Review article

DOI: 10.32415/jscientia_2025_11_2_21-32
EDN: JJLJSA

Liver Dysfunction and Microbiome Imbalance: Their Role in the Development of Allergic Reactions

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Over the past decades, there has been a significant increase in the prevalence of allergic diseases, attributed to multiple factors, including liver dysfunction and gut microbiome imbalance. The liver plays a central role in allergen detoxification, immune response regulation, metabolism of inflammatory mediators, and maintenance of immune tolerance. Impairment of liver function can lead to the accumulation of toxins and metabolic byproducts, contributing to hypersensitivity and inflammatory processes. On the other hand, the gut microbiota actively participates in immune homeostasis and the development of antigen tolerance. Disruptions in its composition provoke systemic inflammation and reduce immune tolerance, thereby enhancing susceptibility to allergic reactions. The interplay between liver dysfunction, microbiota, and allergic responses highlights the complex pathogenesis of allergic diseases. This review examines the mechanisms underlying the relationship between liver function, microbiome composition, and the development of allergic reactions. Restoring liver function and normalizing the microbiome may serve as promising strategies for the prevention and treatment of allergic diseases.

KEYWORDS: gastrointestinal tract, gallbladder, liver, liver dysfunction, microbiome, dysbiosis, parasitic invasion, allergic reaction, allergy

FOR CITATION: Izmailovich MR, Dedova OY, Koshkarbayeva BS, Knaus AA, Seksenova LS, Zharkeeva NB, Madatova KD, Irgizbayeva KM, Sharipzhanova AO. Liver Dysfunction and Microbiome Imbalance: Their Role in the Development of Allergic Reactions. *Juvenis Scientia*. **2025**;11(2):21-32. DOI: 10.32415/jscientia_2025_11_2_21-32.

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© Izmailovich M.R., Dedova O.Yu., Koshkarbayeva B.S., Knaus A.A., Seksenova L.Sh., Zharkeeva N.B., Madatova K.D., Irgizbayeva K.M., Sharipzhanova A.O., 2025

Обзорная статья
DOI: 10.32415/jscientia_2025_11_2_21-32
EDN: JJLJSA

Дисфункция печени и нарушение баланса микробиома: роль в развитии аллергических реакций

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За последние десятилетия наблюдается значительное увеличение распространённости аллергических заболеваний, что обусловлено множеством факторов, включая дисфункцию печени и нарушение баланса кишечной микробиоты. Печень играет центральную роль в детоксикации аллергенов, регуляции иммунного ответа, метаболизме медиаторов воспаления и поддержании иммунологической толерантности. Нарушение функций печени может привести к накоплению токсинов и побочных продуктов метаболизма, способствуя развитию гиперчувствительности и воспалительных процессов. С другой стороны, кишечная микробиота активно участвует в поддержании иммунного гомеостаза и формировании антигенной толерантности. Изменения в её составе провоцируют системное воспаление и снижение иммунной толерантности, тем самым повышая восприимчивость к аллергическим реакциям. Взаимосвязь между нарушениями функции печени, микробиоты и аллергическими реакциями подчёркивает сложность патогенеза аллергических заболеваний. Настоящий обзор посвящён анализу механизмов, лежащих в основе связи между функцией печени, составом микробиоты и развитием аллергических реакций. Восстановление функций печени и нормализация микробиоты могут рассматриваться как перспективные стратегии профилактики и лечения аллергических заболеваний.

КЛЮЧЕВЫЕ СЛОВА: желудочно-кишечный тракт, жёлчный пузырь, печень, дисфункция печени, микробиота, дисбиоз, паразитарные инвазии, аллергическая реакция, аллергия

ДЛЯ ЦИТИРОВАНИЯ: Измайлович МР, Дедова ОЮ, Кошкарбаева БС, Кнаус АА, Сексенова ЛШ, Жаркеева НБ, Мадатова ХД, Иргизбаева КМ, Шарипжанова АО. Дисфункция печени и нарушение баланса микробиома: роль в развитии аллергических реакций. *Juvenis Scientia*. **2025**;11(2):21-32. DOI: 10.32415/jscientia_2025_11_2_21-32. EDN: JJLJSA.

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INTRODUCTION

In recent years, the relationship between biliary system pathology, gut microbiome disturbances, and the development of allergic diseases has been actively investigated. Bile acids play a key role in regulating the gut microbiota. In biliary system disorders, their secretion and composition are altered, leading to dysbiosis, a weakened intestinal barrier, and the activation of inflammatory processes [1].

The biliary system, which includes the gallbladder, bile ducts, and liver, is essential for digestion and metabolism. Disorders such as cholecystitis, cholestasis, and biliary dyskinesia have systemic effects on the body, including the immune system. These conditions can contribute to chronic inflammation and changes in gut microbiota composition, making them significant factors in the pathogenesis of allergic diseases [2].

Allergic diseases, including asthma, atopic dermatitis, and food allergies, represent a growing public health concern. They are characterized by an exaggerated immune response to various allergens and are accompanied by inflammatory processes. Despite extensive research, the pathogenesis of allergic reactions remains multifaceted and not fully understood, particularly concerning the impact of comorbid biliary system disorders [3].

There is increasing evidence suggesting that biliary system dysfunction may contribute to the development of allergic diseases through the activation of inflammatory pathways, disruption of immune regulation, and microbiome imbalance. Additionally, alterations in intestinal epithelial permeability associated with biliary disorders may enhance antigen translocation, triggering immune hyperreactivity [4].

The combined effects of biliary dysfunction and microbiome disturbances represent a complex pathogenic mechanism involving metabolic imbalances, inflammatory cascade activation, and immune shifts [5].

Therefore, investigating the interplay between biliary system disorders, the gut microbiome, and allergic diseases is a crucial task requiring a multidisciplinary approach [1].

MATERIALS AND METHODS

A literature review was conducted using an automated search for relevant sources based on the keywords “gastrointestinal tract”; “gallbladder”; “liver dysfunction”; “microbiome”; “allergic reaction”; “allergy” in scientific databases such as PubMed, e-Library, and manual searches in Google Scholar. The search covered a 10-year period (2014–2024). Sources were selected according to the fundamental context of the study.

In the first stage, a broad collection of articles was gathered, from which the most relevant ones were filtered based on keywords and contextual relevance. In the second stage, the selected sources were analyzed, and key informational segments were extracted and subsequently used in the writing of this review.

RESULTS AND DISCUSSION

The biliary system comprises several anatomical and physiological components that play a crucial role in lipid metabolism and detoxification. The most common pathologies include cholecystitis, cholangitis, and cholestasis, which may result from infections, autoimmune diseases, metabolic disorders, and even stress factors [6]. Bile is essential for fat metabolism, detoxification of fat-soluble substances, and maintaining a normal microbial balance in the gut due to its antibacterial properties. It facilitates the excretion of metabolic byproducts, pharmaceuticals, and endogenous substances (hormones and cellular degradation products). In biliary system pathologies, these processes become impaired, leading to toxin accumulation in the body, systemic inflammatory responses, and increased sensitization to allergens [7].

Insufficient bile flow into the intestines disrupts digestion, weakens the intestinal barrier function, and promotes the absorption of partially digested protein molecules, which possess allergenic properties. Additionally, such molecules may trigger pseudoallergic reactions by stimulating the release of biologically active substances from target cells [8].

Proper digestion and nutrient absorption depend on the neuroendocrine system, gastrointestinal (GI) tract anatomy and function, liver and biliary tract efficiency, as well as the composition and volume of digestive secretions, gut microbiota, and local mucosal immunity. Under normal conditions, food is broken down into safe molecular components, such as amino acids, which do not provoke allergic reac-

tions. The intestinal barrier prevents the penetration of undigested substances that could trigger allergic or pseudoallergic responses [6]. However, inflammatory GI diseases, pancreatic dysfunction, enzymatic deficiencies, and dyskinesia of the biliary and intestinal tracts can lead to increased intestinal permeability, facilitating the absorption of undigested food components. This, in turn, may contribute to food allergies or pseudoallergic reactions [9].

The prevalence of gallstone disease (cholelithiasis) and other biliary system disorders has been rising globally. This trend is attributed to lifestyle changes and the growing incidence of obesity, diabetes mellitus, and metabolic syndrome. The highest prevalence of biliary system diseases is observed in high-income countries, where a Western diet, rich in fats and refined carbohydrates, contributes to metabolic disturbances and an increased risk of gallstone disease and biliary dysfunction [10].

Biliary dysfunction, such as cholestasis or biliary cirrhosis, may lead to toxin accumulation and systemic inflammatory responses, thereby increasing susceptibility to allergic conditions [11]. Research has shown that impaired bile secretion and flow can result in immune system sensitization and elevated levels of pro-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), which play a pivotal role in allergic disease development [12].

Studies indicate that patients with biliary tract diseases, such as cholecystitis or cholangitis, may exhibit an increased predisposition to allergic reactions. This is due to the impact of biliary tract dysfunction on the gut microbiome, which, in turn, affects the immune response. Alterations in the microbiome can disrupt the balance between pro-inflammatory and anti-inflammatory processes, thereby promoting the onset of allergic conditions [12].

KEY MECHANISMS OF BILIARY PATHOLOGY IN THE DEVELOPMENT OF ALLERGIC REACTIONS

Biliary dysfunction plays a crucial role in the development of allergic reactions by disrupting key metabolic and immune processes. Figure 1 outlines four primary mechanisms linking impaired bile metabolism to increased allergy susceptibility.

These mechanisms include toxin accumulation, liver dysfunction, immune system dysregulation, and gut microbiome alterations, all of which contribute to heightened allergic responses. Understanding these connections can help to develop targeted strategies for managing allergic diseases associated with biliary pathology.

1. Impaired Metabolism of Allergens and Toxins and Its Impact on the Immune System

In biliary system disorders (e.g., cholestasis), bile excretion is disrupted, leading to the accumulation of metabolites capable of triggering or exacerbating allergic reactions. Biliary pathology results in toxin retention, which increases the overall burden on the immune system. Under these conditions, the likelihood of an exaggerated immune response to otherwise harmless substances rises, manifesting as allergic reactions [5].

When bile flow is obstructed, substances such as bilirubin, bile acids, and toxins accumulate in the body, potentially leading to hepatic dysfunction and systemic toxicity. The liver is responsible for detoxifying allergens and metabolizing various compounds. In cases of hepatic impairment, metabolic byproducts, including allergens, may not be properly broken down, increasing their bioavailability. The accumulation of toxic substances can alter immune function, leading to heightened sensitivity to allergens. Once the im-

Impaired Metabolism of Allergens and Toxins	Liver Dysfunction	Impact on the Immune System	Disruption of the Gut Microbiome
↑ IL-1, TNF-α Th2 activation	T-cell activation IgE production	Cytokine imbalance Chronic inflammation	Dysbiosis Altered microbiota

Figure 1. Key Mechanisms Linking Biliary Dysfunction to Allergic Reactions [3, 5, 6, 8, 9]

mune system is activated, it triggers an inflammatory response, further exacerbating allergic reactions.

Toxins can also stimulate the production of pro-inflammatory cytokines (e.g., IL-1, TNF-α), which activate macrophages and T-cells, thereby amplifying allergic responses. Furthermore, increased Th2-type helper T-cell activity has been observed following toxic exposure, which is closely linked to allergic reactions. For instance, patients with chronic cholecystitis exhibit an increased susceptibility to allergies, particularly to food additives [3].

2. Liver Dysfunction

The liver plays a central role in allergen detoxification. Impaired hepatic function, such as in cholestasis, can lead to reduced antigen metabolism and increased sensitivity to allergens. If the liver's detoxification capacity is compromised, allergens from food and the environment may accumulate, increasing the likelihood that the immune system will recognize them as foreign threats. This can result in T-cell activation and IgE production, both of which are key drivers of allergic reactions [13].

The liver also regulates histamine levels, a key mediator in allergic responses. Biliary dysfunction can disrupt histamine metabolism, leading to its accumulation in the body and triggering symptoms resembling allergic reactions [14].

Liver Dysfunction and Its Impact on Histamine Metabolism and Allergic Diseases

Histamine metabolism primarily occurs in the liver, where the enzymes histaminase and N-methyltransferase break down histamine, preventing its accumulation and thereby reducing the risk of allergic reactions [15].

In cases of hepatic dysfunction, histamine metabolism slows, leading to elevated histamine levels in the bloodstream. This accumulation intensifies allergic symptoms, such as pruritus (itching) and edema (swelling). Impaired histamine metabolism in liver dysfunction is associated with increased sensitivity to allergens and a higher risk of hypersensitivity reactions [16].

The histamine pathway plays a key role in both true allergic reactions and pseudoallergies, which are not mediated by IgE sensitization. Histamine is primarily produced through the activity of the enzyme histidine decarboxylase (HDC), which catalyzes the conversion of the amino acid histidine into biologically active histamine. According to Ku et al. (2014), bile acids can increase the expression of HDC in gastric cells, thereby enhancing local histamine production and potentially exacerbating inflammatory and allergy-like responses in the gastrointestinal tract [17]. Additionally, as highlighted by Hrubisko et al. (2021), histamine intolerance (HIT) results from an imbalance between histamine intake (via food, microbiota, or enteroendocrine cells) and its degradation, primarily by the enzyme diamine oxidase (DAO) [18]. Liver and intestinal disorders, along with microbiota-associated disruptions, may reduce DAO activity, leading to histamine accumulation and the development of allergy-like symptoms — such as pruritus, urticaria, headaches, diarrhea, and bronchospasm. Thus, the histamine pathway can play a dual role by enhancing IgE-mediated allergic responses and causing pseudoallergic manifestations, especially in the context of hepatobiliary dysfunction and dysbiosis [14].

3. Impact on the Immune System

The liver and biliary system play a crucial role in immune regulation. Inflammatory processes in the liver, such as those occurring in biliary cirrhosis, lead to an imbalance in the production of pro-inflammatory cytokines, which can enhance allergic reactions. For example, Th2 immune responses, which are responsible for allergic reactions, may become activated in the presence of inflammation and toxins [3].

A 2015 study demonstrated that biliary system disorders, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), are associated with immune dysregulation, potentially contributing to allergic reactions. These conditions are often accompanied by cutaneous manifestations, such as pruritus (cholestatic itching), which result from bile flow obstruction. The immune system plays a pivotal role in these processes, further confirming the link between biliary dysfunction and allergic reactions [19]. Chronic inflammation, characteristic of biliary system diseases, activates immune pathways, increasing the likelihood of allergic responses [3].

4. Disruption of the Gut Microbiome

Bile has antibacterial properties in the gut and plays a key role in maintaining microbial balance. Biliary dysfunction can alter the gut microbiota composition, potentially modifying immune responses [20].

This relationship is bidirectional. Zhu Q et al. demonstrated that in acute cholecystitis, patients' exosomes contained elevated levels of Proteobacteria, whereas in chronic cholecystitis, Actinobacteria, Bacteroidetes, and Firmicutes predominated. The study also revealed significant metabolic pathway differences between these groups, including amino acid metabolism, carbohydrate metabolism, and membrane transport [21].

Changes in the gut microbiome can cause cytokine imbalances and disrupt other immune mediators, leading to increased sensitivity to allergens [20]. A healthy microbiome is crucial for recognizing allergens and promoting immune tolerance [22]. The microbiota modulates immune responses, and its dysregulation can result in increased intestinal barrier permeability, facilitating antigen entry into the bloodstream and triggering systemic inflammation [23, 24].

Bacterial imbalance in the gut may also compromise immune defense mechanisms [25]. In 2023, the European Academy of Allergy and Clinical Immunology (EAACI) introduced an updated classification of hypersensitivity reactions, expanding it to nine types. Particular attention was given to Type V hypersensitivity, which is linked to epithelial barrier dysfunction [26].

Epithelial barrier defects, such as weakened tight junctions between cells, can lead to increased tissue permeability, allowing allergens and pathogens to penetrate the body more easily. This activates immune responses, increasing the risk of allergic conditions [27]. Disruptions in microbiota composition — due to poor diet, stress, or antibiotic use — can reduce tight junction protein expression, including claudins and occludins, which weakens intercellular connections and increases barrier permeability [28, 29].

One of the key functions of the microbiome is the modulation of T-regulatory cell differentiation in Peyer's patches. These specialized structures in the gut are a critical component of immune function, shaping the body's response to antigens [30].

Alterations in microbiota composition may shift immune responses toward Th1 or Th2 CD4+ T-cell subpopulations. Under the influence of cytokines, such as interleukins and interferon-gamma, dysbiosis may promote excessive Th1 differentiation, which is associated with chronic inflammation and autoimmune processes. Conversely, a decrease in certain commensal bacteria favors Th2-dominant responses, leading to increased eosinophil activity and elevated IL-5 and IL-13 production. This results in excessive IgE synthesis and a heightened predisposition to allergic diseases [30, 31].

Studies conducted in 2014 highlight the central role of the microbiome in immune system modulation, influencing processes from cellular development to organ and tissue formation. The microbiota exerts these effects through multiple interactions with both innate and adaptive immune pathways [32].

Barcik W and colleagues described the impact of the gut microbiota on asthma development. The connection between the lungs and the gut has been repeatedly demonstrated in studies conducted on both humans and mice. Inducible bronchus-associated lymphoid tissue (iBALT) and gut-associated lymphoid tissue (GALT), both components of the mucosa-associated lymphoid tissue (MALT) system, share similar morphology and functions, including the regulation of local immune responses. An imbalance between symbiotic and pathogenic bacterial strains in the gut and lungs can lead to immune system alterations and inflammatory responses [33].

Studies have shown that changes in the microbiota of the gallbladder and intestines may play a key role in the development of inflammatory and allergic disorders. Additionally, biliary salts released into the intestines have a direct impact on microbiota composition and activity, further exacerbating inflammation and dysbiosis [34].

Another study highlighted the antimicrobial properties of bile acids, which can modulate immune responses by interacting with host cell receptors [35].

THE ROLE OF PROBIOTICS IN IMMUNE TOLERANCE

Lactobacilli and Bifidobacteria play a crucial role in the development of immune tolerance. Probiotics can modulate immune responses in a manner simi-

lar to the natural gut microbiota. Clinical trials have demonstrated the efficacy of perinatal and early probiotic administration in preventing food allergies. The balanced combination of Lactobacillus rhamnosus and Bifidobacterium longum represents a synergistic bacterial symbiosis that enhances each other's effectiveness, promoting optimal gut microbiota colonization from birth and serving as a preventive strategy against both infectious diseases and food allergies. A combined probiotic formulation containing both *Lactobacillus rhamnosus* and *Bifidobacterium longum* appears to be an optimal choice [36].

HELMINTH INVASIONS AS A FACTOR IN MICROBIOME DYSBIOSIS

One of the aspects of microbiome disruption is parasitic invasions. Parasitic invasions can be considered a form of dysbiosis, as they directly influence the composition and function of the microbiota. Helminths and other parasites compete with normal microflora, disrupting its balance [37]. This interaction exacerbates inflammatory processes, impairs the intestinal barrier function, and promotes hypersensitivity reactions, including allergies. Thus, parasitic invasions not only result from microbiome imbalances but also further exacerbate dysbiosis [38].

Helminth invasions are associated with a reduction in microbial diversity, leading to decreased production of short-chain fatty acids (SCFAs), which are essential for anti-inflammatory processes [39].

Increased intestinal permeability in helminth invasions facilitates antigen translocation, allowing parasite antigens and allergens to activate the immune system, thereby contributing to allergic sensitization [40].

Key Mechanisms of Parasitic Invasions in the Development of Allergic Diseases

Parasitic invasions play a significant role in the development of allergic diseases by altering immune responses and disrupting tissue integrity. Parasites can trigger hypersensitivity reactions, promote inflammatory processes, and modulate immune system activity, leading to increased susceptibility to allergies (Figure 2).

These mechanisms include immune hypersensitivity, tissue damage, reduced immune tolerance, and disruptions in bacterial balance. Understanding these interactions may provide new insights into allergy prevention and treatment strategies.

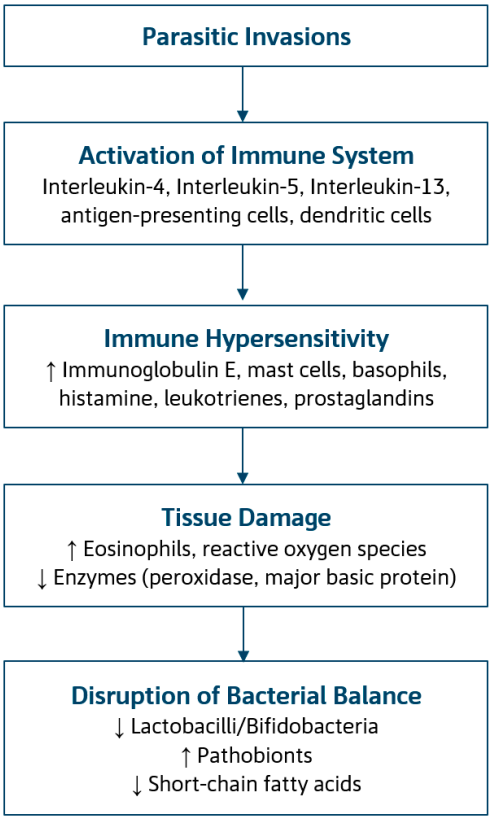

Figure 2. Key Mechanisms of Parasitic Invasions in Allergy Development [7, 8, 23, 28, 32, 33]

1. Immune Hypersensitivity

Parasites stimulate antibody production, particularly IgE, which leads to mast cell degranulation and the release of histamine, prostaglandins, and leukotrienes [41]. These mediators contribute to inflammatory reactions, manifesting as itching, swelling, and bronchospasms [37].

2. Parasitic Metabolites and Tissue Damage

Parasites secrete proteins and enzymes that damage the intestinal mucosa, reducing its integrity and increasing epithelial permeability. This weakens

non-specific defense mechanisms, facilitates immune cell activation, and enhances inflammation, thereby increasing the risk of atopy [30].

3. Reduced Immune Tolerance

Helminths suppress Th1 immune responses while stimulating Th2 responses, leading to increased IgE production and elevated levels of cytokines such as IL-4, IL-5, and IL-13. This promotes the development of type I hypersensitivity and increases the risk of bronchial asthma, atopic dermatitis, and allergic rhinitis. However, in some cases, the immune response to helminths may compete with allergic reactions, potentially reducing their severity [31].

Due to their large size, helminths cannot be cleared through classical phagocytosis. Instead, immune cells release enzymes and reactive molecules, such as reactive oxygen species (ROS) and myeloperoxidase, which amplify inflammatory processes [30].

4. Disruption of Bacterial Balance

Research into parasite-microbiota interactions presents new opportunities for the prevention and treatment of allergic diseases. The use of probiotics and prebiotics has been shown to restore microbial balance and modulate immune responses, thereby reducing allergic manifestations [34].

Numerous scientific studies classify parasitic invasions and allergic diseases as global health concerns [32, 37].

Allergic reactions induced by parasites are often accompanied by a combination of allergic, gastrointestinal, and neurovegetative syndromes. A distinguishing characteristic of parasitic allergy is its chronic nature, recurrent episodes, and resistance to anti-allergic medications, particularly glucocorticosteroids (GCS) [33].

Peripheral eosinophilia and elevated total IgE levels in individuals without a prior history of allergies may indicate parasitic infections [42]. In allergic patients, parasitic invasions should be considered a trigger that exacerbates allergic manifestations and acts as a source of endogenous allergens, further sensitizing the body [43]. Timely diagnosis and targeted treatment of parasitic invasions often lead to significant clinical improvement and alleviation of allergy symptoms [35].

FUTURE RESEARCH DIRECTIONS

Despite these findings, important unresolved questions remain regarding the potential use of helminth-derived molecules for the prevention and treatment of asthma and other allergic diseases [36]. Further research is required to determine the therapeutic applications and long-term safety of helminth-based immunomodulatory treatments.

CONCLUSION

Biliary system disorders, such as cholestasis, cholecystitis, and cholangitis, can significantly contribute to the development of allergic reactions through mechanisms including detoxification impairment, gut microbiome alterations, systemic inflammatory processes, and immune response modulation. Thus, biliary dysfunction, bile secretion disturbances, and microbiota imbalances are important risk factors for allergic diseases. Early diagnosis and a comprehensive therapeutic approach, incorporating liver function restoration and microbiome balance correction, present new opportunities for managing such conditions.

The gut microbiota plays a crucial role in the development and function of the immune system. Microbiome disturbances are linked not only to gastrointestinal disorders and intestinal infections but also to immune dysregulation, including allergic reactions. Studies suggest that a diverse microbiome may reduce allergy risk, while its deficiency or imbalance can contribute to allergic disease development. However, ongoing research is required to fully elucidate the complex interactions between the microbiota and allergic conditions.

The similarities between inflammatory processes in food allergies and parasitic invasions highlight the importance of differential diagnosis in identifying the causes of clinical manifestations. Parasitic invasions may exhibit allergenic properties, potentially triggering allergic reactions. In cases of non-specific allergy-like symptoms, simultaneous allergological and parasitological investigations are recommended to identify the true source of symptoms and determine the most appropriate treatment strategy.

The integration of modern medical diagnostic methods into differential diagnostics will help to prevent unnecessary use of anti-allergic medications and

ensure timely identification and effective treatment of both allergic and parasitic diseases.

Conflict of Interest: The authors declare no conflict of interest.

Funding: The authors declare no funding.

Authors' Contributions: Conceptualization, D.O. and S.L.; methodology, K.B. and K.A.; validation, Zh.N.; formal analysis, I.M.; investigation, Zn.N. and M.Kh.; resources, I.K. and Sh.A.; data curation, I.M.; writing — original draft preparation, Zn.N. and M.Kh.; writing — review and editing, I.K. and Sh.A.; supervision, I.M.; project administration, I. M. All authors have read and agreed to the published version of the manuscript.

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Поступила в редакцию: | Received: 26.02.2025
Поступила после доработки: | Revised: 12.04.2025
Принята: | Accepted: 15.04.2025