FERET, Dominik Maciej, ZAPASEK, Daniel, SZCZEPAŃSKI, Michał, KULIGA, Marcin, BAJAK, Mateusz, SŁOWIK, Julia, INGLOT, Julia, INGLOT, Jadwiga, MAMCZUR, Maciej, and SOWA, Damian. Influence of the Gut Microbiome on the Pathogenesis of Asthma: A Review of Current Research and Therapeutic Options. Quality in Sport. 2024;35:56359. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56359
https://apcz.umk.pl/QS/article/view/56359

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2024. Revised: 05.12.2024. Accepted: 16.12.2024. Published: 16.12.2024.

Influence of the Gut Microbiome on the Pathogenesis of Asthma: A Review of Current Research and Therapeutic Options

Dominik Maciej Feret
Independent Public Health Care Complex No. 1 in Rzeszow
ul. Czackiego 3, 35-051 Rzeszów, Poland
feret.dominik@gmail.com
https://orcid.org/0009-0004-3174-2784

Daniel Zapasek
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
daniel.zapasek@interia.pl
https://orcid.org/0009-0006-1383-1825

Michał Szczepański
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
mszczepanski0202@gmail.com
https://orcid.org/0009-0001-8586-3790

Marcin Kuliga
College of Medical Sciences, University of Rzeszów, Poland
al. Tadeusza Rejtana 16C, 35-310 Rzeszów
marcinkuliga@gmail.com
https://orcid.org/0009-0004-3452-7377

Mateusz Bajak
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland
mateuszbk88@gmail.com
https://orcid.org/0009-0006-8237-1295

Julia Słowik
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland
jj16@interia.eu
https://orcid.org/0009-0003-3821-5090

Julia Inglot
Clinical Provincial Hospital No. 2 in Rzeszów, Poland
Lwowska 60, 35-301 Rzeszów, Poland
inglotjulia@gmail.com
https://orcid.org/0000-0002-6604-7229

Jadwiga Inglot
Clinical Provincial Hospital No. 2 in Rzeszow, Poland
Lwowska 60, 35-301 Rzeszów, Poland
inglotjadzia@gmail.com
https://orcid.org/0000-0002-3071-4392

Maciej Mamczur
Medical Center in Łańcut, Poland
Ignacego Paderewskiego 5, 37-100 Łańcut, Poland
maciej.mamczur@gmail.com
https://orcid.org/0009-0000-2789-1235

Damian Sowa
Clinical Provincial Hospital No. 2 in Rzeszow, Poland
Lwowska 60, 35-301 Rzeszów, Poland
damian_sowa@wp.pl
https://orcid.org/0009-0003-0980-9324

Corresponding author: Dominik Maciej Feret, feret.dominik@gmail.com

Abstract:

Introduction and purpose:

Asthma is a chronic inflammatory disease of the airways. Its pathogenesis may be linked to the gut microbiome, which plays a key role in the immune system. This review analyzes current evidence regarding the influence of the gut microbiome on asthma development, particularly in the context of the gut-lung axis. The aim of this paper is to assess the current therapeutic possibilities for asthma based on the modulation of the gut microbiota.

Materials and methods:

The literature review includes articles from scientific databases (PubMed), selected for their citation impact and relevance to the topic under analysis.

Results:

The gut microbiota affects immune balance by producing short-chain fatty acids (SCFAs) and other metabolites that modulate the body's inflammatory response. Gut dysbiosis may contribute to the development of asthma. The use of probiotics, prebiotics, and a fiber-rich diet has shown beneficial effects in reducing inflammation in asthma. Fecal microbiota transplantation (FMT) may represent a future therapeutic approach, though further clinical research is required.

Conclusion:

Modulation of the gut microbiota is a promising support in asthma therapy. A personalized treatment approach based on the patient's microbiota profile could potentially improve disease control and reduce the reliance on steroids in the future.

Keywords: asthma, gut microbiota, gut – lung axis, probiotics, prebiotics, fiber diet, personalised medicine, fecal microbiota transplantation

Introduction:

Asthma is a chronic inflammatory condition of the respiratory system, manifesting with symptoms such as shortness of breath, wheezing, persistent coughing, and chest discomfort or tightness [1]. These symptoms are a result of ongoing inflammation within the airways. The accumulation of inflammatory cells triggers excessive mucus production and bronchial hyperreactivity, which together lead to the clinical symptoms of asthma. The disease can develop both in childhood and later in life, referred to as childhood-onset asthma and late-onset asthma, respectively. However, special attention is often given to younger patients, as asthma tends to onset more frequently in early childhood [2]. Globally, more than 300 million people suffer from asthma, and the number is expected to rise to 400 million by 2025, marking a significant global health challenge [3]. Despite the prevalence of the disease and extensive research efforts, the precise mechanisms underlying asthma's pathogenesis are still not fully understood. Nonetheless, clear links have been established with genetic predisposition [4, 5], environmental exposures, microbial influences, dietary factors, and personal conditions such as obesity [6].

The gut microbiome, which consists of a vast community of microorganisms—including bacteria, fungi, and viruses—plays an essential role in human health. These microorganisms primarily reside in the gastrointestinal tract, with the highest concentration found in the colon. The gut microbiome is involved in key processes such as digestion, the production of essential vitamins, and the regulation of the immune system. Disruptions in the balance of the gut microbiota, whether through antibiotic use, poor diet, stress, or other factors, can impair these functions, contributing to the development of various diseases, including inflammatory bowel disease and metabolic disorders [7, 8]. Increasing evidence points to a connection between gut microbiome imbalances and the development of asthma, particularly in early childhood [9, 10, 11]. This emerging link highlights the importance of the gut-lung axis, suggesting that maintaining a healthy gut microbiome could manage or even prevent asthma.

Pathogenesis of asthma

Asthma can be categorized into two main types based on its underlying mechanisms and the cells involved: Th2-high asthma and Th2-low asthma. (Figure 1.) [12]

In **Th2-high asthma**, CD4+ cells are crucial, as they release interleukins such as IL-4, IL-5, IL-9, and IL-13. This process occurs in two main phases. The first phase, known as sensitization, involves allergens being presented to Th2 cells, which then produce these cytokines and activate B lymphocytes to produce IgE antibodies. These IgE antibodies attach to mast cells, making them sensitive to allergens. The second phase, called the challenge, happens when the same allergen enters the lungs. This triggers the immediate activation of mast cells, causing them to release mediators that irritate the smooth muscles of the airways, resulting in bronchoconstriction. Additionally, the interleukins facilitate the movement of eosinophils into the lungs, increase the sensitivity of smooth muscles to various factors, and contribute to lung fibrosis. [13, 14]

In **Th2-low asthma**, IL-17 is believed to play a key role in the mechanism. Th-17 lymphocytes are the primary cells responsible for producing this cytokine. IL-17 stimulates epithelial cells and fibroblasts to release chemotactic factors (CXCL1, CXCL5, CXCL8) and granulocyte macrophage colony-stimulating factor (GM-CSF), which attract neutrophils into the lungs. [14]

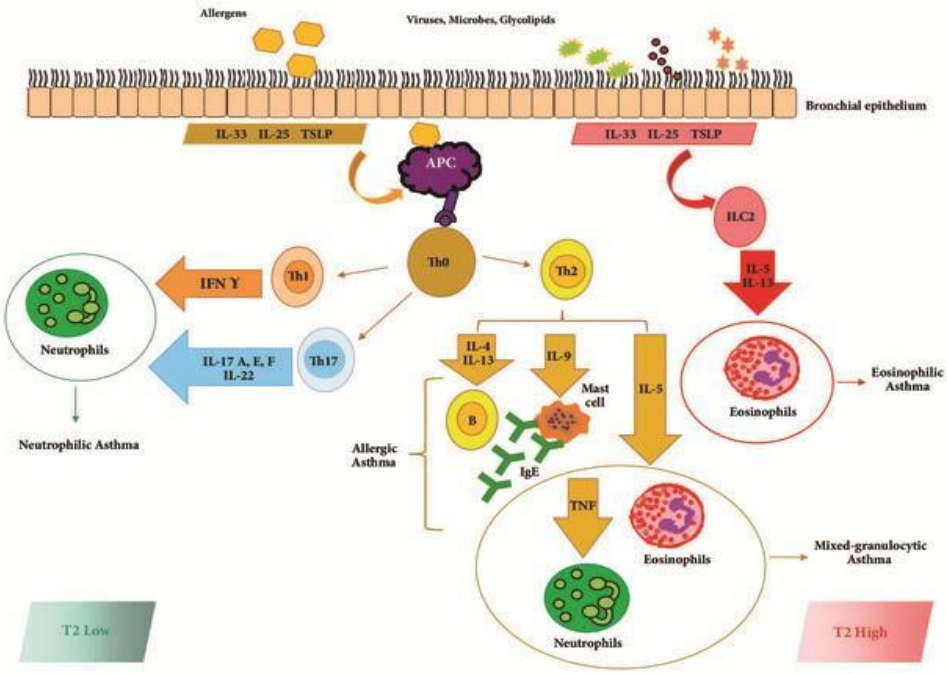

Figure 1. The image depicts the development of asthma with either a Th2-dominant pathway (T2-high) or without Th2 dominance (T2-low). In Th2-high asthma, the activation of Th2 and ILC2 cells leads to cytokine production (IL-4, IL-5, IL-13), resulting in an eosinophilic response. In contrast, Th2-low asthma involves the production of IFN-γ and IL-17, leading to a neutrophilic response. (Gaelone et al., 2018) [12]

The Role of the Gut Microbiome in Immune System Regulation

The gut microbiome plays a vital role in regulating the immune system by affecting various immune pathways and maintaining the body's overall balance. Key elements include microbial metabolites such as short-chain fatty acids (SCFAs), bile acid metabolites (BAs), and tryptophan derivatives (Trps) (Figure 2.). These compounds help shape the differentiation of immune cells, influencing the balance between pro-inflammatory and anti-inflammatory responses. By boosting anti-inflammatory activity - mainly through the increased production of regulatory T cells - the gut microbiome helps prevent autoimmune diseases and excessive immune responses to external antigens. [15]

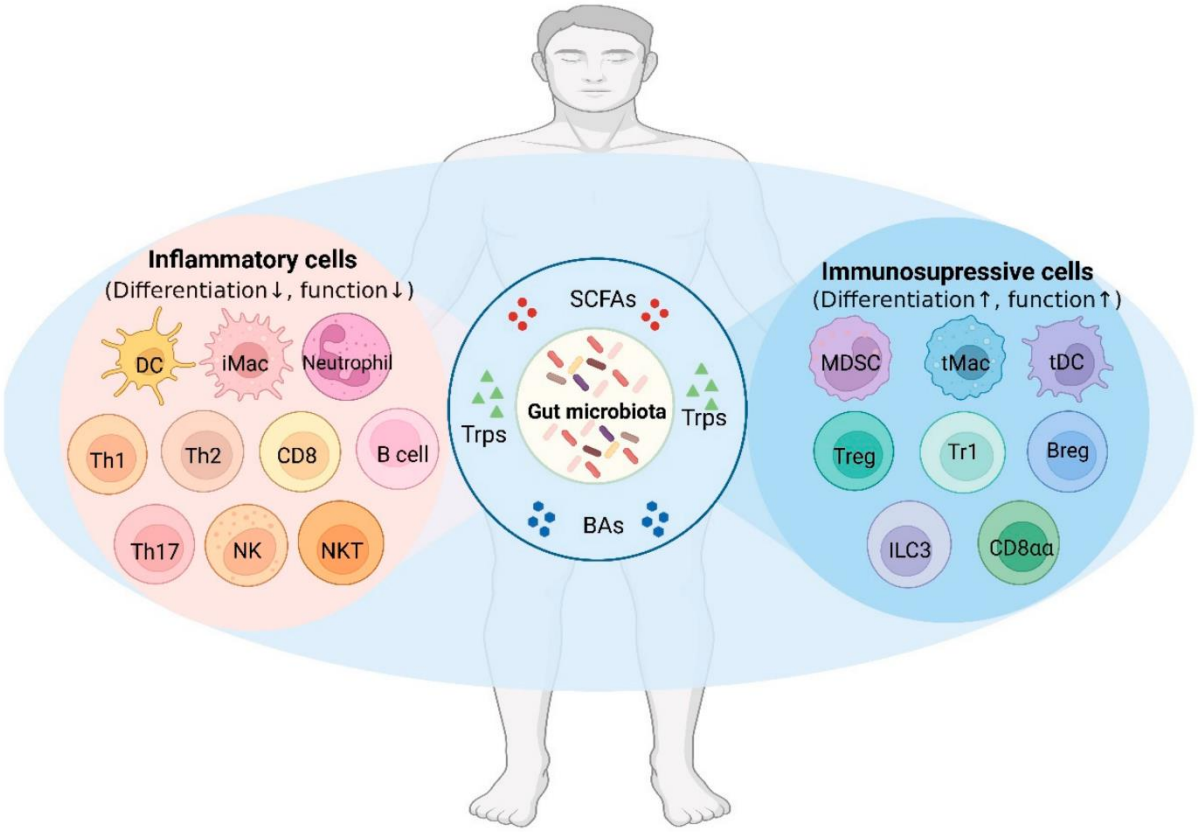

Figure 2. Gut microbiota metabolites, including short-chain fatty acids (SCFAs), tryptophan derivatives (Trps), and bile acids (BAs), help regulate gut and systemic immune balance by supporting immune-suppressive cell activity while restraining inflammatory cells. (Wang J, Zhu N, Su X, et al., 2023) [15]

The connection between the gut microbiome and the immune system also indirectly impacts inflammation in the respiratory system, known as the **gut-lung axis**. This axis functions through communication between the gut and lungs via pathways like the circulatory system or nerve cell migration [16]. When the gut microbiota is imbalanced (dysbiosis), it can lead to increased activity of cells like Th2 and Th17 lymphocytes, which promote inflammation and airway hypersensitivity [17]. These interactions are dynamic and depend on the composition of the gut flora, highlighting the importance of a healthy gut for proper immune function [15].

The gut-lung axis underscores how gut microbiome balance is essential not only for immune health but also for respiratory health. It helps reduce the risk of excessive allergic responses, lowering the chances of inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), or bronchiectasis [16, 18]. Therefore, maintaining a well-functioning gut microbiome can contribute to a healthy respiratory system, which may inform future treatments for inflammatory diseases of the lungs.

Bacterial Groups Influencing the Development and Progression of Asthma

Research indicates that the composition of the gut microbiota has a significant impact on the respiratory system. Certain bacterial species can either increase or reduce the risk of asthma. Studies have found that higher levels of bacteria from the genus *Bacteroides* are associated with an increased risk of asthma, while bacteria from the genus *Ruminiclostridium* have a protective effect. An imbalance in gut flora can lead to immune disorders, and through the gut-lung axis, contribute to inflammatory respiratory diseases. *Ruminiclostridium* also appears to support allergy treatment, suggesting that modulating the gut microbiota could be an effective strategy for managing asthma. [19, 9]

The bacteria present in our surroundings also affect asthma development. A study examining the indoor microbiome in schools in urban and rural areas of China found that asthma symptoms were more frequent in urban areas compared to rural ones [20]. This was linked to differences in the microbial composition of these environments. In rural areas, higher levels of bacteria associated with short-chain fatty acid (SCFA) production, which has a protective effect against asthma and inflammatory diseases, were found.

Another important aspect is the diversity of the gut microbiota. Some studies have shown that reduced bacterial diversity early in life may contribute to asthma development [21]. Children with higher gut microbiota diversity in the first year of life were found to have lower rates of asthma by the age of 5-6. In contrast, an immature microbiome and low abundance of bacteria from the genera *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus* were linked to a higher asthma risk. [21]

Bacteria from the genus *Bifidobacterium*, particularly *B. infantis*, play a crucial role in maintaining proper immune function. Research indicates that a low number of bifidobacteria species, especially those that can metabolize human milk oligosaccharides (HMOs), is associated with a heightened inflammatory response, characterized by excessive activation of Th2 and Th17 cells. Of special interest is the strain *B. infantis EVC001*, which has the complete set of genes needed to break down HMOs. This strain supports the production of SCFAs (such as propionate and acetate), which have anti-inflammatory effects. SCFAs also help develop regulatory T cells (Tregs), which are vital for maintaining immune tolerance both in the gut and across the body. Furthermore, bifidobacteria have been shown to boost the production of interferon-beta, which can enhance the immune response during viral infections by promoting Treg activity. [22]

Microbiotic Interventions

Probiotics

Probiotics, defined as live microorganisms that provide health benefits when taken in adequate amounts, have shown potential for immune support by enhancing digestive system functions. They are gaining increasing scientific interest in the context of treating allergic diseases, including asthma. Their use may alleviate asthma symptoms and reduce the number of exacerbations; however, the evidence on improving spirometry measures remains mixed. While some studies report positive changes [19], meta-analyses highlight a lack of significant impact [23]. Research indicates that probiotics lower exhaled nitric oxide, an inflammation marker in the respiratory tract, among asthma patients. Additionally, patients taking probiotics show improved scores on the Childhood Asthma Control Test, suggesting better asthma symptom control [23, 24, 25].

A specific probiotic, **Lactobacillus reuteri**, appears particularly effective in reducing respiratory inflammation. Studies have found that this probiotic lowers immunoglobulin E levels – a primary driver in allergic responses – and decreases the activity of Th2 cells, which are responsible for producing proinflammatory cytokines Il-5 and Il-13 [19, 26]. Research on the **CCFM1040 strain** shows it may also offer therapeutic potential for asthma patients [27]. This strain reduces respiratory inflammation by modulating the gut microbiota, which leads to symptom improvement. Preliminary evidence suggests that CCFM1040's mechanism of action is linked to the activation of Treg cells. Despite its good tolerance and safety profile, more large-scale studies with extended observation periods are needed to confirm its benefits [27].

Lactobacillus acidophilus strengthens the gut barrier by enhancing the expression of proteins, such as ZO-1 and occludin, which reinforce the intestinal epithelial barrier. This improved cell junction integrity can reduce allergen penetration, thereby limiting the severity of allergic and asthma-related reactions [19, 28].

Lactobacillus rhamnosus also contributes to strengthening the intestinal barrier, preventing excessive immune reactions. Research has shown that this strain activates macrophages and increases the production of interferon alpha and gamma, which boosts the body’s ability to fight infections that can exacerbate asthma symptoms [19, 29]. Studies also suggest a synergistic effect when combined with prednisolone, as it helps alleviate symptoms, potentially reducing the need for higher steroid doses. Futhermore, this strain has immunomodulatory effects, such as lowering proinflammatory Th2 cytokines (Il-4, Il-5, Il-13) and reducing eosinophil and neutrophil counts [29].

Bifidobacterium longum, particularly its subspecies **Bifidobacterium infantis**, is a significant focus of scientific research in relation to asthma**. T**his strain's ability to utilize human milk oligosaccharides (HMOs) allows it to effectively colonize the intestines of breastfed infants, where it serves as a "keystone species" [30]. Its crucial role in modulating the immune response has been demonstrated through the reduction of proinflammatory cytokines (Il-4, Il-13). Additionally, administering this strain has been linked to an increase in beneficial gut bacteria, such as **Faecalibacterium**, which promotes a balanced microbiota and lowers the risk of allergic reactions [19]. These findings, along with further studies, suggest that HMO and **B. infantis** supplementation could aid in the recovery of gut microbiota in formula-fed infants, potentially reducing the risk of asthma following antibiotic therapy [30].

Prebiotics

Prebiotics are dietary components that aren't digested by the digestive system but positively impact health by promoting the growth or activity of beneficial microorganisms, especially in the gut. These include primarily short-chain carbohydrates, such as fructooligosaccharides (FOS), isomaltooligosaccharides (IMO), and xylooligosaccharides (XOS), which bypass the digestive processes of the upper gastrointestinal tract and act as food for beneficial bacteria like *Bifidobacterium* and *Lactobacillus*. Prebiotics are found in various plant-based foods, including whole grains, onions, and garlic [31, 32]. Some studies suggest that specific compounds, like flavonols from cocoa, may also exhibit prebiotic effects [33].

The impact of prebiotics on inflammatory markers in asthma is a subject of research, however, the results remain inconclusive. Not all studies show a clear reduction in inflammatory markers, such as eosinophils, interleukins IL-4, IL-5, IL-13, or FeNO. Potential mechanisms by which prebiotics may influence inflammation include the modulation of gut bacterial microbiota and the production of SCFA, which can impact the immune system. *In vitro* research suggests that prebiotics might help reduce the Th2 humoral response, showing beneficial effects in children. However, results in adult patients are inconsistent and difficult to interpret definitively. The limited statistical power of these studies highlights the need for further, more robustly designed research [34].

Dietary fiber

Dietary fiber is a complex group of plant-derived substances that resist digestion and absorption in the small intestine but can be fermented in the large intestine. Over the years, its definition has expanded to include indigestible carbohydrates (like cellulose, hemicelluloses, pectins, and resistant starch) and non-carbohydrate compounds (such as lignin, saponins, and phytosterols). Dietary fiber is traditionally divided into water-soluble and insoluble types. Soluble fiber –

including pectins and beta-glucans – ferments in the large intestine, stimulating SCFA production, while insoluble fiber – like cellulose – increases stool bulk, enhances intestinal motility, and helps prevent constipation. Recent studies suggest that dietary fiber's benefits extend beyond aiding digestion, with increasing focus on its relationship to gut microbiota and metabolic functions [35].

Dietary fiber plays an important role in the prevention and treatment of inflammatory respiratory diseases, including asthma. Many studies link high fiber intake to better lung health, which is supported by both clinical observations and epidemiological analyses [36, 37]. The National Health and Nutrition Examination Survey (NHANES) from 2013 to 2018 shows a reduced risk of chronic inflammatory respiratory diseases with higher consumption of fiber-rich foods. Moreover, high fiber content was correlated with a lower risk of mortality from chronic inflammatory lung diseases [36].

The mechanisms responsible are multifaceted. Increased production of SCFAs is preceded by the effect of fiber on gut microbiota composition. Moreover, modulating this microenvironment enhances the gut barrier. These effects, beneficial to the body's immune system, lead to a reduction in the production of pro-inflammatory mediators and decrease inflammatory conditions in the lungs [15].

Despite the numerous benefits of high fiber intake, further research is still necessary. Current evidence is based on observational studies that do not establish specific cause-and-effect relationships. Moreover, most studies do not distinguish between different types of fiber, which could be crucial for future dietary treatments. Nonetheless, the findings highlight the importance of promoting a fiber-rich diet as part of the prevention and management of inflammatory lung diseases [36].

Fecal Microbiota Transplantation

FMT Fecal microbiota transplantation (FMT) is a procedure involving the transfer of gut microbiota from a healthy donor to a patient's gastrointestinal tract to treat diseases associated with bacterial flora imbalances. Currently, FMT is primarily used for treating recurrent *Clostridium difficile* infections, a benefit confirmed by multiple studies [38, 39]. The benefits of restoring microbial balance may be significant for patients with coexisting asthma; however, reliable studies on this subject are currently lacking.

Helminths in Asthma

The role of helminths in asthma development, progression, and treatment remains an area of active research. These parasites can influence inflammatory responses in both positive and

negative ways. The negative effects, especially from parasites like *Ascaris lumbricoides*, involve the activation of Th2 cells, which heightens inflammatory responses by releasing cytokines IL-4, IL-5, and IL-13. This immune response helps the body fight off parasites but is also key to the development of allergic reactions, including asthma. Research has found that children infected with these helminths show higher FeNO levels, a marker of increased respiratory inflammation. However, as part of their life cycle, *Ascaris* larvae migrate through the lungs, which can cause significant inflammatory reactions and may be largely responsible for the elevated FeNO levels [40].

However, there are studies on animal models showing effects that could potentially prevent the development of asthma. Helminths such as *Schistosoma mansoni*, *Trichinella spiralis*, and *Heligmosomoides polygyrus* stimulate regulatory mechanisms in the immune system, reducing allergic reactions. Two main mechanisms explain helminths' protective effect. The first, the regulatory network hypothesis, posits that regulatory lymphocytes are activated, which inhibit Th2 cells by releasing IL-10 and TGF-beta, reducing asthma-related inflammation. The second, the saturation hypothesis, suggests that polyclonal IgE antibodies saturate mast cells, blocking allergen-specific IgE from binding and preventing degranulation, thereby halting the allergic response. [41]

Infecting with live parasites isn't practical, so research is focusing on identifying proteins with anti-allergic effects. Proteins like Smteg and Sm22.6 from *Schistosoma mansoni* or AIP-2 from *Ancylostoma caninum* may reduce inflammation and airway sensitivity. By inhibiting the overproduction of pro-inflammatory cytokines and modulating the activity of regulatory cells, these proteins represent a potential avenue for developing asthma vaccines. Current studies yield inconclusive results, but in the future, this could form the basis for new methods of treatment and prevention of allergic asthma. [41]

Personalised Medicine

Personalized medicine is a disease-management approach that emphasizes individualized care based on a patient's unique characteristics – from genetic makeup and environmental factors to personal habits and behaviors. The goal of personalized treatment is to tailor medical interventions to the patient's specific needs, achieving better outcomes. As scientific understanding advances, personalized medicine is becoming increasingly relevant. By exploring the diversity of organisms and the pathomechanisms underlying diseases, we can implement targeted therapies that may prove beneficial for specific individuals. [42]

Personalized treatment in asthma may include modulation of the gut microbiome. Referring to the aforementioned treatment methods, gut microbiome modulation indirectly affects respiratory health. A patient's specific asthma pathogenesis and the gut microbiome profile, shaped by various factors, can guide a targeted therapeutic approach. By analyzing the gut microbiome composition, we can make personalized choices – using probiotics or prebiotics to enhance SCFA production or even starting with targeted antibiotic therapy, which, by removing specific bacteria, shows promise in treating certain neutrophilic asthma phenotypes. [43]

Nevertheless, fully harnessing these interventions requires more research. Despite its promising potential, personalized medicine faces significant challenges. Precision approach requires extensive patient data, which raises privacy concerns and adds high costs to individualized therapies. This approach is likely the future of medicine – as technologies for analyzing patient data and producing customized drugs advance, these solutions may become more accessible. [42, 43]

Conclusion:

The gut microbiome, containing thousands of microorganism species, is vital for immune regulation, and its dysbiosis can lead to inflammation and related diseases. This imbalance extends beyond the gut – immune dysregulation impacts the body more broadly, contributing to respiratory conditions, including asthma. Maintaining a balanced gut microbiota is key to lung health via the gut-lung axis.

The use of probiotics, prebiotics, and dietary fiber can modulate the microbiota and alleviate asthma symptoms. These interventions support the growth of beneficial bacteria that produce SCFAs. These bacteria can reduce inflammation by increasing the number of regulatory T cells and inhibiting pro-inflammatory responses. Using these interventions as an adjunct to asthma treatment shows potential for reducing exacerbations and improving asthma control.

Personalized medicine based on microbiome analysis opens new possibilities for asthma therapy. Adapting prevention and therapy to an individual's unique profile can improve health and quality of life. An example could be the use of specific probiotic strains that support microbiota balance or targeted antibiotic therapy to eliminate specific bacteria.

Despite numerous studies showing promising results regarding the impact of gut microbiota on asthma progression, further well-designed clinical trials are needed to establish clear effects and benefits of these therapies. It is essential to determine which specific bacterial strains have a positive impact on asthma progression and which immune mechanisms are involved in these processes. Additionally, it's essential to develop precise methods for analyzing gut microbiota

composition and refining personalized treatment techniques to identify patient groups most likely to benefit from microbiome-based therapies.

Technological advances are aiming to improve microbiome mapping and to determine the most effective, specific interventions for asthma patients. Including gut microbiome therapies as a complement to conventional asthma treatments may help achieve better disease control, reducing both symptoms and exacerbations. This approach has the potential to lower the required doses of steroids, playing a crucial role in minimizing the long-term side effects of these medications, which are especially concerning for patients in developmental stages.

Disclosures

Author's contribution

Conceptualization – Dominik Maciej Feret, Julia Inglot, Jadwiga Inglot

Formal analysis – Dominik Maciej Feret, Michał Szczepański, Marcin Kuliga

Investigation – Daniel Zapasek, Julia Słowik, Damian Sowa

Data curation – Michał Szczepański, Julia Słowik, Daniel Zapasek

Writing – rough preparation – Dominik Maciej Feret, Jadwiga Inglot, Marcin Kuliga

Writing – review and editing – Julia Inglot, Maciej Mamczur, Mateusz Bajak

Visualization – Damian Sowa, Maciej Mamczur, Mateusz Bajak

All authors have read and agreed with published version of the manuscript.

Funding Statement – No applicable.

Institutional Review Board Statement – Not applicable.

Informed Consent Statement – Not applicable.

Data Availability Statement – The authors confirm that the data supporting this study are available in the article's references.

Conflict of Interest – Authors declare no conflict of interest.

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