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# ASSESSED CORRELATION BETWEEN BIOLOGICAL DIVERSITY OF OROPHARYNGEAL MICROBIOTA AND ATOPIC DERMATITIS SEVERITY AND EXACERBATIONS

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# ОЦЕНКА КОРРЕЛЯЦИИ БИОЛОГИЧЕСКОГО РАЗНООБРАЗИЯ МИКРОБИОТЫ РОТОГЛОТКИ СО СТЕПЕНЬЮ ТЯЖЕСТИ И ЧАСТОТОЙ ОБОСТРЕНИЙ У ПАЦИЕНТОВ С АТОПИЧЕСКИМ ДЕРМАТИТОМ

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**Abstract**

Atopic dermatitis (AtD) is a multifactorial inflammatory skin disease characterized by itching, chronic recurrent course and age–related features of lesions. AtD pathogenesis has not been fully elucidated yet. An important factor for AtD emergence and progression is the imbalance in symbiotic microbiota. The research publications provide a few studies about a role for oropharyngeal microorganisms in AtD immunopathogenesis. The aim of the study is to analyze biological diversity of oropharyngeal microbial communities in varying AtD severity. 97 male patients, aged from 16 to 19 years, with different AtD severity were included in the study. Culture study of oropharyngeal discharge was also performed. Biological material was seeded on the expanded list of growth media and incubated for 5 days at the 37°C. To assess the biological diversity of the oropharyngeal microbiota, the coefficient of constancy (C) was used, in order to classify individual microorganisms as permanent, additional or transient. Statistical data processing was performed using the Stat Tech software (version 4.0.0, Stattech LLC, Russia). While examining biological diversity of the oropharyngeal microbiota in AtD patients, 58 microbial species were isolated and identified. After statistical analysis the significant differences in frequency of isolation, depending on different AtD severity were observed for microbes such as *Streptococcus vestibularis* and *Rothia dentocariosa*. When *R. dentocariosa* is isolated from the oropharynx, the chances of AtD exacerbation emergence decreased by 6 times, whereas in case of *S. vestibularis*, on the contrary, it increased by 5 times. Therefore, identification of transitions of individual microbes from transient to additional and permanent microbiota and vice versa, depending on the AtD stage and severity, allows to analyze an influence of specific microorganisms in AtD pathological processes and to establish definite new microbiological predictors of AtD exacerbation and remission.


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**Keywords:** atopic dermatitis, oropharyngeal microbiota, biological diversity, skin diseases, immunological disorders, microbiome.


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**Резюме**

Атопический дерматит (АтД) - многофакторное воспалительное заболевание кожи, характеризующееся зудом, хроническим рецидивирующим течением и различными возрастными особенностями. Патогенез АтД еще полностью не выяснен. Важным фактором возникновения и прогрессирования АтД является дисбаланс симбиотической микробиоты. Научная литература содержит небольшое количество информации об участии микроорганизмов ротоглотки в иммунопатогенезе АтД. Цель исследования - провести анализ биологического разнообразия микробных сообществ ротоглотки в группах пациентов с различной степенью тяжести АтД и на разных стадиях АтД (ремиссия/обострение). В исследование были включены 97 пациентов с различной степенью тяжести АтД. Также было проведено культуральное исследование выделений из ротоглотки. Посев материала проводили на расширенный перечень питательных сред и инкубировали при температуре 37°С в течение 5 суток. Для оценки биологического разнообразия микробиоты ротоглотки использовался коэффициент постоянства (С), позволяющий классифицировать отдельные микроорганизмы как постоянные, дополнительные или временные. Статистические расчёты проводились с использованием программного обеспечения StatTech (версия 4.0.0, разработчик ООО "Статтех", Россия). В ходе исследования у включенных пациентов было выделено и идентифицировано 58 видов микроорганизмов. В ходе статистического анализа были получены значимые различия в частоте выделения, в зависимости от различной степени тяжести АтД, для таких микроорганизмов, как *Streptococcus vestibularis* и *Rothia dentocariosa*. При выделении *R. dentocariosa* из ротоглотки вероятность возникновения обострения АтД снижалась в 6 раз. При выделении *S. vestibularis* вероятность возникновения обострения АтД, в отличие от *R. dentocariosa*, увеличивалась в 5 раз. Таким образом, выявление переходов отдельных микроорганизмов от транзиторной к дополнительной и постоянной микробиоте и наоборот, в

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зависимости от стадии и тяжести АтД, позволяет нам проанализировать влияние определенных микроорганизмов на патологические процессы при АтД и установить предпосылки для открытия новых микробиологические предикторов обострения и ремиссии АтД.

**Ключевые слова:** атопический дерматит, микробиота ротоглотки, биологическое разнообразие, кожные болезни, иммунологические нарушения, микробиом.


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## 1 Introduction

Atopic dermatitis (AtD) is a multifactorial inflammatory skin disease characterized by itching, chronic recurrent course and age–related features of skin lesions. This is one of the most common skin diseases (from 20% to 40% in the structure of this group), emerging in all countries, mainly in young people of both genders. The prevalence of AtD in Europe has amounted to 15.6%, in the USA – 17.2%, in Japan – 24%, in Russia – 30-35%, reflecting the steady increase in the frequency of AtD detection over the past three decades [20, 28, 29].

The pathogenesis of AtD has not been fully elucidated yet. Presumably, several factors might be the initiators of the inflammatory processes. One of such factors is hereditary determinism, leading to a violation of the skin barrier, defects in the immune system, hypersensitivity to allergens and non-specific stimuli, colonization by pathogenic microorganisms, and also to an imbalance of the autonomic nervous system with increased production of inflammatory mediators [3, 13].

According to the clinical recommendations of the American Academy of Allergy, Asthma, and Immunology (AAAAI), AtD is a chronic inflammatory process of the skin that emerges due to a genetic malfunction, under the influence of external factors , a violation of the skin barrier and a defect in the immune defense [19].

Recent scientific data increasingly indicate that cytokines play one of the main roles in the AtD pathogenesis. In particular, much attention is paid to the proinflammatory cytokines of the IL-36 subfamily: IL-36a, IL-36β and IL-36y and their receptor antagonist IL-36Ra. These molecules are produced by keratinocytes, Langerhans cells and macrophages and they serve as activators of the innate and acquired defense systems [22, 32].

Another important factor contributing to the emergence and progression of AtD is the imbalance of the symbiotic microbiota of the human body [2, 27].


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As a rule, most researches, dedicated to relations between microorganisms and allergic or autoimmune diseases, mainly concentrate on the microbiota of the skin or intestines. At the same time, microbial communities of the upper respiratory tract remain ignored. These anatomical structures are the most diverse and plastic in the composition of the microbiome. The qualitative characteristics of the microbiota in them varies depending on the biotope (nasal cavity, nasopharynx and oropharynx) [5, 10].

Microbiota of the oropharynx is especially interesting in the context of our topic, as it is the most abundant and diverse biotope. The surface of the tonsils is characterized by a particularly high microbial diversity.

The scientific literature provides a certain amount of information about the participation of microorganisms in the immunopathological processes. However, only a small part of data on the involvement of individual oropharyngeal species in the immunopathogenesis of AtD. This fact requires a more detailed further study of the microbial diversity of the upper respiratory tract in patients with varying AtD severity degrees.

Although much is known about the diagnosis and severity assessment of AtD, there are too many ambiguous points about this disease. Additional knowledge about the pathogenesis is needed in order to introduce different biomarkers into practical work for more accurate diagnosis and monitoring of patients' condition. This requires an integrated approach to the problem of AtD, which will take into account various aspects of the pathogenesis of this disease.

Aim of the study is to analyze the biological diversity of oropharyngeal microbial communities in groups of patients at different stages of AtD in order to identify certain microbiological predictors.

## Materials and methods

The study included 97 male AtD patients, aged from 16 to 19. 15 of them had remission, 82 had an exacerbation of varying severity (22 – mild, 53 – moderate and


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7 - severe). Only patients with no exacerbations of other chronic diseases were included.

The semi-quantitative SCORAD (Scoring of Atopic Dermatitis) scale was used to assess the severity of the skin pathological process. The SCORAD scale provides a score assessment of six objective symptoms: erythema, edema/papular elements, crusts/weeping, excoriation, peeling, dry skin.

Atopic dermatitis of mild severity corresponds to a SCORAD value <25, moderate severity - 25-50, and severe atopic dermatitis corresponds to a SCORAD value >50.

A smear was taken from the walls of the oropharynx for cultural examination with a sterile cotton swab. In a tube with a liquid transport medium, the material was delivered to a bacteriological laboratory. The material was seeded on the following growth media: universal chromogenic agar (HiMedia, India), 5% blood agar with mutton blood (HiMedia, India), chocolate agar (HiMedia, India), selective media for the isolation of lactobacilli (HiMedia, India), bifidobacteria (HiMedia, India), clostridium (HiMedia, India), obligate anaerobes (HiMedia, India), veilonella (HiMedia, India), non-fermenting Gram-negative bacteria (HiMedia, India), enterobacteria (HiMedia, India), Saburo agar (HiMedia, India).

The preparation of the material for seeding was carried out by homogenizing it in a liquid Ames growth medium (GEM LLC, Russia), followed by spreading 100 μl of the final suspension on the surface of each growth medium.

Media were incubated in aerobic, microaerophilic (using a $CO_2$ incubator (Sanyo, Japan) and anaerobic conditions (using gas-generating packages (Anaerogaz, Russia), at a temperature of 37 ° C for 5 days.

Colonies of all grown microorganisms were identified using the MALDI-ToF mass spectrometry on the Microflex LT device (Bruker, Germany) by direct application and extended application with the use of formic acid. During identification, the obtained spectra of microorganisms were compared with the database of the Bruker Daltonik GmbH standard library. The accuracy of

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identification was assessed automatically using the MALDI Biotyper RTC software according to the level of the coincidence coefficient (Score) from 0 to 3. The level of 0.000-1.699 was regarded as the result of low-confidence identification, the level of Score from 1.700 to 1.999 was considered as identification on the level of genus; highly reliable identification to the species level was accepted at Score values of 2,000-2.999.

To assess the biological diversity of the oropharyngeal microbiota, the coefficient of constancy (C) was used. According to this assessment, microorganisms were considered as participants of permanent, additional or transient microbiota.

In the case of isolation of individual microorganisms from more than 50% of patients, this microorganism was regarded as permanent. The isolation from patients in the range of 25-50% corresponded to an additional microbiota, isolation less than in 25% of cases corresponded to transient microbiota. Coefficient was calculated using the following formula:

$$C=(p*100)/P$$

In which p – number of isolations of individual microorganisms, P – total number of isolations.

Accumulation, correction, systematization of the obtained data and visualization of the results were carried out in Microsoft Office Excel 2016 spreadsheets. Statistical calculations were performed using the Stat Tech software (version 4.0.0, Stattech LLC, Russia).

A predictive model, reflecting the dependence of a quantitative variable on factors, was created using the linear regression method. The construction of a predictive model of the possibility of a certain outcome was performed using the logistic regression method. The Nigelkirk coefficient $R^2$ served as a measure of certainty, indicating the part of the variance that can be explained using logistic regression.

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For assessment of the diagnostic significance of quantitative signs, during predicting a certain outcome, the ROC curve analysis method was used. The dividing value of the quantitative feature at the cut-off point was determined by the highest value of the Yuden index.

**Results**

During examination of the biological diversity of the oropharyngeal microbiota in AtD patients, 58 species of microorganisms were isolated and identified.

To assess the contribution of different species to biological diversity, for each microbe the coefficient of constancy was calculated in three groups of patients with different severity and in patients with remission.

Microbes of additional and permanent oropharyngeal microbiota are shown in Figure 1.

The only species that can be classified as permanent for AtD patients with all severity degrees was *Neiserria subflava*, which was isolated in 50.9-73.3% of the examined individuals. For the rest of the microbes, three types of patterns were identified: an increase of the coefficient of constancy with the transition from transient to additional and permanent microbiota along with increase of AtD severity (*Streptococcus vestibularis*, *Streptococcus mitis, Actinomyces oris, Rothia mucilaginosa)*; a decrease of the coefficient of constancy with transition to transient species along with increase of AtD severity (*Streptococcus salivarius, Streptococcus parasanguinis, Streptococcus oralis, Staphylococcus aureus, Rothia dentocariosa)*; the absence of significant changes in the coefficient of constancy depending on the AtD severity (*Neisseria flavescens)*.

For individual microorganisms of the first and second groups, significant differences in frequency of isolation were obtained depending on the stage of AtD (remission or exacerbation) (Table 1).


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The isolation of *S. vestibularis* was significantly more often in the group of patients with exacerbations of AtD, whereas *S. oralis* and *R. dentocariosa* were more often isolated in patients with remission.

Above written data, on the one hand, shows the possibilities of the culture method in assessing the biological diversity of the oropharyngeal microbiota. On the other hand, it opens up opportunities for searching for new potential microbial markers that determine the severity of AtD.

The species of microorganisms, which were isolated from the oropharynx with statistically significant differences between patients with different stages and severity degrees of AtD, were also considered as potential microbiological predictors.

To predict the emergence of AtD exacerbation, mathematical models were created, which were characterized by a higher quality of the prognostic test. These models included such microbiological criteria as the isolation of *R. dentocariosa* and *S. vestibularis* from the oropharynx.

For *R. dentocariosa*, the dependence with AtD stage is described by the equation:

$$P = 1 / (1 + e^{-z}) \times 100\%$$

$$z = 1{,}83 - 1{,}83 \times R.d.$$

in which P – possibility of AtD exacerbation, *R.d.*– isolation of *R. dentocariosa* from oropharynx (0 – not isolated, 1 – isolated).

Created regression model is statistically significant (p=0.013). When *R. dentocariosa* is isolated from the oropharynx, the chances of AtD exacerbation emergence decreased by 6 times, which is shown in Figure 2.

For *S. vestibularis*, the observed dependence is described by the equation:

$$P = 1 / (1 + e^{-z}) \times 100\%$$

$$z = 1{,}07 + 1{,}6 \times S.v.$$

in which P – possibility of AtD exacerbation, *S.v.* – isolation of *S. vestibularis* from oropharynx (0 – not isolated, 1 – isolated).


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Created regression model is statistically significant (p=0.021). When isolating *S. vestibularis*, the chances of AtD exacerbation emergence, in opposite to *R. dentocariosa*, increased by 5 times, which is shown in Figure 3.

Depending on the isolation of *S. vestibularis* from the oropharynx, a prognostic model has also been developed to determine the possibility of emergence of moderate AtD by binary logistic regression. The observed dependence is described by the equation:

$$P = 1 / (1 + e^{-z}) \times 100\%$$

$$z = 0{,}39 + 1{,}73 \times S.v.$$

in which P – possibility of emergence of AtD with moderate severity, *S.v.* – isolation of *S. vestibularis* from oropharynx (0 – not isolated, 1 – isolated).

Created regression model is statistically significant (p = 0.004). In the presence of *S. vestibularis* in the oropharynx, the chances of emergence of AtD of moderate severity increased in 5.7 times, which is shown in Table 2.

**Discussion**

The microbiota of the oropharynx is divided into permanent, additional, and transient groups. As an example, *Streptococcus* spp. is a part of the permanent microbiota; coagulase-negative staphylococci, *Corynebacterium* spp., *Haemophilus influenzae* - additional microbiota (25-50% of people); *Enterobacteriacae*, *Pseudomonas* spp., *Moraxella* spp., *Micrococcus* spp. represent a transient group (5-20% of people). The main flora of the tonsils consists of such microorganisms as: *Staphylococcus* spp. (44.3%) and *Streptococcus* spp. (40.2%) [9].

The structure of oropharyngeal microbiota depends on the factors of the pathogenicity of the commensals and on the nature of the interaction between microorganisms and biotope, colonized by them. The published studies show that *Staphylococcus* spp. and *Aerococcus* spp. are most likely to increase virulent properties, and that an indifferent process is detected in the microbiota of a healthy human body, when pathogenic commensals are stabilized by the eubiosis of the tonsils of a healthy person [16].

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In our study, we identified significant variations in the species composition of the oropharyngeal microbiota. This fact allows us to think about its possible functional connection with the emergence of atopic dermatitis. In addition, the question arises whether changes in the microbiota and pathological processes in AtD are interdependent, or is modified microbiocenosis a consequence of AtD?

Most of the studies, dedicated to relations between microorganisms and AtD, focus on the skin or intestinal microbiota. The most common theory about the influence of the human microbiome on the emergence of AtD is associated with the dysbiosis in these loci, which in turn leads to the emergence of inflammatory processes. Defects of the skin and intestinal barrier occur, which leads to the leakage of different bacterial toxins and metabolites into the systemic bloodstream. Among these harmful factors there are such as lipopolysaccharides, metabolic products of tryptophan and serotonin, which can cause immunological dysfunctions [23, 31].

Significant number of researches concentrate on *S. aureus*, the number of which increases significantly in the areas of skin lesions during AtD. As a rule, this is associated with a reduced amount of an important structural skin protein - phyllagrin [12, 17]. On the contrary, some authors consider the predominance of *S. aureus* not only as a consequence of AtD. It is believed that its presence may have a direct connection with the emergence of immunological disorders, especially through the induction of synthesis of such factors as IL-31 and IL-33 [11]. Moreover, increased expression of these molecules is not always associated with the death of epithelial cells – it is associated with the direct presence of *S. aureus* at the locus [6]. It is noteworthy that in our study, with an increase in the severity of AtD, the coefficient of constancy of *S. aureus* in the oropharynx decreased on the contrary.

The oropharyngeal locus is often not paid with enough attention from researchers when studying AtD. And this is despite the fact that, on the one hand, the oropharynx is one of the most microbial-populated biotopes in the human body, and on the other hand, individual oropharyngeal microorganisms are very often associated with other immunological (including allergic ones) disorders [14, 21, 30].

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Perhaps this is due to the close relationship between the microbiota and the immune system, mediated by colonization of the tonsils. Especially interesting is that tonsils are normally colonized by such clinically important microbes in the context of AtD as *Staphylococcus* spp. and *Streptococcus* spp.

Only individual attempts have been made to assess the biological diversity of oropharyngeal microorganisms in relation to the AtD. In some early studies, there was information about a direct correlation between the cutaneous and oropharyngeal microbiota in patients with AtD [4]. Later, targeted studies were conducted to compare the colonization of tonsils, affected and unaffected skin by *S. aureus*, but the difference in results was almost not analyzed [7]. Beheshti et al. [8] conducted a molecular genetic examination of patients with AtD. However, saliva was used as the material, not smears or scrapings, and in addition, the study was linked only to the total load of microbial RNAs and a correlation was found only with a large group of bacteria – *Proteobacteria*.

The most interesting correlations with the stages of AtD in our study were found for *Streptococcus* spp. Scientific works, which investigate the skin microbiota, provided information about a decrease in the number of these microorganisms in the species structure in AtD patients [17]. On the contrary, studies of the correlation between the intestinal microbiota and AtD associate the *Streptococcus* spp. with the onset and progression of this disease [18, 26]. In our study, controversial correlations were established for individual microbes from this genus. Summarizing all the information provided, it is possible to indicate a heterogeneous immunological effect of *Streptococcus* spp.

Regarding the effect of *R. dentocariosa* (which in our study was correlated with a more favorable course of the disease) on the emergence of AtD, no scientific publications were found.

Many allergic diseases are characterized by a pathogenetic relation with the microbiota and the presence of certain microbiological predictors. In the context of AtD, this is the above mentioned increase of *S. aureus* in the composition of the skin

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microbiota. The intestinal microbiota in AtD, in addition to the already described role of *Streptococcus* spp., is characterized by an increased contribution to the species structure from various opportunistic flora (*Parabacteroides* spp., *Clostridium difficile*, *Escherichia coli*) and a decrease in the number of *Lactobacillus* spp. and *Bifidobacterium* spp. [1, 15].

The oropharyngeal microbiota so far lacks microorganisms that could definitely be called predictors of AtD, or predictors of exacerbation or remission. Therefore, the patterns identified in our study should be further analyzed, and the search for such correlations should be continued.

**Conclusion**

Therefore, we have identified significant correlations between the various stages of AtD and the frequency of isolation of individual oropharyngeal microorganisms. Taking into account our data, as well as data on the possible influence of oropharyngeal flora on various immunological processes, we believe that it is necessary to continue work in this direction in order to identify additional microbiological predictors of AtD and its exacerbations. Moreover, studies with a larger studied groups are needed, including a comparison of the microbial diversity between different loci and a deeper analysis of their differences, as well as taking into account various clinical and laboratory parameters, including the level of interleukin expression.


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## ТАБЛИЦЫ

**Table 1.** Analyzed frequency of AtD stage-related isolation for individual oropharyngeal microorganisms.

| Species | Result of culture study | AtD stage | | p |
|---|---|---|---|---|
| | | Remission abs. (%) | Exacerbation abs. (%) | |
| *S. vestibularis* | Isolated | 2 (13,3) | 36 (43,9) | 0,039* |
| | Not isolated | 13 (86,7) | 46 (56,1) | |
| *S. oralis* | Isolated | 6 (40,0) | 13 (15,9) | 0,042* |
| | Not isolated | 9 (60,0) | 69 (84,1) | |
| *R. dentocariosa* | Isolated | 5 (33,3) | 6 (7,4) | 0,016* |
| | Not isolated | 10 (66,7) | 76 (92,6) | |

abs. – absolute number; * – significant differences at $p<0,05$


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**Table 2.** Features of correlation between *S. vestibularis* isolation and odds for AtD moderate emergence.

| Predictors | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | COR; 95% CI | p | AOR; 95% CI | p |
| Isolation of *Streptococcus vestibularis* from oropharynx | 5,655; 1,493 – 21,413 | 0,011* | 5,655; 1,493 – 21,413 | 0,011* |

* – significant predictor's influence (p≤0,05); CI – confidence interval; Unadjusted – odds ratio is unadjusted; Adjusted – odds ratio is adjusted; COR – crude odds ratio (rough odds ratio), i.e. the odds ratio calculated for one of the factors without taking into account the influence of other factors; AOR – adjusted odds ratio (corrected odds ratio), i.e. odds ratio calculated for one of the factors, taking into account the influence of other factors.


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## РИСУНКИ

**Figure 1.** AtD severity-driven Species diversity for permanent and additional oropharyngeal microbiota.

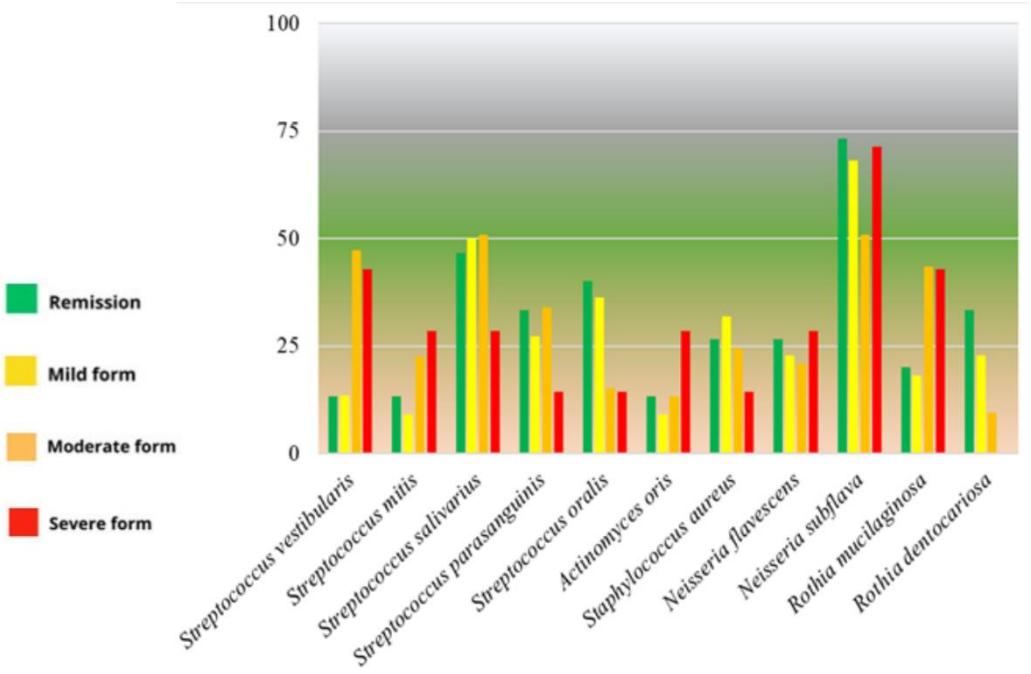



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**Figure 2.** Assessed odds ratio with 95% confidence intervals for isolation of oropharyngeal *R. dentocariosa* as a predictor of emerging AtD exacerbation.

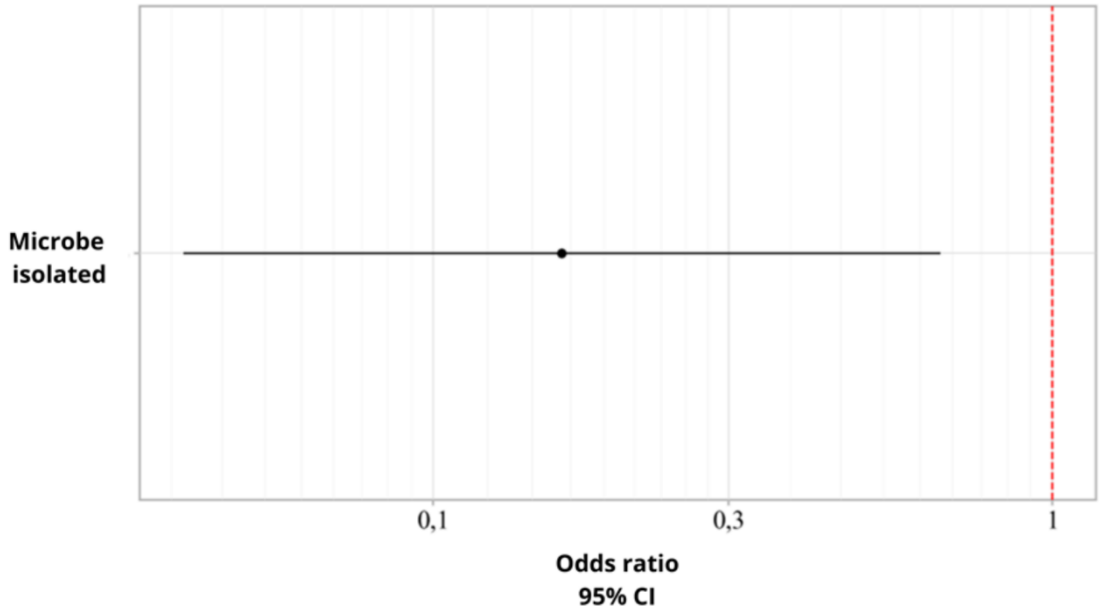



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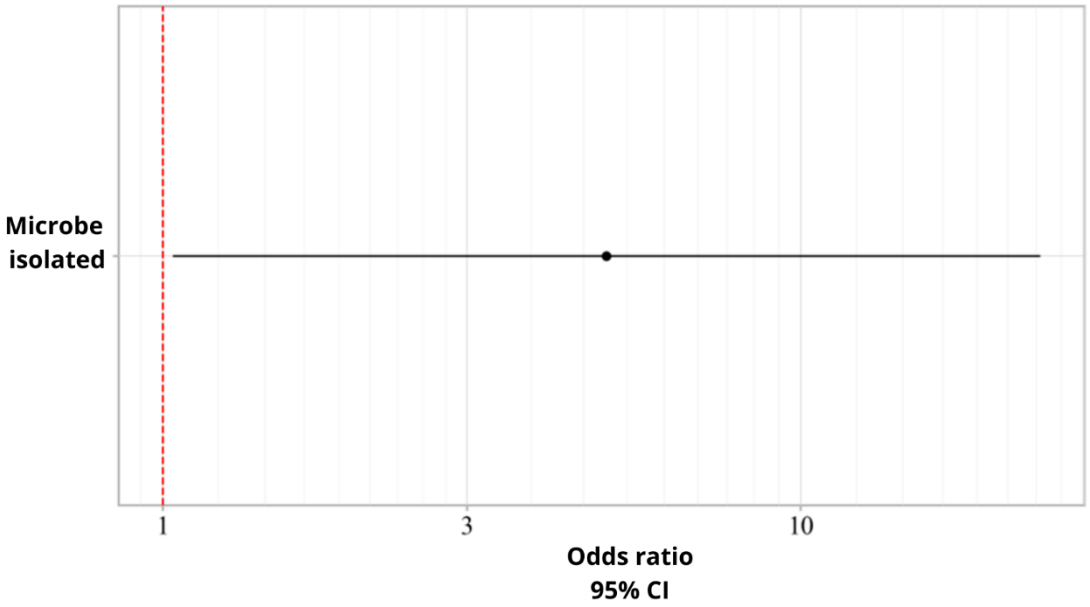
**Figure 3.** Assessed odds ratio with 95% confidence intervals for isolation of oropharyngeal *S. vestibularis* as a predictor of emerging AtD exacerbation.





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# ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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**Блок 3. Метаданные статьи**

ASSESSMENT OF CORRELATION OF BIOLOGICAL DIVERSITY OF OROPHARYNGEAL MICROBIOTA WITH SEVERITY AND EXACERBATIONS IN PATIENTS WITH ATOPIC DERMATITIS

ОЦЕНКА КОРРЕЛЯЦИИ БИОЛОГИЧЕСКОГО РАЗНООБРАЗИЯ МИКРОБИОТЫ РОТОГЛОТКИ СО СТЕПЕНЬЮ ТЯЖЕСТИ И ЧАСТОТОЙ ОБОСТРЕНИЙ У ПАЦИЕНТОВ С АТОПИЧЕСКИМ ДЕРМАТИТОМ

**ASSESSED CORRELATION BETWEEN BIOLOGICAL DIVERSITY OF OROPHARYNGEAL MICROBIOTA AND ATOPIC DERMATITIS SEVERITY AND EXACERBATIONS**

**Сокращенное название статьи для верхнего колонтитула:**

МИКРОБИОТА РОТОГЛОТКИ У ПАЦИЕНТОВ С АТОПИЧЕСКИМ ДЕРМАТИТОМ

OROPHARYNGEAL MICROBIOTA IN PATIENTS WITH ATOPIC DERMATITIS

**Ключевые слова:** атопический дерматит, микробиота ротоглотки, биологическое разнообразие, кожные болезни, иммунологические нарушения, микробиом.

**Keywords:** atopic dermatitis, oropharyngeal microbiota, biological diversity, skin diseases, immunological disorders, microbiome.

Оригинальные статьи.

Количество страниц текста – 11, количество таблиц – 2, количество рисунков – 3.

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| Порядковый номер ссылки | Авторы, название публикации и источника, где она опубликована, выходные данные | ФИО, название публикации и источника на английском | Полный интернет-адрес (URL) цитируемой статьи и/или DOI |
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