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COLONIZATION RESISTANCE AND INTESTINAL MICROBIOTA AS FACTORS OF COUNTERACTION TO THE DEVELOPMENT OF INTESTINAL INFECTIONS (REVIEW)

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Abstract. With the continuing trend of increasing incidence of acute intestinal infections in children in early childhood in recent years, the importance of bacterial pathogens of opportunistic nature has remained. The issues of etiological and epidemiological significance of opportunistic enterobacteria in children without signs of immunodeficiency remain unresolved. There are many levels of protection of the human body from pathogens, which are realized through direct mechanisms of interaction between microbes, and indirect mechanisms mediated by stimulation of the immune system of the mucous membrane by indigenous representatives of the microbiota. Bacteriocins of commensal bacteria can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract. Colonization resistance of intestinal mucous membranes and colonization activity of microbes are directly opposite, but interrelated processes. Opportunistic enterobacteria acquire pathogenicity properties and become dangerous pathogens of infectious diarrhea under certain conditions that are created when the properties of the environment change. The intestinal microbiota, depending on its condition, is actively involved in the prevention, but sometimes also in provoking diarrheal diseases. Currently, *Klebsiella pneumoniae* plays a leading role among the opportunistic pathogens of intestinal infections of community-acquired origin in children of the first three years of life.

Key words: *acute intestinal infections; opportunistic enterobacteria; early childhood; colonization resistance of the intestine; microbiota; Klebsiella pneumoniae.*

КОЛОНИЗАЦИОННАЯ РЕЗИСТЕНТНОСТЬ И МИКРОБИОТА КИШЕЧНИКА КАК ФАКТОРЫ ПРОТИВОДЕЙСТВИЯ РАЗВИТИЮ КИШЕЧНЫХ ИНФЕКЦИЙ (ОБЗОР)

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Резюме. При сохраняющейся тенденции роста заболеваемости детей острыми кишечными инфекциями в раннем детском возрасте в последние годы сохраняется значение бактериальных возбудителей условно-патогенной природы. Вопросы этиологической и эпидемиологической значимости условно-патогенных энтеробактерий у детей, не имеющих признаков иммунодефицита, остаются нерешенными. Существует множество уровней защиты организма человека от патогенов, которые реализуются за счет прямых механизмов взаимодействия между микробами и косвенных механизмов, опосредованных стимуляцией иммунной системы слизистой оболочки индигенными представителями микробиоты. Бактериоцины комменсальных бактерий могут ингибировать патогенные и условно-патогенные микроорганизмы, участвуя в формировании структуры микробиоты желудочно-кишечного тракта. Колонизационная резистентность слизистых оболочек кишечника и колонизационная активность микробов представляют собой прямо противоположные, но взаимосвязанные процессы. Условно-патогенные энтеробактерии приобретают свойства патогенности и становятся опасными возбудителями инфекционных диарей при определенных условиях, которые создаются при изменении свойств среды. Микробиота кишечника в зависимости от своего состояния активно участвует в предотвращении, но иногда и в провоцировании диарейных заболеваний. В настоящее время среди условно-патогенных возбудителей кишечных инфекций внебольничного происхождения у детей первых трех лет жизни лидирующая роль принадлежит *Klebsiella pneumoniae.*

Ключевые слова: *острые кишечные инфекции; условно-патогенные энтеробактерии; ранний детский возраст; колонизационная резистентность кишечника; микробиота; Klebsiella pneumoniae.*

INTRODUTION

With the continuing trend of increasing incidence of acute intestinal infections (AII) in the population of the Russian Federation in the last 10–20 years [1, 2], the high epidemic significance of viral diarrhea in children [3, 4], and a marked decrease in the incidence of shigellosis among children, the importance of AII of opportunistic etiology is retained [5]. A high proportion of AIIs associated with opportunistic representatives of the microbiota (the proportion of AIIs of established bacterial etiology without specifying the pathogen in the total AIIs) is noted in the Astrakhan Region (81.2%), the Republic of Crimea (62.7%), and the Volgograd Region (59.4%), the Republic of Tyva (53.3%) (the national average is 12.8%), which may indicate an insufficient level of implementation of modern methods of laboratory etiological diagnosis [1, 6].

The microbiota in individuals with reduced immunological reactivity is in a state of dysbiosis, in which it is possible to replace indigenous microbial biofilms with polymicrobial biofilms of opportunistic microorganisms that protect them from the effects of innate immunity. As a result, a local infectious process is formed, which, under certain conditions, can become a generalized form by intestinal translocation of microorganisms and their toxins into the lymphatic channel and bloodstream [7, 8].

Currently, the issues of the etiological and epidemiological significance of opportunistic enterobacteria in AII in pediatric patients without the signs of immunodeficiency still remain unresolved.

MECHANISMS PROVIDING RESISTANCE TO COLONIZATION OF THE INTESTINAL MUCOSA

The integrative function of the intestine the protection of the body from pathogens and their translocation to other biotopes is associated with colonization resistance associated with the microbial-tissue complex — an evolutionarily established multifunctional union consisting of the microbiota of the parietal zone of the mucous membrane and underlying tissue structures [9].

"Colonization resistance" is associated with a stable and diverse microbiota in tandem with the absence of inflammation and involves specific interactions between the mucosal immune system and commensal microbes [10]. During all periods of life, the effectiveness of colonization resistance is determined by the optimal quantitative and qualitative composition of the microbiota [11].

The formation of intestinal microbiota begins during the prenatal period; in ontogenesis is a long-term multifactorial process, the violation of which is fraught with the development of various pathological conditions [12]. The formation of the microbiota continues until the child is 7 years of age; its composition is controlled by specific (immune) and non-specific mechanisms [13]. The intestinal microbiota, being the most autonomous and stable microbial community, dominates in quantitative and functional terms compared to that in other biotopes and maintains the required level of immunological reactivity of the organism. The maximum number of bacterial cells (about 10^{14}) lives in the

large intestine, which is tens of times greater than the total number of cells in the human body. In total, from 400 to 1500 species of microbes live in the digestive tract, and the total genome of bacteria contains about 3 million genes, 150 times the size of the genome of the macroorganism [13, 14]. The functional orientation and density of indigenous microbiota is unequal in the upper and lower parts of the digestive tract [15]. The proximal parts of the large intestine are inhabited by microbes attached to the intestinal chyme, the transverse region is inhabited by planktonic bacteria, and the distal parts are inhabited by bacteria associated with the mucous membrane [16]. The main metabolites of the intestinal microbiome, acting at the local level and in the periphery, are short-chain fatty acids (SCFAs) formed during the fermentation of dietary fiber, causing immune, endocrine and neuronal responses due to numerous SCFA receptors [17–19].

Resistance to colonization by bacterial pathogens is one of the most obvious functions of the human intestinal microbiota [20]. Disturbances in the composition of the microbiota reduce colonization resistance and increase the body's susceptibility to intestinal infection. The subtle mechanisms that provide resistance to colonization of the intestinal mucosa, even by fairly well-known and common pathogens, remain poorly understood. Using an experimental model of coli infection in piglets caused by enterotoxigenic strains (ETEC), methods of metagenomics and 16S rRNA sequencing showed that in the fecal microbiota of individuals with developed diarrhea, compared with individuals resistant to this infection, the ratio of *Bacteroides/Firmicutes* (B/F) was significantly lower (Fig. 1). In the jejunum of piglets with diarrhea, an increased percentage of *Lactococcus* (belonging to *Firmicutes)* was detected, and in the feces — a decreased percentage of *Prevotella* (belonging to *Bacteroides*) and an increased percentage of *Escherichia-Shigella*. However, the role of *Lactococcus* and *Prevotella* in the pathogenesis of diarrhea caused by ETEC has not yet been determined [21].

There is evidence of direct and indirect inhibition of some enteric pathogens by host systems [22]. Secondary bile acids (deoxycholic, lithocholic, ursodeoxycholic, allocholic), short-chain fatty acids (acetic, propionic, butyric) and bacteriocins, the production of which depends on the state of the microbiota, as well as the intestinal mucosal and epithelial barriers and competition of microbiota for nutrient substrates with pathogens, are considered as factors for direct inhibition of intestinal colonization. Short-chain fatty acids function as communication between the microbiota and the intestinal epithelium, as well as between different representatives of the microbiota [23].

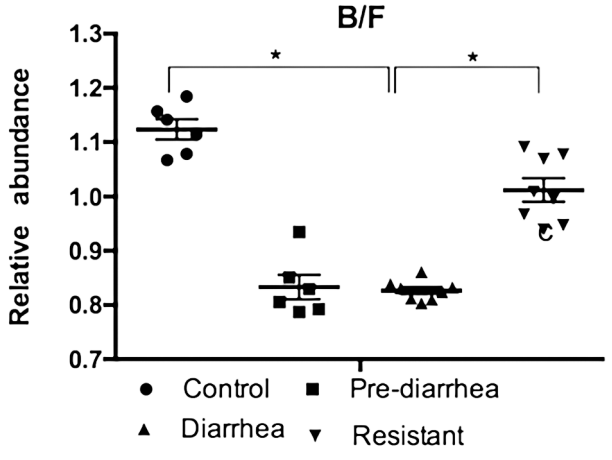

Fig. 1. Analysis of the relative abundance of *Bacteroidetes* (B) and *Firmicutes* (F) in feces using real-time PCR in the control group of piglets (Control), piglets with pre-diarrhea (Pre-diarrhea), those who developed diarrhea (Diarrhea) and those resistant to diarrhea piglets (Resistant) (* — p <0.05, one-way ANOVA) [21]

Рис. 1. Анализ относительной численности *Bacteroidetes* (B) и *Firmicutes* (F) в кале методом ПЦР в режиме реального времени у контрольной группы поросят (Control), поросят с пред-диареей (Pre-diarrhea), развившейся диареей (Diarrhea) и резистентных к диарее поросят (Resistant) (* — p <0,05, односторонний ANOVA) [21]

Indirect inhibition of intestinal colonization by pathogens is carried out by the innate immune system, which plays the role of protection against infectious agents and maintaining tissue homeostasis. The commensal intestinal microbiota and its components, through pattern recognition receptors, maintain the innate immune system in a state of physiological tone due to the balance of the synthesis of pro-inflammatory and anti-inflammatory cytokines and antimicrobial substances [24]. Thus, commensal intestinal microbiota induces the differentiation of CD4 T cells to Th17, which promote resistance colonization of pathogens by releasing the cytokine IL-22. Inhibition of colonization of pathogens is carried out under the influence of antimicrobial peptides, sIgA and other tissue factors of mucous membrane inflammation (Fig. 2) [22].

The relationship between changes in the microbiota and the reactions of the immune system has been established in the normal and reduced states of colonization resistance of the intestinal mucosa. In other words, there are many levels of host protection from pathogens, which are rea-

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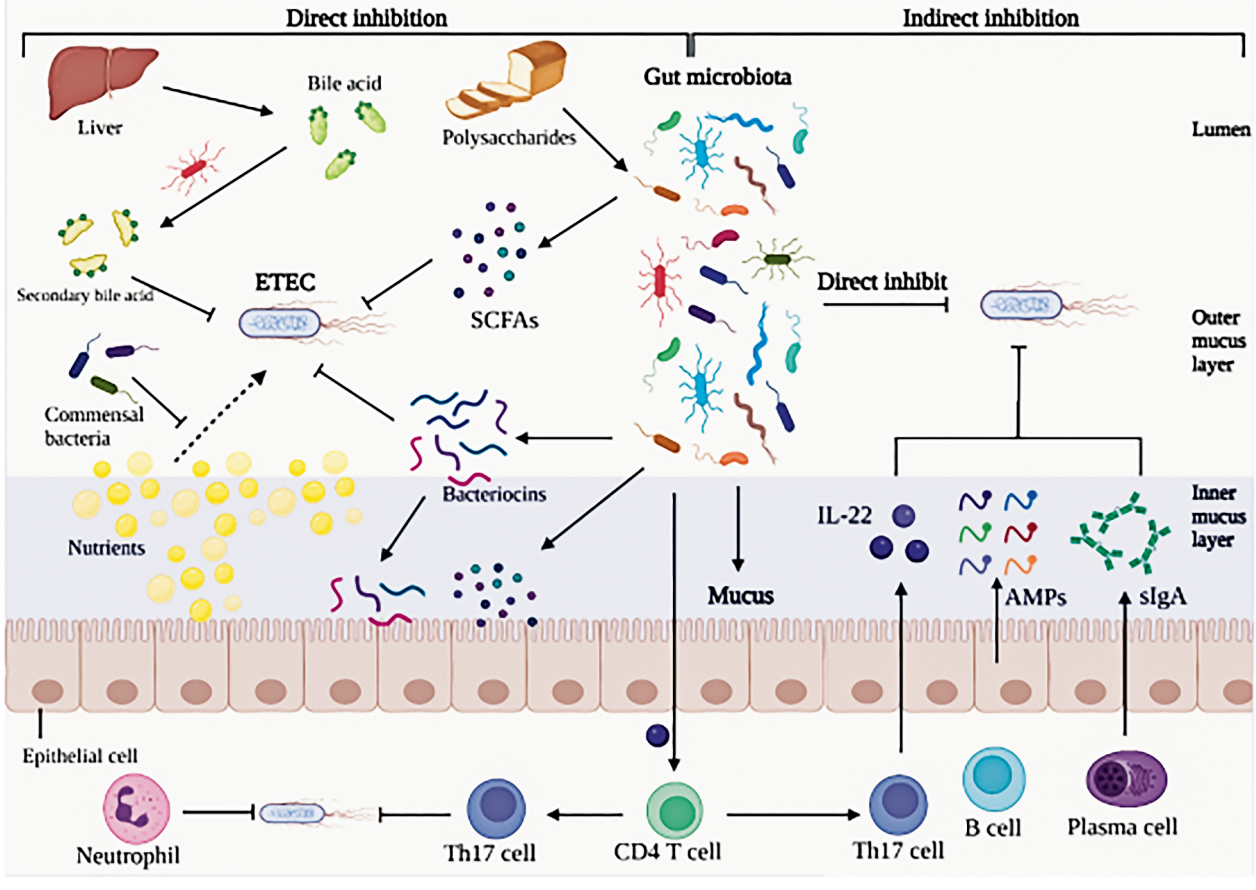

Fig. 2. Mechanisms of direct and indirect inhibition of intestinal colonization by the causative agent of ETEC infection, mediated by intestinal microbiota [22]

Рис. 2. Механизмы прямого и непрямого ингибирования колонизации кишечника возбудителем ETEC-инфекции, опосредованного микробиотой кишечника [22]

lized through direct mechanisms of interaction between microbes, as well as indirect mechanisms mediated by stimulation of the mucosal immune system by representatives of the commensal microbiota that maintain health [10].

INTERACTION BETWEEN BACTERIOCINS OF INTESTINAL MICROBIOTA AND THE IMMUNE SYSTEM

Numerous studies have shown that bacteriocins of commensal microbiota can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract (GIT) and other ecological niches of the body (Fig. 3) [25, 26].

The inhibitory effects of various bacteriocins against pathogens responsible for nosocomial intestinal infections have been proven [27]. Bacteriocins can be used as growth inhibitors of *Enterobacteriaceae* with multiple resistance to antibiotics, including *K. pneumoniae*, *Acinetobacter* spp. and others [28]. Microcin J25, a Gram-negative bacteriocin, exhibits high inhibitory activity against Salmonella and Escherichia coli, which are multi-resistant to antimicrobial drugs [29]. The sites of application of most bacteriocins are in the distal parts of the small intestine and in the colon [30]. The absorption of bacteriocins through the gastrointestinal epithelium and vascular endothelium into the bloodstream has been described [31]. Administration of bacteriocins to mice led to the increase in the number of blood macrophages/monocytes and antibody production due to modulation of the activity of antigen-presenting cells [32].

Antimicrobial molecules produced by commensal microbiota — bacteriocins and SCFAs-strengthen the barrier function of the epithelium by penetrating the inner mucus layer covering the epithelium, providing colonization resistance [22, 33]. In response to the effects of infectious agents, dynamic changes in the intestinal mucosal barrier occur. The rate of mucin secretion is regulated by innate and adaptive immunity. Infection of the

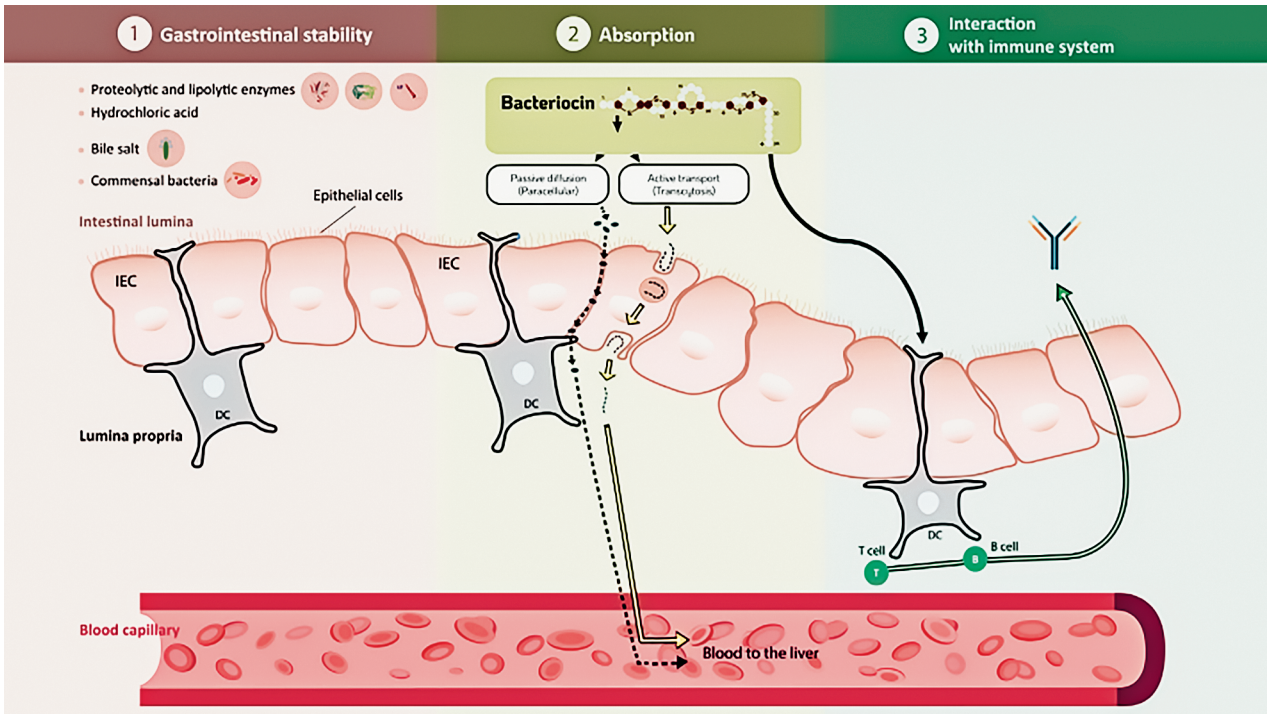

Fig. 3. Interaction of bacteriocins with the gastrointestinal tract and the immune system: 1 — stability of the gastrointestinal tract, including enzyme activity, pH changes, commensal bacteria; 2 — pathways for absorption of bacteriocins by epithelial cells; 3 — interaction of bacteriocins with the immune system [25]

Рис. 3. Взаимодействие бактериоцинов с ЖКТ и иммунной системой: 1 — стабильность состояния ЖКТ, включая активность ферментов, изменения pH, комменсальные бактерии; 2 — пути всасывания бактериоцинов эпителиальными клетками; 3 — взаимодействие бактериоцинов с иммунной системой [25]

intestinal mucosa by pathogens is accompanied by hyperproduction of mucus, antimicrobial molecules and specific immunoglobulins; the rate of their production is influenced by inflammatory factors and microbiota [34].

However, more in-depth studies combining metagenomic and metabolomic approaches are needed to detail the effects of microbial bacteriocins on the composition and balance of the intestinal microbiota [25].

COLONIZATION RESISTANCE AND INTESTINAL MICROBIOTA

Colonization resistance of the intestinal mucosa and colonization activity of microbes are directly opposite, but interrelated processes. Short-chain fatty acids (SCFAs), secreted by bacterial members of the intestinal microbiota, optimize the properties of the intestinal environment. In the case of inflammatory bowel disease, SCFA levels typically decrease, accompanied by an increase in opportunistic adherent-invasive *E. coli* (AIEC). And therefore, SCFA drugs are sometimes prescribed for the treatment of inflammatory bowel diseases [35]. At the same time, the results of a number of studies have shown that SCFAs can enhance the virulence of enterobacteria. It turned out that propionate and butyrate increase the expression of the virulence genes of AIEC, while strengthening the epithelial barrier and reducing the severity of inflammation. Research data show that increasing the colonization activity of the opportunistic pathogen of AII, namely AIEC, due to increased virulent properties, leads to overcoming colonization resistance of the intestinal mucosa [23].

Opportunistic enterobacteria acquire pathogenic properties and become dangerous agents of infectious processes under certain conditions, which are often created when their habitat changes. Metabolites formed during the digestion of fiber can lead to the appearance of pathogenic properties in symbiotic representatives of bacteroids carrying glycoside hydrolases genes that break down starch and are activated in the presence of dietary fiber. For this reason, *B. thetaiotaomicron*, as well as *B. fragilis*, against the background of increasing resistance to antimicrobial peptides and proteins, are capable of enhancing adhesive properties, forming a biofilm, and causing dangerous opportunistic infections [36].

Commensal *E. coli* are exposed to a wide range of antimicrobial agents, which potentiates the increase in antibiotic resistance genes. Changes in the genetic characteristics of *E. coli* place it in the category of opportunistic pathogens causing urinary tract infections, neonatal meningitis, and bacteremia in immunocompetent patients. Contamination of food products by *E. coli*, which has multidrug resistance and high colonization activity, poses a danger to consumers due to the very possible development of infectious diarrhea [37, 38].

Thus, while it was previously believed that the microbiota served as a barrier to pathogens in intestinal infections, today the understanding of microbiota-mediated resistance to pathogens has evolved significantly. It is now clear that the microbiota, depending on its state, not only actively participates in the prevention, but sometimes also in the provocation of infectious diseases [39].

KLEBSIELLA PNEUMONIAE AS A CAUSATIVE AGENT OF NOSOCOMIAL AND COMMUNITY-ACQUIRED INTESTINAL INFECTION IN CHILDREN IN EARLY CHILDHOOD

Everyday practice shows that *Klebsiella pneumonia* plays a leading role among opportunistic pathogens of OCI of community-acquired origin in children of the first three years of life [40–42]. Traditionally, Klebsiella are considered opportunists because they cause infectious lesions of various locations in newborns, immunocompromised individuals and hospitalized patients [43, 44]. At

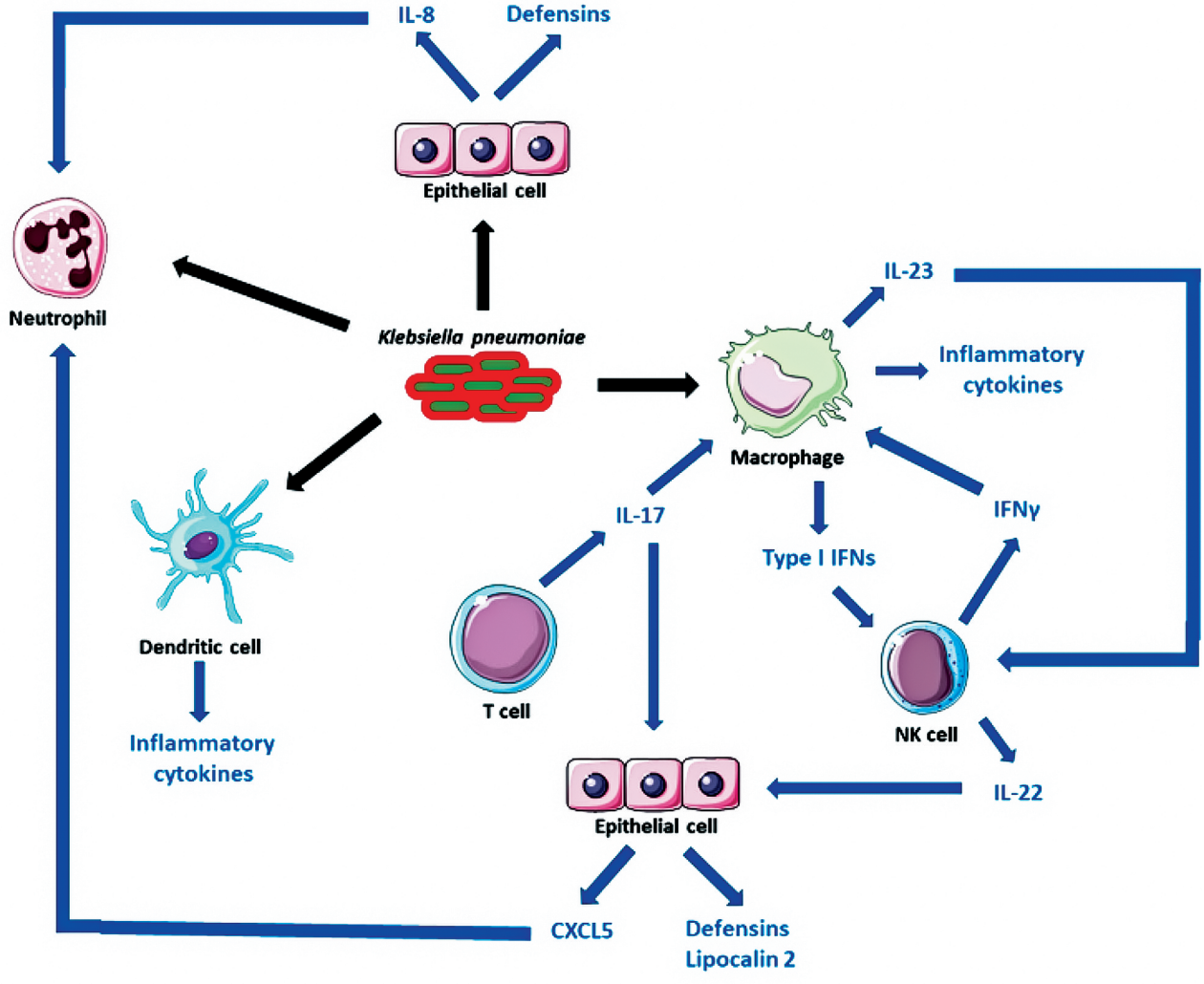

Fig. 4. Mechanisms of innate immunity to infections caused by *K. pneumoniae*. Interactions of *K. pneumoniae* with neutrophils, macrophages, dendritic and epithelial cells are indicated by black arrows; interactions with subpopulations of T cells and NK cells involved in bacterial clearance are indicated by blue arrows [47]

Рис. 4. Механизмы врожденного иммунитета к инфекциям, вызванным *K. pneumoniae*. Взаимодействия *K. pneumoniae* с нейтрофилами, макрофагами, дендритными и эпителиальными клетками отмечены черными стрелками; взаимодействия с субпопуляциями Т-клеток, NK-клеток, участвующими в бактериальном клиренсе, отмечены синими стрелками [47]

the same time, microbes of the genus Klebsiella are often found in the intestinal microbiota of healthy young children [13]. The outcome of colonization of children's intestines with Klebsiella depends on the presence of pathogenicity factors (capsule, lipopolysaccharide, siderophores, types 1 and 3 fimbriae, etc.), the level of contamination of the mucous membrane, colonization resistance, and immune activity (Fig. 4) [45–47].

The manifestation of AII caused by *K. pneumoniae* is a clinical expression of the insufficient effectiveness of the host defense mechanisms against pathogens [48]. The diagnosis of community-acquired AII caused by *K. pneumoniae* is established taking into account the detection of the pathogen in the stool in a high concentration (at least 5 lg CFU/g). And yet, the modern level of studying the biological properties of microorganisms indicates that a quantitative indicator does not always determine the ability of an isolate to cause a disease, the development of which is most associated with the realization of the pathogenic potential of the pathogen, ensuring its participation in the infectious process [49]. Indirect confirmation of the connection between the severity of the virulent properties of *K. pneumoniae* and the intensity of reproduction is the identification of an increase in resistance to ampicillin/sulbactam and to gentamicin with an increase in the concentration of the pathogen in fecal samples from children with AII [50]. Community-acquired cases of intestinal klebsiellosis in children of different ages suggest the possibility of contact, household and foodborne infection [51, 52]. It should be noted, however, that in a comparative aspect, the clinical and epidemiological characteristics of Klebsiella infections of community-acquired and nosocomial origin in children have not been sufficiently studied [53].

OPPORTUNISTIC ENTEROBACTERIA IN COMBINATION WITH VIRUSES IN INTESTINAL INFECTIONS IN CHILDREN

The scientific literature in young children describes combinations of Klebsiella infection with various opportunistic representatives of the *Enterobacteriaceae* family, including co-infections of *K. pneumoniae* with respiratory viruses [54]. Currently, against the backdrop of a widespread increase in co-infections, the issue of AII caused by a combination of opportunistic pathogens with intestinal viruses in children arises [55]. The results of studying the characteristics of clinical and laboratory signs of AII associated with *K. pneumonia* in young children show that the nature and severity of these signs are determined to a greater extent by the combination of *K. pneumoniae* with other opportunistic enterobacteria than by the combination of *K. pneumoniae* with intestinal viruses , thereby confirming the importance of the severity of background intestinal dysbiosis, which is involved in reducing the nonspecific resistance of the body. Identifying differences between mono- and co-infections associated with opportunistic agents may contribute to a more detailed understanding of the pathogenesis of diarrheal diseases.

Recent studies have established that the characteristics of the intestinal microbiome, along with the host genotype and the strength of local immunity, serve as interdependent key factors in the development of infectious diarrhea. In an *in vitro* experiment, it was demonstrated that the attachment of viral pathogens to host intestinal epithelial cells was negatively correlated with the abundance of certain groups of bacteria, such as *Faecalibacterium* and *Ruminococcus* spp., and sIgA titers to noro- and rotaviruses. The authors stated that there is a relationship between host genetics, intestinal microbiota and susceptibility to intestinal infections in humans [56]. Another experimental study demonstrated the preventive effect of using human milk oligosaccharides in rats for rotavirus diarrhea, due to the elimination of intestinal dysbiosis, as well as the immunomodulatory effect of oligosaccharides in the form of an increase in the expression of Toll-like receptors (TLRs), which confirms the active interaction of intestinal viruses with microbiota and the immune system [57].

A signature of pathogen-dependent intestinal dysbiosis based on microbiome analysis using 16S rRNA sequencing was identified in 80 patients with viral gastroenteritis in Ghana. A number of pathogens have been identified that are closely associated with viral diarrhea (*Escherichia-Shigella, Klebsiella and Campylobacter*). Co-infection with these pathogens and enteric viruses has been observed in several cases [58].

Many species of intestinal microbiota bacteria belonging to *Bacillus, Enterobacter, Enterococcus* and *Klebsiella* spp. secrete *enhancin-like proteins* that specifically damage membrane-bound mucins of the intestinal epithelium, leading to disruption of the integrity of the epithelial barrier and the development of viral infection. Deciphering the molecular mechanisms that regulate the interaction of microbiota, bacterial and viral pathogens will in the future become the basis for

the development of promising strategies to combat diarrheal infections [59].

Native-born authors, in experimental studies of the effectiveness of using a metaprebiotic that suppresses pathogens and stimulates the development of indigenous microbes producing antimicrobial exometabolites, on convection white mice, managed to prove the leading role of colonization resistance and normobiota of the digestive tract in ensuring the protection of the sensitive organism from pathogens of intestinal infections and in creating a selective microecological advantage, resisting infectious agents, as a result of bioincompatibility of the "host versus pathogen" type [60].

CONCLUSION

With the continuing trend of increasing incidence of AII in children in early childhood in recent years, the importance of bacterial pathogens of opportunistic nature has remained. The issues of etiological and epidemiological significance of opportunistic enterobacteria in children without signs of immunodeficiency remain unresolved. There are many levels of protection of the human body from pathogens, which are realized through direct mechanisms of interaction between microbes, and indirect mechanisms mediated by stimulation of the immune system of the mucous membrane by indigenous representatives of the microbiota. Bacteriocins of commensal bacteria can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract. Colonization resistance of intestinal mucous membranes and colonization activity of microbes are directly opposite, but interrelated processes. Opportunistic enterobacteria acquire pathogenicity properties and become dangerous pathogens of infectious diarrhea under certain conditions that are created when the properties of the environment change. The intestinal microbiota, depending on its condition, is actively involved in the prevention, but sometimes also in provoking diarrheal diseases. The intestinal microbiome ensures the resistance of the mucous membrane to the colonization of pathogens through the implementation of the following main functions: direct inhibition of pathogens through the production of antimicrobial compounds; maintaining the mucous barrier lining the intestinal epithelium; regulation of local and general immune response; effective use of exogenous and endogenous host nutrients by commensals. A holistic view that includes immunological and microbiological aspects of the intestinal ecosystem reflects the processes that contribute to maintaining intestinal homeostasis and resistance to colonization by pathogens. Currently, *Klebsiella pneumoniae* plays a leading role among the opportunistic pathogens of intestinal infections of community-acquired origin in children of the first three years of life.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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