

# THE ROLE OF THE NASOPHARYNGEAL MICROBIOME IN THE FORMATION OF CHRONIC AND RECURRENT ENT DISEASES IN CHILDREN: CLINICAL SIGNIFICANCE AND PROSPECTS OF PERSONALIZED THERAPY

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## ABSTRACT

The review summarizes current data on the role of the nasopharyngeal microbiome in the development of chronic and recurrent ENT diseases in children, with a particular focus on microbiome-associated biomarkers, host genetic factors, and mechanisms of immune regulation. It has been demonstrated that dysbiosis of the nasopharyngeal microbiota is closely associated with the pathogenesis of adenoiditis, otitis media, rhinosinusitis, and allergic rhinitis, influencing both local mucosal immunity and systemic inflammatory responses. The paper analyzes age-related features of microbiome formation, the interaction between microbial communities and innate and adaptive immunity, as well as the impact of early-life environmental and postnatal factors on microbial colonization. Special attention is given to the role of genetic predisposition in shaping microbial composition and susceptibility to recurrent ENT pathology. Current evidence regarding the association between host genomic variability, immune-response genes, and microbiome diversity is discussed. Modern molecular and metagenomic methods for microbiome assessment, including sequencing technologies and identification of microbial and inflammatory biomarkers, are reviewed together with their clinical interpretation and diagnostic potential. The presented data support the concept that microbiome-derived and genetic biomarkers may become an important basis for personalized approaches to prediction, prevention, and targeted therapy of pediatric ENT diseases. The integration of microbiome profiling into clinical practice is considered a promising direction for precision medicine in pediatric otorhinolaryngology.

**KEYWORDS:** nasopharyngeal microbiome, children, ENT diseases, dysbiosis, immunity, personalized therapy.

## INTRODUCTION

In recent years, more and more attention has been paid to the role of the nasopharyngeal microbiome in the formation of chronic and recurrent ENT diseases in children, since it is this anatomical region that is the first barrier between the external environment and the immune system of a developing organism [1-3]. The imbalance of the nasopharyngeal microbiota is considered as one of the key factors contributing to the development of adenoiditis, recurrent otitis media, chronic rhinosinusitis and allergic rhinitis, which are widespread in pediatric practice. According to the World Health Organization, chronic and recurrent upper respiratory tract diseases are detected in 20-30% of children worldwide, while in a significant proportion of patients, clinical manifestations persist for several years [4]. In the Russian Federation, chronic ENT pathology also occupies a leading place in the structure of childhood morbidity and, according to regional epidemiological studies, occurs in 25-40% of preschool and primary school age children [5].

Despite such a high prevalence, most scientific work has focused on acute infections or pathology of the lower respiratory tract, while the nasopharyngeal microbiome in children has long remained insufficiently studied. [2, 3, 6, 7]. Available studies indicate that colonization of the nasopharynx by opportunistic pathogens can support chronic inflammation and form a tendency to recurrent course of ENT diseases. At the same time, the number of publications devoted to the study of the nasopharyngeal microbiome in healthy children and its age dynamics

remains limited, and the role of the microbiota as a prognostic and therapeutic tool has been covered in fragments [8-13].

Additional interest in this problem arose after the COVID-19 pandemic, as changes in living conditions, including prolonged wearing of masks and a decrease in the frequency of viral infections, could potentially affect the microbial ecosystem of the upper respiratory tract in children [14-18]. The development of high-performance sequencing and metagenomic analysis methods has opened up new opportunities for a detailed assessment of the composition and functions of the nasopharyngeal microbiome and its relationship to immune and inflammatory responses. In the context of the accumulation of disparate data, their systematization and critical analysis become particularly relevant. In this regard, the purpose of this review is to summarize current understanding of the nasopharyngeal microbiome in children, its role in the formation of chronic and recurrent ENT diseases, as well as to assess the prospects for using microbiome-based approaches in the framework of personalized prevention and therapy.

## **FORMATION AND AGE-RELATED FEATURES OF THE NASOPHARYNGEAL MICROBIOME IN CHILDREN**

The formation and age-related features of the nasopharyngeal microbiome in children are a dynamic and multi-stage process that begins at birth and is closely related to the conditions of the early postnatal period [19]. Already in the first weeks of life, the nasopharynx of a child is populated mainly by opportunistic pathogenic and commensal microorganisms, among which *Staphylococcus*, *Streptococcus*, *Moraxella* and *Haemophilus* are most often detected, forming unstable, easily changeable microbial communities. At an early age, the nasopharyngeal microbiota is characterized by a higher colonization density compared to adults, which reflects the immaturity of the local immune response and explains the increased susceptibility of children to respiratory infections. As a child grows, the microbiota gradually evolves from chaotic and variable communities to a more structured and relatively stable microbiome, which is usually observed in the range of one to three years of life [20-22].

The type of feeding has a significant impact on this process: breast milk contributes to the formation of a more balanced microbial profile due to immune factors and oligosaccharides, whereas artificial feeding is associated with other trajectories of microbial colonization. Infections that have been transmitted at an early age also play an important role, which can temporarily or permanently change the composition of the nasopharyngeal microbiota, shifting it towards the dominance of potential pathogens. An additional factor is environmental impact, including overcrowding, hygiene, air pollution, and frequency of contact with other children, especially in organized groups [15].

The early period of life is considered as a critical "window" during which the nasopharyngeal microbiome is most sensitive to external influences and at the same time has a significant impact on the formation of immune regulation [16]. Violations of this delicate balance, including under the influence of antibiotic therapy, can have long-term consequences and be associated with an increased risk of chronic and recurrent ENT diseases. Despite the growing interest in this problem, data on the age-related evolution of the nasopharyngeal microbiome in children remain fragmentary, which underscores the relevance of further research aimed at clarifying the role of breastfeeding, infections, and environmental factors in the formation of a stable and functionally complete microbiome.

## **DYSBIOSIS OF THE NASOPHARYNGEAL MICROBIOME AS A PATHOGENETIC FACTOR IN CHRONIC AND RECURRENT ENT DISEASES**

Adenoids and palatine tonsils, being the most important elements of the lymphoid tissue of the nasopharynx, serve as the primary immune barrier, while it is in this zone that dysbiosis of the nasopharyngeal microbiome can act as a pathogenetic factor in the formation of chronic and recurrent ENT diseases, including adenoiditis, rhinosinusitis, otitis media and allergic rhinitis, which is consistently reflected in the studies of M.V. Drozdova, S.N. Larionova and E.V. Tarnova [3]. The constant exposure of viral, bacterial, and allergic agents to adenoid tissue creates conditions for microbial imbalance, in which the physiological mechanisms of mucosal protection gradually transform into chronic inflammation, complementing the clinical observations presented by G.I. Markov and co-authors [6] in the analysis of nasopharyngeal tonsil hypertrophy.

Anatomical and immunological features of adenoids allow us to consider them not only as an organ of local protection, but also as a potential reservoir of persistent microorganisms that support dysbiosis of the nasopharyngeal microbiome and contribute to the prolonged course of adenoiditis and recurrent upper respiratory tract infections. As emphasized by A.E. Sirbu and co-authors [23], the microbiome of the upper respiratory tract is a dynamic ecosystem, violations of which at an early age can form a predisposition to chronic inflammation, allergic rhinitis and rhinosinusitis. At the same time, the microbiota of the nasopharynx determines not only the probability of infection spreading to the paranasal sinuses and middle ear, but also the severity of clinical manifestations and the frequency of recurrence of otitis media, which is confirmed by data from domestic and foreign authors. A significant contribution by M.V. Drozdova and co-authors [3] is to identify a link between changes in the microbial composition of the nasopharynx and activation of mucosa-associated lymphoid tissue, accompanied by impaired production of secretory IgA and an imbalance of effector and regulatory T cells.

The persistence of opportunistic pathogenic microorganisms such as *Staphylococcus aureus*, *Haemophilus* spp., and *Streptococcus* spp., often in biofilms, demonstrates mechanisms for maintaining chronic inflammation and the development of adenoid hypertrophy with the formation of obstructive symptoms [17]. Repeated viral and bacterial episodes against the background of an altered microbiome additionally contribute to the dysfunction of the auditory tube and create prerequisites for recurrent otitis media, which logically complements the concept of prevention and conservative treatment proposed by G.I. Markov and co-authors [3]. Summarized data presented in the table 1 [17, 19, 24, 25]. They clearly reflect the differences in microbial patterns in the main forms of chronic and recurrent ENT pathology and allow us to compare them with the clinical manifestations of the disease.

**Table 1: Characteristics of microbiome changes in chronic and recurrent ENT diseases**

ENT is a disease	Key microbiome changes	Predominant microorganisms	Pathogenetic significance
Chronic adenoiditis	Reduction of microbial diversity	<i>Staphylococcus aureus</i> , <i>Haemophilus</i> spp.	Persistence of inflammation
Recurrent adenoiditis	Growth of opportunistic taxa	<i>Streptococcus</i> spp.	Frequent exacerbations
Chronic rhinosinusitis	The imbalance of the commensals	<i>Moraxella catarrhalis</i>	Maintaining inflammation
Recurrent rhinosinusitis	Microbiota instability	<i>Haemophilus influenzae</i>	Increased risk of relapses
Otitis media	Colonization of the nasopharynx by pathobionts	<i>Streptococcus pneumoniae</i>	The spread of infection
Recurrent otitis media	Biofilm formation	<i>Staphylococcus aureus</i>	The chronic course
Allergic rhinitis	Reduction of protective bacteria	<i>Corynebacterium</i> spp.	Immune dysregulation
Combined ENT pathology	Severe dysbiosis	Mixed flora	Aggravation of the clinical picture

In general, an analysis of the literature suggests that dysbiosis of the nasopharyngeal microbiome should be considered not as a secondary consequence of the pathological process, but as a significant pathogenetic mechanism of chronic and recurrent ENT diseases, which indirectly indicates the prospects for more individualized preventive and therapeutic approaches.

### **INTERACTION OF THE NASOPHARYNGEAL MICROBIOME AND THE IMMUNE SYSTEM OF THE CHILD'S BODY**

The interaction of the nasopharyngeal microbiome and the immune system of the child's body is a multilevel process in which innate and adaptive immune mechanisms are formed under the constant influence of microbial stimuli of the mucous membrane of the upper respiratory tract [8]. According to clinical observations by N.N. Pirogov [26], persistent viral infection of the oropharynx is able to change the local microbial environment and maintain chronic inflammation, which indirectly reflects a violation of immune regulation against the background of reduced antiviral tolerance.

In childhood, the nasopharyngeal microbiome is actively involved in the "training" of innate immunity, influencing the activity of the epithelial barrier, the production of antimicrobial peptides and cytokines, as well as the nature of the primary inflammatory response. The studies of E.P. Karpova, A.V. Gurov and K.Y. Burlakova [1] complement these ideas, demonstrating that changes in the microbial composition of the nasopharyngeal mucosa in chronic adenoiditis and exudative otitis media are accompanied by signs of immune imbalance and maintenance of prolonged inflammation. As adaptive immunity matures, the nasopharyngeal microbiota begins to influence the differentiation of T-lymphocytes, the production of secretory IgA, and the formation of immune tolerance to commensal microorganisms and environmental antigens.

A violation of this delicate balance associated with dysbiosis can lead to a shift in the immune response towards chronic inflammation or allergic reactivity, which is especially significant for children with repeated infections and atopic manifestations [27]. In this context, modern approaches, including analytical and digital methods, mentioned by F. Indrio and co-authors [28], open up possibilities for a more accurate analysis of the complex relationships between the microbiome and the immune system of a child. Taken together, the data from various authors allow us to consider the nasopharyngeal microbiome not as a passive background, but as an active participant in the formation of innate and adaptive immunity, which determines the balance between inflammation and immune tolerance in childhood.

### **MODERN METHODS OF NASOPHARYNGEAL MICROBIOME RESEARCH IN PEDIATRICS**

Modern methods of studying the nasopharyngeal microbiome in pediatrics are based primarily on molecular genetic approaches, among which 16S rRNA sequencing occupies a central place due to the possibility of a

culture-free analysis of the taxonomic composition of microbial communities and the identification of age and environmental features of colonization in children [29-31]. The use of this method has allowed a number of authors, including Dzidic M. and co-authors [32, 33], to demonstrate that early exposure to antibiotics has a long-term effect on the formation of the respiratory microbiome, which must be taken into account in the clinical interpretation of data in pediatric patients. At the same time, 16S rRNA sequencing has methodological limitations related to insufficient resolution at the species level and lack of information on the functional activity of microorganisms, which reduces the accuracy of interpreting the results in a clinical context [34-37].

In this regard, metagenomic sequencing is becoming increasingly used, which makes it possible to assess not only the structure of nasopharyngeal microbial communities, but also their metabolic potential, as well as their interaction with environmental factors. So, in the research of Boniardi L. and co-authors [38] have shown that exposure to atmospheric pollutants in early childhood leads to functional shifts in the microbiome of the nasal cavity, which are not always detected using exclusively taxonomic analysis. To visually represent the sequence of stages of microbiome research in pediatrics, the work uses a scheme reflecting the process of selecting clinical material, choosing an analytical method (16S rRNA sequencing or metagenomics), bioinformatic data processing and their clinical interpretation. This scheme makes it possible to trace the relationship between the methodological approach and the results obtained, as well as to emphasize the limitations of each stage of the study [39]. In general, an analysis of modern publications shows that a correct assessment of the nasopharyngeal microbiome in children is possible only with an integrated approach combining the use of various molecular methods and their interpretation based on clinical data.

### **PROSPECTS FOR PERSONALIZED THERAPY OF ENT DISEASES IN CHILDREN, TAKING INTO ACCOUNT THE MICROBIOME**

Current data show that the nasopharyngeal microbiome in children is formed under the influence of many factors of early age and plays a significant role in the course and recurrence of ENT diseases, which justifies the need to switch to personalized therapeutic approaches [40-42]. The high frequency of antibiotic use in pediatric practice, on the one hand, remains an important treatment tool, and on the other hand, it contributes to the disruption of microbial balance and colonization of opportunistic microorganisms, which requires more rational and reasonable use [43-46]. The results of microbiome studies performed using 16S rRNA sequencing demonstrate differences in the composition of the nasopharyngeal microbiota in children depending on recent antibiotic therapy and emphasize its effect on the risk of otopathogen persistence [38]. Against this background, probiotics are considered as a potential component of personalized therapy aimed at restoring microbial balance and indirectly modulating the immune response of the mucous membrane. Experimental and clinical data indicate that the interaction of various components of the microbiome, including bacterial and fungal communities, can form heterogeneous inflammatory reactions, which is important for the individual selection of therapeutic tactics.

The use of microbiomic markers also opens up prospects for predicting colonization by resistant pathogens and optimizing antibacterial therapy in children with severe or recurrent ENT pathology [47]. Thus, microbiome-based therapy involves an integrated approach, including the balanced administration of antibiotics, the use of probiotics, and consideration of the functional activity of microbial communities. To clearly summarize these provisions and their practical application, the main recommendations for personalized therapy are presented in table 2, where they are systematized taking into account the clinical significance and possible limitations in pediatric otorhinolaryngological practice.

**Table 2: The main recommendations for personalized therapy of ENT diseases in children, taking into account the microbiome**

The therapeutic approach	Microbiome rationale	Expected clinical effect	Restrictions and comments
Rational use of antibiotics	Reduction of antibiotic-induced nasopharyngeal dysbiosis	Reduction of relapses and colonization by pathobionts	Requires strict clinical indications
Probiotic therapy	Support for microbial diversity and immune homeostasis	Reducing the incidence of upper respiratory tract infections	The effect is strain- and age-dependent
Microbiome-oriented monitoring	Identification of dysbiosis patterns	Personalization of treatment tactics	Limited availability of methods
Prevention of repeated courses of antibiotics	Prevention of breeding of resistant microorganisms	Stabilization of the nasopharyngeal microbiome	Requires an interdisciplinary approach
Correction of environmental factors	Reducing the negative environmental impact on the microbiome	Maintaining a stable microbial profile	Difficulties in controlling factors

Comprehensive personalized strategy	Integration of microbiome and clinical data	Long-term improvement of treatment outcomes	More research is needed
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The recommendations presented in Table 2 summarize the main approaches to personalized therapy of ENT diseases in children, taking into account the microbiome, systematizing them by clinical significance, expected effect, and possible limitations of use in pediatric otorhinolaryngological practice. However, a number of aspects of microbiome-based treatment remain poorly understood and require further clinical and experimental studies.

## CONCLUSION

The analysis of the literature shows that the nasopharyngeal microbiome plays a significant role in the formation of chronic and recurrent ENT diseases in children and affects the features of their clinical course. Microbiota dysbiosis is considered not only as a consequence of the inflammatory process, but also as an independent pathogenetic factor that supports chronic inflammation and a tendency to relapse. The interaction of the microbiome with innate and adaptive immunity determines the balance between the inflammatory response and immune tolerance in childhood. Modern molecular research methods expand the possibilities of studying the microbiome, but their clinical application requires careful interpretation and standardization. In general, the presented data emphasize the prospects of personalized therapy of ENT diseases in children, taking into account the microbiome, while a number of issues remain open and require further clinical and experimental research.

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#### **Contribution of the authors**

The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

**Conflict of interests.** The authors declare that there is no conflict of interest