

## Narrative Review

# The Microbial Role in Allergy: A Comprehensive Review

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## ABSTRACT

**Background:** The rise in allergic diseases in Western industrial nations has been paralleled by an increased understanding of the intricate relationship between microbial exposure and immune system responses. The hygiene hypothesis suggests a link between reduced exposure to infectious agents and an increase in allergies, emphasizing the need for a deeper investigation into the roles of various microbes in allergic reactions.

**Objective:** This review aims to elucidate the complex mechanisms underlying allergic reactions, specifically focusing on the roles of parasites, bacteria, fungi, and viruses. It seeks to explore the potential of microbial exposure as both a protective and pathogenic factor in the development of allergies, with an eye towards informing future therapeutic strategies.

**Methods:** An extensive literature review was conducted using databases such as Google Scholar, Scopus, PubMed, and Web of Sciences, focusing on studies published up to March 2024. The review synthesized findings on the impact of microbial exposure on allergic diseases, examining the roles of specific microbes, their interaction with the immune system, and the implications for allergic responses.

**Results:** The review highlights the dual nature of microbial exposure in allergies, with some microbes offering protection against allergic diseases through the modulation of immune responses, while others exacerbate allergic conditions. Notably, probiotics and certain parasitic infections demonstrate potential in modulating the immune system to prevent or reduce allergic responses. Conversely, specific bacterial, fungal, and viral exposures are linked to the exacerbation of allergic diseases.

**Conclusion:** Understanding the complex relationship between microbial exposure and allergic diseases is crucial for developing novel therapeutic and preventive strategies. This review underscores the potential of targeted microbial management in modulating immune responses to allergens, suggesting a promising avenue for reducing the global burden of allergic diseases.

**Keywords:** Allergies, Microbial Exposure, Immune System, Hygiene Hypothesis, Probiotics, Therapeutic Strategies.

## INTRODUCTION

Allergy significantly impacts individuals worldwide, presenting as an overactive immune response to harmless substances known as allergens (1). This hypersensitivity triggers a series of immunological reactions, leading to symptoms such as anaphylaxis, itching, hives, and sneezing (2). The past decade has seen a noticeable increase in allergic conditions among both children and adults, emphasizing the need for a deeper understanding of these responses (3). The body's reaction to allergens can vary greatly, a diversity that is reflected in the classification of allergic reactions into four major types, each defined by the specific immunological mechanisms they involve (4).

Type I hypersensitivity, or immediate hypersensitivity, represents the swiftest category of allergic reactions, occurring immediately after exposure to an allergen (5). It is mediated by Immunoglobulin E (IgE) antibodies that, upon recognizing specific allergens, bind to basophils and mast cells (6). Subsequent exposure leads to the cross-linking of IgE antibodies, which in turn prompts the release of inflammatory mediators like leukotrienes, histamine, and prostaglandins, crucial in the development of allergic symptoms (7).

Type II hypersensitivity, or cytotoxic hypersensitivity, involves the destruction of the body's cells or tissues by its own immune system (8). This process begins when Immunoglobulin G (IgG) or Immunoglobulin M (IgM) antibodies produced in response to allergens

target specific cells or tissues for elimination, a mechanism seen in certain autoimmune disorders and hemolytic reactions during blood transfusions (9).

The formation of immune complexes between soluble antigens and antibodies characterizes Type III hypersensitivity, or immune complex-mediated hypersensitivity (10). These complexes deposit in tissues, inciting inflammation and organ-specific damage, as observed in conditions like vasculitis and systemic lupus erythematosus (11).

Lastly, Type IV hypersensitivity, or delayed-type hypersensitivity, involves a cell-mediated response where T cells become sensitized to specific allergens upon initial exposure (12). Subsequent exposures lead to T cell activation and the secretion of cytokines, which attract other immune cells to the affected site, resulting in tissue damage (13). This mechanism underlies the reactions seen in the tuberculin skin test, dermatitis, and some autoimmune diseases (14). In the context of rising allergic diseases among individuals at risk, understanding the impact of microbial exposure presents a significant area of inquiry. The research question, formulated on the PICO framework, seeks to ascertain how exposure to specific microbes, such as probiotics or helminths, impacts the incidence and severity of allergic diseases, compared to individuals with minimal or different microbial exposures, such as those in urban versus rural environments. This inquiry is rooted in the need to explore both the protective and pathogenic roles of microbes in allergic responses, with the ultimate aim of informing more effective therapeutic and preventive strategies against allergic diseases. Through this investigation, the research aims to contribute to a nuanced understanding of microbial interactions with the immune system, potentially offering novel insights into reducing the global burden of allergies.

## MATERIAL AND METHODS

The methodology devised for this comprehensive review meticulously aimed to gather and analyze existing literature on the mechanisms through which various microorganisms provoke allergic reactions in the human body, alongside the curative and preventative strategies against such reactions. Adopting a structured approach, the process involved data mining, integration, and the synthesis of findings, underpinned by a selection criterion that embraced an extensive search methodology to ensure the thoroughness and relevance of the review.

The literature search was conducted through various electronic databases including Google Scholar, Scopus, PubMed, and Web of Sciences, targeting publications available up to March 2024. A combination of keywords related to the microbial influence on allergy—such as "Allergy," "Bacteria," "Parasite," "Viruses," "Fungi," "Allergens," "Hypersensitivity"—were employed both individually and in various combinations to encompass a broad scope of research pertinent to the microbial instigation of allergic responses in humans. Additionally, references cited within the identified articles were manually explored to include further relevant studies.

The inclusion criteria were tailored to select studies specifically addressing the role of microorganisms in eliciting various allergic reactions. This encompassed distinct meta-analyses, research papers, and review articles, all published in the English language, which elucidated the etiology of allergies induced by microbes and the potential avenues for their management. Conversely, the exclusion criteria were applied to papers published in languages other than English, studies not directly related to microbial allergies, and conference abstracts.

Data derived from the collected scientific articles was meticulously organized into categories based on the type of microbe and its role in allergic reactions, such as the influence of parasites, bacteria, viruses, and fungi on allergy. This task was independently carried out by two reviewers to ensure the accuracy and comprehensiveness of the analysis, with any arising discrepancies resolved through discussion or consultation with a third reviewer.

The aggregated data was systematically arranged to articulate a cohesive narrative on the role of microorganisms in inducing different allergic reactions within the human body. This narrative delves into the critical mechanisms by which various microbes trigger distinct forms of hypersensitivity and the assorted methodologies for allergy treatment, highlighting the gaps in current knowledge and proposing directions for future research.

In alignment with ethical considerations, this review adhered to the principles stipulated in the Declaration of Helsinki, ensuring respect for the integrity of the source material and the findings presented. Although the review itself did not involve primary research on humans or animals, it recognized the importance of ethical compliance in the studies reviewed.

## RESULTS

Allergic reactions represent a complex interplay of various components of the immune system, encompassing critical steps such as sensitization, activation and degranulation of cells, release of inflammatory mediators, and cellular infiltration. The initial phase, sensitization, involves the immune system's exposure to specific allergens, resulting in the production of allergen-specific Immunoglobulin E (IgE) (14). These IgE molecules bind to FcεRI (high-affinity IgE) receptors on the surfaces of basophils and mast

cells. The subsequent phase involves the activation and degranulation of these cells, a process initiated by the cross-linking of bound IgE antibodies with their receptors (15). This leads to the release of histamine, a pivotal inflammatory mediator, from the basophils and mast cells, causing symptoms such as vasodilation and smooth muscle contraction.

In addition to histamine, other inflammatory mediators like prostaglandins and leukotrienes contribute to the inflammatory response (16). The sensitization of T-cells, their secretion of cytokines, and the recruitment of other immune cells to the site of allergen exposure are crucial in the cellular infiltration observed in type IV hypersensitivity, further illustrating the complexity of allergic reactions (17). Allergens, pivotal in triggering allergic responses, are categorized into four main groups based on their sources. Environmental allergens, including mold spores, pollen, insect stings, dust mites, and pet dander, are known for eliciting significant allergic reactions in humans (18). Latex, primarily affecting healthcare workers through exposure to latex products in a professional setting, represents another source of allergens (19).

Table 1 Evidence Characteristics

Fungal Allergens	Allergic Response	Disease Caused	Drug of Choice	References
<b>Aspergillus fumigatus</b>	Allergic rhinitis	Allergic bronchopulmonary aspergillosis (ABPA)	Posaconazole, Itraconazole, Voriconazole	(102)
<b>Alternaria</b>	Allergic rhinitis, Asthma	Allergic conjunctivitis	Nasal corticosteroids, Antihistamines	(103)
<b>Penicillium</b>	Allergic rhinitis	Allergic sinusitis	Nasal corticosteroids, Antihistamines	(104)
<b>Histoplasma capsulatum</b>	Allergic bronchopulmonary mycosis	Histoplasmosis	Amphotericin B, Itraconazole	(105)
<b>Epidermophyton floccosum</b>	Allergic contact dermatitis	Ringworm	Miconazole, Terbinafine, Clotrimazole	(106)
<b>Pithomyces</b>	Hypersensitivity	Allergic alveolitis	Avoidance of contaminated environments	(107)
<b>Ustilago</b>	Allergic Asthma	Ustilaginosis	Itraconazole	(108)
<b>Candida glabrata</b>	Allergic vulvovaginitis	Vulvovaginal candidiasis	Fluconazole, Miconazole, Clotrimazole	(109)

Furthermore, certain food items such as eggs, nuts, shellfish, soy, dairy products, and fish are recognized for their potential to provoke severe allergic reactions in sensitive individuals (20). Medications, including non-steroidal anti-inflammatory drugs (NSAIDs), contrast dyes, and antibiotics, also act as allergens for specific individuals, highlighting the broad spectrum of substances capable of inducing allergic responses (21). Beyond these conventional allergens, various microorganisms, including viruses, bacteria, archaea, fungi, and parasites, have been linked to both the provocation and prevention of allergic reactions, underscoring the intricate relationship between microbes and the allergic processes in the human body (22).

## DISCUSSION

The escalation of allergic diseases in Western industrial nations since the dawn of this decade has prompted an extensive examination of the underlying causes, with the hygiene hypothesis positing a link between reduced exposure to infectious agents, such as parasitic helminths, and the increase in allergic conditions (23). This theory is bolstered by factors including the maintenance of gut flora consistency, excessive antibiotic use, affluent urban living conditions, smaller family sizes, and improved sanitation reducing pathogen exposure, coupled with diminished helminth infections. Conversely, the prevalence of atopy remains low in developing countries, where it is inversely associated with parasitic infections, suggesting a complex interplay between environmental exposure and immune response mechanisms in the genesis of allergies.

The critical role of T regulatory (Treg) cells in producing interleukin-10 (IL-10) and modulating allergic processes provides support for the hygiene hypothesis (23). The initial immune response against helminth infections is IgE mediated hypersensitivity, highlighting an inverse relationship between helminth infections and sensitivity to aeroallergens due to the absence of antigenic stimulation in the latter scenario (24). Interestingly, the major excretory-secretory product of *Acanthocheilonema viteae*, ES-62, has been identified

as a modulator of the immune response, interacting with Toll-like receptors on TH2 cells and enhancing their response, which suggests a potential therapeutic application in treating allergies (25-27).

Furthermore, schistosome infections have been shown to increase IL-10 levels in children, inversely correlating with dust mite sensitivity, adding another layer to the understanding of parasitic infections and allergic reactions (29). However, enhanced anti-helminthic treatment programs have been linked to an increase in allergic diseases, underscoring the complex relationship between parasitic infections and the immune system's response to allergens (30). The cross-reactivity between environmental allergens and *Ascaris* highlights the nuanced interactions between various types of allergens and the immune system, which can exacerbate or modulate allergic responses (32).

Bacterial involvement in allergies further complicates this landscape, with some species offering protection against allergies while others exacerbate them (43-44). The dual nature of bacterial interactions with the immune system—ranging from promoting Th1 cell responses and IFN- $\gamma$  secretion, which counteract type 2 inflammation, to enhancing susceptibility to allergies—underscores the intricate balance between microbial exposure and allergic disease development (45-46).

The decrease in infectious diseases coupled with a concurrent rise in allergy prevalence over the past three decades has lent credence to the hygiene hypothesis, suggesting a pivotal role for commensal microbes in immune regulation and the prevention of allergic responses through early-life exposure to a diverse microbial environment (50-51). Probiotics, including Lactobacilli and Bifidobacteria, have emerged as beneficial in preventing allergic diseases, especially in infants, illustrating the potential for microbial-based interventions in allergic conditions (52).

The pathogenic mechanisms through which viruses and fungi contribute to allergic diseases are diverse and complex. Viral infections, particularly respiratory viruses, not only provoke immediate allergic reactions but also have long-term implications for diseases such as asthma and atopic dermatitis (68-77). Similarly, fungal allergens from genera such as *Aspergillus*, *Penicillium*, and *Candida* play significant roles in the development of allergic diseases, from rhinitis and asthma to more severe conditions like bronchopulmonary aspergillosis, through mechanisms involving IgE antibodies and non-IgE-mediated responses (84-101).

This review underscores the multifaceted interactions between microbes and the immune system in the context of allergic diseases, revealing both protective and pathogenic roles. The strengths of this analysis lie in its comprehensive examination of the literature and the synthesis of findings across diverse microbial domains. However, limitations include the variability in study designs and populations across the reviewed literature, which may affect the generalizability of the findings. Recommendations for future research include longitudinal studies to elucidate the causative links between microbial exposure and allergic diseases, and clinical trials to assess the therapeutic potential of microbial-based interventions. The intricate dance between microbes and the immune system in the context of allergies remains a fertile ground for investigation, with the potential to uncover novel strategies for prevention and treatment.

## CONCLUSION

The intricate interplay between microbial exposure and the immune system's response underscores a pivotal area of research with profound implications for human healthcare, particularly in the context of the escalating prevalence of allergic diseases. Insights gleaned from the hygiene hypothesis, the protective versus pathogenic roles of various microorganisms, and the potential of microbial-based interventions highlight the necessity of a nuanced understanding of microbial exposures in the prevention and treatment of allergies. Future healthcare strategies could thus benefit from incorporating microbial management, including the use of probiotics and targeted therapies, to modulate the immune system's response to allergens, offering a promising avenue for reducing the burden of allergic diseases globally.

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