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Intestinal microbiota in children with bronchial asthma

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ABSTRACT

Background. Intestinal microbiota is one of the most important factors determining the state of human health, including its influence on the immunological mechanisms regulating the development of allergic diseases in childhood. The role of intestinal microbiota and the gut – lung axis in the development of bronchial asthma (BA) is an important area of research.

Aim. To analyze the taxonomic composition of intestinal microbiota in children with BA using 16S rRNA gene sequencing.

Materials and methods. The study included patients with BA ($n = 50$, mean age 10.34 ± 2.99 years) and a group of apparently healthy individuals ($n = 49$, mean age 10.3 ± 2.8 years). For all patients, medical history was taken, and physical examination and stool test were performed. Patients with BA were assessed for the level of total and specific immunoglobulin (Ig) E and underwent spirometry. The microbiota composition was analyzed by 16S rRNA gene sequencing with subsequent bioinformatic and statistical analysis.

Results. Significant differences in the composition of the intestinal microbiota (beta diversity) and a decrease in taxonomic diversity (alpha diversity) were found in patients with BA compared to healthy controls. The intestinal microbiota of patients with BA was characterized by an increase in the abundance of *Bacteroides*, *Parabacteroides*, *Lachnospira*, *Roseburia*, *Akkermansia*, *Anaerostipes*, *Sutterella*, *Odoribacter*, *Phascolarctobacterium*, *Butyrivimonas*, as well as unclassified bacteria from the Rikenellaceae families. The intestinal microbiota of children without BA was characterized by greater abundance of bacteria from *Blautia*, *Bifidobacterium*, *Dorea*, *Ruminococcus*, *Streptococcus*, *Eubacterium*, *Acinetobacter*, *Collinsella*, *Lactococcus*, *Catenibacterium* genera and unclassified bacteria from the Clostridiaceae and Coriobacteriaceae families. Significant differences in the quantitative abundance of bacteria were revealed depending on the type of sensitization, the level of total IgE, and the value of FEV1.

Conclusion. The results obtained indicate the differences in the intestinal microbiota composition in children with BA and healthy children.

Keywords: intestinal microbiota, bronchial asthma, 16S rRNA gene sequencing, children

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. Patients over 15 years of age signed an informed consent to participate in the study, for children aged 7–14, an informed consent was obtained from their legally authorized representatives. The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 8946 of 24.01.2022).

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Микробиота кишечника у детей, больных бронхиальной астмой

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РЕЗЮМЕ

Введение. Микробиота кишечника является одним из важнейших факторов, определяющих состояние здоровья человека, в том числе оказывает влияние на иммунологические механизмы развития аллергических болезней в детском возрасте. Роль микробиоты кишечника и оси «кишечник – легкие» в развитии и течении бронхиальной астмы (БА) является актуальной областью исследований.

Цель – провести анализ таксономического состава кишечной микробиоты у детей с БА с использованием метода секвенирования 16S рРНК.

Материалы и методы. В исследование включены пациенты, страдающие БА ($n = 50$, средний возраст $10,34 \pm 2,99$) и группа условно здоровых детей ($n = 49$, средний возраст $10,3 \pm 2,8$). Для всех участников выполнен сбор анамнеза и физикальное обследование, сбор образцов стула. Пациентам с БА проводилась оценка уровня общего и специфического иммуноглобулина (Ig) Е и спирометрия (измерение объема форсированного выдоха за первую секунду (ОФВ₁)). Определение состава микробиоты выполнено с помощью секвенирования гена 16S рРНК с последующим биоинформатическим и статистическим анализом.

Результаты. Установлены значимые различия в составе микробиоты кишечника (бета-разнообразие) и снижение таксономического богатства (альфа-разнообразие) у пациентов с БА в сравнении с детьми без БА. У пациентов с БА увеличена представленность бактерий родов *Bacteroides*, *Parabacteroides*, *Lachnospira*, *Roseburia*, *Akkermansia*, *Anaerostipes*, *Sutterella*, *Odoribacter*, *Phascolarctobacterium*, *Butyrivibrio*, а также неклассифицированные бактерии семейств Rikenellaceae. Кишечная микробиота детей, не страдающих БА, характеризовалась более высоким содержанием бактерий родов *Blautia*, *Bifidobacterium*, *Dorea*, *Ruminococcus*, *Streptococcus*, *Eubacterium*, *Acinetobacter*, *Collinsella*, *Lactococcus*, *Catenibacterium* и неклассифицированные бактерии семейств Clostridiaceae, Coriobacteriaceae. Выявлены значимые отличия в количественной представленности бактерий в зависимости от вида сенситизации, уровня общего иммуноглобулина IgE и значения ОФВ₁.

Заключение. Полученные результаты свидетельствуют о различиях состава микробиоты кишечника детей, страдающих БА, и условно здоровых детей.

Ключевые слова: кишечная микробиота, бронхиальная астма, секвенирование 16S рРНК, дети

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Информированное согласие на участие в исследовании дети старше 15 лет подписывали самостоятельно, для детей 7–14 лет – законные представители. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 8946 от 24.01.2022).

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INTRODUCTION

Bronchial asthma (BA) is a multifactorial chronic respiratory disease that affects more than 250 million people of different ages worldwide [1]. Currently, BA remains a serious public health problem, which is associated with high prevalence, a significant decrease in the quality of life of patients and their families, and significant economic burden to the healthcare system [2]. In this regard, it is relevant to study the pathogenetic factors in the development of BA to elaborate new preventive technologies based on personalized medicine, which is of vital importance in pediatrics.

In recent years, a lot of data have demonstrated an association between the development of BA and the composition of respiratory microbiota in childhood [3–5]. However, in chronic lung diseases, respiratory microbiota changes, and an imbalance in the composition of intestinal microbiota is also noted. Molecular genetic methods for identifying microorganisms have expanded our understanding of the gut microbiome and contributed to the recognition that microbial communities influence host physiology beyond the gastrointestinal tract. According to the concept of the gut – lung axis, the gut microbiome has significant effects on immune regulation and lung function [6, 7].

Circulation through the circulatory and lymphatic systems transports regulatory cytokines and bacterial metabolites, such as short-chain fatty acids (SCFA), to the lungs, where they participate in immune and anti-inflammatory responses, thereby connecting the gut – lung axis [8]. The results of experimental and epidemiological studies demonstrate that the formation of the intestinal microbiota at an early age plays a significant role in the development of BA [9–11]. However, most studies on microbiota in childhood asthma are aimed at investigating a correlation between the composition of bacterial communities in early life and the risk of developing the disease in adulthood. In the Russian Federation, research on the intestinal and oropharyngeal microbiota in BA in adult population was carried out using molecular genetic methods, demonstrating modification of the microbiome against the background of the disease [12, 13].

The aim of the study was to analyze the taxonomic composition of intestinal microbiota in children with BA using 16S rRNA gene sequencing.

MATERIALS AND METHODS

A cross-sectional, case-control study included 50 children with BA and 49 apparently healthy children without acute or chronic diseases. Patients with BA were recruited at the Children's Clinic of Siberian State Medical University in Tomsk. Data from a sample of healthy participants from a previous epidemiological study were used as a control group [14].

Criteria for inclusion in the main group: children aged 7–16 years with persistent BA of mild to moderate severity; forced expiratory volume in 1 second (FEV₁) reversibility of more than 12% from the baseline value according to spirometry; basic therapy with inhaled glucocorticoids at a low daily dose as monotherapy or in combination with long-acting β 2-agonists or leukotriene receptor antagonists within 12 months preceding the study. Criteria for inclusion in the control group: apparently healthy children aged 7–16 years without BA or other chronic diseases. Exclusion criteria for all study groups: intake of antibacterial drugs and systemic glucocorticoids within three months preceding the study; intake of eubiotics and/or intestinal infections within one month before the study; presence of clinically significant conditions or diseases that can prevent patients from participating in the study or affect any manipulations or interpretation of the study results; a lack of a signed informed consent.

All study participants were divided into two groups: patients with BA ($n = 50$, mean age 10.34 ± 2.99 years, the ratio of girls to boys 27 / 23) and a group of apparently healthy individuals ($n = 49$, mean age 10.3 ± 2.8 years, the ratio of girls to boys 21 / 28).

The study included history taking and a physical examination. To assess asthma control, we used the Asthma Control Test for children over 12 years of age and the c-ACT in children from 7 to 11 years of age. Patients with BA were assessed for the level of total and specific immunoglobulin (Ig) E (Alkor Bio, Russia) and underwent spirometry (MasterScreen, Germany). To assess the composition of the intestinal microbiota, stool samples were collected using a special stool collection kit with a transport medium (Stool Collection kit, Nobias Technologies).

Sample preparation and sequencing of the V3-V4 region in the 16S rRNA gene

To extract DNA, the Nobias DNA Extraction Kit was used with an extraction protocol that included

homogenization of the stool sample using the bead beating technique and precipitation of inhibitors. Sequencing of the V3-V4 region in the *16S* rRNA gene (341F-801R primers, Litech LLC, Russia) was carried out on the Illumina MiSeq Sequencing System (Illumina, USA).

Analysis of sequencing data

The composition of the samples was determined using the Knomics – Biota platform [15] and QIIME algorithms [16]. Rare and underrepresented bacteria (those that were found in less than half of the samples and did not account for more than 5% in any sample) were excluded from the analysis. The nearest balance method was used to analyze the differences between the groups [17].

The taxonomic abundance and α -diversity were assessed using the Chao1 and Shannon indices after rarefaction to 5000 reads. The Mann – Whitney test was used for statistical analysis. The correlation analysis was carried out using the Spearman's rank correlation coefficient.

Beta-diversity was assessed using the Aitchison distance (after excluding rare microbes) and the Bray – Curtis dissimilarity (after rarefaction to 5000 reads per sample). The PERMANOVA method was used for statistical analysis [18]. Qualitative variables were presented as absolute or relative (%) frequencies. Normally distributed quantitative variables were presented as the mean and the standard deviation $M \pm m$. Quantitative variables with non-normal distribution were presented as the median and the interquartile range $Me (Q_{25}; Q_{75})$. The differences were considered to be statistically significant at $p < 0.05$.

RESULTS

The ACT test revealed that 52% of patients had a well-controlled course of asthma (ACT score ≥ 20), while 48% of patients had the ACT score of 19 or less (20 (18; 24)). According to the laboratory tests, the total IgE level of more than 100 IU / ml was detected in 66% of children with BA. The median total IgE level was 293.5 (82.6; 705.8). Sensitization to household allergens was detected in 50% of patients with BA, to pollen – in 52% of children, to epidermal allergens – in 44% of patients with BA, and to food allergens – in 34% of the examined children. According to spirometry findings in patients with BA, the FEV₁ value was 100.7 (88.9; 111.1).

Taxonomic characteristics

The most abundant phyla in the intestinal microbiota of patients with BA were Firmicutes (71.1 $\pm$ 13.9%), Bacteroidetes (20.2 $\pm$ 14.8%), Proteobacteria (3.4 $\pm$ 6%), Verrucomicrobia (1.2 $\pm$ 2.7%), and Actinobacteria (1.1 $\pm$ 0.6%). The intestinal microbiota of children in the control group was dominated by Firmicutes (73.7 $\pm$ 13.6%), Actinobacteria (14.6 $\pm$ 13%), Bacteroidetes (6.1 $\pm$ 8.1%), Proteobacteria (4.7 $\pm$ 5.9%), and Verrucomicrobia (0.4 $\pm$ 0.8%) phyla. The intestinal microbiota of children with BA was characterized by abundance of Ruminococcaceae (50.4 $\pm$ 13%), Bacteroidaceae (13 $\pm$ 9.6%), Clostridiaceae (5.5 $\pm$ 6%), Lachnospiraceae (5.3 $\pm$ 3.5%), and Prevotellaceae (4.4 $\pm$ 12.5%) families. The samples from the control group were characterized by abundance of Lachnospiraceae (30.6 $\pm$ 14%), Ruminococcaceae (16.6 $\pm$ 8.5%), Bifidobacteriaceae (11.3 $\pm$ 12.6%), and Clostridiaceae (4.4 $\pm$ 3.5 %) families. The most abundant bacterial families in the samples of the studied groups are shown in Fig. 1. Each column in the figure refers to one of the samples. Different colors mark proportions of different bacteria in the sample. The figure shows proportions of the 10 most abundant families, the remaining families are marked with the gray color.

The intestinal microbiota of children with BA at the genus level was dominated by Bacteroides (31.6 $\pm$ 12.6%), Prevotella (4.4 $\pm$ 12.5%), and unclassified bacteria from the Ruminococcaceae (16.1 $\pm$ 5.1%) and Clostridiaceae (5.5 $\pm$ 6%) families. The intestinal microbiota in the control group was represented by Blautia (14.4 $\pm$ 9.4%), Bifidobacterium (11.3 $\pm$ 12.6%), and unclassified bacteria from the Lachnospiraceae (11.7 $\pm$ 6.5%), Clostridiaceae (10.6 $\pm$ 5.2%), and Ruminococcaceae (7.4 $\pm$ 4.4%) families.

Assessing the taxonomic diversity of the intestinal microbiota

The assessment of α -diversity using the Shannon index revealed a decrease in microbiota diversity in children with BA compared to the controls (Shannon index: $p < 0.01$; Fig. 2, a). The assessment of the taxonomic abundance using the Chao1 index revealed no significant differences between the groups (Chao1 index: $p = 0.2$, Fig. 2, b).

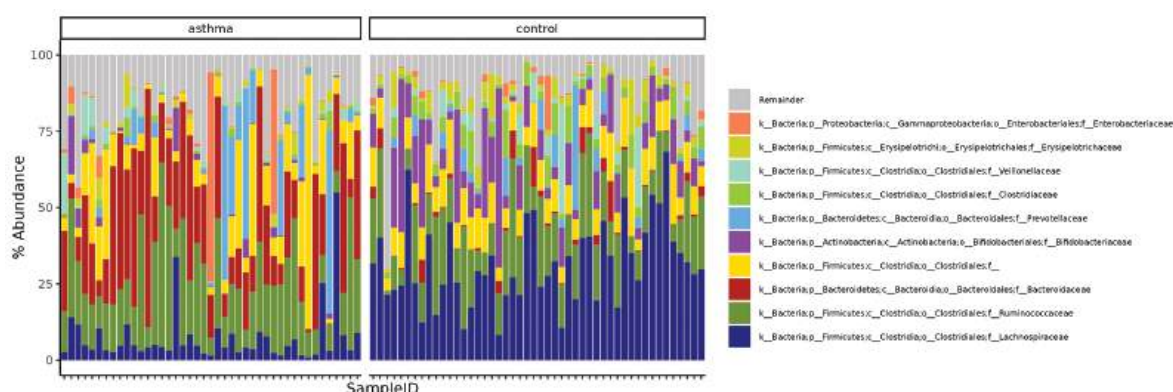


Fig. 1. Taxonomic composition of the intestinal microbiota samples at the family level

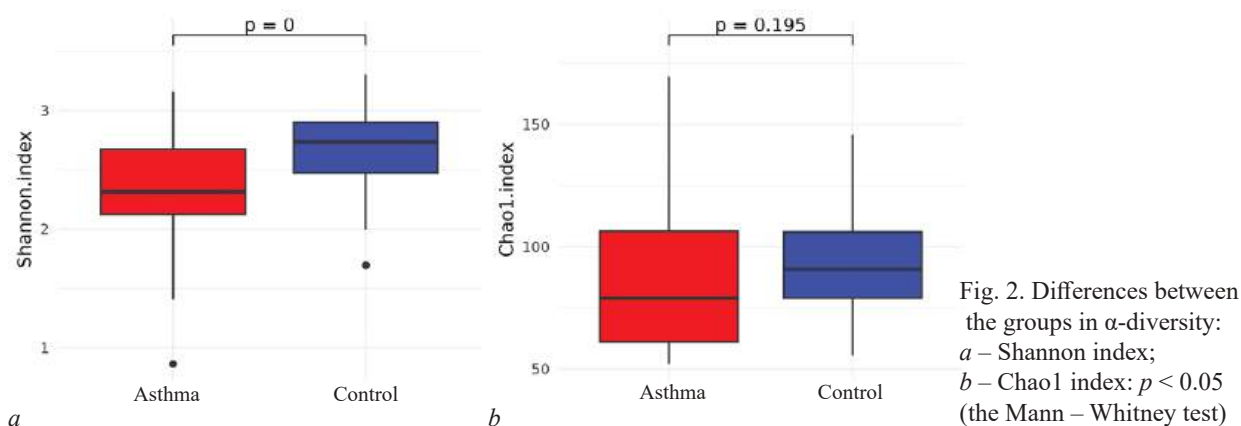


Fig. 2. Differences between the groups in α -diversity: *a* – Shannon index; *b* – Chao1 index; $p < 0.05$ (the Mann – Whitney test)

Beta-diversity of the intestinal microbiota was analyzed using the PERMANOVA method. It revealed significant differences in the microbiota composition between the BA patients and controls (Aitchison distance: $p = 0.001$; Bray – Curtis dissimilarity: $p =$

0.001). Fig. 3 visualizes these differences using the principal coordinate analysis (PCoA). Each point in the figure corresponds to a sample, and the difference between them indicates β -diversity: the closer the points, the more similar their composition is.

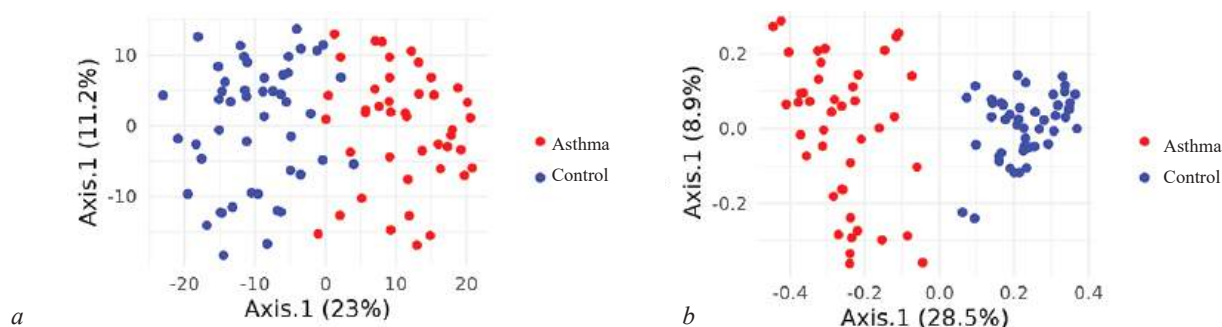


Fig. 3. Visualization of the differences between the samples using the PCoA: *a* – Aitchison distance, which assesses similarity of proportions of prevailing bacteria; *b* – Bray – Curtis dissimilarity, which takes into account the proportions of all bacteria.

Features of intestinal microbiota in BA

The comparative analysis of the intestinal microbiota composition in patients with BA and the control group revealed significant differences in the abundance of 29 taxa ($p < 0.05$). The presence of BA was associated with increased abundance of the *Bacteroides*, *Parabacteroides*, *Lachnospira*,

Roseburia, *Akkermansia*, *Anaerostipes*, *Sutterella*, *Odoribacter*, *Phascolarctobacterium*, *Butyricimonas* genera, as well as unclassified bacteria of the Rikenellaceae, Barnesiellaceae, and Peptostreptococcaceae families of the Mollicutes class, Bacteroidales and Streptophyta orders. The intestinal microbiota in children without BA was

characterized by a higher content of bacteria of the *Blautia*, *Bifidobacterium*, *Dorea*, *Ruminococcus*, *Streptococcus*, *Eubacterium*, *Acinetobacter*,

Collinsella, *Lactococcus*, and *Catenibacterium* genera and the Clostridiaceae and Coriobacteriaceae families (Fig. 4).

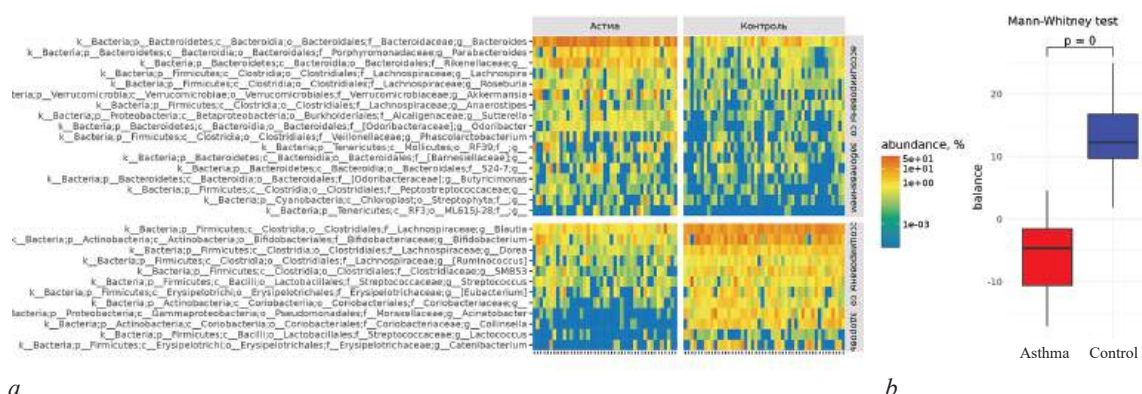


Fig. 4. Differences in the bacterial abundance between patients with asthma and controls: *a* – heatmap showing the abundance of bacteria associated with the presence or absence of the disease, *b* – proportion of bacteria associated with the presence or absence of the disease in the samples obtained from the BA patients and controls (the nearest balance method): each row corresponds to a microorganism, and each column corresponds to a sample; the color of the cell indicates the proportion of bacteria in the sample.

The samples are grouped by the presence of the disease, and microorganisms are grouped by their association with the disease

The comparative assessment of the intestinal microbiota composition was performed in the samples obtained from children with BA depending on the clinical course of the disease, asthma control, the level of total IgE, and sensitization. It was revealed that sensitization to household allergens was associated with an increase in the abundance of the *Peptostreptococcus* genus, and sensitization to epidermal allergens – with increased abundance of the *Bacteroides fragilis* genus. In the intestinal microbiota samples obtained from children with sensitization to food allergens, increased abundance of the *Blautia* genus and a decrease in the *Ruminococcus* and *Dialister* genera were noted. Patients with total IgE levels greater than 100 IU / ml had decreased representation of the *Lachnospira* genus in their intestinal microbiota samples. The correlation analysis revealed a direct correlation of FEV₁ with the abundance of *Bifidobacterium* (0.36; $p = 0.04$), *Streptococcus* (0.39; $p = 0.02$), and *Ruminococcus gnavus* (0.37; $p = 0.03$). There were no significant differences in the taxonomic composition of bacterial communities in patients with ACT scores ≥ 20 and < 20 . The assessment of α - and β -diversity also detected no significant differences between the indices.

DISCUSSION

The intestinal microbiota in patients with BA is characterized by a decrease in the taxonomic diversity, as well as by qualitative and quantitative

changes in the bacterial composition compared to the controls. The taxonomic diversity indicates stability of the microbiota and its resistance to mutations, and a decrease in diversity usually evidences of the presence of a pathological process. Studies have revealed a decrease in the taxonomic diversity of the microbiota in early childhood; such children are subsequently diagnosed with BA [10, 11, 19]. When assessing the taxonomic diversity in children and adults with manifestations of BA, compared to healthy controls, no significant differences in α -diversity were identified [12, 20]. The absence or minimal differences in the taxonomic diversity at an older age suggests that microbial diversity might have a stronger effect on the formation of immunological tolerance and, consequently, the development of BA at an early age [9, 10, 20].

In general, the data obtained in the study groups on the most abundant bacteria at different taxonomic levels are in line with modern ideas about the composition of the intestinal microbiota [21]. We found that the intestinal microbiota composition in children with BA compared to the controls was characterized by a relatively greater abundance of *Bacteroides*, *Parabacteroides*, *Lachnospira*, *Roseburia*, *Akkermansia*, *Anaerostipes*, *Sutterella*, *Odoribacter*, *Phascolarctobacterium*, and *Butyricimonas* and unclassified bacteria of the Rikenellaceae, Barnesiellaceae, and Peptostreptococcaceae families, the Mollicutes class.

Prospective cohort studies showed that an increase in the abundance of *Bacteroides*, *Akkermansia*, *Roseburia*, and *Lachnospira* in the intestinal microbiota of infants, on the contrary, was associated with a decreased risk of developing BA [9, 11].

At the same time, it was shown that at the age of over one year, the differences in the microbiota composition in these cohorts were not significant [9, 11]. Studies revealed the anti-inflammatory potential of these microorganisms and that an increase in their abundance in children with BA might be a compensatory mechanism in response to inflammation of the respiratory mucosa [22]. The study using the Mendelian randomization identified an association between bacteria of the *Butyrivibrio* genus and the development of BA [23]. According to the systematic review, in children with BA, the intestinal microbiota was characterized by an increase in the abundance of *Bacteroides* and a decrease in the abundance of *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Clostridium*, and *Bifidobacterium* [24].

Our study also showed a decrease in the abundance of *Bifidobacterium* in the intestinal microbiota of children with BA compared to the controls. Bacteria of the *Bifidobacterium* genus have an immunomodulatory effect due to stimulation of regulatory T cells [25]. It is suggested that one of the mechanisms mediating interactions within the gut–lung axis is the production of SCFAs by intestinal bacteria [6, 7]. Children with BA are characterized by both an increase (*Anaerostipes*, *Roseburia*, *Phascolarctobacterium*) and a decrease (*Blautia Eubacterium*) in the abundance of SCFA-producing bacteria.

The patients with BA exhibited differences in the quantitative abundance of bacteria depending on the type of sensitization. Studies aimed at assessing microbiota and sensitization to various allergens are scarce. It was shown that sensitization to pet allergens in children with BA was associated with lower diversity of nasal microbiota and *Corynebacterium* sp. and *Staphylococcus epidermidis* compared to children without sensitization [26]. Another study found that the presence of *Ruminococcus* was positively associated with sensitization to casein [27].

CONCLUSION

Following the conducted study, we established that the intestinal microbiota in children with BA is characterized by the decreased taxonomic diversity and differs in the bacterial composition from the

microbiota of apparently healthy children. A number of significant differences in the abundance of bacteria were revealed depending on the type of sensitization and functional parameters of children in BA.

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Sokolova T.S. – conception and design, carrying out of experiments, analysis and interpretation of the data, drafting of the manuscript. Malchuk V.N. – collection and processing of the material, carrying out of experiments, drafting of the manuscript. Fedorova O.S. – conception and design, critical revision of the manuscript for important intellectual content, final approval of the article for publication. Kulenich V.V. – statistical processing of the research results. Odintsova V.E., Koshechkin S.I. – bioinformatic analysis and processing of the research results.

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