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# Metabolic potential of gut microbiota in helminth infections as a way to achieve bronchial asthma control

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**ABSTRACT**

The aim of the review was to analyze modern experimental studies and clinical trials aimed at assessing metabolic activity of gut microbiota in bronchial asthma (BA) and helminth infections.
Being one of the most common chronic heterogeneous respiratory diseases, bronchial asthma secures its place among global health problems of great socioeconomic importance. In recent years, a lot of data has been accumulated indicating that the state of gut microbiota is an important factor determining the state of human health and affecting immune mechanisms underlying the development of allergic diseases in childhood. Dysbiosis of gut microbiota is due not only to changes in its composition, but also to disturbances in its metabolism. In accordance with the "gut – lung axis" concept, maintaining healthy gut microbiota and correcting its disorders, including strategies aimed at activating synthesis of short-chain fatty acids in the intestine, may become a new way to prevent and treat chronic respiratory diseases in childhood. In turn, experimental and epidemiological studies have shown the immunomodulatory activity of helminths. It is assumed that their impact on the composition and function of gut microbiota is one of the mechanisms by which helminths influence the immune response of the host and the course of BA.

**Keywords:** gut microbiota, helminth infection, short-chain fatty acids, bronchial asthma

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# Метаболический потенциал микробиоты на фоне гельминтной инвазии как инструмент управления бронхиальной астмой

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**РЕЗЮМЕ**

Цель – провести анализ современных экспериментальных и клинических исследований, направленных на оценку метаболической активности микробиоты при бронхиальной астме (БА) и гельминтных инвазиях.

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Бронхиальная астма относится к числу глобальных проблем здравоохранения, имеющих большую социально-экономическую значимость, является одним из самых распространенных хронических гетерогенных заболеваний дыхательных путей. В последние годы накоплено множество данных, указывающих на то, что состояние микробиоты кишечника является одним из важнейших факторов, определяющих состояние здоровья человека, в том числе влияющих на иммунные механизмы развития аллергических болезней в детском возрасте. Дисбиотическое состояние микробиоты кишечника обусловлено не только изменениями структуры, но и нарушениями ее метаболизма. В соответствии концепцией «ось кишечник – легкие» поддержание нормальной микробиоты кишечника, коррекция ее нарушений, в том числе стратегии, направленные на активацию синтеза короткоцепочечных жирных кислот в кишечнике, могут стать новым способом профилактики и лечения хронических респираторных заболеваний у детей. В свою очередь, в экспериментальных и эпидемиологических исследованиях показана иммуномодулирующая способность гельминтов. Предполагается, что воздействие на состав и функцию кишечного микробиома является одним из механизмов, посредством которых гельминты влияют на иммунный ответ организма хозяина и течение БА.

**Ключевые слова:** кишечная микробиота, гельминтные инвазии, короткоцепочечные жирные кислоты, бронхиальная астма

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## INTRODUCTION

The increase in the prevalence of chronic noncommunicable diseases, including those of allergic etiology, is one of the main healthcare problems according to world statistics. Investigation of risk factors, development of preventive measures, and search for new approaches to the treatment of socially sensitive diseases are priorities for public health programs. Bronchial asthma (BA) is one of the most common chronic respiratory diseases affecting patients of all ages. Its course is accompanied by a significant decrease in the quality of life of patients and their families, as well as by heavy economic burden. That is why this problem remains highly relevant in the global agenda of medical science [1].

Epidemiological studies suggest a possible association between a high prevalence of allergies and reduced exposure to certain infectious agents and microbiota in childhood as a result of changes in dietary habits, improved hygiene conditions, inappropriate use of antibacterial drugs, and other factors, while living in rural areas, contacts with pets, and higher susceptibility to helminth infections exert a protective effect [2]. Currently, there are several hypotheses that explain the relationship between the prevalence of allergic diseases and environmental changes that have occurred in recent decades, such as urbanization, changes in housing and nutrition, and reduced microbial and parasitic exposure [3–5]. According to the hygiene hypothesis, insufficiency of infectious stimulation in childhood is associated with changes in the immunity that predispose to the development of allergies [3]. Later, the biodiversity hypothesis was put forward, which suggests that contacts with the natural environment enrich the human microbiome, reducing the risk of developing chronic noncommunicable diseases [5].

A lot of data have been accumulated indicating that the gut microbiota is one of the most important factors determining human health, including the effect on the immune mechanisms of the development of allergic diseases in childhood [6]. At the same time, recent studies demonstrate the significance of not only the taxonomic composition of microbiota, but also of its metabolic activity. Along with this, there are data on

the relationship between helminth-induced changes in the microbial composition and suppression of allergic inflammation in BA [7, 8]. Currently, the effects of microbiota – helminth interactions on asthma control remain largely unknown. The aim of this review was to analyze current experimental studies and clinical trials aimed at assessing the metabolic activity of gut microbiota in patients with BA and helminth infections.

## MATERIALS AND METHODS

We analyzed scientific publications of the results of clinical trials and experimental studies aimed at investigating the effect of gut microbiota in asthma against the background of helminth infection. The search was carried out using the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and eLIBRARY (https://www.elibrary.ru/) databases. The review presents original articles published from January 1, 2012 to July 01, 2022. The analysis was carried out according to the following algorithm.

Stage 1. Initial search for publications on the topic of gut microbiota and its metabolites in BA and (or) helminth infection. We used the following keywords in the search: short-chain fatty acids / metabolites / microbiota / asthma or short-chain fatty acids /metabolites / microbiota / helminths. We also searched for studies corresponding to the listed terms in the references in the selected publications.

Stage 2. The titles and abstracts of 1,833 articles selected during the initial keyword search were considered. Reviews and original articles that did not contain data on gut microbiota and its metabolites in BA and / or helminth infection were excluded. Therefore, 52 publications were selected for a detailed analysis.

Stage 3. Evaluation of full texts of the publications ($n$ = 52). At this stage, articles that study the taxonomic composition of gut microbiota without assessing the level of metabolites were excluded. In addition, articles studying the use of a special diet in the experimental model were excluded. Therefore, 9 publications describing gut microbiota and its metabolites in asthma and 6 articles describing gut microbiota and its metabolites in helminth infection were included in the review.

## GUT MICROBIOTA AND ITS METABOLIC ACTIVITY IN BA

Recently, interactions between gut and lung microbiota (the gut – lung axis) and their effect on immunity have been actively studied [9, 10]. In accordance with this concept, maintaining normal gut microbiota or correcting its disturbances can become a tool for prevention and treatment of respiratory diseases. Gut microbiota is a key modulator of immune, metabolic, and cellular functions that responds to inflammatory signals associated with BA; it may mediate disease susceptibility, severity, and phenotype [11].

The results of experimental and epidemiological studies demonstrate that establishment of gut microbiota at an early age plays a key role in the development of BA. Low diversity of gut microbiota in the first month of life is associated with development of the disease at school age [12]. The results of other prospective studies also indicate that low biodiversity and dysbiosis of gut microbiota in infancy are associated with a risk of developing BA in childhood [10, 13, 14].

The analysis of the taxonomic composition of gut microbiota showed that a high risk of BA is associated with a low representation of the *Faecalibacterium*, *Bifidobacterium, Roseburia, Alistipes, Ruminococcus,* and *Dialister* genera and a higher content of *Veillonella* [13, 15]. Another study also showed an association of underrepresented *Bifidobacterium, Faecalibacterium,* and *Akkermansia* genera with a high risk of developing BA [16]. However, in a Canadian cohort study of more than 300 children, the risk of developing BA was associated with a decrease in the relative abundance of *Veillonella* bacteria [14]. Studies have also shown that the composition of gut microbiota differs in patients depending on the severity and phenotype of BA [17]. It was noted that in patients with severe BA, an increase in the *Streptococcus* and *Escherichia-Shigella* genera was revealed [18]. Despite the differences in the gut microbiota composition in various studies, there is an association between low microbiota diversity and abundance of short-chain fatty acid (SCFA)-producing bacteria in children with BA.

One of the potential health biomarkers often considered in microbiome research is relative abundance of bacteria producing SCFAs, such as acetate, propionate, and butyrate [19, 20]. The main producents of butyrate are bacteria of the *Faecalibacterium* genus and the *Ruminococcaceae* and *Lachnospiraceae* families; propionate is mainly produced by *Bacteroides, Propionibacterium, Roseburia,* and *Selenomonas*, while acetate is mostly produced by *Bifidobacterium, Clostridium, Ruminococcus,* and *Lactobacillus* [21]. A decrease in the synthesis of butyrate and other SCFAs leads to a lack of energy supply and degenerative changes in intestinal epithelium. The permeability of the intestinal

barrier for food and bacterial antigens increases, which contributes to the development of chronic inflammatory bowel diseases. This greatly exacerbates the imbalance in the gut microbiota [22]. It is important to note that the anti-inflammatory effects of SCFAs are not limited to the gut. The species diversity of the gut microbiota with an increase in the content of bacteria that ferment plant fibers with the formation of SCFAs is associated with a decrease in T helper 2 cell-mediated allergic airway inflammation [23].

A number of experimental studies with modeling allergic airway inflammation showed that its milder course was associated with ingestion of SCFAs (butyrate, propionate, acetate) or a high-fiber diet [23–27]. It has been shown that oral administration of butyrate to mice was associated with a decrease in the number of eosinophils and neutrophils in bronchoalveolar lavage fluid and an increase in CD25 + FoxP3 + regulatory T cells (Treg) in the lung tissue [25, 27]. It has also been found that the administration of SCFAs to mice during pregnancy had a protective effect against the development of allergies in the offspring [25, 26]. Another study showed that propionate or a high-fiber diet could attenuate house dust mite-induced airway inflammation in mice by activating G protein-coupled receptor 41 (GPR41) [23]. The anti-inflammatory effect of butyric acid and other SCFAs is realized mainly due to the inhibition of histone deacetylase (HDAC) and nuclear transcription factor (NF-κB) and stimulation of Treg, providing a decrease in the production of proinflammatory cytokines and a shift in the Th1 / Th2 balance toward Th1 [28–31].

In the Canadian Healthy Infant Longitudinal Development (CHILD) cohort study, M.-C. Arrieta et al. showed that a reduced concentration of acetate in stool samples of children at the age of three months was associated with a risk of developing BA [14]. Another prospective study showed that infants with high levels of acetate in stool samples were less likely to be diagnosed with food allergies, and a reduced risk of developing BA was noted with high levels of butyrate and propionate [25]. In children with BA, stool samples showed a decrease in butyrate-producing bacteria, including *Faecalibacterium* and *Roseburia spp.,* and a lower level of butyrate compared to the control group [15]. In adult patients with BA ($n$ = 44), regardless of the phenotype of the disease, a significant decrease in the total content of SCFAs in stool samples and a decrease in the absolute concentrations of individual acids and total content of isoacids were revealed compared to the controls [32].

In a randomized, placebo-controlled trial including patients with BA ($n$ = 17), inulin supplementation for one week was shown to improve asthma control as measured by the Asthma Control Questionnaire and reduce eosinophil counts and sputum HDAC9 gene expression [33]. Despite evidence that oral SCFA attenuates allergic inflammation in experimental studies, ways to successfully prevent the development of allergies in humans remain unclear. At present, other metabolites of intestinal bacteria with proinflammatory and anti-inflammatory potential have been studied, such as biogenic amines, polyunsaturated fatty acids (PUFAs), and oxylipins [34–36]. Studies of metabolites in various biological samples (serum, urine, stool samples) in adults and children with BA demonstrate the association of the disease with changes in the levels of certain metabolites, such as tyrosine, tryptophan, sphingolipids, phospholipids, bile acids, PUFAs, SCFAs, etc. [36, 37]. Taken together, these results point to the need to evaluate the metabolic activity of the gut microbiota along with its species diversity.

## EPIDEMIOLOGICAL STUDIES ON THE RELATIONSHIP BETWEEN ALLERGIES AND HELMINTHS

Epidemiological studies found that in regions with high prevalence of helminth infections, not only the prevalence of BA in the population varies, but also the severity of its clinical manifestations. This is thought to be due to the modulating effect of helminths on the human immunity [38–40]. The effect of helminth infection on the course of allergic diseases is realized through various mechanisms and depends on the type of the parasite and the duration and intensity of the infection [40].

Studies in different regions have shown a positive relationship between infection with the nematode *Ascaris lumbricoides* and the prevalence and uncontrolled course of BA, especially in childhood [40–43]. In patients suffering from ascariasis, an increase in the level of immunoglobulin (Ig) E, total and specific to the allergens of *Blomia tropicalis* and *Dermatophagoides pteronyssinus*, was found [43]. Researchers have noted similar effects in patients infected with *Strongyloides stercoralis and Toxocara* [44, 45]. On the contrary, numerous studies have shown a negative relationship between helminth infection *(A. lumbricoides, T. trichuria, Opisthorchis felineus, Ancylostoma, Schistosoma)* and skin test sensitivity or the level of specific IgE to

various allergens [46–49]. Researchers have noted that patients with *Necator americanus* infection have a milder course of BA [40, 50].

The results of epidemiological studies demonstrate a decrease in the risk of allergic diseases in residents of areas endemic for helminth infections [47, 51]. Scientists have observed lower levels of interleukin (IL)-5 and IL-4 and an increase in the production of anti-inflammatory IL-10 in *S. mansoni-infected* asthmatic patients compared to patients not affected by helminth infection [52]. The effect of *O. felineus* infection on the course of BA is characterized by a change in the immune response toward suppression of Th2-dependent mechanisms due to an increase in the expression of genes encoding IL-10 and tumor necrosis factor-β and a decrease in the level of IL-4 and IL-5 [53]. A number of studies have established an association between anthelmintic therapy and the progression of clinical symptoms of allergy and an increase in immune reactivity [53–55].

## METABOLIC ACTIVITY OF MICROBIOTA AND HELMINTH INFECTION

Changes in the abundance and diversity of gut communities vary depending on the helminth species. It has been noted that the presence of helminth infections is associated with an increase in microbial diversity and a rise in the concentration of SCFAs in the large intestine [56, 57]. Influencing the composition and function of the gut microbiome is hypothesized to be one of the mechanisms by which helminths affect host immunity [8].

Experimental studies and clinical trials have shown that helminth infection affects the concentration of SCFAs in the intestine and blood serum. An increase in the total level of SCFAs, acetate, and propionate in the stool samples was revealed to be characteristic of *Heligmosomoides polygyrus infection* in the experimental animals compared to the control group. However, no statistically significant difference in the butyrate content was found [58]. The study by M.M. Zaiss et al. (2015) also demonstrated an association of *H. polygyrus* infection in mice with an increase in the total SCFA and acetate levels [7].

*A. suum* infection is associated with an increase in the content of propionate and butyrate and a trend toward an increase in the concentration of acetate [7]. It has been experimentally shown that transplantation of helminth-modified microbiota in the absence of experimental helminth infection reduces the level of proinflammatory cytokines in recipient mice in a BA model. This can be considered as a potential approach to the prevention of exacerbations of this pathology [7]. It has also been shown that the effect of helminth *infection* on SCFA levels depends on the diversity of the gut microbiota [59]. For example, the concentration of acetate and butyrate in the fecal samples of the laboratory mice infected with *Hymenolepis diminuta* was higher than in the animals with helminth infection against the background of administrated antimicrobial drugs [59].

There are few publications on the assessment of the metabolic activity of gut microbiota against the background of helminth infections in humans which all show contradictory results. This may be due to limited sample sizes, differences between the studied cohorts, and the type of parasitic infection. When assessing the composition of gut microbiota and its metabolites in the stool samples from patients with *S. stercoralis* infection, an increase in microbial alpha diversity and a decrease in beta diversity were revealed along with a change in the abundance of certain types of microorganisms and a decrease in the concentration of SCFAs compared to the participants without helminth infection [60, 61]. According to the results of another study, patients with celiac disease (n=8) and *N. americanus* infection showed no change in the level of SCFAs, but a trend toward an increase in the studied metabolites was noted [7].

Liver flukes can have a significant impact on the gut microbiota and its metabolites. In a study involving children suffering from *O. felineus* infection, an increase in the content of certain bacteria involved in the production of SCFAs and possessing anti-inflammatory potential was revealed (*Lachnospira, Ruminiclostridium, Eubacterium eligens, Faecalitalea, Barnesiella*) [62]. Another experimental study showed that the chronic stage of *O. felineus* infection was associated with an increase in the levels of fatty acids in the blood serum [63]. Infection with another trematode species, *O. viverrini*, in the laboratory animals caused an increase in the abundance of *Methanobrevibacter, Akkermansia,* and *Burkholderia-Paraburkholderia* in the stool samples [64]. However, studies evaluating the level of intestinal metabolites, including SCFAs, have not been performed in patients with *O. felineus* infection.

## CONCLUSION

The conducted systematic review demonstrates the growing interest in the research of microbial metabolites in the context of the “gut – lung axis”

concept and indicates the need to assess not only the taxonomic composition, but also the functional activity of the gut microbiota. The results of modern studies have shown that the main microbiota factors associated with BA are a decrease in the diversity and metabolic potential of the gut microbiota, mainly due to a decrease in the production of SCFAs, and a cooccurring increase in the representation of certain opportunistic bacteria. Experimental studies provide evidence for the effectiveness of a high-fiber diet or oral SCFA in reducing allergic airway inflammation and reducing the risk of developing BA. However, clinical data on the potential of this diet and SCFA for asthma control are currently insufficient.

The analysis of research results indicates that helminths and intestinal bacteria may interact to promote immune homeostasis through anti-inflammatory metabolites, such as SCFAs. Harnessing the immunomodulatory potential of helminths while avoiding side effects associated with infection represents a potential option for managing BA. Currently, the effects of microbiota – helminth interactions on asthma control remain largely unknown and further research is needed to confirm this hypothesis. The disclosure of the role of the gut microbiota and its metabolites as factors of pathogenetic influence and modification of the course of BA in the context of helminth infection presents a prospect for the development of new preventive and therapeutic strategies for BA control.

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