REVIEW ARTICLE

The Role of the Microbiome in the Pathogenesis, Phenotype, and Treatment of Asthma

Safia Gul[1*], Ismail Mazhar[2] and Maryam Maqsood[1]

[1]*Sardar Bahadur Khan Womens' University, Quetta, Pakistan*
[2]*CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan*

Abstract

This review article examines the relationship between microbial communities and asthma, emphasizing the microbiome's significant role in asthma development and therapy. Recent developments in the study of the microbiome have shed light on the intricate role that microbial populations play in the etiology and management of asthma. This paper examines the existing evidence regarding the involvement of microbiome dysbiosis in both the exacerbation and onset of asthma, focusing notably on its impact on inflammation and immune system regulation. The disruption of microbial balance in the gut and respiratory tract has been associated with abnormal immune responses, contributing to airway inflammation and heightened reactivity characteristic of asthma. Additionally, microbial metabolites play a substantial role in shaping airway physiology and immune regulation. Innovations in therapy, such as probiotics, prebiotics, and microbial-based treatments, aim to target the microbiome, potentially enhancing asthma management. In summary, understanding the microbiome's role in the pathophysiology and management of asthma represents a major achievement in respiratory medicine by providing new information and prospects for customized therapy for this long-term respiratory illness.

Keywords: *Microbiome, dysbiosis, asthma, probiotics, prebiotics.*

INTRODUCTION

Hippocrates initially defined asthma as a disorder of dyspnea that may be carried by mental discomfort [1]. Sir John Floyer's writings from the 17th century elucidate the concepts of attacks and triggers and bronchial constriction [2]. As evidence grew over the 20th century, asthma was classified as an inflammatory disease. Over 300 million individuals worldwide suffer from asthma, a long-lasting inciting illness of the airways that is one of the most widespread non-communicable illnesses. Asthma is characterized by obstruction of airflow, increased sensitivity of the bronchial tubes, changes in mucus secretion, structural modifications to the airway walls, and symptoms like wheezing, coughing, difficulty breathing, and chest tightness [3]. Asthma exhibits a multifaceted pathophysiology influenced by immunological, genetic, and environmental factors. Prolonged inflammation of the airway walls, mediated by various immune cells, including eosinophils, innate lymphoid cells, mast cells, and dendritic cells is responsible for inducing airway obstruction. Two distinct forms of asthma are identifiable: neutrophilic and eosinophilic. In eosinophilic asthma, Th2 cells or ILC2s release cytokines such as IL-4, IL-5, and IL-13, driving inflammation that leads to hallmark asthma features like eosinophilia, increased mucus production, heightened bronchial responsiveness, and IgE generation [4]. IL-17 is secreted by Th1 and Th17 cells, and neutrophilic infiltration and interferon-gamma characterize neutrophilic asthma. Patients with asthma, particularly those with severe asthma, have a significantly higher prevalence of comorbid conditions, including depression, obesity, diabetes mellitus, nasal polyposis, allergic rhinitis, cardiovascular diseases, and nasal polyposis.

No single cause of asthma has been identified. Current data suggest that a combination of genetic predispositions and environmental factors contribute to the susceptibility of children to asthma [5]. For many individuals, asthma typically begins during childhood and persists into adulthood with an atopic nature, driven by type 2 immune responses to environmental allergens and microbes. Moreover, the onset of allergies in grown-ups is commonplace and is connected in a few cases to new ecological exposures, which include viral respiration illnesses, irritant exposures, and newly developed allergies or obesity [6]. The genetic material and metabolic byproducts of a diverse range of microorganisms, including bacteria, viruses, fungi, and protozoa, are called the human microbiome. These germs can be found in the lungs, gastrointestinal system, skin, esophagus, and oral cavity, among other body areas. The microbiome is formed and modified through diverse genetic, nutritional, and environmental factors, such as start mode (typically refers to the mode of birth, which significantly influences the initial colonization of an infant's microbiome, the two primary "start modes" are: Vaginal birth and Cesarean Section) age, and antibiotic consumption [7]. Changes in the human microbiome's structure and function influence a range of physiological functions, including intestinal permeability, digestion, metabolism, and immune responses.

The metabolites generated by the gut microbiota function as signaling molecules, influencing the immune

**Corresponding author: Safia Gul, Sardar Bahadur Khan Womens' University, Quetta, Pakistan, E-mail: safiagul34@gmail.com*
Received: May 22, 2024; Revised: October 21, 2024; Accepted: December 09, 2024
DOI: https://doi.org/10.37184/lnjpc.2707-3521.7.35

system and interacting with different body organs. The microbiota-gut-lung, microbiota-gut-skin, microbiota-gut-oral, and microbiota-intestine-mind axis are the names given to these combined effects [8]. Variations in the gut microbiota can significantly influence the emergence of illnesses affecting the skin, brain, lungs, and other systems and organs. Additionally, they may affect ailments including dementia, cognitive frailty, and neurodegenerative diseases. Dysbiosis, or an imbalance in the lung microbiome, is seen in asthma and probably causes the symptoms. Some metabolites produced *via* bacteria, especially short-chain fatty acids, have anti-inflammatory effects on the airways [9]. An explanation for the rise in the prevalence of asthma argues that inadequate exposure to a range of environmental microbes during infancy leads to immune system malfunction.

OVERVIEW OF THE HUMAN MICROBIOME

The human microbiome comprises a varied and ever-changing community of microorganisms that reside in various regions of the human body, including the gastrointestinal tract, skin, respiratory tract, oral cavity, and urogenital tract [10]. Comprised of microorganisms, viruses, fungi, archaea, and other microbes, the human microbiome has complex and symbiotic dating with the human host, influencing several components of fitness and disease. The human microbiome is mostly centered in the intestines. However, bacteria can also be found in the mammary glands, skin, uterus, ovarian follicles, biliary tract lungs, seminal fluid, saliva conjunctiva, and oral mucosa [11]. The overall number of bacteria in the human body is about 3.8×10^{13} (means that the total number of bacterial cells present in the human body is approximately 38 trillion) [12]. The composition of the human microbiome is stimulated *via* an expansion of factors, such as genetics, weight loss program, age, geographic region, lifestyle, medicinal drugs, and environmental exposures [13]. Though significant variability exists among individuals within the microbiome, certain beneficial microbial taxa are typically present across diverse populations.

Lifestyle variables have a substantial impact on the human microbiome, which consists of microbiomes of the stomach, skin, and mouth. The human microbiome's variety and composition are greatly influenced by lifestyle decisions like nutrition, exercise, and environmental exposure [14]. For example, differences in the gut microbiota have been associated with host lifestyle and behavior, and these differences can affect blood levels of illness biomarkers. Exogenous variables, including lifestyle, impact the human skin microbiome, which in turn might affect its makeup. Additionally, social structures and lifestyle impact the composition of oral microbiota, with shared settings and lifestyle having a more significant influence than intrinsic variables like genetics [15]. One crucial lifestyle component that has been shown to significantly impact the human microbiota is diet. Many dietary factors, such as macronutrients, food additives, micronutrients, and salt, as well as nutritional patterns like vegan, high-sugar, vegetarian, ketogenic, gluten-free, high-sugar, Western-style, low-FODMAPS, and Mediterranean diets, can affect the composition of the gut microbiota. Moreover, a variety of factors, including dietary habits and lifestyle decisions, influence the gut microbiome, a complex and dynamic community of bacteria essential to maintaining human health [16]. In addition, lifestyle characteristics common to Westernized populations such as food habits, environmental influences, and sedentary lifestyles—have an impact on the gut microbiome and are associated with an increased vulnerability to metabolic and chronic illnesses that are common in modern civilizations. [17]. In conclusion, lifestyle choices have a substantial impact on the human microbiome, particularly on the variety and makeup of the gut, mouth, and skin microbiomes. These factors, which include industrialization, physical activity, nutrition, and environmental exposures, are major determinants of human health and disease.

THE MICROBIOME IN PATHOGENESIS

Asthma development is significantly influenced by the microbiome, which also affects immune responses and contributes to the variation in illness presentation [18]. Asthma is associated with several factors, including early microbial imbalances in children, abnormalities in the lung microbiome, and dysbiosis in the gut microbiota. Treatments for asthma, such as biologic medications that address Type 2 high asthma, can alter the microbiome, which influences immune function and chronic illnesses like asthma.

Gut Microbiome

The complex community of microbes that live in our digestive tract, known as the gut microbiome, has been recognized as a key component of immune function and other elements of systemic physiology in addition to digestive health [19]. The pathophysiology of asthma, a chronic respiratory disease marked by airway constriction and inflammation, is significantly influenced by the gut microbiota, as recent studies have demonstrated. The gut microbiome affects several processes, such as immunological regulation, metabolizing food and medicinal substances, intestinal epithelial maintenance, and pathogen resistance [19].

Gut-associated lymphoid tissue (GALT) provides both immunological surveillance and defense. GALT is a component of MALT, or mucosa-associated lymphoid tissue, which supports the immune system [20]. To elicit immunological responses against luminal microorganisms and other antigens, GALT has to collect them. Depending on the specific microbial signals, immune cells within lymphoid follicles are prepared to initiate an inflammatory or anti-inflammatory response. M cells are a distinct subgroup of intestinal epithelial cells (IEC) within GALT that are tasked with

the immunological detection of luminal bacteria (where M refers to microfold or membranous) [21]. Moreover, research has demonstrated that microorganisms are essential for the expansion of GALT, for instance, as shown by the significantly undeveloped lymphoid tissues in germ-free animals. Furthermore, the gut microbiome produces various metabolites, including short-chain fatty acids (SCFAs), which have strong immunomodulatory effects [22]. It has been demonstrated that SCFAs encourage the growth of regulatory T cells (Tregs), which are essential for preserving immunological tolerance and limiting excessive inflammation. Changes in SCFA production brought on by dysbiosis can upset immunological homeostasis and aid in the etiology of asthma [23].

Respiratory Microbiome

The genetic material of all microorganisms living in the respiratory system, such as viruses, bacteria, fungi, bacteriophages, and archaea, is collectively referred to as the respiratory microbiome [24]. The microbiota is diverse in asthma and varies with the severity of the disease, the clinical phenotype, the patient's state at that moment, and the underlying cause of inflammation. Research on the lung microbiome has used a range of patient demographics and sample strategies. Notably, compared to healthy people, the lung microbiome in asthmatics exhibits a higher bacterial load. This was first noticed in bronchial brushings and then verified in Broncho alveolar lavage (BAL) and induced sputum samples [25]. According to some research, people with mild asthma who do not use inhaled corticosteroids had less beneficial organisms such as Prevotella and Villanelle and more Proteobacteria, including Haemophilus, Neisseria, and Moraxella [25]. Induced sputum is commonly employed as a substitute for the lower respiratory microbiota, even though it contains secretions from both the upper and lower airways. Variations in the microbial makeup were seen in each sample type when comparing the effects of oral wash, nasal brushing, provoked sputum, and bronchial brushing in individuals with mild asthma [25, 26]. Induced sputum showed a unique microbiome enriched with oral bacteria despite the most significant similarity between it and bronchial brushing [25, 27]. The onset and aggravation of asthma are significantly influenced by viruses. As a result, individuals with asthma have a different respiratory virus repertoire than healthy individuals, with a preponderance of Herpes viruses. More specifically, most of the sputum virome and CMV (comprises cytomegalovirus) and Herpes Simplex Virus 1. Furthermore, the severity of asthma is correlated with elevated levels of both Epstein-Barr Virus (EBV) and CMV.

Asthma endotypes have also been connected to the microbiome; Type 2-high asthmatics show much less fungal diversity than Type 2-low people [25, 28]. Atopy and Type 2 inflammation are linked explicitly to Aspergillus, Alternaria, Fusarium, Penicillium, Cladosporium Trichoderma, Wallemia, and Mycosphaerella [25, 29]. Sensitization is common in severe asthmatics, and Aspergillus is well-identified for persuading allergic symptoms [30]. Moreover, Alternaria can cause allergen-induced airway sensitivity. Wallemia is directly related to sputum eosinophils and has been shown to induce skin prick reactions and positive RAST (Radio-allegro sorbent) testing in asthmatics. Asthma in childhood is common; one in ten children reported having indications in the past year. It usually precedes severe virus-related wheezing episodes in infancy, mostly caused by a respiratory syncytial virus (RSV) and rhinovirus [25, 31]. Several studies have demonstrated that childhood RSV-related wheeze or bronchiolitis incidences are connected to a higher chance of acquiring asthma in the future. The hygiene hypothesis, which contends that irritation exposure plays a part, has long been accepted as a theory explaining the etiology of asthma. Asthma sufferers' symptoms may worsen if exposed to allergens like pollen regularly [32, 33]. According to the hygiene theory, exposure to microbes in early life shields against the emergence of allergies and asthma. This idea suggests that the absence of infections or exposure to potential pathogens during immune system maturation increases the risk of developing atopic illnesses such as asthma. Likewise, wheezing in early childhood and the onset of asthma at the age of five years are associated with the detection of pathogens in the newborn nasopharyngeal microbiome, such as M. catarrhalis, H. influenza, and S. pneumoniae and, using outdated culture-dependent methods [25, 34].

THE MICROBIOME IN ASTHMA PHENOTYPE

In asthma, groups characterized by specific clinical, demographic, or pathophysiological traits are commonly termed phenotypes. For individuals with severe asthma, treatments guided by these phenotypes are increasingly accessible, particularly concentrating on eosinophilic asthma. Clinical phenotypes encompass atopic or allergic, non-allergic asthma, late-onset asthma, asthma with insistent airflow restriction, and asthma associated with fatness [35, 36]. Changes in the microbiome have been connected to several clinical features of asthma, including airway hyper-responsiveness, the degree of airway blockage, and the intensity of symptoms.

When asthmatic patients with airway obstruction present with Broncho alveolar lavage (BAL), their microbiome is typically less diverse in the alpha category and contains fewer Firmicutes, Bacteroidetes, and Actinobacteria at lower concentrations than routine lung function asthmatics [37, 38]. Asthma phenotypes commonly recognized include allergic asthma, also known as asthma with atopy. Atopy indicates an inherited susceptibility to allergies, as seen by elevated IgE reactions to environmental allergens. Many who are impacted have a personal or family history of additional

allergy disorders in addition to the start of asthma during childhood [39].

Additionally, they commonly exhibit eosinophilic inflammation and demonstrate favorable responses to inhaled corticosteroids [40]. A study comparing atopy-free and asthmatic subjects found different microbiome compositions in bronchial brushings. Serological proof of sensitivity to at least one airborne allergen was used to characterize atopy; however, additional markers of eosinophilic inflammation were not specifically contrasted. The results indicated an abundance of Antinomies, Lactobacillus, and Prevotella, in atopic asthmatics, whereas asthmatics without atopy showed enrichment of Aggregatibacter, Homophiles, and Actinobacteria [25, 41].

MICROBIOME AND ASTHMA PATHOPHYSIOLOGY

Immune System Modulation

The immune system's growth and functionality are strongly impacted by the gut microbiota's immunological tolerance and averting exaggerated inflammatory responses, which is supported by a healthy microbiome [42, 43]. Asthma is characterized by an overactive immune response, which can be brought on by dysbiosis reducing the number of Tregs. For example, several species of bacteria, such as Bacteroides and Faecalibacterium, have been shown to enhance anti-inflammatory responses; a decrease in these helpful bacteria has been associated with a higher risk of developing asthma [44].

Airway Inflammation

Another factor contributing to the development of asthma is the lung microbiome. In asthmatic patients, the lung microbiome often changes, becoming less diverse and increasingly dominated by harmful bacteria such as Proteobacteria [45]. These changes can potentially worsen asthma symptoms by increasing airway inflammation. Certain bacteria, such as Moraxella and Haemophilus, have been associated with heightened airway inflammation and hyper-responsiveness, which may intensify the impact of asthma [44].

Microbial Metabolites

Gut bacteria ferment dietary fibers to produce metabolites known as short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate. SCFAs play a crucial role in maintaining the integrity of the gut barrier due to their anti-inflammatory properties [46]. Asthma exacerbations may occur due to increased systemic inflammation, which can result from reduced SCFA production, often caused by a low-fiber diet or microbiome dysbiosis.

MICROBIOME-TARGETED MANAGEMENT STRATEGIES

Probiotics and Prebiotics

Asthma management strategies have included altering the gut microbiome using probiotics (living beneficial bacteria) and prebiotics (dietary carbohydrates that feed beneficial bacteria). Clinical studies have demonstrated that some probiotics, like Lactobacillus rhamnosus and Bifidobacterium breve, can improve immunological control and lessen the frequency of exacerbations and symptoms associated with asthma [47].

Dietary Interventions

Diet is a major factor in influencing the microbiota. Consuming a diet high in fruits, vegetables, and whole grains encourages the growth of good bacteria and the synthesis of SCFAs, which may help lessen inflammation associated with asthma. On the other hand, dysbiosis and poorer asthma outcomes have been linked to a Western diet heavy in fats and carbs. As a result, dietary modifications are a viable asthma management strategy [48].

Fecal Microbiota Transplantation (FMT)

Fecal material transfer (FMT) has been explored as a potential treatment for severe asthma, involving the transfer of healthy donor feces to a recipient. Although FMT is still experimental, it aims to restore a healthy microbiota, potentially improving asthma management and reducing inflammation. While initial research has shown promising results, further studies are necessary to establish the safety and effectiveness of this treatment for asthma patients.

CLINICAL IMPLICATIONS IN ASTHMA DEVELOPMENT

Genetic Predisposition

Genetic factors play a significant role in the development of asthma. Individuals with a family history of asthma or other allergic conditions are at a higher risk. The susceptibility to asthma has been associated with certain genes, such as IL4 and IL13, which regulate the immune system [49]. To effectively manage asthma, personalized medicine must take into account an individual's genetic predispositions, which might affect how they react to environmental triggers and therapeutic interventions.

Early-Life Infections

Asthma risk has been linked to early-life respiratory infections, specifically those brought on by the rhinovirus and respiratory syncytial virus (RSV) [50]. Long-term alterations in the structure and function of the airways may result from these infections' severe induction of inflammation and damage to the airways during crucial stages of lung development. There is a higher chance of asthma and chronic wheezing in children who have severe lower respiratory tract infections in the future.

Allergic Sensitization

Asthma development is significantly influenced by allergic sensitization, especially to indoor allergens such as mold, pet dander, and dust mites. When the immune system reacts to allergens with an IgE-mediated reaction, it creates sensitization, which causes long-term inflammation and hyper-reactivity in the respiratory system. Atopic asthma, the most prevalent type, is characterized by this process [51].

THERAPEUTIC APPROACHES IN ASTHMA MANAGEMENT

Inhaled Corticosteroids (ICS)

The cornerstone of asthma treatment, particularly for those with persistent symptoms, is inhaled corticosteroids. ICS lessens inflammation in the airways, stops flare-ups, and enhances lung function. In individuals who are at risk, starting inhaled corticosteroids (ICS) early can alter the course of the disease and possibly lower the chance of developing severe asthma. To reduce negative effects, such as childhood development retardation, long-term ICS treatment must be carefully managed [52].

Biologics

Treatments for severe asthma that involve biologic medicines that target specific immune pathways, including mepolizumab (anti-IL5) and anti-IgE (omalizumab), have shown promise, especially in individuals with high levels of eosinophilic inflammation or allergic sensitization [53]. With a focus on the underlying causes of asthma in particular patient subgroups, these medicines provide a customized approach.

Bronchodilators

Airflow is improved and bronchoconstriction is relieved with the use of long-acting beta-agonists (LABAs) and short-acting beta-agonists (SABAs). LABAs are used with ICS to provide long-term management, whereas SABAs offer immediate relief during acute exacerbations. However, if anti-inflammatory medication isn't taken in sufficient amounts while using bronchodilators, asthma control may deteriorate and exacerbation risk may rise [54].

ENVIRONMENTAL FACTORS IN ASTHMA DEVELOPMENT

Air Pollution

One of the main environmental risk factors for the onset and aggravation of asthma is exposure to air pollutants, such as particulate matter (PM), ozone (O3), and nitrogen dioxide (NO2). Particularly in those who are genetically predisposed, these pollutants can cause oxidative stress, airway inflammation, and hyper-responsiveness. Children who are exposed to high levels of air pollution in urban settings are more likely to acquire asthma [55].

Tobacco Smoke

One known risk factor for the development of asthma is prenatal and postnatal exposure to tobacco smoke. Pregnant women who smoke can harm the developing lungs of their unborn children and raise their chance of developing asthma and wheezing in the early years of life. Secondhand smoke exposure during pregnancy keeps aggravating asthma symptoms and impairing asthma control [56].

Diet and Obesity

A higher risk of asthma has been associated with dietary factors, such as inadequate intake of fruits, vegetables, and omega-3 fatty acids. Airway remodeling and chronic inflammation may be exacerbated by a diet heavy in processed foods and poor in antioxidants. Furthermore, because obesity modifies lung mechanics and induces a pro-inflammatory state that makes asthma management more difficult, obesity is also a risk factor for asthma on its own.

THE MICROBIOME IN ASTHMA TREATMENT

Asthma immunomodulatory therapies mainly target type 2-related eosinophilic inflammation using corticosteroids and antibodies that target particular cytokine mediators such as IL-5 [57, 58]. However, these approaches are limited for patients who continue to exhibit eosinophilic inflammation after receiving such medications and are ineffectual for those who do not show significant signs of type 2 pathway activation. Enhanced comprehension of the biological drivers behind various asthma phenotypes will facilitate more precise approaches to characterizing asthma in individual patients and determining optimal treatment strategies [59]. Meanwhile, weighing current treatments' efficacy in each patient is crucial against potential risks. For instance, aside from the established clinical side effects of corticosteroids, emerging research indicates that even short-term use of inhaled corticosteroids can impact the bronchial microbiome within six weeks. Previous studies have indicated that a particular member of the airway microbiota, which is more common in steroid-resistant asthma, may influence how macrophages react to corticosteroids, though the long-term effects are yet unknown. Another long-standing treatment strategy is using macrolide antibiotics, which have antibacterial and anti-inflammatory properties [60]. Although meta-analyses have not yielded definitive proof of their efficacy in asthma, several noteworthy individual clinical trials have demonstrated potential. For example, a recent study found that azithromycin helps those with severe asthma have fewer exacerbations [61, 62].

However, evidence of increased carriage of macrolide-resistance genes in the oropharyngeal microbiome raises concerns regarding the evolution of microbial resistance to macrolides [63]. Furthermore, macrolides might have further effects on the microbiota. Better approaches are urgently needed to determine whether asthma patients, especially those on corticosteroid therapy, may benefit from a macrolide cure. These patients may be associated with having a higher burden

or variety of airway microbiota at baseline. Similarly, studies on probiotic use for primary asthma prevention have not produced encouraging results. In conclusion, there is still insufficient clinical data to support the use of probiotics in managing or avoiding asthma [64].

ANTIBIOTIC AND STEROID THERAPY IN ASTHMA (EFFECTS ON MICROBIOTA)

It is increasingly recognized that the microbiota in asthma, along with the use of antibiotics and steroids, plays a significant role in shaping the course and treatment of the disease. While antibiotics are effective against bacterial infections, they can also disrupt the microbial balance in the respiratory and gastrointestinal tracts. This disruption can reduce microbial diversity, which may exacerbate asthma symptoms and lead to negative outcomes. Such effects arise from alterations in the beneficial microbiota that help regulate lung inflammation and immune responses [65].

Steroid therapy, commonly employed to control asthma-related inflammation, has a unique but equally important impact on the microbiota. Corticosteroids, whether inhaled or used systemically, are known to suppress immune activity, which can disrupt microbial communities. Research shows that long-term corticosteroid use can foster the overgrowth of harmful pathogens while reducing beneficial bacteria, creating an imbalance that may influence asthma severity. This microbial disruption weakens the body's defenses against infections, further compromising respiratory health [66].

The use of both antibiotics and steroids can significantly alter the microbial environment in individuals with asthma. This underscores the need to take microbiota health into account when developing treatment strategies for asthma, as these therapies may lead to lasting microbial imbalances that influence disease progression and outcomes.

GUT AND LUNG MICROBIOTA IN ASTHMA

Although increasing evidence points to a connection between the gut and lung microbiota and asthma, the relationship remains complex and not yet fully understood. Numerous studies have suggested that alterations in gut and lung microbial communities may impact asthma severity and immune responses, but proving a direct causal link is still difficult. Observational research indicates that gut dysbiosis may affect lung immunity through mechanisms like the gut-lung axis, where microbial metabolites influence respiratory health. However, direct cause-and-effect evidence is still limited [66].

Most existing research highlights associations rather than clear causality. While reduced microbial diversity due to antibiotic use or environmental factors has been linked to worsening asthma outcomes, the mechanisms driving these interactions are still under investigation. The microbiota may impact asthma development through indirect pathways, but more research is needed to determine whether changes in the microbiome directly cause the onset or worsening of asthma. Current evidence suggests that, although strong associations exist, causality between microbiota alterations and asthma has yet to be conclusively proven [65].

THE MICROBIOME AND ASTHMA SYMPTOMS

ACT (The Asthma Control Test) an authenticated measure based on patient-reported outcomes, is frequently used to assess symptomatology in asthma [67]. According to the ACT, worsening symptoms are correlated with an elevated bacterial load, particularly of Proteobacteria. On the other hand, the production of certain anti-inflammatory compounds by Actinobacteria is associated with a reduction in symptoms. Moreover, they are the leading cluster related to FKBP5 manifestation, a sign of steroid receptiveness, which may indicate that they are involved in the response of symptoms to treatment [25]. The microbiome may be impacted by the varied microbial makeup across clinical characteristics, even if symptom exacerbation corresponds with increased treatment, which may also be related to the dysbiosis exacerbation correlated with increasing illness severity.

CONCLUSION

The possibility that some beneficial microorganisms may have a major influence on the development of asthma may assist in explaining the complex interaction between the microbiota and asthma. Antibiotic use in childhood and adulthood is strongly correlated with the occurrence of asthma. However, a lower risk of getting asthma has been linked to the "farm effect," early exposure to natural green areas, and exclusive nursing; the gut flora mediates this relationship throughout the early years of life. It has been demonstrated that having older siblings in the family helps the immune system and gut microbiome mature, possibly reducing the threat of asthma in younger children. Contact with definite ecological microbes during infancy may be critical in immune system development and asthma prevention. The mechanisms underlying the development of asthma are significantly impacted by the interactions between the microbiota and the host's immune system. The host's immune system is subjected to molecular alterations by bacteria and their metabolites. These changes impact cellular responses, cell differentiation, and the release of pro- and protective substances such as interleukins, antibodies, and cytokines. Due to unbalanced immunological responses, dysbiosis in the microbiome can interfere with inflammatory processes and possibly hasten the onset of allergy diseases, most notably asthma, by allowing opportunistic pathogens to infiltrate the body. Numerous studies have evaluated the efficacy of different treatment modalities in asthma. Specific dietary treatments, probiotics, and prebiotics may have preventive or therapeutic effects, but more high-quality research is required to draw firm conclusions.

The role of the microbiome in the pathogenesis, phenotype, and treatment of asthma is increasingly recognized as a critical factor in the broader context of immune system development and disease modulation. Similar to the way epigenetic influences, such as the maternal environment and glucocorticoid exposure, shape fetal programming and the development of pancreatic beta cells, the microbiome exerts significant effects on the immune system. Early-life dysbiosis, or microbial imbalance, has been implicated in an elevated risk of asthma development by disrupting immune responses, promoting chronic inflammation, and hindering the maturation of immune tolerance. Moreover, the specific composition of the microbiome may contribute to the clinical phenotype of asthma, influencing the severity and type of inflammatory responses observed in patients.

FUNDING

This study did not receive any specific grant from public, commercial, or not-for-profit funding agencies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

Maryam Maqsood: Supervised the project, ensured the study's integrity, and handled the submission and revisions process.

Safia Gul: Designed the study, performed literature search and manuscript writing.

Ismail Mazhar: Provided significant intellectual input and offered critical revisions to the manuscript.

All authors read and approved the final manuscript.

REFERENCES

1. Azmeh R, Greydanus DE, Agana MG, Dickson CA, Patel DR, Ischander MM, *et al.* Update in pediatric asthma: selected issues. Disease-a-Month 2020; 66(4): 100886. DOI: https://doi.org/10.1016/j.disamonth.2019.100886
2. Pavord ID, Barnes PJ, Lemière C, Gibson PG. Diagnosis and assessment of the asthma. J Allergy Clin Immunol Pract 2023; 11(1): 1-8. DOI: https://doi.org/10.1016/j.jaip.2022.09.034
3. Mandlik DS, Mandlik SK. New perspectives in bronchial asthma: pathological, immunological alterations, biological targets, and pharmacotherapy. Immunopharmacol Immunotoxicol 2020; 42(6): 521-44. DOI: https://doi.org/10.1080/08923973.2020.1824238
4. Ricciardolo FL, Guida G, Bertolini F, Di Stefano A, Carriero V. Phenotype overlap in the natural history of asthma. Eur Respir Rev 2023; 32(168): 220201. DOI: https://doi.org/10.1183/16000617.0201-2022
5. Diaconu ID, Gheorman V, Grigorie GA, Gheonea C, Tenea-Cojan TS, Mahler B, *et al.* A Comprehensive Look at the Development of Asthma in Children. Children 2024; 11(5): 581. DOI: https://doi.org/10.3390/children11050581
6. Gill R, Kumar R, Singh AP, Singh AP. Diagnosis and management of asthma: A review. Int J Rural Dev Environ Health Res 2024; 8(2): 23-35. DOI: https://doi.org/10.22161/ijreh.8.2
7. Vliex LM, Penders J, Nauta A, Zoetendal EG, Blaak EE. The individual response to antibiotics and diet—insights into gut microbial resilience and host metabolism. Nature Rev Endocrinol 2024; 14: 1-2. DOI: https://doi.org/10.1038/s41574-024-00966-0
8. Manos J. The human microbiome in disease and pathology. Apmis 2022; 130(12): 690-705. DOI: https://doi.org/10.1111/apm.13225
9. Ney LM, Wipplinger M, Grossmann M, Engert N, Wegner VD, Mosig AS. Short-chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. Open Biol. 2023; 13(3): 230014. DOI: https://doi.org/10.1098/rsob.230014
10. Martínez JE, Vargas A, Pérez-Sánchez T, Encío IJ, Cabello-Olmo M, Barajas M. Human microbiota network: unveiling potential crosstalk between the different microbiota ecosystems and their role in health and disease. Nutrients 2021; 13(9): 2905. DOI: https://doi.org/10.3390/nu13092905
11. Logoń K, Świrkosz G, Nowak M, Wrześniewska M, Szczygieł A, Gomułka K. The Role of the Microbiome in the Pathogenesis and Treatment of Asthma. Biomedicines 2023; 11(6): 1618. DOI: https://doi.org/10.3390/biomedicines11061618
12. Sender, R.; Fuchs, S.; Milo, R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol 2016; 14: e1002533. DOI: https://doi.org/10.1371/journal.pbio.1002533
13. Gacesa R, Kurilshikov A, Vich Vila A, Sinha T, Klaassen MA, Bolte LA, *et al.* Environmental factors shaping the gut microbiome in a Dutch population. Nature 2022; 604(7907): 732-9. DOI: https://doi.org/10.1038/s41586-022-04567-7
14. Rachman A. The impact of lifestyle factors on the human microbiome. Med Stud Health J 2024; 1(1): 113-22. DOI: https://doi.org/10.62207/9mmb8t87
15. Bhandary R, Venugopalan G, Ramesh A, Tartaglia GM, Songhay I, Khijmatgar S. Microbial symphony: navigating the intricacies of the human oral microbiome and its impact on health. Microorganisms 2024; 12(3): 571. DOI: https://doi.org/10.3390/microorganisms12030571
16. Pedraza Matute S, Iyavoo S. Exploring the gut microbiota: Lifestyle choices, disease associations, and personal genomics. Front Nutr 2023; 10: 1225120. DOI: https://doi.org/10.3389/fnut.2023.1225120
17. Clemente-Suárez VJ, Beltrán-Velasco AI, Redondo-Flórez L, Martín-Rodríguez A, Tornero-Aguilera JF. Global impacts of western diet and its effects on metabolism and health: A narrative review. Nutrients 2023; 15(12): 2749. DOI: https://doi.org/10.3390/nu15122749
18. Zhao X, Hu M, Zhou H, Yang Y, Shen S, You Y, Xue Z. The role of gut microbiome in the complex relationship between respiratory tract infection and asthma. Front Microbiol 2023; 14: 1219942. DOI: https://doi.org/10.3389/fmicb.2023.1219942
19. Maciel-Fiuza MF, Muller GC, Campos DM, do Socorro Silva Costa P, Peruzzo J, Bonamigo RR, *et al.* Role of gut microbiota in infectious and inflammatory diseases. Front Microbiol 2023; 14: 1098386. DOI: https://doi.org/10.3389/fmicb.2023.1098386
20. Spencer J, Bemark M. Human intestinal B cells in inflammatory diseases. Nature Rev Gastroenterol Hepatol 2023; 20(4): 254-65. DOI: https://doi.org/10.1038/s41575-023-00755-6
21. Kong C, Faas MM, de Vos P, Akkerman R. Impact of dietary fibers in infant formulas on gut microbiota and the intestinal immune barrier. Food Function 2020; 11(11): 9445-67. DOI: https://doi.org/10.1039/x0xx00000x
22. Liu XF, Shao JH, Liao YT, Wang LN, Jia Y, Dong PJ, *et al.* Regulation of short-chain fatty acids in the immune system.

Frontiers in Immunology. 2023; 14: 1186892.
DOI: https://doi.org/10.3389/fimmu.2023.1186892

23. Song XL, Liang J, Lin SZ, Xie YW, Ke CH, Ao D, *et al.* Gut-lung axis and asthma: A historical review on the mechanism and future perspective. Clin Translat Allergy 2024; 14(5): e12356.
DOI: https://doi.org/10.1002/clt2.12356

24. Belizário J, Garay-Malpartida M, Faintuch J. Lung microbiome and origins of the respiratory diseases. Curr Res Immunol 2023; 4: 100065.
DOI: https://doi.org/10.1016/j.crimmu.2023.100065

25. Campbell CD, Gleeson M, Sulaiman I. The role of the respiratory microbiome in asthma. Front Allergy 2023; 4: 1120999.
DOI: https://doi.org/10.3389/falgy.2023.1120999

26. Yuksel N, Gelmez B, Yildiz-Pekoz A. Lung microbiota: Its relationship to respiratory system diseases and approaches for lung-targeted probiotic bacteria delivery. Mol Pharma 2023; 20(7): 3320-37.
DOI: https://doi.org/10.1021/acs.molpharmaceut.3c00323

27. Gao J, Yi X, Wang Z. The application of multi-omics in the respiratory microbiome: Progresses, challenges and promises. Computat Struct Biotechnol J 2023; 21: 4933-43.
DOI: https://doi.org/10.1016/j.csbj.2023.10.016

28. Georas SN, Khurana S. Update on asthma biology. J Allergy Clin Immunol 2024; 153: 1215-28.
DOI: https://doi.org/10.1016/j.jaci.2024.01.024

29. Van Tilburg Bernardes E, Gutierrez MW, Arrieta MC. The fungal microbiome and asthma. Front Cell Infect Microbiol 2020; 10: 583418.
DOI: https://doi.org/10.3389/fcimb.2020.583418

30. Rajagopal TV, Kant S, Verma SK, Kushwaha RA, Kumar S, Garg R, *et al.* Aspergillus sensitization in bronchial asthma: A separate phenotype. Allergy Asthma Proc 2020; 41(1): e26-e32.
DOI: https://doi.org/10.2500/aap.2020.41.190008

31. Papadopoulos NG, Apostolidou E, Miligkos M, Xepapadaki P. Bacteria and viruses and their role in the preschool wheeze to asthma transition. Pediatr Allergy Immunol 2024; 35(3): e14098.
DOI: https://doi.org/10.1111/pai.14098

32. Annesi-Maesano I, Cecchi L, Biagioni B, Chung KF, Clot B, Collaud Coen M, *et al.* Is exposure to pollen a risk factor for moderate and severe asthma exacerbations? Allergy 2023; 78(8): 2121-47.
DOI: https://doi.org/10.1111/all.15724

33. Pham DL, Le KM, Truong DD, Le HT, Trinh TH. Environmental allergen reduction in asthma management: an overview. Front Allergy 2023; 4: 1229238.
DOI: https://doi.org/10.3389/falgy.2023.1229238

34. Di Simone SK, Rudloff I, Nold-Petry CA, Forster SC, Nold MF. Understanding respiratory microbiome–immune system interactions in health and disease. Sci Translat Med 2023; 15(678): eabq5126.
DOI: https://doi.org/10.1126/scitranslmed.abq5126

35. Chevereau-Choquet M, Thoreau B, Taillé C, Marchand-Adam S, Morel H, Plantier L, *et al.* Smoking, urban housing, and work-aggravated asthma are associated with asthma severity in a cross-sectional observational study. J Asthma Allergy 2024: 69-79.
DOI: https://doi.org/10.2147/JAA.S424546

36. Cheng ZX, Wu YX, Jie ZJ, Li XJ, Zhang J. Genetic evidence on the causality between gut microbiota and various asthma phenotypes: A two-sample Mendelian randomization study. Front Cell Infect Microbiol 2024; 13: 1270067.
DOI: https://doi.org/10.3389/fcimb.2023.1270067

37. Hufnagl K, Pali-Schöll I, Roth-Walter F, Jensen-Jarolim E. Dysbiosis of the gut and lung microbiome has a role in asthma. In: Seminars in immunopathology. Berlin/Heidelberg: Springer Berlin Heidelberg 2020; Vol. 42, No. 1, pp. 75-93.
DOI: https://doi.org/10.1007/s00281-019-00775-y

38. Aghapour M, Ubags ND, Bruder D, Hiemstra PS, Sidhaye V, Rezaee F, *et al.* Role of air pollutants in airway epithelial barrier dysfunction in asthma and COPD. Eur Respirat Rev 2022; 31(163): 210112.
DOI: https://doi.org/10.1183/16000617.0112-2021

39. Baloh CH, Mathias RA. Recent progress in the genetic and epigenetic underpinnings of atopy. J Allergy Clin Immunol 2023; 151(1): 60-9.
DOI: https://doi.org/10.1016/j.jaci.2022.10.027

40. Mormile M, Mormile I, Fuschillo S, Rossi FW, Lamagna L, Ambrosino P, *et al.* Eosinophilic airway diseases: From pathophysiological mechanisms to clinical practice. Int J Mol Sci 2023; 24(8): 7254.
DOI: https://doi.org/10.3390/ijms24087254

41. Ling X, Jie W, Qin X, Zhang S, Shi K, Li T, *et al.* Gut microbiome sheds light on the development and treatment of abdominal aortic aneurysm. Front Cardiovasc Med 2022; 9: 1063683.
DOI: https://doi.org/10.3389/fcvm.2022.1063683

42. Okolie MC, Edo GI, Ainyanbhor IE, Jikah AN, Akpoghelie PO, Yousif E, *et al.* Gut microbiota and immunity in health and diseases: A review. Proc Indian Natl Sci Acad 2024; 1-8.
DOI: https://doi.org/10.1007/s43538-024-00355-1

43. Fiyouzi T, Pelaez-Prestel HF, Reyes-Manzanas R, Lafuente EM, Reche PA. Enhancing regulatory T cells to treat inflammatory and autoimmune diseases. Int J Mol Sci 2023; 24(9): 7797.
DOI: https://doi.org/10.3390/ijms24097797

44. Kim YC, Sohn KH, Kang HR. Gut microbiota dysbiosis and its impact on asthma and other lung diseases: potential therapeutic approaches. Korean J Intern Med 2024; 39(5): 746-58.
DOI: https://doi.org/10.3904/kjim.2023.451

45. Valverde-Molina J, García-Marcos L. Microbiome and asthma: microbial dysbiosis and the origins, phenotypes, persistence, and severity of asthma. Nutrients 2023; 15(3): 486.
DOI: https://doi.org/10.3390/nu15030486

46. Shin Y, Han S, Kwon J, Ju S, Choi TG, Kang I, *et al.* Roles of short-chain fatty acids in inflammatory bowel disease. Nutrients 2023; 15(20): 4466.
DOI: https://doi.org/10.3390/nu15204466

47. Garg AP, Ateeq A, Bisht N, Patil B. Management of asthma using probiotics. Explor Asthma Allergy 2024; 2(1): 9-32.
DOI: https://doi.org/10.37349/eaa.2024.00026

48. Zhang P. The role of diet and nutrition in allergic diseases. Nutrients 2023; 15(17): 3683.
DOI: https://doi.org/10.3390/nu15173683

49. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell 2021; 184(6): 1469-85.
DOI: https://doi.org/10.1016/j.cell.2021.02.016

50. Berdnikovs S, Newcomb DC, Hartert TV. How early life respiratory viral infections impact airway epithelial development and may lead to asthma. Front Pediatr 2024; 12: 1441293.
DOI: https://doi.org/10.3389/fped.2024.1441293

51. Vitte J, Vibhushan S, Bratti M, Montero-Hernandez JE, Blank U. Allergy, anaphylaxis, and no allergic hypersensitivity: IgE, mast cells, and beyond. Med Princ Pract 2022; 31(6): 501-15.
DOI: https://doi.org/10.1159/000527481

52. De Vleeschhauwer F, Casteels K, Hoffman I, Proesmans M, Rochtus A. Systemic adverse events associated with locally administered corticosteroids. Children 2024; 11(8): 951.
DOI: https://doi.org/10.3390/children11080951

53. de Oliveira DE, Leitão CG, Falcão FO, de Paiva Torquato JP, Neto JD, de Castro MA, *et al.* Immunobiological therapy in the treatment of severe asthma. Res Soc Develop 2024; 13(5): e14513545933.
DOI: https://doi.org/10.33448/rsd-v13i5.45933

54. Krings JG, Beasley R. The role of ICS-containing rescue therapy versus SABA alone in asthma management today. J Allergy Clin Immunol Pract 2024; 12(4): 870-9.
DOI: https://doi.org/10.1016/j.jaip.2024.01.011

55. Ma Y, Zhao H, Su Y. Ozone pollution and acute exacerbation of asthma in residents of china: An ecological study. J Asthma Allergy 2023; 2024: 951-60.
DOI: https://doi.org/10.2147/JAA.S422476

56. Kithara C, Kuniyoshi KM, Rehan VK. Preterm birth, developmental smoke/nicotine exposure, and life-long pulmonary sequelae. Children 2023; 10(4): 608.
DOI: https://doi.org/10.3390/children10040608

57. Shen K, Zhang M, Zhao R, Li Y, Li C, Hou X, *et al.* Eosinophil extracellular traps in asthma: Implications for pathogenesis and therapy. Respirat Res 2023; 24(1): 231.
DOI: https://doi.org/10.1186/s12931-023-02504-4

58. Jasemi SV, Khazaei H, Morovati MR, Joshi T, Aneva IY, Farzaei MH, *et al.* Phytochemicals as a treatment for allergic asthma: Therapeutic effects and mechanisms of action. Phytomedicine. 2023; 2023: 155149.
DOI: https://doi.org/10.1016/j.phymed.2023.155149

59. Sardon-Prado O, Diaz-Garcia C, Corcuera-Elosegui P, Korta-Murua J, Valverde-Molina J, Sanchez-Solis M. Severe asthma and biological therapies: now and the future. J Clin Med 2023; 12(18): 5846.
DOI: https://doi.org/10.3390/jcm12185846

60. Armillei MK, Lomakin IB, Del Rosso JQ, Grada A, Bunick CG. Scientific rationale and clinical basis for clindamycin use in the treatment of dermatologic disease. Antibiotics 2024; 13(3): 270.
DOI: https://doi.org/10.3390/antibiotics13030270

61. Tashiro H, Takahashi K, Uchida M, Kurihara Y, Sadamatsu H, Takamori A, *et al.* Effect of azithromycin on exacerbations in asthma patients with obesity: Protocol for a multi-center, prospective, single-arm intervention study. Int J Environ Res Public Health 2023; 20(3): 1861.
DOI: https://doi.org/10.3390/ijerph20031861

62. Parnham MJ, Norris V, Kricker JA, Gudjonsson T, Page CP. Prospects for macrolide therapy of asthma and COPD. Adv Pharmacol 2023; 98: 83-110.
DOI: https://doi.org/10.1016/bs.apha.2023.03.002

63. Van Dijck C, Laumen JG, de Block T, Abdellati S, De Baetselier I, Tsunamis A, *et al.* The oropharynx of men using HIV pre-exposure prophylaxis is enriched with antibiotic resistance genes: A cross-sectional observational metagenomic study. J Infect 2023; 86(4): 329-37.
DOI: https://doi.org/10.1016/j.jinf.2023.02.006

64. Garg AP, Ateeq A, Bisht N, Patil B. Management of asthma using probiotics. Explor Asthma Allergy 2024; 2(1): 9-32.
DOI: https://doi.org/10.37349/eaa.2024.00026

65. Shimokawa C, Kanaya T, Hachisuka M, Ishiwata K, Hisaeda H, Kurashima Y, *et al.* Mast cells are crucial for induction of group 2 innate lymphoid cells and clearance of helminth infections. Immunity 2017; 46(5): 863-74.
DOI: https://doi.org/10.1016/j.immuni.2017.04.017

66. Nightingale K, Lin KM, Ravenhill BJ, Davies C, Nobre L, Fielding CA, *et al* . High-definition analysis of host protein stability during human cytomegalovirus infection reveals antiviral factors and viral evasion mechanisms. Cell Host Microbe 2018; 24(3): 447-60.
DOI: https://doi.org/10.1016/j.chom.2018.07.011

67. Wu TD, Diamant Z, Hanania NA. An update on patient-reported outcomes in asthma. Chest 2024; 165(5): 1049-57.
DOI: https://doi.org/10.1016/j.chest.2024.02.010