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Features of Healthy Colonization of the Intestine in Children

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ABSTRACT
Until recently, it was believed that the intestines of the fetus in the womb are sterile (except in cases of intrauterine infection). Previously applied culture methods (growing bacteria on nutrient media) made it difficult to identify representatives of the microbiota in biological samples. However, modern molecular genetic technologies have made it possible to detect the content of microorganisms in the meconium, placenta and amniotic fluid. The flora of the original feces turned out to be quite diverse, it is dominated by staphylococci and enterobacteria. The microbiome of the placenta and amniotic fluid is not diverse, it is dominated by proteobacteria. The microbiome of the amniotic fluid affects the formation of the intestinal microbiota of the fetus, and the microbial composition of meconium depends on the duration of gestation. This proves that the process of formation of the intestinal microbiota of a child begins in the prenatal period and occurs under the influence of the transfer of microorganisms from the mother to the fetus. Thus, by influencing the microbiome of a pregnant woman, it is possible to influence the process of microbial colonization of the baby's intestines.

The relationship between microorganisms inhabiting the human digestive tract and the occurrence of diseases was established at the end of the XIX century by the French scientist Louis Pasteur. Russian scientist I.I. Mechnikov, professor at the Pasteur Institute in Paris, Nobel Prize winner, who studied the effect of intestinal microflora on health, suggested that "intestinal auto-intoxication" can be reduced by correcting the intestinal microbiota and replacing proteolytic microbes that produce toxic substances with beneficial lactobacilli. He discovered the ability of lactic acid bacteria to have a beneficial effect on health and increase life expectancy. In the future, attempts to change the composition of the intestinal microbiota using live non-pathogenic bacteria were also made by other scientists. So, Henri Tissier (Pasteur Institute) at the beginning of the last century for the first time isolated Bifidobacterium from a newborn breastfed for its subsequent administration to children suffering from acute diarrhea. German scientist Alfred Nestle in 1917 he isolated a non-pathogenic strain of Escherichia coli, he became the first example of a probiotic not associated with lactic acid bacteria. Despite such a long history, the problem is still relevant today. Microorganisms inhabit all the surfaces of the human body that come into contact with the external environment and resist its effects. The human microflora consists of 1014 bacteria, which exceeds by more than 10 times the number of the body's own cells [1,2]. Distinguish the microflora of the skin, mucous membranes, vagina, intestines. The digestive tract contains about 60% of the entire microbiota of the body; 15% – in the oral cavity, nasopharynx, larynx; 14% is represented on the skin; 11% – in the genitourinary system [3]. The microbial landscape is also unevenly represented in various parts of the digestive tract. The number of bacteria increases as you move down the intestinal tube from top to bottom. There are very few bacteria in the esophagus, and they are related to the bacteria of the oral cavity. In the stomach, massive microbial colonization is prevented by hydrochloric acid, bile and pancreatic enzymes. The stomach and duodenum contain a very small number of microorganisms – <103 cells per gram of contents. Lactobacilli and streptococci are mainly present in the stomach and colon. In the small intestine, the number of bacteria progressively increases as it moves towards the large intestine – from 104 cells per gram of contents in the jejunum to 107 cells in the distal parts of the ileum. The large intestine is densely populated with anaerobes – up to 1012 cells per gram of the contents of the lumen, here the number of microorganisms is maximum – more than 500 species of bacteria, they occupy an area of more than 200 m2 and number about 1012 cells. In addition to bacterial cells, the microbiocenosis of the colon contains fungi and protists in minimal quantities, as well as viruses and phages, the number of which may exceed the number of bacteria. In general, intestinal microbes add an average of 600 thousand genes to each human body.

The total weight of the intestinal microflora is about 1.5 kg, and 1 million microbes are localized in 1 ml of intestinal contents [4,5]. The intestinal microflora is conditionally divided into main (obligate), facultative (conditionally pathogenic) and accidental (transient). Obligate microflora is represented by anaerobes (bifidobacteria, propionobacteria, peptostreptococci) and aerobes (lactobacilli, enterococci, E. coli). The ecosystem of the adult human intestine is dominated by two bacterial groups: firmicutes and bacteroids, which account for 90% of the total active microflora, 10% are actinobacteria, proteobacteria, Verrucomicrobia and Fusobacteria. Bifidobacteria make up 80-90% of the intestinal microflora in breastfed children, with a change in diet, the composition of the microbiota approaches that of an adult [6]. Bifidobacteria inhibit the development of various putrefactive and pathogenic organisms, promote the digestion of carbohydrates. These microorganisms activate parietal digestion and participate in the utilization of food substrates; by association with the intestinal mucosa, they form an intestinal barrier and prevent the penetration of microbes and toxins into the internal environment of the body; they have high antagonistic activity to pathogens and opportunistic bacteria due to the production of organic fatty acids. In addition, bifidobacteria synthesize organic amino acids (lactic, acetic, folic, amber, etc.), which reduces the pH of the intestinal contents and prevents colonization by foreign bacteria, and also participate in the synthesis of vitamins B, C, D, E, K and contribute to the diffusion of calcium, iron, vitamin D ions through the intestinal walls. Lactobacilli colonize the newborn's body in the early postnatal period at the time of its passage through the birth canal and subsequently successfully fight pathogens throughout the life of the macroorganism. In the process of vital activity, lactobacilli form antibiotic substances: lactolin, lactocidin, lysozyme, which suppress putrefactive microorganisms, primarily proteus, and have an antagonistic effect against pathogens of acute intestinal infections. In the process of metabolism, lactobacilli form lactic acid, which participates in fermentation processes and, by lowering the pH, creates an environment unfavorable for the development of pathobionts.

Facultative microflora is no more than 1% of the total normoflora. It is represented by bacteria, staphylococci, streptococci, yeast fungi. With a decrease in the body's defenses caused by diseases or adverse effects, it begins to multiply intensively, displacing normal microflora and causing symptoms of dysbiosis. Random (transient) microflora in quantitative terms normally does not exceed 0.01%. Microorganisms of this group easily enter the body with water and food. First of all, the transient microflora includes yeast-like fungi and fungi of the genus Candida.

The intestinal microflora indirectly affects the formation of the child's immune system, and consequently, the state of his health as a whole, the development and course of diseases.

Representatives of the microbial community, especially some types of microorganisms, have a sufficiently high immunogenicity, which stimulates the development of not only local, but also systemic immunity. Activation of the local immunity link is carried out by enhancing the synthesis of secretory IgA, in turn, the bacterial load on the intestinal lymphoid apparatus stimulates cellular and humoral immunity [9]. Currently, it is generally recognized that the immune response of the body is formed under the influence of bacteria. Microflora, creating an antigenic load on the intestinal lymphoid apparatus, participates in the formation of food tolerance or the development of food allergies [10, 11].

When studying gut microbiocenosis in children with atopic dermatitis, which debuted against the background of polyvalent food allergies, a significant decrease in the content of protective bifidoflora and increased vegetative growth of strains of Staphylococcus aureus, bacteria of the genus Klebsiella, Proteus, hemolytic Escherichia coli, fungi of the genus Candida were revealed [13].

It is obvious that violations of the composition of the intestinal microflora in the early neonatal period can be a trigger mechanism that triggers a cascade of reactions leading to the development of atopy in childhood. In turn, the development of allergic inflammation in the intestinal mucosa changes the living conditions of intestinal microorganisms, which affects the composition of the microflora. Regardless of whether dysbiotic shifts lead to the development of allergic reactions or are their consequence, microbial imbalance in the intestine inevitably affects the functioning of the macroorganism and aggravates the course of allergic diseases.

The effect of intestinal microflora on immune function is due to the presence of a large number of organized lymphoid structures in the mucous membrane of the small intestine (Peyer's plaques) and large intestine (isolated lymphoid follicles), which are involved in the capture and sampling of antigens, as well as in the induction of adaptive immune responses.

According to modern research, intestinal dysbiosis is one of the factors affecting the severity of the course and frequency of recurrence of gastrointestinal diseases such as ulcerative colitis, allergic colitis, postinfectious irritable bowel syndrome, and is also involved in the pathogenesis of colon neoplasms.

Increasing attention is being paid to the role of microbiota in the pathogenesis of necrotizing enterocolitis (NEC). The predominance of microorganisms such as Enterobacteriaceae and Pseudomonadaceae and a decrease in the number of Firmicutes were found in the intestinal microflora of children with NEC. According to V. Moi et al., early colonization of the small intestine by some species of enterobacteria and clostridia may be a predictor of the subsequent development of NEC [5]. Excessive growth of bacterial flora is one of the mandatory mechanisms of NEC pathogenesis. Currently, the role of intestinal microflora in the pathogenesis of autism is widely discussed.

Thus, intestinal microbiocenosis is an optimal balance of many different microorganisms, which in general have a significant impact on the macroorganism. The harmonious relationship between intestinal bacteria and their host is a symbiotic relationship. Violation of this balance is fraught with the development of symptoms of intestinal dysbiosis. Violation of the composition of the intestinal microflora (qualitative or quantitative, with violation of its properties) is designated by the term "dysbiosis", which was introduced by the German scientist Alfred Nissle at the beginning of the last century. The modern term for microbiota imbalance is "dysbiosis".

The term "dysbiosis" (or "dysbiosis") denotes not an independent nosological unit, but a set of symptoms caused by a violation of the microbial balance. The syndrome can be a manifestation or complication of the underlying disease, which explains the absence of such a diagnosis as "intestinal dysbiosis" in the International Classification of Diseases. Thus, dysbiosis of the digestive tract is a symptom complex, which is based on a violation of the quantitative and qualitative balance of the intestinal microflora, developing against the background of a number of pathological conditions and diseases.

In foreign literature, to determine the state of intestinal dysbiosis, the terms "bacterial overgrowth syndrome" (small intestinal bacterial overgrowth syndrome (SIBOS)) are most often used or "enhanced growth syndrome" (overgrowth syndrome).

Each person has his own composition of the intestinal microbiota, due to his genotype, the nature of primary microbial colonization at birth and dietary habits.

The use of medications, especially antibiotics, the encounter with viruses and bacteria, errors in the diet lead to an imbalance of the microflora. The restoration of the microbial landscape after antibiotic treatment takes place for a long time, during this period the child is most vulnerable to opportunistic infections due to the low content of beneficial microorganisms necessary to suppress pathogens, which dictates the need to correct dysbiosis during this period with the help of pharmaceuticals [13].

Measures aimed at restoring the microbial landscape of the intestine can be presented in the form of the following algorithm:

- identification and treatment of the underlying disease that led to the development of dysbiosis;
- suppression of the activity of pathogenic and opportunistic flora;
- replacement of protobionts with beneficial bacteria and provision of favorable conditions for their growth and reproduction.

To correct dysbiosis, drugs are used, the action of which is aimed at maintaining and restoring the quantitative and qualitative composition of the intestinal microflora. Probiotics, prebiotics and synbiotics are used for this purpose. The use of these drugs has a positive effect on the intestinal environment populated by billions of symbiotic microbes, thereby having a beneficial effect on human health. In general, the functions of both probiotics and prebiotics correlate with the functions of microbes colonizing the human digestive tract. The targets on which probiotics act are the cells of the host organism and/or bacteria inhabiting the digestive tract of the macroorganism. Prebiotics serve as a source of nutrition for beneficial representatives of the microflora and indirectly have a positive effect on human health. Synbiotics combine the properties of probiotics and prebiotics.

The use of probiotics and prebiotics is aimed at optimizing the symbiotic relationship between the microbiota of the digestive tract and the host.

The positive effects of these pharmaceuticals go beyond the gastrointestinal tract and spread to other organs and systems of the body, but the main point of application of their action is the intestine.

Probiotics can be contained in food products (for example, in fermented dairy products), be an integral part of biologically active additives (dietary supplements) or have the status of a medicinal product. Probiotics act on the intestinal microbiota, affecting the intestinal immune system, interacting with symbiotic or potentially pathogenic microbes, generating metabolic products. As a result of this interaction, the formation of antagonism with potential pathogens, improvement of the environment in the intestinal lumen, strengthening of the intestinal wall barrier, the development of negative feedback with inflammation and the formation of an immune response to antigenic challenges are noted.

Probiotics have the following immunological effects: activate local macrophages, increasing the presentation of antigen to B-lymphocytes and increasing the production of secretory IgA both locally and systemically; model the cytokine profile; form tolerance to food allergens. Non-immunological effects of probiotics include participation in digestion and competition for nutrients with pathogens; acidification of intestinal pH to create an unfavorable environment for pathogens; production of bacteriocins to inhibit pathogens.

A prebiotic is a selectively fermented ingredient that is formed with specific changes in the composition and/or activity of the gastrointestinal microbiota and thereby has a positive effect on the health of the host.

The concept of prebiotics was proposed by Gibson and Roberfroid in 1995 [10]. The mechanism of action of probiotics is based on the fact that they are not digested in the digestive tract and have a beneficial effect on the health of the body by influencing the host's own beneficial bacteria. These substances affect the gastrointestinal bacteria by increasing the number of beneficial anaerobic bacteria and reducing the population of potentially pathogenic microorganisms.

Prebiotics are dietary substances, mainly consisting of non–starch polysaccharides and oligosaccharides. The most common prebiotics are oligofructose, inulin, galacto–oligosaccharides, lactulose, breast milk oligosaccharides. Prebiotics are part of biologically active additives (dietary supplements), most of them are an integral part of various food products (cookies, cereals, chocolate, dairy products). Natural prebiotic oligofructose is found in many foods, such as wheat, onions, bananas, honey, garlic and leeks. Also, oligofructose can be isolated from chicory root or enzymatically synthesized from sucrose. Artificially synthesized oligofructose is a part of many pharmaceutical preparations.

Currently, synbiotics are becoming more and more widespread – innovative and, as a result, more effective drugs for restoring the microflora of the digestive tract.

Synbiotics are products containing both probiotics and prebiotics that have a positive effect on health.

When taking synbiotics, as a result of the action of the prebiotic component, not only the effective colonization of beneficial bacteria of the digestive tract occurs, but also the stimulation of the body's own microflora by creating favorable conditions for the reproduction of representatives of normal microflora. The weight gain of beneficial microbiota, in particular bifidobacteria, has a positive effect on human health by producing components that inhibit potential pathogens, reducing the level of ammonia in the blood and activating the production of vitamins and digestive enzymes.

Prebiotic and probiotic in the composition of synbiotics mutually potentiate the positive effects of each other, which makes the use of these drugs highly effective for the correction of intestinal dysbiosis. Currently, as a result of numerous clinical studies, the effectiveness of probiotics, prebiotics and symbiotics in the complex therapy of a number of nosologies has been proven. According to the recommendations, some probiotic strains are effective for reducing the severity and duration of acute infectious diarrhea in children. The use of probiotics reduces the duration of diarrheal syndrome in children by approximately 1 day. There is strong evidence that probiotics are effective for the prevention of diarrhea in adults and children receiving antibiotic therapy, and probiotics can also reduce the risk of developing C. difficile-associated diarrhea in children receiving antibacterial drugs [12]. Inclusion of certain probiotic strains in H. eradication schemes. pylori can be effective in increasing the rate of eradication [3]. The prebiotic lactulose is used to treat functional constipation and hepatic encephalopathy. Some probiotic strains and the prebiotic oligofructose are effective for improving the immune response. Evidence of an enhanced immune response was obtained in studies aimed at the prevention of acute infectious pathology (nosocomial pneumonia in children, flu episodes in winter). It has been shown that some probiotics are effective and safe in the complex therapy of ulcerative colitis of mild and moderate activity to achieve a higher degree of response and remission in both adult and pediatric populations [4].

Probiotic strains and prebiotics reduce abdominal flatulence and bloating in irritable bowel syndrome, some strains can reduce visceral pain sensitivity and improve well-being, thereby improving the quality of life of patients with functional abdominal pain [5,6]. It has been proven that some probiotic strains reduce the duration of crying in infants with intestinal colic, as well as symptoms associated with lactose intolerance [7,8]. Probiotic supplements reduce the risk of NEC in premature newborns. Evidence-based indications for prescribing probiotics, prebiotics and synbiotics in children are summarized by the World Gastroenterological Organization in "Global Practical Recommendations: Prebiotics and Probiotics" (2017). The effectiveness of strains LGG, Lactobacillus reuteri, Lactobacillus acidophilus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Saccharomyces boulardii in the treatment of acute gastroenteritis in children has been proven [11]. The administration of probiotic strains LG, Saccharomyces boulardii is indicated for antibiotic-associated diarrhea [2,3], and strains LGG Bifiidobacterium bifidum and Streptococcus thermophilus are recommended for the prevention of nosocomial diarrhea in children [4]. When included in the scheme of eradication therapy H. The pylori strain of Saccharomyces boulardii reduces the risk of side effects of therapy and reduces the eradication time [14], Lactobacillus reuteri DSM reduces the crying time in infants with intestinal colic who are breastfed [6].

Of interest are modern synbiotics containing several cultured beneficial bacteria (lactobacilli, bifidobacteria), as well as prebiotics (fructooligosaccharides). Synbiotics contribute to the restoration and normalization of intestinal microflora in children. The lactobacilli contained in their composition inhibit the growth of protobionts, thereby providing a protective function of the body and strengthening the immune system, and bifidobacteria are involved in the synthesis of proteins, amino acids and vitamins.

The prebiotic effect of synbiotics is realized due to the presence of fructooligosaccharides (oligofructose) in the preparation, which stimulate the reproduction of beneficial bacteria and inhibit the development of pathogens, stimulate intestinal peristalsis and contribute to the normalization of gastrointestinal function.

Synbiotics can be prescribed to children from an early age, they are produced in the form of acid-resistant granules that successfully overcome the acid barrier of the stomach, thanks to which most of the probiotic bacteria reach the intestines.

Taking synbiotic is indicated when prescribing drugs that can lead to qualitative or quantitative changes in the composition of the microflora of the digestive tract. Indications for the appointment of synbiotics are diarrheal syndrome resulting from the administration of antibacterial drugs, postinfectious colitis, flatulence and / or violation of the nature and frequency of stool against the background of disaccharidase (lactase) deficiency or food allergy.

Conclusion: Thus, the microflora of the digestive tract has a significant impact on the development and health of the child, protects the body from adverse environmental influences, strengthens local and systemic immunity, reduces the risk of allergic reactions. The use of synbiotics helps to reduce the number of cases of flatulence, reduces the duration of abdominal pain and diarrheal syndromes, has a beneficial effect on the restoration of intestinal biocenosis.

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