. With a decrease in CD, an increase in the number and spectrum of pathogenic bacteria occurs, and the possibility of the development of an infectious process arises. The stability of the composition of the intestinal microflora in a healthy person is maintained with the participation of a number of mechanisms. The leading host factors limiting bacterial growth in the small intestine are hydrochloric acid and intestinal motility. The composition of the intestinal microflora is influenced by the integrity of the intestinal mucosa, the secretion of mucus, digestive enzymes, Ig, especially sIgA, the volume of desquamated intestinal epithelium, as well as food components. The factors of bacteria that maintain their normal composition in the intestine include: competition for the use of nutrients; change in the intraluminal pH level; production of toxic metabolites, enzymes, antibiotics such as "colicins", oxygen utilization by aerobes [131]. The colonizing ability of microorganisms (in particular, lactobacilli) is strictly specific for a particular individual.Studies on volunteers show that auto-microorganisms provide a very rapid restoration of the normal state of the intestinal microflora [20,80,93].

Bifidoflora forms an association with the intestinal mucosa (covers the epithelium in the form of shingles), providing physiological protection of the intestinal barrier from penetration into the internal environment of metabolites formed as a result of the vital activity of bacteria, from endotoxins formed during the death of bacteria. Non-mobilized bacteria have a resistance many times lower than with CR [34,51,93,]. BP components are: mucus; IgA 1 and IgA2 associated with mucus glycoproteins; glycocalyx with its normal rheological parameters, ensuring the resistance of the epithelium to bacterial and chemical agents and a number of low

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molecular weight intestinal metabolites, which are associated with CR of the mucous membrane in relation to UPM and pathogenic microorganisms; indigenous microflora and its metabolites, which protect the intestinal mucosa from degradation, physical and chemical aggression, from the adhesion of pathogenic microbes, the action of bacterial and other toxins. The postepithelial barrier includes blood flow, which provides phagocytosis, humoral immune responses and other defense mechanisms, as well as the functioning of the preepithelial and epithelial barriers. An important protective role is played by the intestinal lymphatic system, which includes intraepithelial T-lymphocytes, Peyer's (Peyer) plaques and the lamina propria (Lamina propria) of the intestinal mucosa, as well as a number of regulatory substances (prostaglandins, enkephalins, growth factors, secretin, sulfidryls, etc.) which enhance the protective functions of the mucous barrier [16,93,123].

Feces contain a large but inconsistent amount of potentially pathogenic bacteria, which are more common in vegetarianism, in disorders of the immune system or in gastric diseases accompanied by low acidity. They can cause translocation of microorganisms into the blood or adjacent organs, contributing to the development of infection (sepsis, endocarditis, recurrent cystitis, etc.) and their spread in the environment, with subsequent infection of others. Intestinal bacteria can live in the lumen of the intestine, freely moving in it, or permanently inhabit the mucous membrane, forming "parietal" and "luminal" microflora. The acidic environment of the stomach prevents the multiplication of microorganisms that enter it from the oral cavity with food. After passing through the gastric barrier, microorganisms find themselves in more favorable conditions and multiply in the intestine with sufficient heat and nutrients, as in a thermostat.Under the condition of a normal physiological state, the relationship "macroorganism - microflora" has a symbiotic character, while the microorganisms inhabiting the human gastrointestinal tract perform a variety of vital functions, including providing the processes of digestion and absorption, intestinal trophism, synthesis of vitamins, enzymes, amino acids. The complex relationship between the saprophytic bacterial flora and the macroorganism determines the states of eubiosis and dysbiosis. In the first case, the microflora is represented by non-pathogenic microorganisms that occupy their biological niches in certain quantitative and qualitative ratios. Violation of the number, proportions and type of bacteria can lead to dysbiosis and infections. Recognizing the possibility of the existence of such a pathological condition, it should be emphasized that such a nosological unit does not exist. This is a stable violation of the species spectrum, quantitative ratio and qualitative characteristics of microorganisms of obligate and facultative microflora with a significant decrease in the protective role of indigenous microflora [8,17,51,93]. Dysbacteriosis and dysbiosis are different concepts. Dysbacteriosis (synonyms - excessive bacterial growth in the intestine) is a microbiological assessment of changes in the composition and quantitative ratio in the microbiocenosis of the gastrointestinal tract. Dysbiosis is a more general concept: it is a microbiological imbalance in the body, which over time manifests itself with local symptoms, and then general disorders that aggravate the course of various diseases.Dysbiosis cannot be used as the main diagnosis, it is always secondary and

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has no specific clinical equivalents. They are not talking about treatment, but about the correction of this condition. The reasons for the disturbance of the intestinal biocenosis are varied. The main ones are gastrointestinal diseases, inadequate diets, acute intestinal infections, medications, including antibiotics, that disrupt the immune status of the intestine and its motility. Distinguish between a compensated form of intestinal dysbiosis, when clinical manifestations are absent, and violations of the microflora CR are detected during bacteriological analysis, and decompensated, which is divided into three stages according to the level of bifidumbacteria content: the first stage - bifidumobacteria more than 105 / ml, intestinal dysfunction is observed, an association of opportunistic microorganisms reaches threshold values, which is clinically manifested by dyspeptic syndrome; the second stage is bifidumobacteria less than 105 / ml, UPM prevails; dyspeptic fermentative syndrome occurs; the third stage is a further decrease in the number of bifidumobacteria with a predominance of pathogenic flora, there is a putrid dyspeptic syndrome and intoxication syndrome. The term "intestinal dysbiosis" includes: 1) changes in the quantitative and qualitative composition of microflora in different biotopes (small and large intestine); 2) the emergence of optional UPM. For example, in mucin of a mucosal area affected by a tumor, the frequency of sowing bifidobacteria is 40-66% lower than in other pathological conditions. On the mucous membrane of the diverticulum and polyp, bifidobacteria and staphylococci are noticeably more common. The inflamed mucosa quite often contains clostridia ($p < 0.05$) and candida, but less often - bifidobacteria [18]. Depending on the type of intestinal lesion, different sowing rates from mucin of enterobacteria, not belonging to the genus Escherichia {Proteus ssp., Enterobacter ssp., Citrobacter ssp., Klebsiella spp., Hafnia ssp., Were recorded. and etc.). So with diverticulosis, this figure was 100%, with tumors - 80%, inflammation - 64.7%, polyposis - 25%, and in areas with unchanged mucosa - only 20% [32]. Nevertheless, mucin of the intestinal wall mucin with diverticulosis and polyposis was distinguished by a lower specific content of bifidobacteria and lactobacilli, and with inflammation - a higher specific concentration of enterococci and candida. The dependence of the adhesive properties of lactobacilli and Escherichia on the functional state of the gastrointestinal mucosa is interesting. Thus, microbes isolated from mucin of the inflamed mucosa differed significantly from strains obtained from unaltered tissue. In the inflamed areas, 40% more adherent and extremely few coadhesive cells were found. Obviously, the inflamed tissue creates the prerequisites for the accumulation of highly adhesive strains in the mucosa. This fact may be due to the fact that with inflammatory lesions of the intestinal wall, the physicochemical properties of the synthesized mucin change, as well as the bioavailability of the biotope.In addition, lactobacilli, located in the parietal mucin of the inflamed areas, were clearly defective in their ability to form microcolonies [18]. The presented data demonstrate the mechanism of formation of dysbiotic shifts in inflammatory diseases of the gastrointestinal tract.

Microbiocenosis of the vagina and cervical canal

The microbiocenosis of the birth canal is very diverse and rich in species. The components of the normal microflora are diverse, nature has endowed this part of the mother's body with

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peculiar protective properties, in which there are many even strictly anaerobic microorganisms. If we compare the microbial species of the birth canal with the microflora of other areas of the body, we find that the microflora of the birth canal of the mother is similar to the main groups of microbial inhabitants of the body of the future young organism, that is, the child receives obligate representatives of his normal microflora when passing through the birth canal of the mother. Further colonization of the child's body comes from this evolutionarily grounded microflora received from the mother. In a healthy mother, the fetus in the uterus is sterile until the onset of labor. However, the correctly formed (selected in the process of evolution) normal microflora of the mother's body fully inhabits its body not immediately, but in a few days, having time to multiply in certain ratios.

A distinctive feature of the vagina is that its mucous membrane communicates with the external environment and is always bacterially seeded (Table 4).The microflora of the vagina includes both microorganisms that form the microflora and non-pathogenic bacteria that have come from the outside, UPM and pathogenic bacteria. The vagina with its inherent microflora form a single ecosystem in which the vaginal environment controls the microflora, and the microflora, in turn, affects the vaginal environment [56,73,150,151]. Vaginal discharge normally contains 108-1012 CFU / ml of microorganisms, while facultative anaerobic bacteria are 103-105 CFU / ml, anaerobic - 105-109 CFU / ml [63,105,144]. The normal microbial landscape of the vagina and cervix includes about 60 species of bacteria related to microaerophiles, facultative and obligate anaerobes. In this case, associations from 2-5 sometimes to 10-15 microorganisms are possible (Table 4) [49,144, 150,155,].

Table 4

Species composition of the vaginal microflora of healthy women of reproductive age

Types of microorganisms	Frequency of xcretion (%)	Ability to cause disease
Microaerophilic bacteria		
Lactobacillus spp. L. fermentum L. crispatus L. jensenii L. gasseri L. acidophilus L. plantarum L. brevis L. delbruckii L. salivarius	71-100	-
Gardnerella vaginalis	6-60	+
Obligate anaerobic gram-positive bacteria		
Lactobacillus spp.	5-30	-
Bifidobacterium spp. B. bifidum B. breve B. adolescentis B. longum	12	-

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Clostridium spp.	10 - 25	+
Propionibacterium spp. P.	25	-/+
Mobiluncus spp.	-	+
Peptoniphilus asaccharolyticus	80 - 88	+
Finegoldia magna	53	+
Anaerococcus prevotii	32	+
Peptostreptococcus tetradius	32	4-
Obligate anaerobic gram-negative bacteria		
Bacteroides spp. B. ureolyticus B. fragilis B. vulgatus B. ovatus B. distasonis B. uniformis B. caccae B. multiacidus	9-13	+
Prevotella spp. P. bivia P. disiens	60	+
Porphyromonas spp. P.	31	+
Fusobacterium spp. F.	14-40	-
Veillonella spp.	11-14	-

According to various sources, UPM concentrations range from 103 to 105 CFU / ml [505]. Monocultures of aerobic and anaerobic microorganisms of the vagina can be obtained relatively rarely; microbial associations of different composition are distinguished much more often [75]. A characteristic feature of the normocenosis of these biotopes is the predominance of anaerobic microflora with a concentration of 108-109 CFU / ml. Healthy women have an average of 108'1 aerobic and 109'1 anaerobic CFU per ml of material from the vagina [109,121,126,155]. The total number of bacteria in the vaginal microcenosis ranges from 103 to 10b-108 CFU / ml; in a few works on the study of the normal microflora of Cc - up to 102 CFU / ml [11,112,145].

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Table 5

Types of microorganisms Frequency of excretion (%) and Ability to cause disease

Facultative anaerobic gram-positive bacteria		
Corynebacterium spp. C. aquatum C. minutissimum C. equi C. xerosis C. bovis	30-40	-
Corynebacterium enzymicum	8-10	Возбудители
Staphylococcus spp. S. epidermidis S. saprophyticus	62	+
Streptococcus viridans	30-40	+
Streptococcus agalactiae	10-20	Respiratory diseases, meningitis, septicemia in newborns
Enterococcus faecalis	30-40	+
Семейство	5-30	+
Escherichia coli Enterobacter spp. Klebsiella spp. Proteus	2-10	+
Pseudomonas aeruginosa	2-10	+
Mycoplasma hominis	2-15	+
Ureaplasma urealyticum	6-7	+
Mycoplasma fermentans	2-5	-
Yeast-like mushrooms		
Candida albicans Candida tropicalis Torulopsis	15-20	+

Notes: "+" - the presence of a sign; "-" - no sign.

The mucous membranes of the genital tract in apparently healthy women of reproductive age are seeded mainly with Lactobacillus spp. (72-100% of cases at a concentration of 103-108 CFU / ml); coagulose-negative staphylococci (CNS) and Corynebacterium spp. (60-80% at a

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concentration up to 104 CFU / ml); Bacteroides spp. (6-65%), Prevotella spp. (55-60%) and Peptostreptococcus spp. (30-90%) - up to 103-104 CFU / ml; Micrococcus spp. (35%). There is also G. vaginalis (up to 10%, as a rule, but it can be detected in 60% at a concentration of up to 104-106 CFU / ml); E. coli (5-30%) and Streptococcus spp. (30-40%) with a concentration of 103-104 CFU / ml; M. hominis (2-50% up to 104 CFU / ml); U. igea - lyticum (6-50% up to 103 CFU / ml). G. Vaginalis is often found in associations with U. Urealyticum (53.8%) or M. Hominis (30.6% -54%). In rare cases (0-5%), Mobiluncus spp. Is found in vaginal secretions. It is believed that mycoplasmas cannot be representatives of the normal flora of the vagina [55,107,115,129,135,139,159,161,164,169].

Dederlein's lactic acid sticks (lactobacilli, the number reaches 109 CFU / ml) and diphtheroids predominate in the vagina of a healthy woman. There is a balance between lactobacilli on the one hand and gardnerella and anaerobes on the other. Against the background of species diversity, the leading place in the microbiocenosis of the vagina of women of reproductive age is occupied by lactobacilli of aerobic and anaerobic nature (more than 10 species) - microaerophilic, producing H2C> 2 (71-100%), less often anaerobic (5-30%) gram-positive rods - representatives of the genus Lactobacillus.Among these microorganisms, facultative anaerobic acid- and peroxide-producing predominate.

In clinically healthy women of reproductive age, lactobacilli of one species or several varieties predominate in the vagina: L. crisptus, L. iners and L. gasseri ... However, in some cases, lactobacilli can be replaced by other lactic acid bacteria: Atopobium, Megasphaera and / or Leptotrichia species. It is proposed to distinguish between women with "normal" vaginal flora (lactobacilli predominate) and women with "wrong" vaginal flora (non-lactobacillary flora predominant). In clinically healthy patients, in 60% and 100% of cases, the absence and decrease in the content of Lactobacillus spp. into the vagina (at the generally accepted rate of 106'8 CFU / ml); monocultures of CNS, S. viridans group, E. coli (103'4 CFU / ml) are found in urine samples. At the same time, in clinically healthy women, clinical and instrumental examination revealed the absence of UGT pathology; the presence in 100% of cases of I-II degree of purity of the secretion of the mucous urogenital organs in the absence of "key" cells and yeast-like fungi [7,41,42,69,125,134,141,143,155,158].

Bifidobacteria, part of the vaginal microcenosis, like bacteria of the genus Lactobacillus belong to Dederlein's microflora. In healthy women of reproductive age, they are detected with a lower frequency (12%) at concentrations of 103-107 CFU / ml. Bifidobacteria synthesize amino acids and vitamins that are actively used by the host's body in its metabolism.

Peptostreptococci are the third constituent of Dederlein's microflora.The number of anaerobic cocci in the vaginal discharge is 103-104 CFU / ml. Despite the fact that peptostreptococci are part of the normal flora of the female genital tract, they are often found in septic abortions, tubo-ovarian abscesses, endometritis, and other severe infections of the female genital tract. In association with other anaerobic bacteria, peptostreptococci are isolated in a large number of cases in bacterial vaginosis. Propionobacteria are commensals of the human body (excreted with a frequency of up to 25%). They have immunostimulating

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properties. Normally, they are excreted in amounts not exceeding 104 CFU / ml [52, 168]. Normally, the quantitative level of porphyromonads, veilonella and fusobacteria does not exceed 103 CFU / ml, and of bacteroids and prevotellus - 104 CFU / ml [112,151,161,158,162]. In the vagina of clinically healthy women, corynebacteria are found in an amount of 104-105 CFU / ml [124,159]. Genital mycoplasmas, staphylococci are found in an amount of no more than 104 CFU / ml [105,129,156, 145,156,157]. The number of streptococci in vaginal discharge varies considerably and is usually 104-105 CFU / ml. Enterobacteriaceae {Escherichia coli, Proteus spp., Klebsiella spp.), As well as Pseudomonas aerugenosa, occur in an amount of 103–104 CFU / ml and can be an etiological agent of UGI [131, 157, 165]. Fungi of the genus Candida are determined in amounts up to 104 CFU / ml, without causing pathological processes. Yeast-like fungi of the genus Candida: C. albicans, C. tropicalis and Torulopsis glabrata (formerly Candida glabrata) are detected in the vaginas of healthy women in 15-20% of cases. C. albicans is the most characteristic species, determined in 80-90% of women whose vaginas are colonized by Candida fungi. The number of yeast-like fungi may increase during pregnancy. This is due to the fact that with physiological suppression of cellular immunity that occurs in pregnant women and aimed at eliminating the possibility of rejection of the developing fetus, favorable conditions are created for the growth and reproduction of yeast-like fungi. It was revealed that S.albicans has the ability to attach to vaginal epithelial cells using special surface structures, and also to produce gliotoxin, which can disrupt the viability and function of human leukocytes [61]. Consequently, the normal inhabitants of the vaginal mucosa in women of reproductive age are in 72-100% of cases Lactobacillus spp. (103-108 CFU / ml); CNS and Corynebacterium spp. (60-80% each), as well as Bacteroides spp. (6-65%), Prevotella spp. (55-60%) and Peptostreptococcus spp. (30-90%) - in a moderate amount (up to 104 CFU / ml) [69,121,164,169,173].

The living conditions of microorganisms in the vagina and endocervix differ significantly and are associated not only with the morphological characteristics of a particular epitope, but also with the characteristics of factors local immunity, which can determine individual differences in the species composition of the vaginal and cervical microbiocenosis. In the vagina, a slightly greater variety of species is noted: in 82% of the examined, the difference in microbial associations in the vagina was revealed 1.5 times more often, representatives of gram-positive coccal microflora and the family of enterobacteria were found [55, 121]. The study of the species composition of the microflora of the vagina and cervical canal in healthy fertile women showed the predominance of staphylococci (34.48% and 38.9%, respectively) and lactobacilli (27.6% and 22.2%, respectively), a smaller percentage were corynebacteria (10 , 34% -16.7%, respectively), streptococci (6.9% - 11.1%, respectively), and enterobacteria (10.34%) were sown only from the vaginal mucosa [41].At the same time, the concentration of microorganisms in the cervical canal was 104.75-105'18 CFU / ml for lactobacilli, 103'57 CFU / ml for staphylococci, 105'2 CFU / ml for streptococci, 104 CFU / ml for enterococci, 103'3 CFU / ml.

There is a close relationship between the biocenosis of the vagina, the level of physical and sexual development, the formation of the immune system. The state of the vaginal microflora in girls differs significantly in three

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different age periods: up to 8 years (prepubertal period), from 9 years to the onset of menarche (phase I of the pubertal period) and menstruating girls up to 17 years of age (phase II of the pubertal period) [6,44] ... In the prepubertal period, the vagina in newborn girls is sterile in the first hours of life. However, by the end of the first day after birth, it is colonized by aerobic and facultative anaerobic microorganisms. The sIgA has a minimal protective role. Until 4-6 weeks after birth, the pH of the vaginal discharge is about 4.0, lactobacilli dominate in the vaginal contents. 6 weeks after birth, the reaction of vaginal secretion is alkaline, the pH ranges from 7.0 to 8.5. The flora is scarce, more often coccal. Staphylococcus epidermidis and Staphylococcus saprophyticus are the most common representatives of the aerobic and facultative anaerobic microflora of the normal vaginal biocenosis. In the microbial landscape, Table 5

E. coli, enterobacteria and streptococci were isolated. The composition of the normal microflora of the vagina in 70% of the examined girls includes bacteria with hemolytic properties. Characterizing the distribution of the proportion of hemolytic colonies, it should be noted that in 30% of the examined hemolytic bacteria are not detected at all, in 6.7% of girls the entire microflora is represented by bacteria with hemolytic properties, the number of colonies of which is 103-104. In 36.7% of girls, the proportion of hemolytic bacteria among all grown colonies is 40-50%, 60-90% of hemolytic colonies in the vaginal microflora are recorded in 26.7% of those examined. It is believed that lactobacilli and bifidobacteria are representatives of the normal microflora of the vagina of adult women. However, in girls of prepubertal age, bifidobacteria and lactobacilli are also detected in isolated cases (Table 5).

Vaginal biocenosis of healthy girls 6-8 years old

Microorganisms	Number of colonies, CFU / ml	Specific
Lactobacilli	10^2	6,7
Bifidobacteria		10
Streptococcus lactic acid	10^2	13,3
E. coli	10^2- 10^1	26,7
Staphylococci	10^2- 10^4	53,3
Streptococci	10^2- 10^5	80
Other aerobes	10^2- 10^5	56,7

When studying samples of vaginal secretion of girls, IgG is detected in all samples, IgM - in 80.0%, and IgA - in 96.7% of cases. The main part of IgA is represented by the secretory form (only sIgA was detected in 50%). In the first phase of puberty, the pH of the vagina of the environment decreases from 7.2 to 5.8. The amount of discharge from the vagina increases. In vaginal smears, mixed flora (cocci or small sticks) is determined. In bacteriological research, Staphylococcus epidermidis and Escherichia coli are most often sown. Lactobacilli are detected in 34.3% of girls, bifidobacteria - in almost half of the surveyed (Table 6).

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Table 6

Vaginal biocenosis healthy girls from 9 years old to menarche

Microorganisms	Number of colonies, CFU / ml	Specific gravity, %
Lactobacilli	10*(2)-10*(3)	34,3
Bifidobacteria	10*(2)-10*(3)	48,5
Lactic acid streptococci	10*(3)	43,2
E. coli	10*(2)-10*(3)	28,4
Staphylococci	10*(2)-10*(4)	44,7
Streptococci	10*(2)-10*(4)	
Enterobacteria	10*(2)-10*(3)	4,5

When studying samples of vaginal secretion of girls, IgG, IgM are detected in 65.2%, and IgA (it was completely represented by sIgA) - in 73.9% of cases, respectively. In the II phase of puberty, the vaginal environment becomes slightly acidic, and its pH is in the range of 4.0-4.5. In a smear from the vagina - rod flora. Lactobacilli are determined in more than 80% of cases. In 42% of girls, the entire microflora is represented by lactobacilli. Among the accompanying microorganisms, the most common are epidermal staphylococcus, Escherichia coli, lactic acid streptococcus (Table 7).

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Table 7

Results of bacteriological examination of menstruating girls under 17

Microorganisms	Number of colonies, CFU/ml	Specific gravity,%
Lactobacilli	10^{l}-$10^{'}$	84,2
Bifidobacteria	10^{J}-10^{4}	51,2
Lactic acid streptococci	10^{4}-10^{5}	41,6
Staphylococci	10^{4}	67,7
Escherichia coli	10^{3}-10^{4}	23,8
Streptococci	10^{J}	3,2
Enterobacteria	10^{J}	6,4

When studying samples of vaginal secretion of girls, IgG is detected in 100%, and the numerical values of IgA and IgM levels are zero in 57.7%, sIgA in 96.2% of cases. The composition of the vaginal microflora can vary depending on the hormonal status. Vaginal microflora can change in different phases of the menstrual cycle.

According to some authors, the least number of microorganisms is determined during menstruation, and according to others, during menstruation, a more intensive growth of microflora is determined than 7 days after its end. Menstrual blood is thought to be a nutrient medium that supports the growth of microorganisms. The sowing frequency and the number of strictly anaerobic and most aerobic representatives of normal microflora are higher in the proliferative phase than in the secretory phase. With the onset of menopause, the level of estrogen, glycogen and redox potential in the genital tract significantly decreases, the number of lactobacilli and bifidobacteria decreases, the pH of the environment becomes neutral. The qualitative composition of microflora is also depleted, and the total content of bacteria also decreases. Obligate - anaerobic bacteria prevail among the microorganisms found in the vagina. In pregnant women, the concentration of glycogen in the vagina increases, which creates favorable conditions for the life of lactobacilli. The rate of colonization of the genital tract by yeast microorganisms and lactobacilli increases. The number of lactobacilli increases significantly compared to the level in non-pregnant women.At the same time, the number of bacteroids and other non-spore-forming strict anaerobes decreases, as well as aerobic gram-positive coccoid and gram-negative rod-shaped bacteria. These changes peak in the third trimester of pregnancy. Morphofunctional, physiological and biochemical changes in the genital tract during pregnancy lead to the fact that the vaginal microflora becomes more homogeneous.

CR is provided by a combination of various factors, which include the normal microflora of the cervical canal and vagina, secretory and serum Ig, cytokines, chemokines, bactericidal products (complement, lysozyme, lactoferrin,

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etc.), as well as phagocytic cells. Representatives of the normal flora live in the body in the form of a biofilm consisting of cellular mucin, bacterial exopolysaccharide and microcolonies of bacteria contained within this matrix. The levels of indicators and the dynamics of changes in the factors of the antibacterial innate immune system are individual for a particular person, which must be taken into account when assessing them [177]. KR maintains the stability of the population, species and quantitative composition of the components of normal microbiocenosis, determines the resistance of the mucosal epithelium to colonization by UPM (including those that are part of the normal microbiocenosis) and pathogenic microorganisms, their excessive reproduction and spread outside the ecological niche.Thus, bacteria - representatives of the normal microflora of the vagina, closely interacting with each other and with the cells of the vaginal epithelium, create and maintain a high Cr of the vaginal biotope, but sometimes they can cause inflammatory processes of UGT. Due to the fact that the vaginal microflora, in addition to the protective function, also performs a number of other important functions (enzymatic, vitamin-forming, immunostimulating, etc.), it is usually considered as an indicator of the state of the vagina. CR is provided by a combination of various factors: on the mucous membranes, it is primarily mucin, which forms a rather complexly organized biolayer. All protective tools are built into mucin and function in it: resistant microflora, secretory antibodies, various bactericidal molecules, such as lysozyme, lactoferrin, toxic metabolites of oxygen, nitrogen, opsonins. Examples of such biocidal proteins are lysozyme and vaginal a-lysines, which are released primarily by platelets. Lysozyme, in addition to the pronounced lithic activity in relation to primarily gram-positive bacteria, is able to enhance the phagocytic activity of neutrophils. This protein can provide the body's natural tolerance to foreign agents: first, due to the participation of lysozyme in the regulation of immune and metabolic processes; secondly, by enveloping genetically foreign material, lysozyme protects it by neutralizing and removing damaging components from the body. Among the factors of the humoral link of the local protection of the reproductive system, Ig plays one of the main roles. IgG, IgA, IgD, IgE are determined in varying amounts in the secretions of the vagina, cervical canal, uterus and fallopian tubes. Local synthesis, primarily sIgA, which differs from serum in its structure and properties, is of decisive importance in the origin of secretory Ig [150]. Characteristic changes in the structure of IgA (polymerization and sc attachment) occur during the passage of serum IgA through the mucous membranes [148,149]. A comparative study of the production of Ab with local and parenteral administration of antigen made it possible to obtain additional evidence for the synthesis of Ig directly in the lymphoid cells of the mucous membranes and secreting glands [110,156,171,182]. The second mechanism for the appearance of Ig in secretions is their receipt from the serum. Normally, the intake of Ig into secretions is very limited. The highest concentration of IgG is determined in the secretion of the cervical canal (in contrast to other secretions such as saliva, tears, milk, intestinal juice, in which sIgA is the dominant component); its main source in the secretion of the cervical canal is blood transudation. As for IgM, it is practically not found in healthy women, or its concentration is insignificant; this Ig appears in the inflammatory process of

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the reproductive sphere, and to a greater extent in the acute process than in the chronic [37,45,60,63,78,105,].The presence of IgA-Ab and IgM-Ab in the mucus of the cervical canal is explained by their production, first of all, by local lymphoid tissue and intake from the bloodstream (IgA-Ab, IgM-Ab and IgG-Ab). These Ab are also able to stimulate phagocytes to kill bacteria. So, for example, with bacterial vaginosis, the Ig content in the blood practically does not change, and their level in the vaginal secretion undergoes significant changes. Against the background of a decrease in IgA, the level of IgM increases markedly. Their significant increase is explained by the fact that IgM constitute the main part of Ab against lipopolysaccharide O-antigens (endotoxins) of gram-negative bacteria, which replace lactoflora in this disease. A decrease in IgA leads to a decrease in the number of opsonized bacterial cells. As a result, their phagocytosis becomes less likely. The anti-chlamydial activity of the secretions of the vagina and cervical canal is known [154]. In the urine were found "phosphate inhibitors" of chlamydial infection.

One of the main factors of local anti-infectious protection of the reproductive tract is the normal microflora of the vagina. Vaginal colonization of healthy women usually occurs with lactobacilli and group B streptococci. Normal vaginal microflora, along with other factors, provides CR of the genital tract. The quantitative and qualitative composition of the vaginal microflora depends on the age, endocrine status of the woman. Lactobacilli predominate not only in the vagina, but also in the distal urinary tract, which prevents the colonization of the lower urinary tract by uropathogenic microorganisms.Colonizing the vaginal mucosa, lactobacilli participate in the formation of an ecological barrier and thereby ensure the resistance of the vaginal biotope to colonization by generally recognized pathogens and UPM. The protective properties of lactobacilli are realized in different ways: due to antagonistic activity (inhibiting the growth of gram-negative bacteria and staphylococci), the ability to produce lysozyme, hydrogen peroxide, endobiotics (substances whose action is similar to antibiotics) and adhesive properties. However, the main mechanism providing the CR of the vaginal biotope is the ability of lactobacilli to produce acid. Lactic acid is a metabolic product of lactobacilli. It is formed in the process of destruction of glycogen of the vaginal epithelium by lactobacilli and determines the acidic reaction of the vaginal contents (normal pH is 3.8-4.5). Lactobacilli produce lactic acid in quantities sufficient to create a pronounced acidic environment of the vaginal discharge, and, thereby, prevent the reproduction of acidophobic bacteria. Hydrogen peroxide-producing lactobcilli are detected in the vaginas of most healthy women, and are absent or significantly reduced in women with bacterial vaginosis or vaginitis. Peroxidase, a mediated system of lactobacilli, is one of the most important protective mechanisms of normal vaginal microflora [49,76,104,111,120,125,147,174]. Bifidobacteria - acid-producing microorganisms, are involved in maintaining low pH values in the vagina. Bifidobacteria adhere to the surface of vaginal epithelial cells, are capable of producing bacteriocins, lysozyme, alcohols, which also ensures their participation in the creation and maintenance of CR in the vagina in relation to UPM and pathogenic microorganisms. Propioni bacteria are commensals of the human body. Due to the organic acids they produce, these bacteria can participate in

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maintaining the CR of the vagina [32, 168]. It was found that C. albicans can produce the so-called anti-neisseria, a factor that can suppress the reproduction and colonization of the vagina by N. gonorrhoeae [61]. Clostridium difficile located in the genital tract secretes a creosole-like substance, and infected epithelial cells secrete nitric acid, which suppresses the multiplication of chlamydia [59]. The protective effect of normal microflora is also due to the blockade of adhesion receptors for transient microorganisms, the production of antimicrobial substances, detoxification of xenobiotics (including those of microbial origin) due to their adsorption or biotransformation, induction of local immunity. Unrepaired ruptures of the cervix, which also disrupt the anatomical structure of the lower genital area, are of importance [75].Anaerobic bacteria compete with other microorganisms for nutrients and receptors on epithelial cells; production by anaerobic bacteria of antimicrobial compounds - organic acids, which reduce the pH of the vagina, the content of bacteriocins and bacteriocin-like substances, and, possibly, biosurfactants. CR is determined by phagocytic activity (the ability to kill) leukocytes and a sufficient number of humoral factors - opsonins, which promote the killing process.

Representatives of the normal vaginal microflora, closely interacting with each other and with the cells of the vaginal epithelium, create and maintain a high CR of the vaginal biotope, but sometimes it can cause inflammatory processes of UGT. The role of the resistance of the vaginal biotope to exogenous infection is especially evident in the example of SHISH. In case of impaired CR, the incidence of syphilis and AIDS increases by 3 times. With colpitis, syphilis occurs 1 time in 3-5 contacts, HIV 1 time in 50 contacts, while without colpitis 1 in 12-15 and 1 in 150 contacts, respectively. According to the data of numerous epidemiological studies, among infectious and inflammatory diseases of the female genital organs, inflammatory processes are becoming increasingly important, the etiological agent of which is UPM and fungi (U. urealyticum, Bacteroides spp., Corynebacterium spp., Candida spp., Etc.), which are integral part of the normal microflora. Str. agalactiae can cause severe respiratory diseases, meningitis, septicemia, often leading to death in newborns [129,159].Greening streptococci can cause postoperative inflammatory complications. Enterococci are often found in inflammatory diseases of the urinary and reproductive system. Enterobacteriaceae - E. coli, Proteus spp., Klebsiella spp., As well as P. aerugenosa are found in the amount of 103-104 CFU / ml and can be an etiological agent of UGI [131,157,165]. Despite the fact that peptostreptococci are part of the normal flora of the female genital tract, they are also often found in septic abortions, tubo-ovarian abscesses, endometritis, and other severe infections of the female genital tract. In association with other anaerobic bacteria, peptostreptococci are excreted in a large number of cases in bacterial vaginosis. The absence of a specific picture of inflammation, a sluggish and often asymptomatic course complicate the diagnosis of these diseases, which can contribute to the chronicity of the process and the development of complications. Only quantitative studies that determine the ratio of individual types of microorganisms both in the vaginal fluid and on epithelial surfaces, the determination of their biological properties can fully characterize the microbiocenosis of the vagina. [5,57,140,142,175]. The pathogenic properties of strictly anaerobic gram-negative bacteria

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are associated with their enzymatic systems. Thus, B. fragilis has hyaluronidase, collagenase, fibrinolysin, immunoglobulin proteases, heparinase, and sialidase. B. fragilis also have other pathogenic factors such as capsular polysaccharide. In addition, bacteroids of the fragilis group are capable of producing catalase, which allows them to resist the action of H2O2 produced by lactobacilli. Various proteases and collagenases have been found in bacteria of the genus Porphyromonas.

Thus, man and the environment are a single ecological system in a state of biological balance between macro- and microorganisms.The human microflora is the basis of its microecology and has a direct impact on the vital activity and state of the macroorganism. Microbiocenosis is a kind of dynamic microecological system that contributes to the creation of more or less uniform conditions for the normal life of the autoflora and performs or regulates numerous functions of the macroorganism. Indicators of the state of microbiocenoses reflect the state of reactivity of a macroorganism - the ability of an organism to respond to the effects of the external environment by changing its vital activity, which ensures its adaptation to various living conditions. The skin, respiratory, urogenital and gastrointestinal tract, conjunctiva of the eye, oral mucosa, constantly exposed to a variety of foreign substances and microorganisms, perform their own barrier function. The mucous membranes of the open cavities of the macroorganism are a single system. The barrier function of these areas is determined by the state of colonization resistance (CR) - the ability of microflora and a macroorganism in cooperation to protect the ecosystem of mucous membranes from pathogenic microorganisms. CR can be considered as an integrating component of local immunity. Representatives of microflora are present in the biotopes of the body in the form of microcolonies fixed to certain receptors, enclosed in a biofilm, which, like a glove, covers the skin and mucous membranes of open cavities and consists, in addition to microorganisms, of exopolysaccharides of various compositions, as well as mucin [22,27,45, 53.88].

Children's health is the main characteristic of the health of the population. Currently, there is a high prevalence of respiratory diseases among children of preschool and school age. The onset of most bronchopulmonary diseases is associated with the development of pathological processes in the mucous membrane of the upper respiratory tract and the oropharynx, which normally retains and eliminates about 70% of the inert and aggressive antigenic material coming from outside. The initiation of any infectious and inflammatory process begins with the attachment of bacteria to the surface of the host's susceptible tissue. Depends on the ratio of the levels of indigenous microorganisms and opportunistic microflora (UPM) that form a given biotope [45,84,83,124].

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