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The role of microbiome in the formation of child health (literature review)

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The review is devoted to the microbiome interactions with physiologic and pathologic processes that have place during child organism development. Modern data concerning the questions of the microbiome formation in children are examined, beginning from the intrauterine fetus development and further during the process of ontogenesis. Characteristics of the microbiota content and functional activity in infants are presented. Influence of changed microbiota on the disease development in the child age is described. Analysis of the data available is performed with appreciation of medicines used for the improvement of microbiome health at different forms of child pathology.
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Key words: microbiome, microbiota, metabolites, diseases, inflammation, dysbiosis, immunity, probiotics, prebiotics, synbiotics, enterosorbent.

Child microbiome and factors influencing its formation

More then 18 years have passed from the time when there was formulated the scientific definition of microbiome as a unique human organ, which comprises microbe communities of different ecologic niches [150]. Since then, the study of microbiome has begun with great progress. In particular, many investigations with very interesting results have been done in the framework of the Human Microbiome Project [244]. When realizing this project, a great number of microbiome characteristics has been obtained, microbiome has been shown to influence different processes of the human organism, including metabolic brain mechanisms [19, 35, 39, 40, 59, 63, 73, 77, 83, 226, 227, 245, 258, 268, 269, 275].

Of special interest are the questions of the microbiome formation in children, as the growth and development of the child organism and its health in further life depends on how this process is physiological.

Initial microbiome formation in the child biotopes has its characteristic specifics that significantly distinguishes from others tissues, organs and systems.

This process occurs mainly at the perinatal and infant age; it is under the influence of many factors, in particular, the state of mother microbiome, features of infant feeding, mother diet during pregnancy and breast feeding, quality of breast milk, application of medicamental therapy (especially antibiotics), the state of environment etc.

Resent experiments have cast doubt on the previous notions about sterility of the fetus during placental period. Classical conception that the first contact of the child organism with microbes occurs in maternal generative passages was shaken. In a number of studies, convincing evidences have been obtained that the process of microbe system formation begins as early as during the period of intrauterine development of fetus due to the presence of unique placental microbiome in the organism of pregnant woman, which existence has not been even suspected not very long ago.

First information that the microbiome may be formed in mammals still before the birth appeared in 2008. Researchers from Complutense University of Madrid added milk with marked microorganisms into the food of pregnant mice. One day before estimated delivery date, the mice were underwent cesarean section in sterile conditions; in newborn mice, meconium was analyzed and marked bacteria were revealed in it [119].

In 2009, American researchers isolated bifidobacteria and lactobacilli DNA from placenta of 34 women [220]. As far as living microorganisms were not detected by cultivation on nutritional media, the authors supposed the translocation of nucleic acids through placental membrane. According to the researchers, nucleic acids, revealed in placenta, might promote much earlier development of Th-1-type immune mechanisms through activation of Toll-9-like receptor [220].

The ability of pregnant women microbiota to overcome placental barrier was convincingly proofed in 2012 by a group of scientists from the University of Valencia that discovered bacteria from the genera *Lactobacillus and Escherichia* in meconium of 20 newborns [100]. At that, lactobacilli dominated approximately in half newborns and escherichia prevailed in the other half. Dependence between lactobacilli and escherichia from different external factors and physiological features of mother organism were not clearly ascertained; however, the authors assumed that the content of newborn microbiome depended

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on the life style of pregnant woman, her diet and physical activity [100].

Later, the presence of microorganisms in meconium was confirmed by other researchers [92, 178, 236]. The authors of these studies have shown that the predominance of opportunistic microorganisms in meconium was associated with the infant predisposition to allergic and respiratory diseases.

Transitory colonization of germ-free mice during pregnancy assured innate immunity maturing in their germ-free offsprings, which gave better defense against infections [90]. Infections play an important role in disorders of the child development; therefore, these results suppose that translocation of microbe products from mother to her fetus may be very important for the immunity maturation and, possibly, for the child development after birth.

In 2014, researchers from Texas children's hospital in Houston identified genetic sequences of bacteria from placenta in 320 women. Tissues were taken at once after birth on the inside of placenta, therefore, the samples did not contact with the microbiota of parturient canal. In these tissues, a surprisingly wide array of bacteria was discovered. This testifies to the existence of a unique placenta microbiome, which, undoubtedly, is very important for the fetus development and further formation of the child microbe system [20].

Metagenome analysis revealed five basic types of adult human microbiome: *Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes* and *Fusobacteria* [20].

Unexpected was the fact that these microorganisms differed from the women intestinal and vaginal micro-symbionts; they were identical to the bacteria widely present in the biocenosis of oral cavity. In view of such differences between placental microbiomes in women that carried a full term child and that had preterm child (up to 37 weeks of pregnancy), the conclusion was suggested that pathological placental microbiome might be a risk factor of the preterm delivery. Besides, there was shown that the content of placental microflora is under the negative influence of the infectious diseases, which the mother had berore delivery; these are mainly infections of the urinary tract in the first trimester of pregnancy [262].

It should be noted that microflora of oral cavity was already found in amniotic fluid earlier. Thus, in 2002, fusobacteria and streptococci, identical to the microflora of oral cavity, were isolated from amniotic fluid of pregnant women with planned cesarean section. Then, the researchers supposed that amniotic fluid was infected with opportunistic microorganisms, because of their translocation from oral cavity through bloodstream, and proposed to consider this phenomenon as a marker of pregnancy complications [32].

Recently, a group of Australian researchers from the Edith Cowan University and the University of Western Australia also confirmed the availability of microbes in placenta, amniotic fluid and newborn meconium. In these microbiomes, a wide spectrum of bacteria was determined that were widely spread on skin, in oral cavity and human intestine [236].

Undoubtedly, inherent placental microbes carry out a significant influence on the growth and development of the fetus and on its microbiome. This indicate more large influence of the woman microbiome on her child health than it was supposed earlier. Moreover, the results obtained are an additional evidence of the close interconnection between the organism local biocenoses; the last are united into a single microbe ecological system that takes part in different functions and reactions of other organs and systems and provides and maintains homeostasis.

Therefore, in normal conditions, child adaptation to the life in the world of microbes begins long before birth; furthermore, intrauterine microbe surrounding influences both fetus development and physiological state of birth as well as postnatal health of the child. Contact with symbiotic microorganisms already in the mother's womb is a major mechanism of the long-term adaptation of fetus and its immunological apparatus to the life in the world of microbes, where the newborn finds itself after the birth. In this connection, a matter of great consequence may be the improvement of woman microbiome well before pregnancy with maintaining its normal state during pregnancy and the period of newborn breast feeding, that is, in the periods, when the microflora of woman organism has the most effect on the establishment of the child microbiome. In addition, attention should be paid not only to the state of intestinal and vaginal biocenoses, but also to all other biotopes, including oral cavity.

Later on, during the birth and postnatally, the child become actively colonized with mother strains from other biotopes — intestine, vagina, skin, breast milk.

As H. Makino et al. (2013) have shown, mother intestine is the most important source for colonizing her child with physiologic microorganisms, in particular, bifidobacteria. According to the available data, naturally born healthy infants, acquire, during first three days after birth, from one to

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seven bifidobacteria strains from mother intestinal microbiome [164].

Child gestational age is an important factor that influences the process of colonization with the formation of child microbiome. In premature infants, colonization of mucous membranes with symbiotic microorganisms passes frequently at a much slower rate; their biocenoses are more variable and with lesser diversity in comparison with healthy full-term children [85, 156, 164]. According to the available information, preterm birth may be connected with disturbed microbiome of mother [18, 51, 127, 206].

According to D.A. Chernikova et al. (2018), microbiomes in preterm children differ by their diversity depending on gestational age [51]. In such children, early colonizers of their biotopes are often opportunistic representatives of the genera *Staphylococcus, Escherichia, Streptococcus, Enterococcus, Klebsiella, Clostridium, Candida* etc. [5, 15, 17, 96, 118, 119]. At the same time, saccharolytic anaerobes from the genera *Bifidobacterium* and *Lactobacillus*, usual for intestine of healthy full-term children, can not always be discovered in sufficient quantity in feces of preterm children [15, 164]. Delayed colonization and reduced diversity of intestinal microbiota in preterm children may be connected with their maintenance in aseptic conditions of intensive care units and delayed feeding *per os* [156]. Besides that, large application of antibiotics in such children also may be an important factor disturbing microbiota content [10, 11, 198]. In view of this, preterm children may be more susceptible to disorders of gastrointestinal tract functions with development of infectious diseases, for example, such severe pathology as necrotizing enterocolitis [11, 37, 53, 180].

Mode of delivery plays a noticeable role in the formation of adequate child microbiome. According to data available, the fecal flora of naturally born children is most similar to mother vaginal communities with dominance of the genera *Lactobacillus, Prevotella* and *Atopobium*. Contrary, in children with cesarean delivery, fecal bacterial content is mostly close to mother skin microbiota with dominance of bacteria from the genera *Staphylococcus* and *Corynebacterium* [94, 118, 156].

On evidence of H.E. Jakobsson et al. (2014), children with cesarean delivery (unlike naturally born) had much lower microbe diversity in intestinal biotope during first two years of their life with slow establishment of populations from the type *Bacteroidetes* and reduced Th1- response [115].

Cesarean delivery children are often colonized with potentially pathogenic clostridia species. Such children microbiome contains low quantity of bifidobacteria but bacteria of the species *Clostridium difficile* are significant and appear in intestine already at the first days of life [198]. At the same time, microbiome of vaginaly born children contains rather high populations of bifidobacteria, in particular, the species *Bifidobacterium longum* and *B. Catenulatum*, with rare representatives of the species *Clostridium difficile* [156, 198].

Last years, rather interesting correlations were discovered between specific microbe taxons (especially from intestine microbiome) and the macroorganism genotype [35, 40, 59, 91, 136, 227]. One such association was observed between expression of mother gen fucosyl transferase-2 (FUT2) and the colonization of infant intestine with bacteria of the genus *Bifidobacterium*. Infants, born from mothers with absent secretion of this enzyme (FUT2–/–), had delayed intestine colonization with representatives of the genus [28, 154]. As is well known, this genus encodes main component adapted to metabolize oligosaccharides of mother milk [24, 28, 234]. It should be noted that bacteria *Bifidobacterium* play key role in maintaining infant health due to regulation of intestinal permeability and reduction of inflammation [52].

Last years, special attention has been given to the proliferation of bifidobacteria of the subspecies *B. longum. spp. infantis* in the newborn intestine. These bacteria are unique for the infant organism as they have in their genome a special cluster of 43,000 bp [86, 151, 152, 229]. This cluster contains 30 genes and four of them are coding enzymes that decompose breast milk oligosaccharides to monosaccharides [86, 134]. This group of enzymes contains sialydase, fucosidase, N-acetyl-β-hexosaminase and β-galactosidase.

According to E. Rosberg-Cody et al. (2004), certain bacterial strains, in the content of healthy infant microbiota, may produce conjugated isomers of linoleic acid, which, as was shown, possess antitumoral and anti-inflammatory properties [216]. Infants born by cesarean section are devoid mother vaginal and intestinal microflora in their organisms; accordingly, such infants have much prolonged and unhealthy formation of biocenoses and more subjected to colonization by hospital strains, dysbiosis development and infectious diseases [4, 10, 11, 13, 18, 156, 277].

Therefore, early colonization is initiated by placental microbiome in uterus, but after birth, it is defined mostly by microorganisms that are trans-

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located into the infant organism from vagina, intestinal tract and skin of mother [85].

The mode of infant feeding is very significant for the microbiome formation. Of great importance are the first portions of colostrum that enter into the infant intestinal tract immediately after the birth; it contains not only valuable nutritious, immune and bifidogenic factors, but also living microflora and plays a large part in the formation of physiologic microbiome [10, 45, 55, 66, 95, 110, 119, 146, 166, 179, 190]. It is estimated that 25–30% of infant bacterial microbiota comes from breast milk [193].

Oligosaccharides of breast milk play a special part in the formation of healthy infant microbiome with prevalence of physiologic bifidobacteria. Mother milk/colostrum comprises 5–23 g/l of oligosaccharides [143, 280], which, at lactose-reducing end, contain fucosyl and/or sialyl N-lactose-amine units [41]. Joining of these units leads to the creation of more than 200 different structures of mother milk oligosaccharides (HMOs), which distinguish by their size, charge and sequences [41].

HMOs are known by their anti-adhesive properties — they may bind pathogen bacteria preventing them from adhesion to targeted mucin oligosaccharides or epithelial cells [184]. In particular, anti-adhesive activity of free HMOs was described for pathogen bacteria *Streptococcus pneumonia* [25], enteropathogenic *E. coli* [25, 56], *Listeria monocytogenes, Vibrio cholera* [56], *Salmonella fyris* [56], as well as for human immunodeficiency virus (HIV) [106]. Presumably, glycolipids and glycoproteins of woman milk also take part in defense mechanisms against such pathogens as *Pseudomonas aeruginosa* [153], *Noroviruses* [117], *Vibrio cholera* [18] and *Rotovirus* [273].

A number of molecules in mother milk and colostrum supplement innate immunity and may influence the content of child microbiome. Fatty acids and peptides in the content of milk belong to antimicrobial factors and some of them may be activated at partial milk digestion [203, 241]. Local and system immunity of newborn may also be modulated by such milk components as secretory IgA, lactoferrin, lysozyme, lipoprotein-lipase and soluble signal molecules [148]. Milk is well known by its inhibiting action on pathogen microbes, but it also exerts positive selective influence on symbiotic microbiota. Accumulating data testify that the child organism receives with mother milk living bacterial cells and products, which promote adjustment of tolerant responses in child [162, 199].

Earlier, an opinion has been generally accepted that milk of healthy women was sterile with the possibility of its contamination only with skin microflora in the field of mammary gland, but lately a specific microbiome of breast milk was discovered. Its bacterial community, undoubtedly, performs the important function in the formation of child microbe ecologic system [28, 54, 79].

According to the results of a group of Spanish and Finnish scientists, healthy woman milk contains hundred species of different bacteria [167, 168]. At that, colostrum differs by the most diversity; it contains more than 700 microorganisms [190].

A. Donnet-Hughes et al. (2010) showed that dendritic cells of mucous membranes take part in the process of the microbiota translocation from the gut to tissues of mammary glands during the lactation period [66]. L. Fernandez et al. (2013) detected some mechanisms responsible for the translocation of mother microbiota into colostrum and breast milk. According to the authors, this takes place at the late pregnancy and during lactation period with the participation of gut monocytes [79].

In the normal condition, breast milk microbiota is an additional dose of physiologic bacteria that enters *per os* the child digestive tract [79, 119, 166]. These bacteria protect the child from infections and favor maturation of its immune system. On the other part, dysbiosis of mammary gland, due to proliferation of opportunistic microorganisms, may cause development of mastopathy and increase the risk of child contamination with harmful microflora [79, 172].

Breast milk of healthy woman is an effective natural synbiotic that plays an essential part in the formation and optimization of the immune system in postnatal period. During lactation period, microbe content in milk changes and species diversity decreases; this associates with increasing abundance of own infant microflora and, accordingly, necessity in the inflow of new species with breast milk lowers. At this stage, bifidogenic and immune factors of milk may have greater influence on the formation of microbiome and immune system. Breast milk is also an important source of secretory immunoglobulin (sIgA), which is important for infant with its passive neonatal immunity [172].

Time of the first breast feeding and further natural feeding substantially influence the formation of healthy child microbiome. During lactation period, physiologic bacteria considerably cumulate on the surface of nipples and areolae of gland in the feeding women; from here, they enter into the milk and in child digestive tract and favour the development of microbiome [45, 146].

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Mode of child nutrition influences the integration of its microbiome into the functioning of child digestive system. This regularity was revealed on children of the first year that were maintained on natural or artificial feeding. Lactose and oligosaccharides, coming in with the breast milk, stimulate the growth of intestine physiologic microbiota with prevalence in it of the genera *Bifidobacterium* and *Lactobacillus*; while, at artificial feeding with milk formula based on cow milk, streptococci, bacteroids and representatives of the family Enterobacteriacea predominate in the content of gut microbiome.

Children on breast-feeding differ from the ones fed with adapted mixture formula. The first have more healthy gut microbiome with prevalence of bifidobacteria and lactobacilli, they are more stable to infectious and allergic diseases an have developed mechanisms of the immune response [18, 10, 11, 45, 95].

Depending on feeding, spectrum of bacterial metabolites in the gut and the character of metabolic processes may also change. At natural feeding, acetate and lactate prevail in the products of fermentation, while acetate and propionate dominate at artificial feeding. Protein metabolites (phenol, cresol, ammonia etc.) are largely produced in the gut at artificial feeding. At that, detoxicant function of the digestive system against these products is reduced. In children on milk formula, activities of β-glucuronidase and β- glucosidase are also higher, which is typical for some representatives of the genera *Bacteroides* and *Closridium*. Such modifications of the microbiome content may result in both decrease of metabolic functions and direct damaging of the gut [276].

Therefore, neonatal age is a complex period of the microbiome formation; it plays a significant role in the infant adaptation to the life outside the mother organism. This process is influenced by a variety of factors; this explains why neonatal microbiome is so unstable and vulnerable to the action of endo- and exogenous influences. Available information suggests that the microbiome may partially be modified during the life, but initial development of this unique organ may have a particular importance for the formation of the microbiome central core that is stable to further modification. Dysregulation of microbiome in the initial, critical period during infancy may have long-lasting effects on the immune and metabolic functions and its repairing is very difficult [84, 177].

Changes of child microbiome during of ontogenesis

Microbiome formation continues several years and deeply depends on the state of the microbe ecology of mother organism, mode of delivery, feeding and maintenance of child. It is believed that the period from ovum fertilization to two-year age represents a critical window for the growth and development in the early childhood [214]. This prenatal and early postnatal period is characterized by rapid maturing of metabolic, endocrinous, nervous and immune ways that profoundly influence the growth and development of the child. All these ways develop jointly in strong interdependence and in dependence of internal and external signals [214].

In the view of a number of researchers, a rather firm configuration of steadily inhabited bacteria is achieved in children approximately in 4-year age [43, 161, 272]. At the same time, results of J. Cheng et al. (2015) testify that gut microbiota may often be unstable even in 5-year age [50]. According to the data available, main changes in the content of microbiome take place between 2-year age and sexual maturation of the organism [29].

Autogenic succession may be especially clear observed during first 2–3 years of child life; it passes several stages: before introduction of additional feeding, after introduction of additional feeding, after introduction into the diet of solid food, after termination of breast-feeding. Changes in the microbiome content may be influenced also by physiological processes in the child organism during its growth, such as establishment of immune and enzymatic systems, the change of hormonal background in juvenile age and so on [161].

Successive replacement of microbiota in early life plays an important role in the development and maturation of endocrine, mucosal immune and central nervous system [214].

P. Ferretti et al. (2018) have studied microbiome development from birth to 4 months after birth on 25 pairs «mother-child» [81]. They showed that the initial infant microbiome contained mother skin, oral and fecal strains; at that, the variability in each site was very large, in spite of the fact that all infants were born vaginally. According to the authors, transmission from skin and vagina was not long lasting and the child gut microbe content had the most similarity to the mother gut microbiome on the 4-th month after the birth [81].

American scientists observed some regularities of the microbiome formation in practically healthy children; they concluded that the diet changes and

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child age had the most importance in this process [137]. Phylogenetic diversity of microbiome increases noticeably with the increase of child age and the introduction of additional food [137, 191]. The transfer of children to solid food leads to rapid and steady changes of their gut microbiota. First weeks after birth, the gut metagenome community contains mainly genes responsible for the fermentation of lactose and oligosaccharides of breast milk. However, with introduction of solid food, the authors noticed sharp increase of genes associated with decomposition of vegetable carbohydrates, degradation of xenobiotics, and synthesis of a large spectrum of short chain fatty acids (SCFA), vitamins and amino acids [137].

While determining the diet of a first year child, one should take into account the successive establishment of metabolic functions and its dependence on food. In normal state, mucin decomposition begins alter 3 months of life, synthesis of coprostanol — in the second half-year, synthesis of urobilinogen — in 11–21 months of life. At the normal formation of gut microbiome, activities of β-glucuronidase and β-glycosidase, are rather low during the first year of life [68].

J.E. Koenig et al. (2011) studied gut microbiome in children over a period of more then two years. Studies, performed with the use of 16S rRNK pyrosequencing, showed that introduction of solid food into the diet of a child on breast milk led to the abundant increase of the type *Bacteroidetes* in their gut [137]. Other group of researchers, M. Fallani et al. (2010), with the use of fluorescent hybridization *in situ*, studied the content of gut microbiome in 531 children before weaning and 4 weeks after the first feeding with solid food. They found out significant increase of the species *Clostridium coccoides* and *C. leptum* together with lowered quantity of the genus *Bifidobacterium* [74].

Therefore, children food is an important regulator of functional microbiome diversity, which corresponds to different age-related stages of life. After weaning, child microbiome quickly becomes identical to adult microbiome; it gains new properties including possibility to use new complex high-energy nutrients.

Multitude of exogenous factors influence the formation of microbiome, however, hereditary features also should be taken into account. A number of studies have showed that, during first year of life, the microbiome content in twins has much more overlapping elements as compared with unrelated children. Clear evidence of relations between genetic structure of macroorganism and its microbiome has been obtained on mice models [156]. These results extend our knowledge about genetic factors of macroorganism that influence the assemblage of gut microbiome. For example, under the influence of environmental parameters, microbiome in genetically susceptible children may promote health disorders connected with immunity [156].

Therefore, a number of factors promote population of child biotopes with physiologic microflora, which reinforces child adaptation to new more aggressive environment.

Connection of child microbiome with immunity and other organs and systems

The formation of infant microbiome takes place in the close relation with development of mucosal and systemic immunity, physiologic maturation, nervous and endocrinous systems. Therefore, inhabiting biotopes with physiologic microbiota prevents from disturbances in homeostatic links, and from pathologies associated with vitamin and mineral metabolism, in particular, rachitis, iron-deficient anemia etc. [39, 93, 94, 107, 130, 189, 199, 233, 276].

Physiologic microbiota provides stimulation necessary for development of fully functioning and well-balanced immune system; the last includs not only homing of B- и T-cells to lamina propria, spreading and maturation of IgA-plasmacyte and production of IgA, but also induction of tolerance to safe food and microbe antigens [43, 63, 87, 96, 172, 268, 275].

Newborns and early age children are characterized by transient immunodeficiency, which concerns mostly humoral immunity. To some extent, this accounts for more frequent microbiome anomaly in the first year children as compared with older ones. Physiologic insufficiency of local gut immunity during first three months of child life is partially compensated by intake of protective factors with breast milk, such as sIgA, lysozyme, lactoferrin, complement, properdin, lactoperoxidase etc. [116, 188, 205].

Training of adaptive immune response to microbe colonization needs the growth of subset of inherent lymphoid cells and all lymphoid tissue with establishment of mutualistic relationship between macroorganism and its microsymbionts.

Initial microbe colonization leads to substantial changes of mucosal and system immunity. Maturing of the immune system is initiated still at the stage of fetus, but it grows and transforms

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very dynamically during the first months after birth and in childhood [184]. Newborns are characterized by the low expression of jointly stimulated molecules, low differentiation of dendritic cells, weakened phagocytosis, poorly developed interactions between dendritic cells, T- lymphocytes and regulatory T-cells as well as low cytotoxic activity of T-cells [141, 247]. Mother immunoglobulin G penetrates into fetus though placenta; due to its activity, newborn has no specific immune reactions, including local immunity of mucous membranes owing to minimal levels of IgA [129]. These features of the newborn organism were convincingly confirmed in experiments on animals. For example, in the germ-free mice and mice in the first days of microbe colonization, Peyer's plaques have less size, lamina propria contains low cell number and also lower levels of $CD4^+$ and $CD8^+$ T-lymphocytes [72, 257]. Besides, mucous membrane of the small gut rarely contains intraepithelial lymphocytes and plasmatic cells, the levels of secretory immunoglobulin (sIgA) are considerably lowed and expression of genes and markers of gut macrophage activation are suppressed [72, 176].

Using germ-free animals, M. Gomez de Aguero et al. (2016) showed considerable influence of mother microbiota on the early postnatal development of innate immunity in descendants. According their results, monocolonization of germ-free animals during pregnancy with the strain *E. coli* HA107 influenced the quantity of innate gut leukocytes in newborns in early postnatal period; as compared with sterile control, this also increased innate lymphoid cells (ILC) in small intestine and their general number, especially cells from subset $NKp46^+ROR\gamma t^+$ ILC3 [90].

Last year studies on experimental animals brought in some clarity into our understanding how gut microbiota within several days of colonization may program gut mucous membrane to maintain balanced immune response [69, 71, 87]. Results of these studies indicate that, during early stage of life, the biology of macroorganism undergo rather large changes in answer to colonization with microbiota. According to S. El Aidy et al. (2016), macroorganism encounters antigenic stimuli that evoke responses, including activation of genic network associated with different diseases [73]. Therefore, anomalous shifts in the process of infant development at this early phase may have long-lasting effects on the state of its health [58]. Accumulated data suggest singular critical window in the early stage of life; during the window, all full-scale organization of adequate homeostatic symbiosis of macroorganism with its microbiota is permitted. During this period, disturbed responses may lead to the development of pathologies in further life [44].

In postnatal period, digestive system maturing is of a large value; this system, like the immune one, should be prepared for the creation of mutualistic relations with microbiome. Studies on experimental animals showed that microbiota initiates significant changes of gut morphology [235]. These changes affect the architecture of villi, crypt depth, stem cell proliferation, blood vessel density, mucous layer properties and maturing of lymphoid tissue that is connected with mucous membrane.

In germ-free mice, in the distal part of small intestine, villi are longer and thinner than in conventional animals. Besides, at the absence of microbiota, villi have less complex vascular network, and gut crypts are less deep and contain less quantity of growing stem cells. In germ-free mice, mucous is thinner with changed properties. Such animals also contain very small quantity of isolated lymphoid follicles, immature Peyer's plaques and immature mesenteric lymph nodes (MLN); the levels of both immunoglobulins A (IgA) and antibacterial peptides (AMP) are lower then in conventional animals. In conventional animals, polysaccharide A (PSA), produced by *Bacteroides fragilis*, induces $CD4^+CD25^+FOXP3^+$-regulatory T-cells (Treg), which possess anti-inflammatory effect and suppress immune responses. On the opposite side, other studies showed that segmented filamentous bacteria (SFB) could induce the growth of T-helper 17 cells (TH17) that exert anti-inflammatory effect [235].

Microbiome plays a critical role in nutrient production and macroorganism metabolism and influences digestion, absorption and energy storage. At the beginning of life, all metabolic paths that are connected with development may be disturbed; immature microbiota cannot protect gut barrier, which may lead to blunting villi, mucous degradation, increased gut permeability and immune response abnormality. Such gut disorders may result in dysfunction of gut environment, chronic system inflammation, infectious diseases and diarrhea; each of these factors may disturb child development. Dysbiosis may also disturbs metabolism of key nutrients, including essential amino acids, with violation of the normal child development. At defective content of gut microbiome, normal production of growth hormones may change [214].

Central place in the functioning of intestinal microbiome and its interaction with macroorga-

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nism is possessed by mucous layers. Mucus thickness depends on the concentration of microbiota that regulates mucin production by special gut cells in small and large intestines. Obligate gut microbiota, presented in neonatal age mainly by bifidobacteria, actively decomposes complex O-linked glycans (mucins) and produces short chain fatty acids (SCFAs), which serve as the important source of energy and anti-inflammatory factor, and are toxic for many pathogens.

Large intestine epithelial cells utilize SCFAs, especially butyrate, which supply them by 60–70% with energy and promote strengthening of the mucous membrane barrier [78]. SCFAs also regulate the metabolism of glucose and lipids and immune functions [177]. Butyrate, acting as the inhibitor of histone-deacetylase, takes part in producing and maintaining the level of regulatory T-cells [177].

Intestinal barrier is very important for adequate functioning of the intestine and its formation largely depends from microbiota. As is well known, the main function of the intestinal barrier is regulation of absorption of nutrients, electrolytes and water from intestinal lumen into bloodstream together with nonadmission of pathogen microbes and toxins [131]. Intestinal barrier regulates molecular exchange between the environment and macroorganism through influence on the balance between tolerance and immunity to one or several antigens. These functions are maintained by a number of structures, including mucous layer and monolayer of epithelial cells connected by tight joints. Mucous layer, containing sIgA and antimicrobial peptides, covers the epithelial cells. It facilitates nutrient transport and serves as a protection from bacteria invasion [121]. Intestinal barrier is in the close and permanent interaction with gut microbiota, which disturbances may have serious consequences for maintaining key barrier functions [17].

Impermeability of the internal mucous layer for microbes is ensured by high concentration of antimicrobial peptides and secretory immunoglobulins as well as tight junctions.

Tight junctions are complex protein structures, composed of transmembrane proteins — cloudin, occulin and triculin that are joined with plasmatic membranes through ties between epithelial cells with formation of barrier between cells [57]. The structure of intestinal barrier in fetus was shown to form already to the end of the first trimester of pregnancy [131]. Epithelial cells with microvilli, goblet and enteroendocrine cells appear at the 8-th week of pregnancy, while tight junctions may be found out at the 10-th week. Functional development of intestinal barrier continues after birth and the diet influences it considerably [249]. Disturbance of this process leads to the underdevelopment of intestinal barrier, which may be observed in premature infants, and predisposes to the dysimmunity. Early in life, development of gut microbiota and intestinal barrier overlap. Intestinal barrier, functioning as protection, may be modified by gut microbiota and its metabolites. Mechanisms, underlying epithelial barrier regulation, are rather complex and examined only partially.

Physical and psychoneurological child development depends on the content of microbiome. Relations between development of gut and brain in infants is a field of modern studies of microbiome. Early microbiota colonization was shown to go in parallel with neuron migration. Establishment of microbiome during the first 2–3 years of child life coincides with critical periods of brain growth, myelination and synaptic brain clearance. Therefore, optimization of microbiome establishment in the early age is an important factor that favours the physiological development of brain [108, 209, 223, 256, 269].

Thus, the microbiome processes, taking place at the beginning of life, are the foundation for forming and maintaining child health. Therefore, we should have perfect approaches to optimize the formation of physiologic microbiome, which regulates interactions between the organism and environment and promotes the optimal child adaptation to the extrauterine conditions of life.

Any changes in the microbiome formation are a serious risk of diseases in early child life and their chronical passing in the future.

Microbiome disturbances and their link with pathology in the child age

At present, increasing number of specialists considers microbiome as a modulator of diseases. Last year, a number of works has appeared with detailed description of functional relationships between microbiome disturbances (dysbiosises) and a broad spectrum of pathologies in children [3, 4, 18, 32, 137, 160, 187, 199, 207, 214, 216].

In adults and children of the older age, dysbiotic disturbances are caused by modification of already formed microbiome, while, in children of early age, disbioses take place against the background of abnormalities of natural rather fragile initial microbiota. Neonatal microbiome distur-

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bances became chronical very rapidly; and pathological microbiome, generated in the early age, cannot be easily normalized later on.

The formation of infant microbiome is inseparably tied with the ontogenetic development of mucosal and systemic immunity; therefore, dysbiosis leads to disturbances not only in the microbiota content but also in the system of immune response to microbe antigens.

Children on artificial or early mixed feeding are devoid of protective factors of breast milk. Development of disbioses, allergies and other pathologies is observed much frequently in such infants. Atypical gut colonization during first weeks of infant life increases its susceptibility to immune and metabolic diseases [149, 188].

In particular, replacement of natural child feeding by artificial mixtures lead to the failure of the synthetic and exchange properties and to the impaired supplying of trophic and energetic substrates to the gut epithelium. Modification of the microbiome content results in overload of immature child immunity with microbe antigens, which may favour the formation of an inadequate immune response, inflammation and metabolic disorders.

Mother microflora plays a key role in the formation of infant microbiome; accordingly, the state of women microbe system is the main factor that defines both establishment of physiological microbiome in child and development of dysbiotic abnormalities. Immunologically immature organism of the newborn in in the neonatal age, that is, during the period of most active formation of its own microbe ecosystem, is completely dependent on the functioning of mother indigenous microbiota. Her healthy oral, vaginal, gut and skin microflora are supported by microbes and prebiotic factors of breast milk; all these factors promote selective proliferation of most physiologic microbe symbionts in the child biotopes, and favours postnatal adaptation of newborn organisms [4, 14, 16, 18, 19, 88, 188, 198].

At the same time, pathologic changes of mother microbiome are a source of child infection with microflora dangerous for his health. This indicates how responsible attitude a woman should have to her health and the state of her microbiome in order to prevent dysbiotic complications in her child.

In connection with complicated multifactorial and multistage process of physiologic microbe colonization, newborns and small children are the most vulnerable contingent of population, as they may have serious microbiome disorders. Even microflora of healthy child that receives mother milk may change significantly. However, at natural feeding, infants receive with breast milk a wide spectrum of immune and microbiological protective factors that optimize the formation of healthy child microbiome and effective immune system.

Vast biologic potential of microbiome and its unique role in generation and maintaining of child health is well understood. Close attention of scientists and medical practitioners to this question should help optimizing the process of establishing microbe system in peri- and postnatal periods in order to maintain it in healthy state in future.

Strong changes of microbiome at the early stage of its formation are the most dangerous, as they may lead to unfavorable consequences not only in child age but also at subsequent stages of human life. In particular, it is supposed that microbiome damage owing to treatment with antibiotics in early child age may significantly increase the risk of gut inflammatory diseases in mature age [198, 226, 230, 258].

The influence of environmental factors on the gut colonization of children born by cesarean section is highly important. On such infants, researchers have observed delayed formation of stable bifidoflora and high levels of opportunistic bacteria of the species *Enterococcus faecalis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Staphylococcus epidermidis* and *Staphylococcus haemolyticus* [15, 17, 228]. Such microbe contamination disturbs the processes of immune adaptation, lowers gut protective barrier and favours development of inflammation.

Formation of gut microbiome at early stages of the child growth is of great importance for the prophylaxis of obesity [228]. Some studies have identified differences in microbiome content assosiated with body weight [174]. For instance, longitudinal study by M. Kalliomaki et al. (2008), with the use of modern molecular-genetic methods (FISH) and flow cytometry, has shown relation between lowering of bifidobacterial species during the first year of life and obesity in such children in the age of 7 years. In children with extra mass in the age of 6 to 12 months, the level of infantile bifidobacterial species (*B. breve, B. infantis* and *B. longum*) was lower then in children with normal body mass. Also in children with obesity in 7-year age, the level of bacteria *Staphylococcus aureus* was significantly higher on the first year of life as compared with children that had normal indexes of body mass at the school age [127].

Physiological colonization of child biotopes plays an important role in preventing allergy [95, 105]. A number of studies has describe the

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content of microbiome in infants with developed allergic disturbances [38, 124, 197].

Studies by A. Shreiner et al. (2008) have revealed marked differences in the content of gut microflora in healthy and allergic children [232]. Normal microflora inhibits the process of food histidine decarboxylation, which lowers the synthesis of histamine and reduces the risk of food allergy in children. Antiallergenic properties of helthy microbiome are supplemented with strong barrier function of epithelial biofilm that prevents penetration of food allergens and toxic substances thought gut wall into blood flow.

Epidemiological researches showed greater risk of allergic diseases in children born by cesarean section [105]. The cause of this may consist in colonization of infant gut with skin or hospital microflora, for example, with opportunistic bacteria of the genera *Staphylococcus* and *Acinetobacter*; their redundant populations disturb normal establishment of the immune system. Late beginning of infant breast feeding and prophylactic using by mother of antibacterial preparations also have negative effect.

Epidemiologic studies have shown that microflora of atopic and non-atopic infants is different. M.A. Johansson et al. (2011) revealed that infants of non-allergic parents are more frequent colonized with lactobacilli; that indicates the role of mother microflora in protection from allergic diseases. In gut microbiome of healthy children, bifidobacteria of the species β. *longum* and *B. breve* are prevalent, while children with eczema have colonization of adult type with domination of the species *B. adolescentis*. In newborns, having gut colonized with bacteria of the species *Staphylococcus aureus* and *Clostridum difficile*, atopy was observed in later childhood [120].

Gut microbiota provides strong source of stimuli for macroorganism. The path for the first allergic reactions often arises in gastrointestinal tract, and food allergy represent common problem in children with atopic eczema. Violation of barrier in gut mucous membrane lead to increased penetration of antigens through mucosal barrier and to the change of transfer pathways. This results in the formation of distorted immune responses and the release of proinflammatory cytokines with further impairment of barrier functions. In turn, such inflammatory state lead to increased gut permeability; thus, in genetically susceptible individuals, we observe vicious circle of self-amplified allergic responses and dysregulation of immune reaction in response to antigens.

Preterm delivery is the primary cause of neonatal mortality and child disability. Premature newborns distinguishes by immature digestive tract and insufficient preparation of mucous membranes for their colonization with physiologic microflora; they make a group of increased risk for development of necrotizing enterocolitis, sepsis, meningitis and other serious diseases with high rate of fatal outcome [137, 159].

Index of infant mortality was significantly reduced due to a number of organizational measures in the system of mother and child health protection, such as organization of intensive care units in maternity homes with their modern equipment. However, this gave rise to new complex problems, connected with wide using of invasive diagnostic and therapeutic methods. As a result, new forms of nosocomial infections appeared, in particular, bacteremias, associated with the use of catheters, and pneumonias after artificial ventilation of the lungs.

Premature infants have much higher risk of complications after birth, including necrotizing enterocolitis. It is supposed that a risk factor of necrotizing enterocolitis is disturbed gut microbiota, which favours increased susceptibility of premature infants to systemic infections [37, 53, 61, 180, 182, 192, 228, 261].

Necrotizing enterocolitis (NEC) is a very dangerous life disease, provoking gut necrosis; it may also affect other organs, including brain with consequences much serious than damages of digestive system. NEC affects 5–10% infants that were born with the mass less then 1500 g. In spite of progress in child care, this disease is lethal in about 30% cases [82] and is associated with prolonged intellectual disability.

M. Hallstrom et al. (2004) detected in gut microbiome of newborns with necrotizing enterocolitis high concentrations of opportunistic microorganisms from the genera *Enterococcus* and *Candida* that, according to the authors, may play an important enteropathogenic role in the course of the disease. At that, microbiome of infants that were prematurely but normally born contained much less populations of opportunistic microorganisms as compared with premature infants born by cesarean section [99].

Breast milk is a rather effective means for prophylaxis of necrotizing enterocolitis; it facilitates gut colonization with helpful microflora, which exerts health-improving function on mucous membrane and raises the protective function of the organism.

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Premature infants are frequently delivered by cesarean section; they are given antibiotics and may have problems with feeding. Moreover, premature infants have functionally immature digestive tract with low level of acidity in the stomach, as a result of insufficient secretion of gastric acid, and they need more frequent feeding. These circumstances lead to increased content of potentially pathogenic bacteria in gastrointestinal tract and to lesser microbe diversity in such children in comparison with full-term infants [27, 48].

Low body mass at birth is an important risk factor of neonatal mortality and various diseases; this is caused by immaturity of immune system and barrier mechanisms of infant gastrointestinal tract as well as frequent using of invasive diagnostic and treatment procedures.

Premature newborns kept in intensive care units may contain a special microbe flora, which is substantially modified and with higher levels of opportunistic species, as compared with the microbiota of full-term infants. In microbiome of premature newborns, J.C. Madan et al. (2012) revealed, among facultative anaerobes, prevalent staphylococci of the species *Staphylococcus epidermidis* and *Staphylococcus aureus*, enterobacteria of the genus *Klebsiella* and enterococci, while clostridia were widespread among obligate anaerobes [159].

At violation of gut microbiome establishment, direct bilirubin, released with bile, undergoes enzymatic action of β-glucuronidase from intestinal wall with the producing of toxic unconjugated (non-direct) bilirubin. The last is absorbed in intestine, enters blood flow and may increase intoxication and jaundice, which is especially dangerous in newborns so as ductus (Arantius) venosus is still functioning in them [188]. The processes of calcium and iron absorption, synthesis of many vitamins and assimilation of D- and E-vitamins are also disturbed.

It should be taken into account that the microbiome destabilization lead to lowering of its detoxication properties; accordingly, loading on child liver significantly increases and may result in hepatocyte damage and development of hepato-biliary pathology.

Child pathologies are a serious problem of neonatology and pediatrics. Child organism substantially differs from the adult one by the structure and functions of different organs and systems with continuous morpho-functional changes, associated with growth and development; accordingly, child organism has greater susceptibility to infectious factors.

According to WHO, infectious diseases make up about 63% among causes of mortality in children [1, 15].

Infectious pathology of the fetus and newborn occupies one of leading places in the structure of morbidity and mortality during neonatal period. Treating perinatal infections of newborns with antimicrobial preparations that traditionally are used in neonatology (mainly cephalosporins and aminoglycosides of the third generation) lead to marked disturbances of the process of gut colonization. At that, studies testifies gut colonization with bacteria, resistant to utilized antibiotics (enterobacteria, enterococci, staphylococcus et al.), as well as fungi [11, 12].

Opportunistic fungi of the genus *Candida*, which can be considerably stimulated with medicamentous therapy (especially antibiotics), frequently become a danger to the life of premature infants. Causative agents of neonatal candidiases possess very high pathogenic potential; they can provoke sepsis and severe neurologic diseases in premature infants [34, 159, 163, 187].

The risk of invasive mycotic infections is much higher in premature infants with very small body weight at birth if they receive antibiotics in the complex of intensive therapy. Metagenomic analysis of microbiome of newborns with small body mass determined high concentrations of aggressive fungus species from the genus *Candida* in their gut biocenosis, which possess high invasive activity [145, 165].

In biocenoses of children with very low body mass, after antibiotic therapy there was observed poor species diversity of bacterial flora with predominance of antibiotic resistant bacteria, in particular, representatives of the species *Staphylococcus aureus* and *Enterococcus faecium*, which in many cases may become an etiological factor of sepsis [159, 161, 180, 218].

At present, there is not a single antibacterial preparation, which could act only on pathogenic microorganisms and do not affect indigenous flora. Gut microbiocenosis disturbances, associated with the use of antibiotics, lead to lowered resistance to the organism colonization; this creates favorable conditions for both infection of a patient with exogenous nosocomial strains and raised virulence of opportunistic autoflora.

Scientists from Wageningen University (the Netherlands) showed that using antibiotics in mother or child interferes with the formation of microbiome even at breast feeding of the infant. In their gut microflora, such infants contained predominantly enterococci, clostridia and escherichia with the complete absence of bifidobacteria [76].

Frequent antibiotic usage in child age is associated with increased risk of the resistance to anti-

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biotics [185]; this may occur due to the changes in microbiome and may predispose to the increased risk of diseases, including obesity [30] and inflammatory gut diseases [270].

Antibiotic-associated diarrhea (AAD) is an example of the negative influence of antibiotics on the infant organism. Most researchers suppose that etiologic factor of AAD is clostridia, in particular, the one of the species *Clostridium difficile*. This microorganism gives about 10–20% cases of AAD [23, 64].

French researches, on basis of their results, came to the opinion that antibacterial therapy not always lead to the newborn colonization with clostridia. These microorganisms overfill all hospital environment, which, in most cases, is the source of child colonization [80]. On the contrary, according to S. Matsuki et al. (2005), infection of newborn with clostridia in maternity hospital takes place from mothers. It has been establish, that 50–70% newborns may play a role of the carriers of the species *Clostridium difficile*, which may be connected with low colonization resistance of the intestine in the children of early age [169]. Intake of antibiotics may selectively increase the aggressive potential of clostridia and favour the development of the disease.

As was shown, besides *Clostridium difficile*, other microorganisms may also be causative agents of antibiotic-associated diarrhea in newborns and early age children, for example, representatives of the species *Pseudomonas aeruginosa, Clostridium perfringens, Salmonella sp., Klebsiella oxytoca*, fungi of the genera *Candida* etc. [228]. At that, according to Y.G. Kim et al. (2017), some clostridia species effectively protest infant digestive tract from colonization with pathogens [133].

Epidemiological studies, performed by Denmark scientists, testify that using antibiotics in early childhood is an unfavourable prognostic factor for the development of some gut inflammatory diseases. 500 thousand newborns were included in a perspective study, during which all volume of antimicrobial therapy was taken into account. The analysis showed that morbidity from Crohn's disease substantially increased in infants that were given antibiotics in the first years of life. Besides, the risk of the disease increased proportionally to the number of courses of antibiotic therapy [112].

In spite of life-saving functions of antibiotics, accumulated data suppose that early and repeated using of antibiotics and, possibly, other medicaments in the child age is an important factor influencing the microbiome, which may increase the risk of further diseases.

The state of child microbiome may be associated with the risk (at a later time) of many serious diseases, in particular, chronic intestine disease, endocrine, autoimmune, allergic and other pathologies. Special attention of specialists is drawn by the possible relationship between changes of microbiome in children and development of mental pathology. For instance, autism has been associated with differences in the content of microbiome [108, 209, 223, 245, 278].

It is known that brain possesses extensive metabolic ability during childhood; it makes up 5–10% from total body mass and is responsible for almost 50% basic metabolic energy of the body, and is especially sensitive to lowered energy consumption [214]. Due to the ability of gut microbiota to regulate the quantity of incoming energy, microbiome may play a regulatory role in the development of the nervous system during first years of child life. Parallel maturing of both microbiome and CNS in early life testifies the possibility to promote physiological development of nervous system in children through optimization of microbe establishment [223, 269].

Some works show that microbiome plays a role in the immune response at vaccination [63, 279]. At vaccine introduction, higher quantities of bacteria from the type *Actinobacteria* and *Firmicutes* were associated with much strong humoral and cellular response, while relatively high numbers of *Proteobacteria* and *Bacteroidetes* were associated with reduced responses [102, 109].

Numerous studies of the last decade convincingly testify that the establishment of healthy microbiome in child is an important factor for the formation of normal immune system and prevention of many chronic diseases. That is why, measures, oriented at optimization of microbiome processes in early childhood are of urgent interest for microbiologist, neonatologist and pediatricians.

Modern approaches to optimization of microbiome formation and its maintaining in children

Probiotics take up a special place among means used to optimize formation of healthy microbiome in early child age.

Already in XVIII century in the Netherlands, cultured buttermilk was proposed for feeding sucking children that suffered from dyspepsia. Later on, a number of products for child nourishment appeared that were enriched with cells of lactococci [31]. With development of microbiology and methods of bacterial therapy, increasing data confirmed beneficial effect of lactococci and bifido-

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bacteria on the health of suckling children; this favoured the production of large assortments of child products that contained these microorganisms [144].

In recent years, employment of probiotics in neonatology and pediatrics significantly increased. Results of researches show beneficial effect of some probiotics on the course of a number of gut diseases; they may be used with benefit at diarrhea, food allergy and other types of pathology [8, 12, 15, 37, 53, 135, 140, 180, 237, 258, 281].

Despite all complications of postnatal microbiome formation, this microbe organ in the stage of its formation may be much easier restored to the normal state as compared with microbiome restoration in older children and adults.

Choice of probiotics for newborns and small children has a key importance to get positive results. «Child» probiotic must have a number of biologic properties, and, first of all, reliably proved its safety. To prevent remote undesirable effects on the child health, one should not routinely use many probiotics containing microorganisms, which are not typical for child microbiome, as well as many additional ingredients of non-microbe origin. Of importance is optical configuration of the used substances. It is well known that L(+)-lactic acid is physiological for the human organism. And, on the contrary, D(-)-lactic acid is much worse tolerated, as it firstly transforms under the influence of D-2-hydroacid dehydrogenase and only thereafter may be assimilated by the organism [19]. Entering into child organism, D(-)-lactic acid may provoke acidoses, especially in small children [208, 209, 252].

Nowadays, results available show reasonability of using probiotics to improve microbiome in newborns and small children.

Probiotics, based on saccharolytic bacteria of the genera *Lactobacillus* and *Bifidobacterium*, are mostly used in neonatology and pediatrics, which, foremost, is accounted for by non-pathogenic profile of these microorganisms. Besides, such probiotics possess a number of other useful properties, which, in particular, include xenobiotic detoxication [12, 171], vitamin biosynthesis [14, 13, 15, 101], useful metabolic effects [17, 19, 135, 181], positive influence on the transit of intestinal contents [170], competition with pathogenic bacteria for nutrients and binding sites [19, 47], modulation of the immune response [19, 173].

Probiotics became wider used for prophylaxis of necrotizing enterocolitis, which is characterized by high mortality rate in premature newborns with low body mass at birth [37, 53, 140, 180, 194, 254]. This disease quickly affects gut mucous membrane, with removing off some parts of it. Breast milk is a rather effective means for preventing necrotizing enterocolitis; it favours gut colonization with useful microflora that improves health of mucous membrane and increases protection of the organism. To increasing favourable influence of breast milk, probiotics may be used orally.

In newborns that do not receive breast milk, enrichment of the diet with probiotic additives, which optimize the process of healthy microbiome formation, is very important for preventing necrotizing enterocolitis. Many studies showed efficiency of probiotics applied for this purpose [53, 89, 140, 147, 157, 194, 217, 218, 224, 254, 255].

Metaanalysis of 9 randomized, placebo-controlled trials with inclusion of 1425 premature newborns showed that probiotics appreciably lowered frequency of necrotizing enterocolitis in children; besides, their usage also significantly lowered mortality from this disease in children with body mass less then 1000 g at birth [22]. The authors of the metaanalysis are persuaded in the usefulness of applying probiotics in premature children for prophylactic purposes.

Randomized trial was carried out in Taiwan on 367 children with very small body mass at birth; it showed that, additionally to breast-feeding, everyday twofold intake of probiotic, containing strains of the species *Lactobacillus acidophilus* and *Bifidobacterium infantis*, lowered frequency and severity of necrotizing enterocolitis [157].

Another placebo-controlled trial was performed in perinatal center Shaare Zedek (Israel) on 72 infants with very low body mass. The infants were given probiotic mixture from the species *Bifidobacterium infantis, B. bifidum* and *Streptococcus thermophiles*; necrotizing enterocolitis was diagnosed only in 3 infants (4%), while in control group (n=73) with infants on breast or mixed feeding, 12 (16,4%) infants were diseased. At that, severe form of necrotizing enterocolitis (stage 2 or 3 according to Bell-test) was in 1 infant from probiotic group, while 10 such cases were diagnosed in control group among 73 patients (14%) (P =0,013) [37].

Japanese scientists in their review have summarized data of clinical trials on application of probiotic strain *Bifidobacterium breve* M-16V in premature newborns [271]. To estimate the protective effect of the strain in prophylaxis of necrotizing enterocolitis and other infectious diseases in premature newborns, there was performed clinical trial with participation of 338 children with very

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low body mass (total time of trials was 5 years). The children were given the probiotic *B. breve* M-16V in doze 10^9 cfu/day from the first hours after birth; control group (226 premature children) were not given the probiotic. As it turned out, the frequency of necrotizing enterocolitis and total frequency of infectious diseases were reliably lower in the group receiving bifidobacteria as compared with control [271].

G. Deshpande et al. (2007) carried out metaanalysis of randomized, controlled trials and showed that prophylactic application of probiotics in premature newborns can lower frequency of necrotizing enterocolitis by 30% [61]. Thus, results of many researches convincingly testify that probiotics based on physiologic bacteria may serve as an effective measure for preventing necrotizing enterocolitis and other infectious diseases in premature newborns.

Studies have shown positive effect of probiotics on the dynamics of growth and weight in children. For example, in a twice-blind study, performed on 105 infants of 0–2 month age, infants were given milk formula, containing probiotic strains *Lactobacillus rhamnosus* GG ATCC 53103 (107 cells/g); they better grew and gained weight as compared with infants that were given the same diet but without addition of probiotic [248]. In other study, the authors showed that fermented milk, containing lactobacilli *L. acidophilus* (10^8 cells/g), improved growth and weight indexes in children [221]. These results were explained by increased food conversion and, as a result, improved digestibility of food ingredients.

Placebo-controlled studies showed that full-term infants, which, from the first day of life, were given probiotic with *Lactobacillus plantarum*, had colonization of mucous membranes with lactic-acid bacteria that inhibited proliferation of opportunistic gram-negative flora predominating in children on placebo [213].

Well demonstrated is clinical efficiency on children of some probiotics in treatment of lactose intolerance [201], antibiotic-associated diarrhea (AAD) [19, 23, 33, 64, 123], atopic diseases [77, 114, 122, 124, 125, 126, 211, 240] and rotavirus gastroenteritis [195].

In the metaanalysis, G. Bernaola Aponte et al. (2013) showed that probiotics might be an effective means at chronic (persistent) diarrhea in children. Inclusion of probiotics based on physiologic bacteria into treatment schemes decreased stool frequency and duration of diseases. Unfavourable side effects of used probiotics were not detected in the study [36].

Cohrane Systematic Reviews [123] showed efficiency of some probiotics in preventing antibiotic-associated diarrhea (AAD) in suckling children. Analysis of 16 trials with participation of 3432 children allowed concluding that dozes of probiotic bacteria higher then $5x10^9$ cells/day reliably lowered risk of AAD. In some trials, prophylactic effect against acute gut diseases in infants was shown for bifido-containing probiotics [23, 237]. The authors emphasize that the effect of preparations administered depended on the used strains and dozes.

Three-strain probiotic mixture was more effective in treating early age children, which appeared in decreased acuity of diarrhea and in lowered stay in a hospital [605].

According to L.Vitetta и et al. (2014), probiotics at inflammatory gut diseases in most cases gave positive effect [251]. X.L. Liu et al. (2013) testify that administration of probiotics to children of early and preschool age resulted in lowered probability of diarrhea [158].

In randomized, double-blind, placebo-controlled trial with participation of 742 hospitalized children, Hojsak et al. (2010) revealed lowered of risk of nosocomial infections of gastrointestinal tract and respiratory airways in the group of children that every day were given a probiotic strain of the species *Lactobacillus rhamnosus* in 100 ml of cultured milk [104]. In another randomized, double blind, placebo-controlled trial with participation of 624 children (1–4 years), Sazawal et al. (2010) showed lowering rate of dysentery and respiratory infections in the group of children that during a year were given the culture *Bifidobacterium lactis* with milk [225]. According to systematic review of J.A. Applegate et al. (2013), inclusion of probiotics into the therapy of acute diarrhea in children younger then 5-year reduced diarrhea duration and stool frequency beginning from the second day of the disease [26]. N. Phavichitr et al. (2013) showed that probiotic, containing species *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, in the therapy of children hospitalized with acute diarrhea led to shortening of their hospitalization [202]. H. Szajewska et al. (2013) in their metaanalysis evaluated 15 randomized clinical trials with participation of 2963 children with acute gastroenteritis; they showed that intake of the probiotic strain *Lactobacillus rhamnosus* (LGG) lowered duration of diarrhea [238].

Some probiotics based on lactobacilli could decrease the risk of gastro-intestinal colonization with fungi of the genera *Candida* with further in

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premature newborns from the intensive care unit. Children that were given probiotics had lesser neurologic abnormalities during first year of life as compared with the control group [215].

Increasing data indicate higher effectiveness of polyspecies probiotics. Clinical trials showed that such probiotics were more effective when treating children with antibiotic-associated diarrhea [242].

According to modern recommendations, all patients that were given antibiotics should take a course of probiotic prophylaxis. These recommendations should be based on experimental and clinical data of the sensitivity of probiotics to different antibacterial preparations. Some studies have shown that the intake of probiotics based on lactic-acid bacteria may prevent lowering of gut lactobacilli at antibiotic application [33, 103, 140, 204, 243, 282]. According to other results, simultaneous intake of antibiotics with probiotics is possible, when probiotic microorganisms are resistant to antibacterial preparations. In this respect, poly-species probiotics are more effective [1, 138, 175].

Scientists of the department of child infections of A.A. Bogomolets National medical university analyzed effectiveness of the home multiprobiotic Symbiter® in the complex treatment of children with infectious pathology (purulent meningitis, lacunar tonsillitis, pneumonia). Control group of children (n=36) had standard therapy of a basic disease with antibacterial preparations (penicillin, ceftriaxone, cefotaxime). Primary group (n=34) was additionally given multiprobiotic Symbiter®, which is resistant to most widespread antibacterial means. The preparation was prescribed for all period of antibiotic therapy and during 10 days after its cessation. Multiprobiotic Symbiter decreased main and side symptoms of antibiotic therapy connected with gastrointestinal tract (diarrhea, abdominal pain, meteorism, vomiting); the authors concluded about reasonability of its inclusion into complex therapy of infectious diseases [1].

Frequent problem in children of the first months of life is intestinal colic. For the most part, colics appear as a result of child gastrointestinal tract adaptation to new conditions [266]. At frequent colics, formation of gut microbiota in children became disturbed; in view of this, probiotic mixtures are proposed in the diet [231].

Italian researchers from Torino University showed positive influence of some probiotic lactobacilli at intestinal colics on the state of newborns and infants of the first months of life. Similar results were obtained also in other studies [98, 113]. According to the data available, probiotics based on lactic-acid bacteria lower intensity of intestinal colics, decrease the frequency of regurgitation and vomiting and favorably influence gut peristalsis in premature newborns.

F. Savino et al. (2007) established that in children with colics, gut microflora contains lesser quantity of lactic-acid bacteria; instead, anaerobe gram-negative prokaryotes are rather frequent. In randomized, blind, prospective trial, 7-day course of lactobacilli probiotic showed considerable lowering of colic symptoms in 95% infants in comparison with control group, where only 7% children responded to simethicone therapy ($p < 0.01$) [224].

According to the data available, breast feeding with addition of bifidobacterial probiotics may maintain optimal content of gut microbiome and improve responses to vaccines in early child age. Dysbiotic microbiota, modifying mechanisms of T-lymphocytes development, may by indirect way change the response to vaccination. M.N. Huda et al. (2014) suppose that probiotics at vaccination may be especially useful for early year children that are subjected to frequent infectious diseases, hospitalizations and antibiotic prescription, which damage child microbiome [109].

According to some researches of early age children, bifidobacteria, predominant in their gut microbiome, may stimulate growth of thymus and immunologic responses to both vaccines — oral and parenteral. At the same time, decrease of bifidobacteria and increase of opportunistic microorganisms promotes the system inflammation, development of immunosuppression and lesser response on the vaccination [109, 175].

One of most important medical problems is prevention of allergic diseases in children. A number of clinical trials on allergy prophylaxis with the use of probiotics was successful. It is believed that child susceptibility to allergy is defined by the microbiome violation. A. Shreiner et al. (2008) revealed appreciable differences in gut microflora between healthy and allergic individuals with the possibility of reducing allergies by using some probiotics [232].

In a number of studies, atopic diseases in infants were prevented through the intake of probiotics by both mother during pregnancy and infant after its birth [67, 122, 135, 196, 210].

Antiallergic effectivity of probiotics is significantly higher in infants on breast feeding, especially when probiotics are also used by the mother during pregnancy and breast feeding [67]. Breast milk contains important immunoregulatory factors, such as TGF-β and IgA, which may protect infant from allergic diseases [212]. Biological mechanisms, responsible for such properties of

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breast milk, are studied still insufficiently and further researches are needed.

Joint studies with prenatal and postnatal probiotic usage showed considerable decrease of general eczema manifestation and/or IgE-associated eczema in 6 from 9 randomized clinical trials with participation of children up to 2 year old [67, 124, 132, 142, 186, 263]. In three trials, such effects were not observed [21, 111, 139].

2012 Metaanalysis detected significant lowering of eczema risk in 2-7 year old children, when women took probiotic lactobacilli during pregnancy, as compared with placebo and probiotics of other content [65]. In two other trials with the use of different probiotic mixtures, eczema decreased in a year [132] and in three months, accordingly [186].

K. Wickens et al. (2008) has studied effect of two types of probiotics against placebo and showed that the stain *L. rhamnosus* HN001 significantly lowered total eczema and IgE-associated eczema on the 2 year, however, it has no influence on the state of sensitization [264].

According to S.I. Woo et al. (2010), 12-week intake of *L. sakei* KCTC 10755BP by small children also led to lowering of atopic dermatitis and thrice decreased the disease activity comparing with children that were given placebo [265].

Analysis of the results available confirms considerable differences between probiotics in their biologic activity. Consequently, while planning clinical trials with probiotics, careful analysis should be done of not only species, but also strain content.

It should be noted that, in spite of positive effect of a number of probiotics, some researchers observed also increased incidence of asthma-like symptoms, two [139] and seven years after probiotic intake was finished [126]. Therefore, it is very important to take care of tested groups over a period of several years in order to clear up the duration of probiotic influence on the health of children.

At application of probiotic strain *L. paracasei* F19, lowering of general eczema cases was observed after 13 months [260]. Overall, these researches show that only postnatal application of probiotics may be insufficient to lower clinical symptoms of allergic diseases; therefore, early period of life, when we may influence microbiome and immune function, may begin before birth. Because of differences in trial organization, it is rather hard to obtain significant conclusions. Apparently, only prenatal using of probiotics is insufficient, they should be used also in postnatal period.

F. Campeotto et al. (2011) studied efficiency of a probiotic culture, based on *Bifidobacterium brevis* and *Streptococcus salivarius subsp. thermophiles*, on premature infants. Infants with gestational age 30–35 weeks were given the probiotic and the authors observed lowering of proinflammatory markers, associated with some features of gastrointestinal tolerance [46].

According to P. Van Baarlen al. (2009), probiotic based on *Lactobacillus plantarum* induces tolerance to food allergens owing to initiation of AhR-signaling path within mucous membrane [246].

Increasing results confirm reasonability of using probiotics to prevent respiratory diseases in children. Double blind, placebo-controlled, randomized study was performed from 1 December 2000 till 30 September 2002 in 14 centers of child-care in province Beersheba (Israel). Healthy, full-term infants of 4 to 10 month age were included in the study. Duration of observation for each participant was 12 weeks. Probiotics based on lactobacilli and bifidobacteria considerably lowered disease frequency in children with respiratory pathology and shortened the disease duration, which allowed diminishing the doze of administered antibiotic [259].

Microbiota modulation was proposed as a preventive means against usual cold and influenzal symptoms in children [155, 274]. In double blind, placebo-controlled, randomized study, 326 children 3 to 5 year old were given during 6 months twice a day probiotic strain *Lactobacillus acidophilus* (n=110), the mixture of strains *L. acidophilus* и *B. animalis lactis Bi-07* (n=112), or placebo (n=104). To the end of the study, children taking one-strain or combined probiotic had considerable lowering of frequency and duration of states with higher temperature, cough and rhinorrhea as compared with placebo group [155].

Randomized, placebo-controlled, study showed improvement of mucosal immunity and decreased frequency and severity of intestinal and respiratory diseases in children that were given yoghurt, containing the probiotic strain *L. rhamnosus* CRL1505. Frequency of infectious diseases decreased from 66% in placebo-group to 34% in the group that received yoghurt with probiotic. At that, in children that received yoghurt, severity of such diseases, as fever, decreased and the need in antibiotics lowered [250].

One more randomized, clinical trial with the participation of 110 healthy children in the age of 1 month to 4 years showed prophylactic efficiency of multiprobiotic Symbiter in respect of seasonal respiratory diseases. 3-month course of the multiprobiotic lowered severity of acute respiratory viral infection in children and dura-

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tion of main symptoms of the disease; probability of the disease complications was also lower and, accordingly, the need in antibacterial preparations decreased [2].

According to A.M. Deasy et al. (2015), probiotic based on the species *Neisseria lactamica* in the form of nasal drops lowered colonization of meningitis causative agent *Neisseria meningitides*. It is supposed that these effects are realized due to the mechanisms of competing interactions between microorganisms or through innate immune responses, which become activated at the availability of necessary symbionts [60].

Treatment with modification of microbiome content, including faecal transplantation and probiotic usage, improved some symptoms of child autism [128, 219].

In view of numerous results available, usage of probiotics for prophylaxis and treatment of dysbiotic violations in children represents large interest. At the same time, prophylactic usage of probiotics in neonatology still induces many discussions.

In particular, according to one opinion, prescription of prebiotic preparations to practically healthy newborns is unreasonable, as it may interfere with replantation of mother physiological strains. However, it should be taken into account that at once after the birth the child finds itself in the world, which is closely peopled with opportunistic microorganisms, among which nosocomial strains present a special hazard for its health. In adults, most part of exogenous microflora is perished due to mechanisms of specific and nonspecific protection, while newborn organism is less defended from the outer microbiological attack. Therefore, substantial part of microbe cells, entering into its organism, has a chance to survive and disturb the mechanisms of its microbiome formation.

Main protection of the newborn organism is the contact with the body of healthy mother and natural feeding. In most cases, such preventive mechanisms are not sufficiently effective. In particular, this may be seen in the fact that currently the phase of transitory dysbiosis in healthy newborns persists not less then a month and sometimes may lasts 2–3 years, while in the past this phase lasted only 6–8 days [4].

Neonatal age is characterized by maximal tension of all organism adaptive reactions; in this state, the spectrum of microflora, contacting with the organism, and the degree of its aggressive properties have extremely large importance. Newborn organism is very vulnerable; it is subjected to high risk of colonization with hospital strains of potential pathogens with their penetration into near-epithelial biofilms. «Defective» biofilms of high stability may form; they promote development and chronization of pathological processes not only in digestive tract but also in other organs and systems [7, 8, 13].

At neonatal infections, traditional usage of antibacterial preparations complicates still more the formation of healthy microbiome; this lead to selective advantages of opportunistic microflora due to the proliferation of antibiotic-resistant bacterial clones. Moreover, there is a danger of candido-mycoses, pseudomembranous enterocolitis and other complications.

Therefore, probiotic optimization of the microbiome formation in newborns, including premature infants, is one of effective approaches to their successful postnatal adaptation.

Until the present time, there are disagreements concerning effectiveness of probiotics on newborns in different clinical situations; it, to a considerable degree, is associated with using in studies of preparations with different content. There is common opinion about reasonability of using probiotics. However, clinical effect of a number of preparations has not been demonstrated; such effect was mechanically transferred from other preparation with similar species content. Such situation is inacceptable, as among great diversity of strains for each species of microorganisms, only some of them possess high probiotic effectiveness.

Therefore, medical and prophylactic usage of probiotics, based on physiologic bacteria, in neonatology and pediatrics is one of perspective methods for making healthier child population. Safety and simplicity of their application attract growing number of specialists to the methods of probiotic therapy and prophylaxis. At the same time, large introduction of «child» probiotics into the practice requires further studies to optimize their application.

Besides probiotics, prebiotics, fermented milk products and some enterosorbents may be used for making healthier child microbiome.

Prebiotics are food components, chiefly oligosaccharides, which, because of their structural organization, are not digested in small intestine; they are fermented in large intestine by anaerobic saccharolytic bacteria, which promotes the growth of their population in the microbiome. It is obvious that the greatest positive effect has prebiotics known as short chain fatty asides (SCFA).

Prebiotics may be used in the content of child mixtures. According to S. Fanaro et al. (2005), combination of galacto-oligosaccharides (GOS)

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and fructo-oligosaccharides (FOS) in the ratio close to their content in breast milk may stimulate the growth of bifidobacteria. Such mixture may influence the distribution of certain species among gut microflora and change faeces pH and the levels of SCFA, brining their concentrations closer to the content in the gut of infants on breast feeding [75].

M. Haarman and J. Knol (2005), using similar prebiotic mixtures on allergic children, showed their ability to induce bifidobacteria content close to healthy children on breast milk feeding [97]. Along with other means for improving microbiome, prebiotics increase functioning of newborn immune system and protect the organism from pathogens [42, 222].

Complex of probiotics with prebiotics — synbiotics — are also of significant interest. Many specialists suppose that prebiotics synergistically interact with probiotics and exercise a significant positive influence on the state of microbiome and the health of intestinal tract.

In the study K.G. Wu et al. (2012), children with eczema (from moderate to severe) were threated during 8 weeks with the combination of lactobacilli strain from the species L. salivarius and FOS. Such treatment gave significant lowering of the illness severity as compared with the children that were given only FOS; but, in the study, placebo group, needed for reliable comparison, was absent [267].

Advantage of fermented milk products in child feeding has been proved in many researches. In particular, regular consumption of probiotic products lead to quick restoration of physiologic microbe balance in biotopes of intestinal tract, favours the treatment of peptic ulcer, colitises, acute gut infections, improves the state of patients with metabolic disorders.

Some types of enterosorbents also enter to the group of means for microbiome improvement. Mechanism of their action is mainly caused by sanitization of gut lumen and improvement of the conditions for functioning of physiologic microbiota.

Enterosorption is a non-invasive method of the efferent therapy. With the choice of adequate sorbent, it may promote effective purification of the organism from allergens, mediators, the products of allergic and inflammatory reactions, metabolites, toxins, active peroxide compounds, viruses and other substances. Improvement of biotopes optimizes conditions for functioning of physiologic microbiome [6, 9, 19].

At present, we may choose a large assortment of different enterosorbents; however, not all of them are effective at microbiome disorders, especially in children.

Enterosorbents based on clay minerals are perspective for using in pediatrics; for example, smectites that are characterized by small particles and ability to form gels with cytomucoprotector properties. Smectites possess high adsorptive, water-retaining and ion exchange properties [6, 9]. Of large interest is their ability to sorb gut viruses; therefore, they are effective at enterovirus infections [9, 239]. Smectite was shown to suppress infectivity of 90% rotavirus inoculum at minimal concentrations during a minute of their contact [239].

Fundamental researches the authors led to the creation of a new generation of effective enterosorbents of the series Symbiogel®; they showed high results in the complex scheme of microbiome improvement in children. This series enterosorbents ensure effective sanitization of intestine tract, improvement of protective mucous layer of gut wall and conditions for active vital activity of physiological bacteria.

Conclusion

Numerous studies of the last two decades show that microbiome makes a substantial contribution into formation and maintaining the child health. It takes part in essential physiologic processes from the moment of conception and guides the development of child organism. Biologic potential of microbiome and its unique role in maintaining the child health are enormous. Scientists and medical practitioners should give special attention to the process of microbe system formation in pery- and postnatal periods in order to preserve it in healthy state in the future. Anomalies in the structure of microbiome associate with a wide spectre of diseases; therefore, its optimization and improvement in the early age is an extremely important factor for improving the health of children and adults.

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