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The Role of Intestinal Microbiota in the Development of Severe Wheezing Syndrome in Children with Acute Bronchitis

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Abstract **Background:** The intestinal microbiota is a key component in maintaining homeostasis and immune protection. Disruption of its normal composition reduces local enteral immunity, suppresses cytokine and antibody production, and increases the risk of infections and allergic reactions. **Objective:** To assess the role of intestinal microbiota in the development and severity of wheezing syndrome in children with acute bronchitis. **Methods:** A total of 150 children aged 1–3 years were examined: 120 with acute bronchitis and wheezing syndrome (ABWS) (33 mild, 51 moderate, 36 severe), 30 with acute bronchitis without wheezing, and 20 healthy controls. Intestinal microbiota composition was analyzed by standard bacteriological methods. Statistical significance was determined at $P<0.05$, $P<0.01$, and $P<0.001$. **Results:** Children with ABWS demonstrated significant dysbiotic changes. Counts of bifidobacteria and lactobacilli were markedly decreased ($P<0.001$), while opportunistic microorganisms (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus*, *Candida* spp.) were significantly increased ($P<0.01$–0.001). The degree of microbial imbalance correlated directly with the severity of wheezing. **Conclusion:** Intestinal dysbiosis contributes to the pathogenesis and severity of wheezing syndrome in children with acute bronchitis. Probiotic therapy aimed at restoring intestinal microbiota may improve disease outcomes and should be considered in treatment strategies.

Keywords Intestinal microbiota, Dysbiosis, Acute bronchitis, Wheezing, Children

1. Introduction

One of the unique systems ensuring the stability of the internal environment of the human body is the intestinal microbiota. Disturbance of its normal composition leads to a decrease in local enteral defense, caused by reduced levels of lysozyme in secretions and low concentrations of the secretory component of IgA. As a result, suppression of the immunological function of the normal microbiota leads to decreased B-lymphocyte blast transformation, impaired antibody formation, and inhibition of α-interferon, interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α) synthesis, which increases the incidence of allergic and autoimmune reactions [1,2].

Consequently, any alteration in the composition of the intestinal microbiota sharply reduces the body's anti-infectious resistance and modifies the immune response to bacterial, food, and drug antigens. In some cases, activation of the virulence mechanisms of commensal microorganisms may occur, allowing them to acquire pathogenic properties that aggravate the underlying disease [3,4].

Previous studies have shown that approximately 59% of patients with recurrent bronchitis demonstrate intestinal dysbiosis characterized by a decrease in bifidobacteria and *Escherichia coli* with normal enzymatic activity, along with the appearance of hemolytic *Staphylococcus*, *Proteus*, and increased numbers of *Candida* species. Alterations in intestinal microbiota have been observed in 88.6% of young children with respiratory diseases and in 94.5% of those with recurrent bronchitis [4,5].

Despite the wide prevalence of bronchitis and numerous publications devoted to various aspects of acute bronchitis with wheezing syndrome in young children, several unresolved issues remain. These include inconsistencies in terminology, unclear etiological factors, the influence of allergic mechanisms, and the lack of consensus regarding its pathogenesis and age-specific development. Moreover, clear differential-diagnostic criteria are absent, and the roles of microelement imbalance, immune dysfunction, and intestinal microbiota disturbances have not been fully elucidated. Currently, there is no unified pathogenetically justified model for the treatment and prevention of this condition [6–14].

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Objective: To study the role of intestinal microbiota in the development of severe wheezing syndrome in children with acute bronchitis.

2. Materials and Methods

The present study included 150 children aged 1–3 years with bronchopulmonary pathology (BPP). Among them, 120 patients were diagnosed **with** acute bronchitis accompanied by wheezing syndrome (ABWS). These 120 children were divided into three groups according to disease severity:

- **Group I:** 33 children with mild ABWS;
- **Group II:** 51 children with moderate ABWS;
- **Group III:** 36 children with severe ABWS.

The comparison group consisted of 30 children with acute bronchitis without wheezing, and the control group included 20 practically healthy children of the same age.

Diagnosis was established based on anamnesis, clinical examination, laboratory findings, radiographic data, functional tests, and immunological assessments.

Microbiological Analysis

Microbiological examination of the intestinal microbiota was performed according to the standards of modern clinical microbiology. The degree of intestinal microbial colonization was evaluated using bacteriological culture methods. Stool samples were inoculated on liquid and agarized nutrient media. The isolated colonies were identified by determining the genus, species, and strain of microorganisms based on their morphological, cultural, enzymatic, and antigenic characteristics.

Statistical Analysis

All microbiological data were processed statistically using a Pentium-IV personal computer **and** Microsoft Office Excel 2016 software package. Four main levels of statistical significance were accepted:

- **High significance:** $P < 0.001$
- **Moderate significance:** $P < 0.01$
- **Low (borderline) significance:** $P < 0.05$
- **Insignificant (non-reliable):** $P > 0.05$

3. Results

To assess the qualitative and quantitative composition of the intestinal microbiota in young children with acute bronchitis accompanied by wheezing syndrome (ABWS), 120 children aged 1 to 3 years were examined. The study was conducted on the first day of hospital admission and again on days 10–14 after the completion of treatment. The **comparison group** included 30 healthy children of the same age and sex.

It is important to note that none of the children received medications prior to the study that could have induced or exacerbated intestinal dysbiosis. Clinical manifestations of intestinal microbiocenosis disorders were observed in the majority of patients (85.71%) and were characterized by symptoms of **dyspeptic syndrome**. Regurgitation occurred in 40% (33.3 ± 4.32), abdominal distention and flatulence in 30% (30.8 ± 4.23), vomiting in 22% (18.3 ± 3.55), stool disorders in 61% (51.2%), and tongue coating in 38% (66.0 ± 4.56%) of children with ABWS.

An analysis of the intestinal microbiota in the acute phase of the disease, depending on the severity of wheezing syndrome, is presented in **Table 1**. Significant qualitative and quantitative disturbances of the intestinal microbiota were identified across all study groups.

Table 1. Intestinal Microbiota Composition in the Acute Phase of Disease in Children with Acute Bronchitis Depending on the Severity of Wheezing Syndrome (M ± m)

Genus and Species of Microorganisms (log CFU/g)	**Healthy Children** (n = 30)	**Group I** (Mild Wheezing Syndrome) (n = 33)	**Group II** (Moderate Wheezing Syndrome) (n = 51)	**Group III** (Severe Wheezing Syndrome) (n = 36)	P	P1	P2
Bifidobacteria	8,27 ±0,10	5,58 ±0,5	3,37 ±0,2	2,72 ±0,2	<0,05	<0,001	<0,001
Lactobacilli	8,37 ±0,1	6,33 ±0,5	3,8 ±0,25	2,14 ±0,12	<0,05	<0,001	<0,001
Escherichia coli (with normal enzymatic activity)	6,77 ±0,2	5,73 ±0,4	5,8 ±0,3	4,72 ±0,3	<0,05	<0,01	<0,01
Conditionally pathogenic microorganisms (*Proteus*, *Klebsiella*, *Enterococcus*, etc.)	2,48 ±0,2	3,1 ±0,3	3,14 ±0,2	4,22 ±0,31	<0,05	<0,01	<0,01
Staphylococcus aureus	0,41 ±0,2	0,8 ±0,1	0,9 ±0,1	1,92 ±0,2	<0,05	<0,01	<0,01
Candida spp.	2,39 ±0,3	2,85 ±0,3	4,02 ±0,3	5,11 ±0,31	<0,05	<0,001	<0,001

Note:
P — significance of differences between groups of children with acute bronchitis and wheezing syndrome (ABWS) and the control group;
P_1 — significance of differences between groups with mild and severe wheezing syndrome;
lg — decimal logarithm, base 10 ($lg_{10}x = x$);
CFU/g — colony-forming units per gram, indicating the number of microbial cells in 1 gram of sample.

In children of **Group I (mild ABWS)**, the number of bifidobacteria during the acute phase was significantly lower — (5.58 ± 0.46) log CFU/g — compared to healthy subjects (8.27 ± 0.10 log CFU/g) ($P < 0.001$). The level of lactobacilli was (6.33 ± 0.50) log CFU/g versus (8.37 ± 0.09 log CFU/g) in the control group ($P < 0.001$). Additionally, quantitative and qualitative alterations were observed in *Escherichia coli* populations, with a significant reduction in total *E. coli* count to (5.73 ± 0.42) log CFU/g compared to (6.77 ± 0.24) log CFU/g in the comparison group ($P < 0.01$).

The composition of **conditionally pathogenic microorganisms (CPM)** in patients with mild ABWS showed an increase in *Candida* species, reaching (2.85 ± 0.29) log CFU/g versus (2.39 ± 0.28) log CFU/g in healthy children ($P < 0.01$). The content of *Staphylococcus aureus* (including hemolytic strains) was (0.8 ± 0.13) log CFU/g compared to (0.41 ± 0.51) log CFU/g in the control group ($P < 0.01$). Furthermore, a statistically significant increase ($P < 0.01$) was observed in the number of conditionally pathogenic bacteria (*Proteus*, *Enterobacter cloacae*, *Citrobacter*, *Klebsiella pneumoniae*, etc.), reaching (3.1 ± 0.25) log CFU/g versus (2.48 ± 0.18) log CFU/g in healthy children.

The analysis of data obtained from children in **Group II (moderate wheezing syndrome)** revealed pronounced dysbiotic changes in the large intestine, manifested by both qualitative and quantitative alterations of the intestinal microbiota.

During the acute phase of the disease, none of the children in this group had a normal level of bifidobacteria (10^8 CFU/g). The mean count was significantly lower—(3.37 ± 0.20) log CFU/g—compared with healthy children ((8.27 ± 0.10) log CFU/g) ($P < 0.001$). Similar changes were observed for lactobacilli, whose count averaged (3.88 ± 0.25) log CFU/g versus (8.37 ± 0.09) log CFU/g in the control group ($P < 0.001$).

All patients in this group demonstrated a statistically significant ($P < 0.001$) decrease in the population of *Escherichia coli*—(5.80 ± 0.30) log CFU/g—compared to healthy children. *Candida* fungi were identified in significantly higher quantities, approximately twice the levels found in controls ($P < 0.01$). The titers of conditionally pathogenic microorganisms (CPM) also increased, reaching (3.14 ± 0.22) log CFU/g compared with (2.48 ± 0.18) log CFU/g in the control group ($P < 0.01$). *Staphylococcus aureus* (including hemolytic forms) was detected in (0.90 ± 0.10) log CFU/g, which was significantly higher than in children without pathology ($P < 0.01$).

The study of the intestinal microbiocenosis in **Group III (severe wheezing syndrome)** revealed marked disturbances in both the qualitative and quantitative composition of aerobic and anaerobic microorganisms. There were pronounced quantitative alterations in the anaerobic flora and a shift in the species profile of conditionally pathogenic microorganisms.

In this group, during the acute phase, the number of bifidobacteria was almost four times lower—(2.72 ± 0.20) log CFU/g—compared with healthy children ((8.27 ± 0.10) log CFU/g) ($P < 0.001$). A similar pattern was observed for lactobacilli, whose concentration decreased to (2.14 ± 0.12) log CFU/g versus (8.37 ± 0.09) log CFU/g in controls ($P < 0.001$).

Furthermore, qualitative and quantitative changes in the *Escherichia coli* population were observed, characterized by a significant reduction in total counts to (4.72 ± 0.30) log CFU/g ($P < 0.05$). The species composition of CPM in this group differed notably from that of healthy individuals. The highest titers were observed for *Candida* species, reaching (5.11 ± 0.31) log CFU/g compared with (2.39 ± 0.28) log CFU/g in controls ($P < 0.01$).

Staphylococcus aureus was detected in (1.92 ± 0.20) log CFU/g, while in the comparison group it was only (0.41 ± 0.51) log CFU/g ($P < 0.01$). In addition, there was a statistically significant increase ($P < 0.01$) in the total count of conditionally pathogenic bacteria to (4.22 ± 0.31) log CFU/g.

4. Conclusions

1. The results of this study demonstrate the presence of both qualitative and quantitative disturbances in the intestinal microbiocenosis of children with acute bronchitis accompanied by wheezing syndrome (ABWS) of varying severity. The majority of patients (85.71%) exhibited clinical manifestations of large intestinal microbiota imbalance in the form of dyspeptic syndrome.
2. Examination of the intestinal microbiota revealed significant qualitative and quantitative alterations across all age groups. These were characterized by a marked reduction in the counts of bifidobacteria ($P < 0.001$), lactobacilli ($P < 0.001$), *Escherichia coli* with normal enzymatic activity ($P < 0.001$), as well as an increase in yeast-like fungi ($P < 0.001$), *Staphylococcus* spp. ($P < 0.01$), and other conditionally pathogenic microorganisms ($P < 0.05$). The detected dysbiotic changes, along with laboratory findings of altered intestinal flora composition during the acute phase of ABWS, indicate the necessity for targeted correction of intestinal microbiota disturbances, particularly through the use of probiotic therapy.
3. As the severity of wheezing syndrome increases, the degree of intestinal dysbiosis also intensifies, with a higher frequency of microbiocenotic disturbances. This correlation is confirmed by statistically significant differences in dysbiosis rates between the studied groups ($P < 0.01$).

Study Limitations

This study has several limitations. First, it was conducted in a single specialized pediatric center, which may limit the generalizability of the findings to broader populations. Second, the sample size was relatively small, which could reduce the statistical power to detect subtle associations between intestinal microbiota composition and clinical severity of wheezing syndrome. Third, the study design did

not include long-term follow-up, preventing assessment of changes in microbiota over time or after treatment. Finally, potential confounding factors such as dietary habits, environmental exposures, and previous antibiotic use were not fully controlled. These limitations should be considered when interpreting the results.

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Authors' Contributions

Kamola Rakhmatillayevna Muratova – study conception and design, patient recruitment, supervision, manuscript drafting.

Furkat Mukhitdinovich Shamsiev – clinical data acquisition, analysis, interpretation, and critical revision of the manuscript.

Nilufar Irgashevna Karimova – microbiological analysis, data interpretation, literature review, manuscript editing.

All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

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