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Significance of microbiota in treatment, prevention and rehabilitation of patients with diseases of internal organs in residents of the Tyumen region and the extreme north

368

Importancia de la microbiota en el tratamiento, prevención y rehabilitación de pacientes con enfermedades de órganos internos en residentes de la región de Tyumen y el extremo norte.

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Abstract

This literature review summarizes the results of the assessment of the survey of microbial associations of upper respiratory tract systems in residents of the Tyumen Oblast and the Far North of different age groups. The features of upper respiratory tract biotopes: nasal and oral cavities are characterized. And also the retrospective analysis of diagnostics of treatment and rehabilitation of healthy residents of the above-mentioned regions and patients with various cardiovascular diseases, respiratory diseases and musculoskeletal system was carried out.

The oral micro biota represents an exceptional large ecosystem and is considered the most accessible for scientific research. Modern sources speak about the essential role of opportunistic microorganisms: Staphylococcus aureus and Pseudomonas aeruginosa, in the

occurrence of various infectious diseases and complications. The study of human oral cavity, description of its species composition allows one to trace the interaction of micro- and macro-organism to understand the mechanisms of impact of microorganisms, as well as their metabolites on the formation of unhealthy conditions and the human body as a whole. This review article provides a description of the human upper respiratory tract microbiome. Including a great attention is paid to complications associated with cardiovascular pathology, pathology of the respiratory system, urinary system, which may arise due to disturbance of the balance of the microbiome in the human body.

The results of the study prove the significance of studying the relationship between the microbiota of the oral and nasal cavities and the risk of upper respiratory tract

infections and cardiovascular complications, which makes it possible to correct treatment and increase rehabilitation potential.

Keywords: micro biome, oral cavity, upper respiratory tract, acute tonsillitis, cardiovascular diseases, Staphylococcus aureus, Pseudomonas aeruginosa.

Resumen

Esta revisión de la literatura resume los resultados de la evaluación del estudio de las asociaciones microbianas de los sistemas del tracto respiratorio superior en residentes de la Región de Tyumen y el Extremo Norte de diferentes grupos de edad. Las características de los biotopos del tracto respiratorio superior: se caracterizan las cavidades nasales y orales. También se llevó a cabo el análisis retrospectivo del diagnóstico del tratamiento y la rehabilitación de los residentes sanos de las regiones antes mencionadas y de los pacientes con diversas enfermedades cardiovasculares, respiratorias y del sistema musculoesquelético.

La microbiota oral representa un gran ecosistema excepcional y se considera el más accesible para la investigación científica. Las fuentes modernas hablan del papel esencial de los microorganismos oportunistas: Staphylococcus aureus y Pseudomonas aeruginosa, en la aparición de diversas enfermedades infecciosas y complicaciones. El estudio de la cavidad bucal humana, la descripción de su composición de especies permite rastrear la interacción de los microorganismos y macroorganismos, comprender los mecanismos de influencia de los microorganismos, así como sus metabolitos, en la formación de condiciones no saludables y en el cuerpo humano como un todo. Este artículo de revisión proporciona una descripción del microbioma del tracto respiratorio superior humano. Se presta gran atención a las complicaciones asociadas con patología cardiovascular, patología del sistema respiratorio y del sistema urinario, que pueden surgir debido a una alteración del equilibrio del microbioma en el cuerpo humano.

Los resultados del estudio demuestran la importancia de estudiar la relación entre la microbiota de las cavidades bucal y nasal y el riesgo de infecciones del tracto respiratorio superior y complicaciones cardiovasculares, lo que permite corregir el tratamiento y aumentar el potencial de rehabilitación.

Palabras clave: microbioma, cavidad bucal, tracto respiratorio superior, amigdalitis aguda, enfermedades cardiovasculares, Staphylococcus aureus, Pseudomonas aeruginosa.

Introducción

The micro biota of the upper respiratory tract in healthy adults is much less well understood. It has been suggested that the micro biota may be one of the factors influencing the development of infection, worsening or improving the course of the disease¹.

In the scientific literature, there is insufficient information on the study of micro biota in the inhabitants of the Far North, as well as in the immigrant population living for more than 5 years, who have undergone long-term adaptation to its extreme conditions². Given the relevance of studying the relationship between the intestinal micro biota, considered as a separate organ of the human body, there is a need for this study to identify the role in the health of the indigenous population and people coming to live permanently in the Far North. Also, these studies should be conducted to detail and systematize the features of micro biota in people living in different climatic geographical zones of Russia³.

Currently, special attention is paid to the treatment and rehabilitation of diseases caused by the most common opportunistic microorganisms such as Pseudomonas aeruginosa, Staphylococcus aureus and Streptococaceae. Pseudomonas aeruginosa is an opportunistic pathogenic microorganism (APM) that causes lesions only when the immune system response is reduced^{4,7}.

Staphylococcus aureus can normally live for years on the skin, mucous membranes and in the intestines without causing harm. Thus, the bacterium permanently lives in the nasopharynx of about 20% of people, episodically - in 60%. But in stressful situations - when immunity is reduced, after trauma or surgery - Staphylococcus aureus can cause staphylococcal infection^{6,18}.

Streptococcus aureus is a UPM that normally inhabits human mucous membranes and skin, and is constantly present in the oral cavity, nasopharynx, large intestine, and vagina⁸.

The multisystem and clinical diversity of symptoms of synehaemia infection is reflected in the number of complications of this condition. The most frequent negative consequences include generalization of the infectious process, infectious-toxic shock, necrotizing colitis, abscessing, gangrenous changes, sluggish course of infection in the mucous membranes of the ear, oropharynx, nose, conjunctiva, formation of meso tympanitis, bronchiectasis, creeping corneal ulcer, partial or complete deafness, unilateral blindness⁹.

Staphylococcal infection manifests itself depending on the organ affected. It manifests as folliculitis, boils, carbuncles, scalded skin syndrome, tonsillitis, bronchitis,

pneumonia, pleurisy, otitis media, arthritis, meningitis, endocarditis.

B-haemolytic group A streptococcus (BHSGA) often affects the upper respiratory tract. Diseases associated with Streptococcaceae are divided into primary (otorhinolaryngeal diseases, as well as skin lesions) and secondary (glomerulonephritis)^{9,10}.

Today, many patients undergo therapy every year to avoid recurrence of the infectious process. Treatment is aimed at strengthening the immune system. And also the main task is to reduce the risks of complications associated with diseases of the cardiovascular system, respiratory system¹¹.

In view of the fact that the active infectious process has a direct impact on the course of the patient's CVD, contributing to their exacerbation.

We would like to consider in more detail several diseases that are currently included in the list of topical infections.

Acute tonsillitis, an infectious disease that can be caused by viruses of single-stranded, double-stranded DNA, single-stranded RNA. Streptococcus pyogenes is considered the most common causative agents. The route of transmission of the virus is airborne. Autoinfection through normal oral flora is also possible^{12,13}.

The occurrence of recurrent episodes of sore throat with minor complaints suggests recurrent acute tonsillitis (RAT). One of the popular complications of ROT is considered to be tonsil fibrosis and peritonsillitis¹⁵.

Beta-haemolytic group A streptococcus (BHSA) can cause infections of the respiratory system (pneumonia, empyema), cardiovascular system (endocarditis), lymphatic system (lymphangitis, lymphadenitis), and urinary system (acute glomerulonephritis)¹⁶.

Community-acquired pneumonia (CAP) is an acute lung lesion of infectious-inflammatory nature. The causative agents of pneumonia can include: Streptococcaceae, Streptococcus pneumoniae, Staphylococcaceae, Klebsiella pneumoniae, Haemophilus influenzae, Legionellaceae, Herpesviridae, Influenza Virus and Parainfluenzae. Complications of pneumonia are divided into pulmonary (obstructive syndrome, abscess, lung gangrene) and extrapulmonary (endocarditis, myocarditis, meningitis, glomerulonephritis)¹⁶.

It is necessary to dwell on an extremely important and relevant block: study of oral microbiota, analysis of antibiotic resistance, selection of antibiotic therapy. To competently determine the complex of treatment and rehabilitation measures for patients with somatic diseases, it is necessary to study in detail the morphology and properties of microorganisms, including the determination of antibiotic sensitivity, as well as to take into account the symbiotic approach in the context of macro- and microorganisms^{18,19,20}.

Materials and methods

The Russian and foreign literature in PubMed, Web of Science for the last 5 years was analyzed, using analytical, statistical, comparative methods of research, analysis of case histories and outpatient records of residents of the Tyumen region and the Far North.

Results

To date, a wealth of data has been presented on the interaction between the microbiota and its host in vivo. A huge amount of research is devoted to the role of microbial associations in the pathogenesis of infectious diseases of the human oral cavity, such as caries and periodontitis, while the influence of microorganisms on the development of other diseases remains almost unexplored.

The microbiota of the oral cavity is anatomically and physiologically the initial section of the gastrointestinal tract (digestive conveyor belt) and the entrance gate that determines the colonization resistance and development of the microcosm of other biotopes of the digestive and bronchopulmonary systems. Previous studies have shown that the oral and gut micro biota of healthy individuals share a number of interdependent common features. The oral micro biota reflects the state of the microflora of the entire gastrointestinal tract and can be used for a comprehensive assessment of the gastrointestinal microflora at the stage of preventive evaluation.

Today, there is no doubt that the microflora of the gastrointestinal tract, and in particular of the oral cavity, is a vast spectrum of microorganisms that contains bacteria, protozoa, fungi and viruses. The relationship between bacteria and viruses in the oral cavity is mainly the subject of investigation in infectious diseases, but the qualitative and quantitative parameters of the viral component of the microflora in healthy individuals are hardly ever established.

The human upper respiratory tract is formed by several different anatomical niches, different in the level and form of contact with the external environment, as well as in the level of oxygenation, which affects the com-

position of the taxonomic micro biota. Such anatomical structures include: nasal vestibule, nasal cavity, which includes 3 nasal passages, as well as paranasal sinuses, nasopharynx and oropharynx. Some microorganisms are common to all anatomical structures, in general it is typical for them to be differentiated by levels.

Of the entire human upper respiratory system, the nasal vestibule has the maximum contact with the external environment. The nasal vestibule contains vibrissae, which form a hair net that stops large ($>3 \mu\text{m}$) particles, as well as serous and sebaceous glands. The skin fat absorbed by the glands causes colonization by lipophilic bacteria such as *Staphylococcus*, *Cutibacterium* and *Corynebacterium*, which are able to convert skin fats to short-chain fatty acids.

Additional factors that cause *Corynebacterium* and *Staphylococcus aureus* to multiply are an oxygen-enriched environment and humidity.

An oxygen-enriched environment and high humidity are ancillary causes that promote the increase of *Corynebacterium* and *Staphylococcus aureus*.

The nasal cavity warms and humidifies the inhaled air.

The nasal cavity is lined with mucus (mucin), its function is to trap microparticles that have not been trapped in the nasal vestibule.

There are few nutrients in the nasal mucosa; also, the presence of organic acids and inorganic salts does not favor the growth of microorganisms.

Bacteria of the Actinobacteria type, especially *Corynebacterium* and *Cutibacterium*, are most abundant in the nasal cavity. Most of these bacteria are symbionts. Species of the genus *Corynebacterium* are associated with constancy of the nasal cavity microbiome and reduced possibility of infections in children. At the same time, species of the genus *Cutibacterium* (formerly *Propionibacterium*) are often found in the nasal cavity of adolescents, in particular *C. acnes*, which is considered a factor in acne. It is also most represented in the nasal cavity of adults^{14,22}.

The nasal cavity is largely inhabited by archaea of the genus *Methanosphaera* and *Methanobrevibacter*, which are seen in the human gut, and *Nitrososphaera*, most commonly found on the skin. The paranasal sinuses are lined by the mesenteric epithelium. Their function is to moisten and warm the inhaled air. The paranasal sinuses were thought to be normally sterile. Studies have been carried out to identify microbial taxa in the sinuses of healthy people, namely a number of species specifically - a number of species belonging to the order Lactobacillales-*Lactobacillus sakei*, *Carnobacterium alterfunditum*, *Enterococcus mundtii* and *Pediococcus pentosaceus*²¹.

In the nasopharynx, humidified and warmed air follows into the lungs. Consequently, in the nasopharynx there are microorganisms found in the vestibule of the nose and nasal cavity - bacteria of the genus *Staphylococcus*, *Dolosigranulum*, *Corynebacterium*, *Streptococcus* and others.

According to one study, 4 types of microbial profiles are distinguished depending on the dominance of a particular genus of microorganism *Streptococcus*, *Fusobacterium* or *Moraxella*, as well as a mixed type²³.

The literature suggests that the oropharynx is the main source of microorganisms inhabiting the lower respiratory tract.

Based on the available data, it is concluded that some bacteria (e.g. *Corynebacterium ssp.*) are found in all parts of the upper respiratory tract. However, it is possible to distinguish species that are found only in some sections. The diversity of the micro biota increases from the nasal vestibule to the oropharynx.

Therapy of patients with bacterial diseases caused by the above-described microorganisms is complicated by the high prevalence of opportunistic microorganisms with resistance to ABP, up to polybiotic resistance, the difficulty of proper selection of antibiotic therapy regimens and the emergence of secondary complications that reduce the effectiveness of treatment, as a consequence reducing the rehabilitation potential, which leads to a longer period of recovery of the patient.

When choosing the treatment of pneumonia, timely detection and treatment of concomitant diseases is important.

In the conclusion of the analysis of the development of upper respiratory tract diseases, it is necessary to focus on monitoring the effectiveness of drug treatment and the timeliness of the beginning of the stage of the complex of rehabilitation measures, including increased physical activity. In case of incorrect selection of antibiotic therapy and non-compliance with doctor's recommendations, patients may develop the following complications: cardiovascular diseases (endocarditis), respiratory tract organs (pneumonia), urinary system (glomerulonephritis).

An important step is the study of antibiotic sensitivity and the properties of the oral and nasal micro biota to determine effective therapy. Treatment adjustments with antibiotic prescription are required for proper effective treatment and rehabilitation measures.

The importance of the micro biome for human health is now generally recognized. It plays an essential role in human defense against pathogenic microbes and in the functioning of the immune system. A great diversity of micro biome in healthy people has been found. Disturbance of the balance of the microbiological environment has an impact on the progression of various human pathological conditions.

Research on the microbiome in Russian inhabitants, including its northern territories, is insufficient. Large domestic studies are needed to clarify the nature of the micro biome in people living in harsh climatic conditions.

The detailed characterization of micro biome features and mechanisms of influence on human health in the Far North will contribute to solving important and priority problems of developing technologies for health saving and increasing the life expectancy of the population in these conditions.

The results of the study prove the importance of studying the relationship of oral and nasal cavity micro biota with the risk of upper respiratory tract infectious diseases and cardiovascular complications, which allows to correct the treatment and increase the rehabilitation potential.

It is necessary to correct the micro biota of the oral cavity towards the prevalence of representatives of normobiotics, including the use of probiotic preparations. They can become an additional means of prevention and medical treatment of a number of diseases, as well as increase the adaptive capacity of a person in the extreme conditions of the Far North environment.

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References

1. Starikova E.V., Galeeva Y.C., Ilyina E.N.. The role of the upper respiratory tract microbiome in human health: biotopes and variability. *Pulmonology*. 2022; 32 (5): 745-754
2. Oral cavity microbiota and its role in the formation of the human microbiome (literature review) / A. M. Samoukina, Y. A. Alekseeva, O. A. Gavrilova, M. V. Nasonova // *Modern Dentistry: from tradition to innovation: proceedings of the international scientific-practical conference, Tver, 15-16 November 2018* / Edited by M. N. Kalinkin, B. N. Davydov, O. A. Gavrilova, I. A. Zhmakin, K. B. Bakanov. - Tver: State budgetary educational institution of higher professional education Tver State Medical Academy of the Ministry of Health of the Russian Federation, 2018. - C. 336-340.
3. General microbiology and microbiota of the oral cavity: Testbook / M. I. Zaslavskaya, T. V. Makhrova, N. I. Ignatova [et al.]. - Nizhny Novgorod: Publishing House of the Privolzhsky Research Medical University, 2021. - 92 p.
4. Detection of carriage of antibiotic-resistant strains of nasopharyngeal biotope biotope in patients of planned surgical profile / K. A. Voronin, D. S. Solovyova, M. S. Mezhakova, O. A. Malyugina // *Week of Youth Science - 2024: proceedings of the All-Russian scientific forum with international participation, dedicated to the 300th anniversary of the Russian Academy of Sciences, Tyumen, 30 March 2024*. - Tyumen: LLC 'Pechatnik', 2024. - C. 239. - EDN ALWGAG.
5. Mezhakova, M. S. Analysis of antibacterial properties of Bifidobacterium vifidum supernatant against staphylococcus aureus 928, staphylococcus aureus 25923 / M. S. Mezhakova // *Week of Youth Science - 2023: proceedings of the All-Russian scientific forum with international participation, dedicated to the 60th anniversary of the Tyumen State Medical University, Tyumen, 23-25 March 2023*. - Tyumen: RIC 'Iveks', 2023. - C. 236-237. - EDN YYTOTR.
6. Characterisation of intermicrobial interactions of Gram-positive and Gram-negative associative microbiota on the example of the association of Pseudomonas aeruginosa c Bifidobacterium bifidum and Staphylococcus aureus / V. V. Leonov, L. V. Leonova, T. N. Sokolova [et al.] // *Medical Science and Education of the Urals*. - 2016. - T. 17, № 2(86). - C. 91-94. - EDN WDEGWH.
7. Morin CD, Déziel E, Gauthier J, Levesque RC, Lau GW. An Organ System-Based Synopsis of Pseudomonas aeruginosa Virulence. *Virulence*. 2021 Dec;12(1):1469-1507. doi: 10.1080/21505594.2021.1926408. PMID: 34180343; PMCID: PMC8237970..
8. Guntinas-Lichius O, Geißler K, Mäkitie AA, Ronen O, Bradley PJ, Rinaldo A, Takes RP, Ferlito A. Treatment of recurrent acute tonsillitis-a systematic review and clinical practice recommendations. *Front Surg*. 2023 Oct 10;10:1221932. doi: 10.3389/fsurg.2023.1221932. PMID: 37881239; PMCID: PMC10597714..
9. Sidell D, Shapiro NL. Acute tonsillitis. *Infect Disord Drug Targets*. 2012 Aug;12(4):271-6. doi: 10.2174/187152612801319230. PMID: 22338587.
10. Klemens A, Brunner FX. Differenzialdiagnose der akuten Tonsillitis. Stippchen, Fibrinbeläge oder einseitige Schwellung? [Acute tonsillitis]. *MMW Fortschr Med*. 2008 Oct 16;150(42):44-5. German. doi: 10.1007/BF03365623. PMID: 18985909.
11. Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. *Indian J Pediatr*. 2001 Dec;68(12):1135-8. doi: 10.1007/BF02722930. PMID: 11838568; PMCID: PMC7091368.
12. Munck H, Jørgensen AW, Klug TE. Antibiotics for recurrent acute pharyngo-tonsillitis: systematic review. *Eur J Clin Microbiol Infect*

- Dis. 2018 Jul;37(7):1221-1230. doi: 10.1007/s10096-018-3245-3. Epub 2018 Apr 13. PMID: 29651614.
13. Houborg HI, Klug TE. Quality of life after tonsillectomy in adult patients with recurrent acute tonsillitis: a systematic review. *Eur Arch Otorhinolaryngol.* 2022 Jun;279(6):2753-2764. doi: 10.1007/s00405-022-07260-7. Epub 2022 Jan 19. PMID: 35044507.
 14. Sih TM, Bricks LF. Optimizing the management of the main acute infections in pediatric ORL: tonsillitis, sinusitis, otitis media. *Braz J Otorhinolaryngol.* 2008 Sep-Oct;74(5):755-762. doi: 10.1016/S1808-8694(15)31387-2. PMID: 19082359; PMCID: PMC7110967.
 15. Barros RR. Antimicrobial Resistance among Beta-Hemolytic Streptococcus in Brazil: An Overview. *Antibiotics (Basel).* 2021 Aug 12;10(8):973. doi: 10.3390/antibiotics10080973. PMID: 34439023; PMCID: PMC8388994.
 16. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. *Med Clin North Am.* 2019 May;103(3):487-501. doi: 10.1016/j.mcna.2018.12.008. Epub 2019 Mar 7. PMID: 30955516.
 17. Zhou Y., Mihindikulasuriya K.A., Gao H. et al. Exploration of bacterial community classes in major human habitats. *Genome Biol.* 2014; 15 (5)
 18. Koskinen K., Reichert J.L., Hoier S. et al. The nasal microbiome mirrors and potentially shapes olfactory function. *Sci. Rep.* 2018; 8 (1): 1296.
 19. Tizzano M., Gulbransen B.D., Vandenbeuch A. et al. Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. *Proc. Natl. Acad. Sci. USA.* 2010; 107 (7): 3210–3215.
 20. Lemon K.P., Klepac-Ceraj V., Schiffer H.K. et al. Comparative analyses of the bacterial microbiota of the human nostril and oropharynx. *mBio.* 2010; 1 (3)
 21. Ta L.D.H., Yap G.C., Tay C.J.X. et al. Establishment of the nasal microbiota in the first 18 months of life: Correlation with early-onset rhinitis and wheezing. *J. Allergy Clin. Immunol.* 2018; 142 (1): 86–95.
 22. Ramakrishnan V.R., Feazel L.M., Gitomer S.A. et al. The microbiome of the middle meatus in healthy adults. *PLoS One.* 2013; 8 (12): e85507.
 23. Abou-Hamad W., Matar N., Elias M. et al. Bacterial flora in normal adult maxillary sinuses. *Am. J. Rhinol. Allergy.* 2009; 23 (3): 261–263.