

PART III. OTHER
DZIAŁ III. RÓŻNE

THE ROLE OF MICROBIOTA IN THE DEVELOPMENT OF ALLERGIC DISEASES

ROLA MIKROBIOTY W ROZWOJU CHOROÓB ALERGICZNYCH

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Summary

Scientific progress, industrial development, urbanization, and the “sterile” way of life have a significant negative side, namely, the sustained growth of allergic diseases. The “hygienic theory” is used to explain the unceasing increase in the incidence of allergies in the population. At the same time, an important link in the development of allergic diseases is the microbiological environment and our own microbiota. In our literature review we gathered new data on the pathogenetic relationships between the violation of the quantitative and qualitative composition of our microbiocenosis and the development of allergic diseases. The basic mechanisms by which microbiota influence the development of an allergic process have been established, in particular: influence on T-cell immunity, synthesis of cytokines, etc. In this review, particular attention is paid to factors that lead to microbiocenosis and contribute to the development of allergies. Among them it is worth to highlight inappropriate nutrition, “sterile” style of life, widespread using of antiseptics and antibiotics, etc. Therefore, the most important step in the prevention of allergic diseases is the modification of lifestyle, breastfeeding of children, frequent staying in the open air and contact with nature, rational use of antiseptics and antibiotics.

Keywords: microbiota, microbiome, allergic diseases, hygienic theory

Streszczenie

Negatywnym aspektem postępu naukowego, rozwoju przemysłowego, urbanizacji i „sterylnego” stylu życia jest stały wzrost zachorowań na choroby alergiczne. Zależność tę wyjaśnia tzw. „teoria higieniczna”, tłumacząca nieprzerwany wzrost liczby alergii wśród społeczeństwa. Równie istotnym czynnikiem w rozwoju chorób alergicznych jest środowisko mikrobiologiczne i nasza własna mikrobiota. W tym artykule staraliśmy się zebrać nowe dane na temat zależności patogenetycznych, pomiędzy naruszeniem ilościowego i jakościowego składu naszej mikrobiocenozy, a rozwojem chorób alergicznych. Podstawowe mechanizmy wpływu mikrobioty oraz procesu powstawania alergii zostały już ustalone, są to przede wszystkim: wpływ komórek T na odporność, synteza cytokin, itp. Obecnie, szczególną uwagę poświęca się czynnikom, które prowadzą do powstawania mikrobiocenoz i przyczyniają się do rozwoju alergii. Należą do nich m.in. niewłaściwe odżywianie, „sterylny” styl życia, częste stosowanie środków antyseptycznych i antybiotyków. Z tego powodu najważniejszym krokiem w profilaktyce chorób alergicznych jest zmiana stylu życia, karmienie dzieci piersią, częste przebywanie na świeżym powietrzu, kontakt z naturą i rozsądne stosowanie środków antyseptycznych i antybiotyków.

Słowa kluczowe: mikrobiota, mikrobiom, choroby alergiczne, teoria higieniczna

Introduction

Allergic diseases form a genetically heterogeneous group of chronic, immune-dependent diseases [1, 2]. Over the last few decades, allergic diseases have become one of the main health problems of the modernized world. The prevalence of atopic dermatitis, food allergy, and asthma has increased dramatically, especially in western societies. It is estimated that between 20% and 30% of people living in western countries suffer from at least one form of allergic diseases [3, 4, 5, 6]. They are more common among children than adults. Almost 700 million people suffer from allergic respiratory diseases worldwide, namely bronchial asthma and allergic rhinitis [1, 7]. According to recent reports, in the United States there are 15 million children and adults with food allergies

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[8, 9, 10]. The prevalence of allergic diseases has increased over the last few decades, but at different rates in different regions of the world [1, 11]. At present, bronchial asthma is considered the most common chronic non-infectious disease among children [11]. In some industrialized countries, the prevalence of asthma is close to 35-40%, while in other regions it is less than 5% [1, 12, 13]. In addition, the prevalence of asthma is increasing in many low and middle income countries [1, 3, 5, 6, 14, 15].

It is interesting that the number of children and adults suffering from allergic diseases is almost twice as high in cities as in villages. Many researchers combine this fact with the so-called “hygienic hypothesis,” according to which an avalanche-like increase in the incidence of allergic diseases is observed predominantly in highly developed countries, and this is due to a decrease in the effects of antigens found in the environment, the widespread use of antibiotics, the use of chemical additives in production, nutrition, and a very “sterile” lifestyle [6, 16, 17]. Indeed, an increase in the incidence of allergic diseases in industrialized countries has coincided with a widespread distribution of vaccines, the use of antibiotics, a decrease in the size of the family, and the improvement of household amenities [14, 16].

The negative impact of allergic diseases is huge both on sick people and their families and society. They negatively affect the quality of life, are a significant psychological burden for the family, and increase comorbidities and the risk of death [1, 3, 18, 19]. In addition, the economic burden of these diseases is extremely high [1, 7, 20, 21].

According to the “hygienic theory”, the less people are exposed to parasites and microbes, the more this leads to excessive reactivity of the immune system and the development of allergic diseases [17]. Consequently, the impact of microorganisms on the environment and the state of our own microbiome is an important factor that can affect the development of allergic diseases. This is the subject of our review of literature.

Human microbiota

The term “microbiome” was proposed in 2001 by the Nobel Prize winner Joshua Lederberg to describe the ecosystem of symbiotic and pathogenic microorganisms inhabiting the human body. Lederberg believed that microorganisms in the human body play an important role in health and development of diseases [22, 23, 24].

Recent studies using molecular genetic techniques (sequencing of 16S genes of ribosomal RNA of amplified bacterial nucleic acids derived from feces or biopsy of the intestinal mucosa) demonstrated an incredible complexity of human intestinal microbiota consisting of more than 1000 phylotypes, 80% of which still have not been cultivated [25, 26]. Adults contain about 100 billion bacteria only in the intestines, and the microbiome occupies approximately 90% of the cells in the human body [28]. The human genome consists of about 21,000 genes encoding proteins [29], and microbiota can contain about three million genes [22, 27, 30], which is 100 times greater than the human genome [24, 31, 32]. It is believed that the human microbiota is as unique as the fingerprints of a person [27].

The microbiome (microbiota) of a human is a set of microbiocenoses that colonize all surfaces of the human body, including the skin, respiratory system, gastrointestinal tract and genitourinary system [34, 35].

The microbiome can be considered a “new system organ” since its contribution to human health and disease development was discovered by researchers 20 years ago [22, 25, 33].

The same microorganisms do not occur in all parts of the body. The source of nutrients, humidity conditions, and presence or absence of oxygen affect the nature of microorganisms that can multiply in one or another area. Therefore, the microbiota of the skin, oral cavity, vagina, intestines and others are isolated [27]. The largest part (about 60%) of the microflora inhabits different regions of the gastrointestinal tract, approximately 15-16% is accounted for by the oropharynx. The urogenital tract, except the vaginal section, is inhabited rather weakly. Other microorganisms are accounted for by the skin [36]. In the digestive tract, there are more than 500 different types of microorganisms with the biomass of 2.53 kg [36]. Together, the macroorganism and the microflora constitute a single ecological system that is in a state of homeostasis or eubiosis [36, 37].

The composition and functions of the human intestinal microbiome develop during the first years of life [22]. Despite the widespread belief that the fetal gastrointestinal tract is sterile, recent studies have shown that preterm infants have many contacts with bacteria contained in the amniotic fluid, even if there has been no rupture of membranes or chorioamnionitis before [41, 42]. At birth, children are in contact with the bacterial flora of the vagina and the mother’s anus [41]. Despite this, the microbiota of the child’s intestines is finally formed after birth [3, 8, 27, 32, 35].

After birth, the newborn’s intestine is temporarily dominated by *Enterobacteriaceae* and *Staphylococcus* [17, 43]. The establishment of stable intestinal microbiota is generally accompanied by two major transitions in childhood. The first transition occurs shortly after birth, during lactation, and leads to predominance of bifidobacteria and some lactic acid bacteria in the intestines [1, 17, 44].

The second transition occurs when weaning a child from breastfeeding or with the introduction of solid foods (complementary feeding) [17, 44, 45, 46, 47]. With the decrease in the amount of oxygen in the intestines, anaerobes of the *Bacteroides* and *Clostridium* genera appear [35]. The Bifidobacterium flora is gradually replaced by the adult-type microorganisms and is mainly represented by bacteria of the *Bacteroides*, *Prevotella*, *Ruminococcus*, *Clostridium*, and *Veillonella* genera, which colonize the intestines of the child [49]. In the end, in approximately three years, a typical intestinal microbiota, which is typical for adults [1, 17, 31, 39, 40, 42, 49], is established.

In elderly people, there is another change in the composition and number of microorganisms. There is a significant reduction in the number of *Bacteroides* and *Bifidobacterium*; thus, *Clostridium*, *Eubacterium*, and *Fusobacterium* begin to dominate. The result is an increase in the pH of the intestinal contents to about 7.0-7.5, which may be a cause of diseases of the digestive system in the elderly people [32, 40].

It is important to note that the intestinal microbiotas are distinct among people living in developed and underdeveloped countries, also among urban and rural residents [17].

The microbiota controls numerous metabolic functions, many of which have still not been recognized [34, 50]. Normal microflora performs a number of important functions to ensure the full functioning of the human body, namely: trophic, protective, metabolic, vitamin-forming, endocrine, anti-mutagenic and anti-carcinogenic functions in addition to effects on brain function and behavioral reactions [16, 25, 32, 36, 38, 40, 52, 53, 54].

Importantly, the immunogenic function of microbiota include the following:

- constant interaction with the immune system of the intestine, regulation of the immune response, and the formation of immunological tolerance;
- secretion of proinflammatory cytokines [16, 36, 39, 52, 53];
- regulate the balance between Th-1 and Th-2 cell activity [22, 56, 57].

Additionally, microbiota is the largest source of antigenic stimuli, which contributes to the development of postnatal immunity due to the maturation of the gastrointestinal-associated lymphoid tissue (GALT) [3, 15, 54, 55].

Consequently, the human microbiome is a complex system that is capable of influencing the human body through communication with many organs and systems, synthesizing a large number of biologically active compounds, and controlling the release of substances with other organs [38].

Relationship of microbiota and allergic processes

As it has been noted earlier, intestinal microbiota plays a decisive role in the regulation of the immune system [1]. The intestinal epithelium expresses a variety of pathogen recognition receptors, including Toll-like receptors (TLR) and nucleotide-binding oligomerization domain receptors that activate the immune response against pathogenic microorganisms [1, 16]. In particular, microbiota closely contact the immune system of the intestine through the system of 11 TLRs, each of which recognizes a certain microbial molecular structure [38]. In this case, the immune system is capable of recognizing pathogenic bacteria and intestinal commensals, reacting to pathogens, but at the same time remaining tolerant to commensals. These mechanisms are quite complex and include intestinal epithelial cells, TLRs, dendritic cells, and T-regulatory (T_{reg}) cells [1, 58].

In a healthy state, microbiota have some mucus-like taxons that regulate the production of IL-22, which stimulates the formation of the protective mucous layer by the mucous membrane of the intestines. This barrier is protective and reduces the ability of food allergens to cross the epithelial barrier and enter the microcirculation system. After activation by allergens, epithelial cells secrete cytokines, including TSLP, IL-33 and IL-25, which activate dendritic cells and ILC2 to promote the formation of Th2 cells [59].

T-helper (Th)-2 cells are characterized by the production of IL-4, IL-5, IL-9, IL-13, and the production of allergen-specific IgE that promotes the development and maintenance of an allergic inflammatory process, while Th1-cells produce $TNF\alpha$ and $IFN\gamma$, which promote modulation of cell-mediated immunity [1, 22, 58, 60].

In the classical paradigm, the induction of Th2 cytokine reactions also acts to inhibit Th1 activity (typically via $IFN-\gamma$), which helps maintain an allergic phenotype. The stability of this Th1/Th2 balance is also regulated at the gene level through the functions of the transcription factors GATA-3 (Th2) and T-bet (Th1) [3, 31, 39].

Bacterial colonization of the intestine affects the differentiation of precursor T-cells in Treg-cells or different types of Th-cells such as Th1, Th2 and Th17 [61]. Treg-cells suppress the differentiation of precursor T-cells into Th-cells [61] and have various anti-inflammatory effects, including inhibition of inflammatory activity of mast cells, basophils and eosinophils, suppression of IgE synthesis, and IgG4 induction [17, 62].

Numerous studies indicate the importance of the balance of T-helpers (Th1, Th2, Th17, regulatory T-cells) as the main factor in the development of allergic diseases [16, 22]. The physiological microbiota leads to the

differentiation of Tregs and the release of IL-10, which play a key role in maintaining the Th1/Th2 balance [24]. In this case, when the normal state of the microbiota is violated, Tregs contribute to the promotion of the Th2 lineage [63]. These cells produce cytokines such as IL-4, IL-5, IL-9 and IL-13, which regulate both the activation of B-cells and the synthesis of IgE, as well as the migration of the activated eosinophils, mast cells, and CD4 + T-cells to the site of affection. This leads to the development of allergic diseases [8, 14, 36, 43, 64].

A number of intestinal bacteria, including *lactic bacteria*, *bifidobacteria*, *bacteroides*, *clostridia* and *streptococci* [65], as well as bacterial metabolites such as butyric acid and propionic acid [15, 66, 67], polysaccharide A (produced by *Bacteroides fragilis*) are capable of inducing Treg-cells (more precisely, their peripheral type of pTreg) in various experimental models in mice or cell culture [15, 67, 68]. Clinical studies have also shown that probiotic bacteria reduce the formation of Th2 cytokines [69].

The development of allergies in children is associated with a decrease in the level of lactobacilli and bifidobacteria [35]. These bacteria have strong anti-inflammatory properties [70], which are not limited to induction of iTreg IL-10, since the introduction of lactobacilli in mice, carrying defective IL-10 gene still causes inhibition of intestinal inflammation [70]. Their activity is mediated by dendritic cells that secrete IL-10 and TGF- β , which stimulate the formation of iTreg, and also inhibit Th1, Th2 and Th17-dependent response [35].

Consequently, as evidenced by a large number of studies, there is a link between the intestinal microbiology and the emergence of allergy [5, 17, 34]. It has been shown that in patients suffering from allergic diseases (asthma, atopic dermatitis, food allergy) there is an imbalance in the microbiome: disbacteriosis of respiratory system, skin and digestive system [71].

Intestinal microbiota and allergy

During the last 15 years, numerous epidemiological studies have been done on the relationship between the microbiotic composition of the intestines and the risk of developing an allergy. The vast majority of these studies indicate that the change in the microbiome in childhood is associated with allergic sensitization and allergic manifestations, especially atopic dermatitis [16, 42].

The first study, devoted to the study of the hypothesis that allergic disease is associated with aberrant microbiota in childhood, was carried out in Sweden in the 1990s [39, 72]. Then, Bjorgsten et al. [72] investigated differences in the microbial composition of the intestine between allergic and non-allergic children, as well as between children living in Sweden and Estonia. After that, a number of epidemiological studies revealed differences in the microbial composition of the intestine between allergic and non-allergic children, although the differences were not always consistent. Indeed, allergic infants were more often colonized by bacteria of the *Bacteroides* genus and rarely colonized by *Acinetobacter* and *Clostridium* bacteria [17].

After that, a large number of studies were conducted. Thus, it has been established that atopic children have lower rates of *lactic bacteria*, *bifidobacteria* and *bacterial strains* [73]. Systematic review of Melli et al. [74] on the role of intestinal microbiota and allergic diseases among children has shown that in children with intestinal allergy, more bacteria such as *B. fragilis*, *E. coli*, *Clostridium difficile*, *Bifidobacterium catenulatum* and *B. bifidum*, as well as smaller amounts of *B. adolescentis*, *B. bifidum* and *lactobacilli* have been found [1]. In their study Ling et al. [75] reported a decrease in *Bacteroidetes* and an increase in the percentage of *Firmicutes* (including *Clostridiaceae*) in 5-month-old children with food allergies [39].

As it has been noted by Kalliomaki et al., in atopic patients' intestines there are more clostridia and less bifidobacteria than in non-atopic people, which has led to a decrease in the ratio between bifidobacteria and clostridia [15, 16, 76].

The reduced prevalence of bifidobacteria in children with allergies [78] has not been confirmed in all studies [16, 78, 79]. Some authors report that the limited diversity of bifidobacteria is associated with allergy [80], but again it has not been confirmed in other studies [15, 16]. However, it became clear that the properties of intestinal bifidobacteria primarily depend on strains, especially in immuno-stimulating properties [15, 81]. The change in the species composition of bifidobacteria during allergies is indicated by a large number of researchers [75, 82, 83]. Ouwehand et al. [82] revealed a higher prevalence of *Bifidobacterium adolescentis*, but the lower one of *Bifidobacterium bifidum* in children with eczema or atopic eczema compared with healthy children [14].

C. difficile was associated with all atopic symptoms and sensitization [15]. Colonization of faeces at the age of 3 weeks with *Clostridium coccoides* subcluster XIVa bacteria is described as an early indicator of possible asthma in further life [15, 84]. *Bacteroidaceae* is also associated with the development of allergies, although, as for clostridia and bifidobacteria, the results are contradictory [15]. Fujimura et al. indicate that children with a high risk of atopic dermatitis and asthma show a decrease in the relative number of such bacteria as *Bifidobacterium*, *Akkermansia* and *Faecalibacterium*, against the relatively high number of individual fungi such

as *Candida* and *Rhodotorula* [17, 85]. The study of gastrointestinal microbiota in children with food allergy to milk proteins showed more bacteria of the *Lactobacillus* genus and fewer enterobacteriaceae and bifidobacteria in microbiological cultures, as well as more *Clostridium* bacteria [71].

However, presently there are no definite bacterial taxons or separate microbiota subgroups that are always associated with allergic diseases [39, 42]. Taking this into account, some studies have shown that early diversity of intestinal microbiota may be more important than the presence or absence of specific taxons [86, 87, 88]. Several prospective studies have shown that the decline in microbial diversity precedes the development of eczema [86, 88, 89], allergic rhinitis [87], and asthma [39, 86], but not atopic dermatitis [42].

Microbiota of the respiratory tract and allergy

For many years, there has been an assumption that microflora plays a key role in the development of asthma. The bronchial epithelium has a characteristic microbiome, distinct from healthy people and asthmatics [5]. In studies performed with the help of traditional methods (microbiological cultures), an increased number of atypical bacteria, especially *Chlamydophila* and *Mycoplasma* in sputum and fluid after bronchoalveolar lavage in patients with asthma, was detected in comparison to the control group. While studying the lower respiratory tract of patients with asthma, the dominance of proteobacteria, in particular *Haemophilus*, *Moraxella*, *Neisseria* and *Streptococcus* was found. During active inflammation with asthma, there has been a loss of species diversity of the microflora and an increase in the number of proteobacteria, whereas with hormone resistant asthma, *streptococcus* and *M. catarrhalis* have been prevalent in sputum [71].

In addition, the lungs of adults with asthma contain far more bacteria than the lungs of people without asthma. In addition, individuals with severe forms of bronchial asthma have a greater bacterial diversity than patients with moderate asthma [5, 22].

Microbiota of skin and allergy

A characteristic feature of the skin microbiome in patients suffering from atopic dermatitis is the domination of *Staphylococcus aureus* [37, 73, 90]. In this case, the harmful effects are probably mediated through the development of factors of staphylococcal virulence, including superantigens that stimulate type 2 immune responses and reduce the activity of regulatory T-cells: cytolysins, serine proteases, and lipases that damage the skin barrier. The colonization of *S. aureus* occurs as a result of dysfunction of the skin barrier (for example, reduction of the expression of filaggrin) and increased expression of IL-4 and IL-13. These disorders can occur as a result of genetic and immune reactions caused by allergens or mechanical damage [37].

The aggravation of allergic diseases is characterized by an increased number of pathogenic *S. aureus* (which leads to a general decrease in microbial diversity). In mice, the δ -toxin secretion of *S. aureus* induces degranulation of mast cells and exacerbates allergic sensitization to the antigen model applied to the skin [17]. In patients with atopic dermatitis, there is a decrease in the microbial diversity of the skin during the exacerbation of the disease [17, 71].

Risk factors for the development of allergy, associated with microbiota

Studies of the links between changes in microbiota composition and a sharp increase in the prevalence of allergy as the "hygiene hypothesis" proposed by D.P. Strachan in 80's, began with clinical observations [5, 91]. Thus, epidemiological studies have shown a link between lower incidence of allergies in many families and children, who are brought up in rural areas, especially in early childhood [73, 92]. There was a reduced risk of allergic diseases in the presence of some individual factors, including the lack of antibiotic therapy in childhood, exclusive breastfeeding during the first 4 months of life, vaginal birth, and the presence of domestic animals [71]. Today, the reduction of microbial effects (and the growth of allergic conditions) is also associated with improved hygiene [3].

Changes in the microbial environment of a person are more often associated with a change in lifestyle during the last 15-20 years [16, 93]. The increasing prevalence of allergic events, such as asthma or atopic dermatitis, is actually a result of low levels of bacterial exposure during childhood. In some way, children are deprived of immunological stimuli. To a certain extent, this is due to the fact that the inhabitants of the civilized countries spend almost 90% of their time in a built environment, with about 70% of the time spent in their apartments or houses and are less outdoors [94]. In fact, it means leaving the environment, in which the microbiome of a person should develop. In particular, it has been shown that in the United States, children who are raised in an internal (home) environment are more likely to suffer from asthma and atopy [15, 95].

A particularly interesting topic is the relationship between the increased prevalence of allergic diseases and the increased hygiene of life in the 21st century. The increase of the sterility of our environment, the widespread use of antiseptics and antibiotics (for treatment, at home, consuming with food) and the simultaneous migration of people from villages to cities significantly reduced human contact with the microbiological world. As a result, our immune system in search of new "opponents" began to actively react to substantially harmless particles of food or pollen [37, 53].

Further evidence of the role of microorganisms in the development of allergic diseases stems from the independent study of microbial exposure associated with pet owners. The influence of dogs and, to a lesser extent, cats in childhood, protects against the development of allergic diseases [96]. Fujimura et al. (2010) showed that bacterial communities in household dust from homes, where dogs or cats were present, were significantly richer and more diverse than those, who did not have domestic animals and, according to the author, most of the bacterial taxons from the environment were found in the microbiome of the man's intestinal [15, 97]. This is confirmed by studies, which in particular indicate a reduction in the prevalence of asthma and other allergic diseases in children living on the farm [39, 98, 99, 100]. Most researchers attribute this to the fact that children on farms and in the countryside are exposed to more diverse microflora than children, who do not live on farms [14, 22, 101].

It has also been established that the effect on the skin of gram-negative *gamma proteobacteria*, common in the soil and on plants such as *Acinetobacter*, is associated with a decrease in the risk of atopy developing in teenagers [102].

In parallel with this, excessively harsh hygiene practices of a mother and disturbed vaginal flora leads to a weak colonization of the birth canal with lactic bacteria [72]. It should also be noted that the consumption of sterile industrial products by the mother reduces the production of lactic acid by bacteria. Thus, too harsh hygiene during labour, as well as disturbed vaginal flora with a decrease in the proportion of lactic bacteria leads to an increase in the prevalence of atopy in children, as shown by studies made in Sweden and Estonia [72].

As it has been already mentioned, microbial colonization of the intestine usually begins at birth, and this process primarily affects the maternal microbiota of the birth canal and the way of the childbirth (Caesarean section or delivery via natural way). During natural births, newborns are in contact with the bacterial flora of the vagina and the anus of the mother. The sterile environment in which the baby is found during Caesarean section disturbs the colonization described above [41]. After Cesarean section the colonization of the intestine occurs with delay and the composition of microbiota changes [24]. Thus, the microbiome of 1-month-old children, who were born via Cesarean section, contains more *Clostridium spp.*, *Klebsiella spp.*, *Enterobacteriaceae*, *Bacteroides spp.*, *Bifidobacterium spp.* and *Escherichia coli* [1, 6, 103, 105]. This effect lasts more than 6 months in newborns and greatly increases the risk of atopy, asthma, and allergic rhinitis [1, 104, 105]. This is confirmed by numerous studies, which report that children born via Caesarean section are more likely to develop asthma and atopy, allergic rhinitis, and food allergies [17, 31, 104, 106].

The method of feeding a newborn child also influences the formation of microflora of the gastrointestinal tract of children. Breastfed infants develop flora, which is dominated by bifidobacteria and lactobacilli that make up 60-91% of the intestinal microflora [107], while artificial feeding contributes to the development of *C. perfringens*. This is due to the composition and properties of breast milk, which contains a high concentration of lactose and casein, has a low content of calcium phosphate, and therefore reduces the buffer capacity. It was shown that a decrease in pH in the intestinal lumen inhibits the growth of bacteroids, clostridia and *E. coli*, but does not affect bifidobacteria [6]. Bifidobacteria, producing acetic and lactic acids, inhibit the growth of pathogenic strains, in particular *E. coli* and *Clostridium* [6, 32].

In addition, breast milk contains many factors that modulate and promote the development of the immune system in childhood, including immunoglobulins such as IgA and IgG, antimicrobial compounds such as lysozyme and lactoferrin, cytokines such as TGF- β and interleukin 10 (IL-10), and lymphocytes. In particular, cytokines, such as IL-10 and TGF- β , in breast milk contribute to the tolerance of the host immune system to the intestinal bacteria and contribute to the development of IL-10 by the child [17, 108].

Furthermore, recent studies have shown that breast milk is not sterile. It contains up to 600 different types of bacteria [109]. These are mainly bacteria such as *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, and *Weissella*, as well as some species of *Bifidobacterium* [17, 110]. Children who have been breastfed for at least 4 months have a reduced risk of developing asthma [111].

The use of antibiotics at an early age has profound implications for the development of intestinal microbiota. The use of antibiotics in infants changes the composition of intestinal microbiota in relation to a large number of proteobacteria and a low prevalence of actinobacteria populations [112], reduces the overall diversity of microbiota in a child, and promotes the formation of antibiotic resistant strains of bacteria [17, 113].

In addition, it has been noted that taking antibiotics during the first month of life is linked to decreases in the number of anaerobic bacteria (*Bifidobacterium*, *Bacteroides*) in relation to enterococci, enterobacteria and coagulase-negative staphylococci [24, 114]. *Clostridium difficile* infection is one of the possible complications of antibiotic therapy. Thus, the longer the antibiotic therapy and the wider spectrum of the drug, the greater the risk of infection with *C. difficile* [27].

According to some epidemiological studies, the use of antibiotics at an early age increases the sensitization of the organism [115], increases the risk of developing allergic diseases, such as asthma, atopic dermatitis, and allergic reactions to cow's milk [116]. An alternative system using antibacterial agents can be inhaled antibiotics in inflammatory respiratory diseases [117, 118].

Conclusions

A review of scientific studies indicates the association between the allergic diseases and the state of microbiota. This connection is realized due to the ability of the microflora to affect the activity of the T-cell arm of immunity, the formation of interleukins and other cytokines, interaction with the receptors of the intestinal epithelium, and recognition of antigens. Accordingly, a violation of the quantitative and qualitative composition of microbiota can increase the risk of hypersensitization and allergic diseases. Violation of microbiocenosis can be caused by many factors, in particular: the birth of children via Cesarean section, inappropriate feeding, a "sterile" way of life, wide use of antiseptics and antibiotics, etc. All these factors can lead to the violation of the quantitative and qualitative composition of microbiota and, accordingly, to the increased risk of developing allergic diseases. The most important steps in the prevention of allergic diseases is modification of lifestyle, breastfeeding of children, frequent exposure to the fresh air and contact with nature, and rational use of drugs. In our opinion, these recommendations are basic, without which successful prevention and treatment of allergic diseases is impossible.

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