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REVIEW

Systemic Immune Dysregulation in Allergic Rhinitis: Mechanisms, Comorbidities, and Implications for Targeted Therapy

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Abstract: Allergic rhinitis (AR) has traditionally been regarded as a localized inflammatory disorder of the nasal mucosa. However, accumulating evidence indicates that AR is associated with systemic immune dysregulation characterized by peripheral eosinophilia, altered T helper cell polarization, circulating cytokine imbalances, and widespread inflammatory signaling. This systemic immune disturbance contributes to the frequent coexistence of AR with asthma, atopic dermatitis, and other immune-mediated conditions. These associations support the concept of AR as part of a unified airway and systemic allergic disease spectrum. In this review, we summarize current insights into the immunopathogenesis of AR from both local and systemic perspectives. We focus on epithelial barrier dysfunction, type 2 immune responses, and immune cell trafficking between the upper and lower airways. We further discuss emerging systemic inflammatory biomarkers and their potential clinical relevance in disease stratification and management. Finally, we highlight recent advances in allergen immunotherapy and targeted biologic therapies, emphasizing their implications for precision treatment of AR and its comorbidities. Recognizing AR as a manifestation of systemic immune dysregulation may facilitate improved disease classification and support the development of more effective, individualized therapeutic strategies.

Keywords: allergic rhinitis, systemic immune dysregulation, type 2 inflammation, comorbidities, allergen immunotherapy, biologic therapy

Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease mediated by immunoglobulin E (IgE), primarily characterized by immune responses in the nasal mucosa. Typical symptoms include nasal congestion, clear rhinorrhea, frequent sneezing, and nasal itching. However, accumulating evidence suggests that AR is associated with systemic immune dysregulation rather than being confined to local nasal inflammation. These symptoms severely affect the quality of life of patients, leading to decreased learning, work, and social productivity.[1] Epidemiological data indicate that 10–40% of the global population is affected by AR, and prevalence continues to rise, adding substantially to the healthcare and socioeconomic burden.[2,3] Growing evidence supports AR as a condition associated with systemic immune dysregulation that contributes to disease persistence and comorbidities.

AR has long been managed as an upper-airway disorder, yet multiple studies now indicate that nasal inflammation can align with broader immune alterations beyond the nasal mucosa.[4,5] Some patients may exhibit signs of systemic immune activation, characterized by an increase in eosinophils in peripheral blood and elevated serum cytokine levels, even in the absence of typical respiratory symptoms.[6] Moreover, AR is often comorbid with asthma, atopic dermatitis (AD), allergic conjunctivitis, and metabolic syndrome, further supporting its systemic nature.[7]

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Viewing AR as a syndrome of systemic immune dysregulation has significant scientific and clinical implications. From a basic research perspective, this shift in understanding prompts us to re-examine its pathogenesis and the construction of immune networks. Clinically, this transition requires expanding treatment strategies from traditional local therapies to systemic immune regulation, including precision diagnosis, systemic treatment, and long-term disease management. To explore the question of whether AR should be regarded as a systemic disease, this article provides a comprehensive analysis based on literature from the past decade. This review focuses on recent advances in understanding allergic rhinitis as a manifestation of systemic immune dysregulation. We summarize key local and systemic immunological mechanisms, discuss the association between allergic rhinitis and common comorbidities, and highlight implications for emerging targeted and precision therapies.

Diagnostic Methods and Immune Phenotype Classification of AR

Clinically, the diagnosis of AR relies on typical symptoms, allergic history, and a series of objective testing methods.[8] Typical symptoms include recurrent sneezing, clear rhinorrhea, nasal itching, and nasal congestion, often triggered or exacerbated by exposure to specific allergens.[9] Skin prick tests and serum-specific IgE (sIgE) tests are commonly used tools for identifying sensitizing allergens and excluding non-IgE-mediated rhinitis.[10] Additionally, nasal endoscopy helps assess nasal mucosal edema, the nature of secretions, and the presence of nasal polyps, providing a basis for disease classification and treatment decision-making.[11]

According to the "Allergic Rhinitis and its Impact on Asthma" (ARIA) guidelines, AR can be classified into intermittent and persistent types based on symptom duration, and further categorized by severity and impact on quality of life.[12] This classification system not only considers the frequency and intensity of symptoms but also evaluates the impact on sleep, daily activities, work, and learning efficiency, helping to identify high-risk individuals who require intensified treatment.[13] Moreover, some studies have classified patients based on immune phenotypes (such as Th2-high and eosinophilic types), laying the foundation for precision treatment.[14]

For disease assessment, the Total Nasal Symptom Score (TNSS) and Visual Analog Scale (VAS) are commonly used quantitative tools that directly reflect symptom burden.[15] Quality of life assessment tools, such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), evaluate the impact of the disease on the patient's overall health across multiple dimensions, including work, learning, sleep, and emotions.[16] It is noteworthy that studies have shown that TNSS and RQLQ scores correlate with peripheral eosinophil counts and serum Th2-related cytokine levels, suggesting that symptom scores may reflect the potential influence of systemic inflammation. This helps facilitate the transition from local symptoms to a comprehensive evaluation of the systemic immune status.[17]

Local Immune Mechanisms Underlying AR

The pathogenesis of AR has traditionally been thought to be initiated by local inflammatory responses in the nasal mucosa, characterized by IgE-mediated immediate and late-phase immune reactions.[18] During local inflammation, various cells and molecular pathways interact, including the disruption of nasal mucosal barrier function, infiltration of inflammatory cells, and the cascade release of inflammatory mediators.[19]

The nasal epithelium not only serves as a mechanical barrier but also plays an important role in immune regulation. In AR patients, nasal mucosal tight junction proteins (such as occludin and claudin) are often downregulated, leading to increased barrier permeability, allowing allergens to penetrate more easily into the submucosal layer.[20] Damaged epithelial cells secrete thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33), and IL-25, which act as "upstream alarm signals" that activate innate immune cells, particularly type 2 innate lymphoid cells (ILC2), further amplifying local inflammatory responses.[21] Mast cells are central effector cells in local allergic reactions.[22] When sensitized individuals encounter allergens, the allergens bind to IgE-FcεRI complexes on the surface of mast cells, triggering degranulation and the release of histamine, leukotrienes, and prostaglandins, leading to typical symptoms of nasal itching, sneezing, and rhinorrhea.[23] Mast cells drive immediate allergic responses through degranulation and also contribute to late-phase inflammation via cytokine release. Their activation promotes downstream recruitment of eosinophils and amplification of type 2 immune responses within the nasal mucosa.[24,25] These findings further support the theory of AR as a systemic immune dysregulation disorder.

In late-phase immune responses, the sustained infiltration of eosinophils is a major feature of chronic inflammation in the nasal mucosa.[26] Recent studies have found that in AR patients, the number and function of eosinophils, Th2 cells, and ILC2 cells in peripheral blood exhibit significant abnormalities.[27,28] The release of eosinophil cationic proteins and other basic proteins not only causes tissue damage but also promotes further disruption of epithelial barrier function.[29] Eosinophils maintain a positive feedback loop of inflammation through factors like IL-5 and IL-13, driving the persistence of local inflammation, which explains the chronic nature of AR.[30] Th2 cells play a key role in local immune responses by secreting IL-4, IL-5, and IL-13, promoting IgE production, eosinophil recruitment, and mucus secretion.[31] At the same time, Treg cell dysfunction or a reduction in their number is commonly observed in rhinitis patients, weakening the suppression of inflammatory responses.[32] Recent research has shown that Th17 cells and their secretion of IL-17 also contribute to nasal mucosal inflammation, particularly in relation to neutrophil recruitment and the development of chronic inflammation.[33] Therefore, the local immune response in AR is not purely Th2-biased but represents a composite manifestation of immune system imbalance.

Moreover, increasing evidence suggests that there is bidirectional communication between nerve fibers and immune cells in the nasal mucosa.[34] Neuropeptides (such as Substance P and CGRP) released by sensory nerve endings can directly enhance mast cell activity, thereby exacerbating local inflammatory responses. Conversely, inflammatory mediators lower the threshold of nerve endings, further triggering neurogenic inflammation.[35] This mechanism helps explain why some patients exhibit heightened nasal reactivity even without clear allergen exposure. These local immune events can align with systemic immune activation through circulating mediators and immune cell trafficking, providing a mechanistic link to extra-nasal comorbidities.

Systemic Immune Dysregulation in AR

Systemic immune dysregulation in AR refers to persistent immune abnormalities beyond the nasal mucosa, including circulating inflammatory cells, cytokine imbalance, and altered immune phenotypes (Figure 1). Although AR primarily manifests as nasal symptoms, increasing evidence indicates that locally activated type 2 immune cells can enter the circulation and participate in inflammatory responses in other organs. This pattern supports a bidirectional interaction between local nasal inflammation and systemic immune activation.

Although AR primarily manifests as local nasal discomfort, recent studies have shown that AR is not only a product of local immune responses but may also reflect systemic immune system dysregulation.[36] AR patients often exhibit abnormal immune cell profiles in peripheral blood, and these locally activated immune cells, particularly Th2 cells and ILC2 cells, can migrate through the bloodstream to various parts of the body, triggering systemic inflammatory responses.[37,38] For example, eosinophil spillover occurs not only in the nasal region but also increases significantly in systemic allergic reactions such as asthma and AD, further supporting the theory of AR as a systemic immune dysregulation disorder.[39] These findings suggest bidirectional interactions between local nasal inflammation and systemic immune activation rather than a simple unidirectional spillover model.

The role of ILC2 cells in AR has gained widespread attention in recent years. These cells are activated not only in the nasal mucosa but also in peripheral blood and other organs (such as the respiratory tract and skin), where they mediate immune responses.[40] This phenomenon of cell migration and activation reveals the immune association between AR and other immune diseases, such as asthma and AD. Elevated levels of inflammatory cytokines are commonly detected in the serum of AR patients, compared to normal populations.[41] Once immune cells are activated, the massive secretion of cytokines is not limited to the nasal mucosa but also affects systemic immune responses through the bloodstream.[42] For example, IL-33, as an upstream alarm signal, has been shown to play a critical role in AR and other immune-mediated diseases. Its levels are elevated not only in the nasal mucosa but also in the serum, correlating closely with the onset of asthma and skin allergic reactions.[43] Similarly, IL-25 and TSLP also activate the systemic immune system through the bloodstream, further exacerbating systemic inflammation, suggesting that the immune response in AR may extend beyond the local nasal region.[44] Together, these findings support a systemic immune network model in which epithelial-derived alarmins and type 2 immune cells orchestrate both local and systemic inflammation, as illustrated in Figure 1.

Moreover, in addition to the "spillover effect" of cytokines, AR patients often exhibit signs of systemic inflammation. Studies have found that systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-

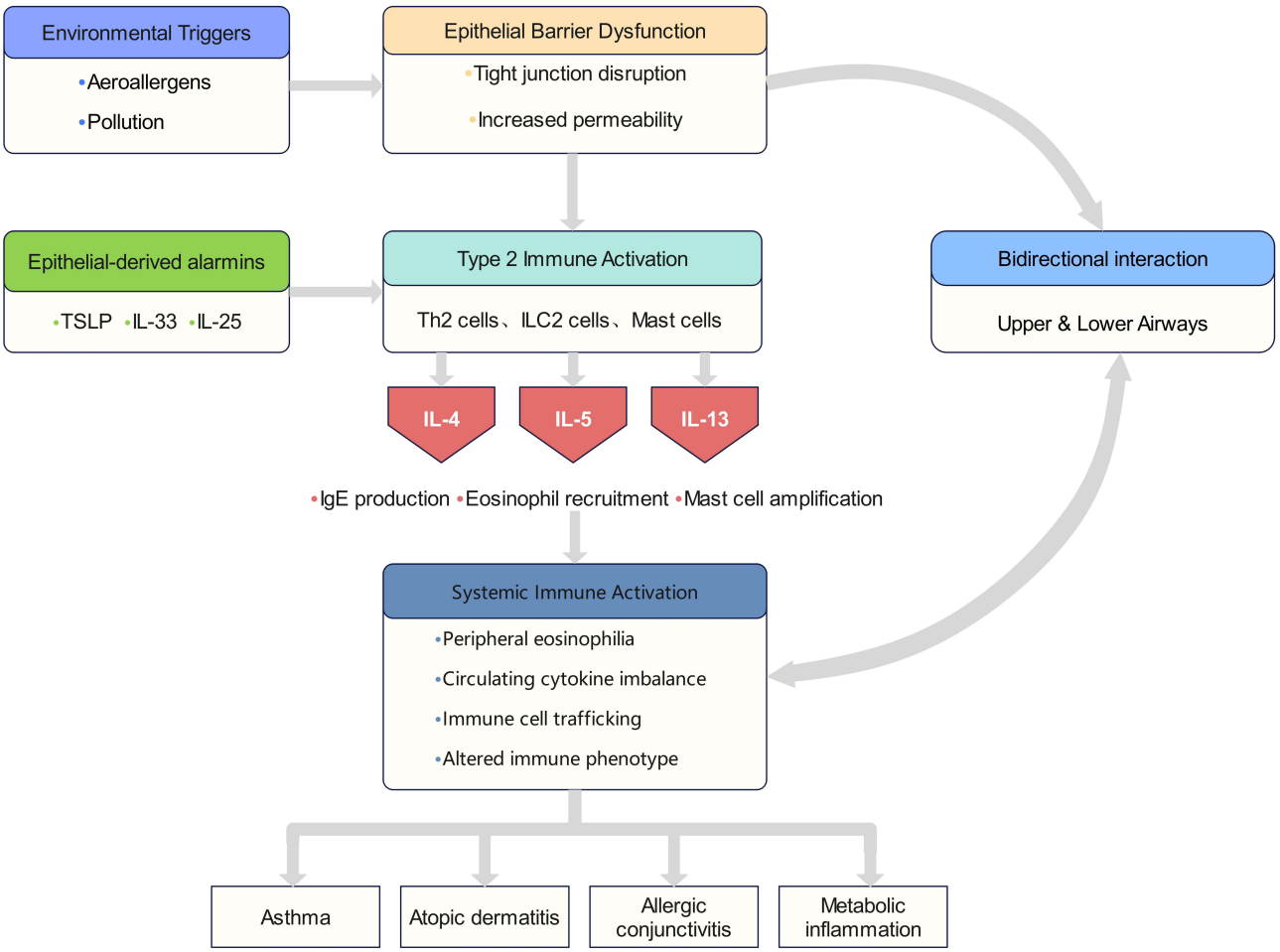

Figure 1 Systemic immune dysregulation model of allergic rhinitis. Allergen-induced epithelial barrier dysfunction triggers the release of alarmins (TSLP, IL-33, IL-25), which activate Th2 and ILC2 cells and promote type 2 cytokine production (IL-4, IL-5, IL-13). This cascade drives eosinophil recruitment, IgE production, and amplification of local inflammation. Immune cell trafficking and circulating cytokine imbalance extend local responses into systemic immune activation, contributing to comorbidities such as asthma and atopic dermatitis. Bidirectional interactions between upper and lower airways further sustain chronic inflammatory signaling.

lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and pan-immune inflammation value (PIV) are significantly elevated in peripheral blood.[5] In some patients, immune cell subpopulations remain in a chronically activated state in the circulatory system, further supporting the notion of AR as a systemic immune response disorder.[45] These systemic immune alterations may partially explain disease severity heterogeneity and variable treatment responses among patients with allergic rhinitis.

At the epigenetic level, increasing evidence suggests that AR may involve alterations in gene expression regulation.[46] Studies have found changes in the methylation patterns of certain key genes in eosinophils and T cells in AR patients. These genetic alterations not only affect local immune responses in the nasal mucosa but may also influence the immune status of peripheral tissues.[47] For example, genes related to Th2 cell responses, such as IL-4 and IL-13, exhibit epigenetic regulatory changes in rhinitis patients, potentially leading to sustained immune system activation.[46–48]

These findings indicate that AR is not merely localized inflammation in the nasal region; its underlying immune mechanisms reflect systemic immune dysregulation. AR is often comorbid with asthma, AD, allergic conjunctivitis, and other immune-mediated diseases. These diseases share the common feature of excessive immune activation and abnormal responses to external allergens, further supporting the hypothesis of AR as a "systemic allergic state".[49] With deeper research into the concept of immune tolerance, increasing evidence suggests that immune tolerance is disrupted in AR patients, leading to enhanced local immune responses and abnormal systemic immune reactions.[50,51] This immune

dysregulation not only prolongs the duration of rhinitis but also increases the risk of other immune diseases, suggesting that AR may represent a clinical manifestation of systemic immune dysregulation.

Comorbidities of AR and Its Association with Other Immune Disorders

As a common immune-mediated allergic disease, AR is often comorbid with various other immune disorders. Recent studies have shown that AR is not only a manifestation of localized allergic reactions but is often associated with respiratory diseases (such as asthma), skin diseases (such as AD), and metabolic disorders (such as obesity and metabolic syndrome).[52–54] These comorbidities provide new insights into understanding the systemic immune response mechanisms of AR.

The comorbidity of AR and asthma has long been a key topic in clinical and basic research. The unified airway theory proposes that AR and asthma share a common pathophysiological foundation, both being triggered by allergic reactions, with the nasal and lower respiratory tracts forming a unified immune response system.[55] Studies show that about 40% of AR patients also have asthma, and approximately 80% of asthma patients have concomitant allergic rhinitis, a phenomenon closely related to the extension of localized allergic responses to the lower respiratory tract.[56] The activation of mast cells and eosinophils in the nasal mucosa not only triggers immune responses in the upper respiratory tract, but these cells also migrate through the bloodstream to the lower respiratory tract, causing chronic inflammation in the bronchi.[57] Additionally, cytokines such as IL-4 are elevated in both AR and asthma airways, playing a critical role in nasal inflammation and contributing to asthma exacerbations and progression.[58] These immunological findings support the theory of AR and asthma as "unified airway" diseases.

AD is another immune-mediated disease closely related to AR. Studies indicate that AR and AD often coexist.[59] Both share several common inflammatory pathways in their immune mechanisms, particularly cytokines such as IL-4, IL-5, and IL-13. These cytokines not only promote immune responses in the nose and skin but also stimulate IgE production, further exacerbating the clinical manifestations of allergic diseases.[60,61] Additionally, disruption of the skin barrier function is a common feature between AD and AR. Damage to the skin barrier allows external allergens to invade, which is similar to the impairment of the nasal barrier.[62]

AR patients are also commonly associated with other upper respiratory tract and ear diseases, with allergic conjunctivitis and allergic otitis media being the most frequent comorbidities.[63] Allergic conjunctivitis presents with symptoms such as eye itching, tearing, and redness, and is often comorbid with AR. The immune responses between the two conditions interact, leading to ocular inflammation.[64,65] Studies have found that nasal allergic reactions propagate through the tear ducts and the shared immune system of the upper respiratory tract, leading to immune reactions in the eyes.[66] Allergic otitis media is common in children, with nasal mucosal immune cells from AR patients migrating to the middle ear via the Eustachian tube, resulting in chronic allergic inflammation in the ear.[67] Since these ear conditions are often misdiagnosed as ear infections, delaying proper treatment, it is crucial to recognize the relationship between AR and eye/ear-related diseases for early diagnosis and treatment.

Increasing evidence also suggests a link between AR and metabolic diseases (such as metabolic syndrome and obesity). AR patients often exhibit comorbidities like hypertension and dyslipidemia, which are associated with chronic low-grade inflammation.[68] AR may activate metabolic regulatory systems through chronic inflammation, thereby increasing the risk of metabolic syndrome.[69] Moreover, some studies have found that the systemic inflammatory response in AR may increase the risk of atherosclerosis, which in turn elevates the incidence of cardiovascular diseases.[70] Although these studies are still in the early stages, they already highlight the potential impact of AR on cardiovascular health.

Beyond organ-level comorbidities, AR is also closely associated with sleep disorders and psychological issues. Chronic nasal congestion, nocturnal sneezing, and rhinorrhea can significantly impact sleep quality, leading to difficulty falling asleep, fragmented sleep, and daytime sleepiness. Some patients may also experience snoring or sleep apnea.[71] The decline in sleep quality further affects cognitive function, reducing learning and work efficiency, particularly in children and adolescents. Epidemiological studies have shown that the incidence of anxiety and depression is higher in AR patients compared to the general population, with more severe symptoms correlating with more pronounced

emotional problems.[72] This indicates that the impact of AR extends beyond localized nasal mucosa and should be managed and intervened from a "holistic health" perspective, addressing both physical and psychological well-being.

Clinical Treatment Strategies and Immunotherapy for AR

With the in-depth study of the immune mechanisms of AR, especially the growing recognition of its manifestation as systemic immune dysregulation, traditional local treatments are no longer sufficient to meet clinical needs. Increasing evidence suggests that AR is not only a localized immune response but also a reflection of systemic immune activation. Therefore, treatment strategies should shift from the traditional "local symptomatic treatment" to "systemic immune regulation". This shift not only helps to improve nasal symptoms but also effectively reduces the occurrence and progression of related comorbidities.

The comorbidity of AR and asthma has provided a new perspective for clinical treatment. The unified airway theory proposes that AR and asthma share a common immunological basis, both being triggered by allergic reactions, and the nasal and lower respiratory tracts form a unified immune response system.[73,74] This immunological connection suggests that combined treatment for AR and asthma may be a more effective strategy. Currently, there are combination treatment plans for AR and asthma, primarily involving immunotherapies such as anti-IL-4, IL-5, and IL-13 monoclonal antibodies.[47] By controlling immune responses in both the upper and lower airways, these therapies can significantly improve overall disease control in patients.

The emergence of biologics has brought revolutionary changes to the treatment of AR, particularly in the field of immunotherapy. Traditional treatment methods mainly rely on antihistamines, intranasal steroids, and allergen-specific immunotherapy.[75] However, these methods primarily target symptoms and do not fundamentally alter the immune system's response to allergens. In recent years, biologics such as anti-IL-5 and anti-IL-4/IL-13 monoclonal antibodies have begun to be applied clinically and have shown excellent efficacy. The anti-IgE monoclonal antibody omalizumab can reduce the downstream inflammatory cascade.[76] After three months of omalizumab treatment for moderate to severe AR patients, clinical symptoms significantly improved.[77] The anti-IL-5 monoclonal antibody Mepolizumab works by inhibiting eosinophil activation, reducing eosinophil infiltration, and local inflammation, thereby alleviating comorbid AR and asthma symptoms.[78] A study involving 1189 AR patients showed that after Mepolizumab treatment, symptoms of AR patients with chronic sinusitis improved significantly, and the SNOT-22 score, nasal polyposis score (NPS), and nasal congestion score (NCS) decreased significantly.[79,80] The anti-IL-4/IL-13 monoclonal antibody Dupilumab inhibits Th2 cells and immune-mediated cytokine responses, reducing chronic inflammation caused by immune system over-activation. In particular, in severe AR patients, symptoms of nasal congestion and rhinorrhea were significantly alleviated, and the SNOT-22 score decreased significantly after 2 weeks of treatment. This is particularly important for severe AR patients who are resistant to traditional treatments.[81,82] These clinical data support the transition from local treatment to systemic immune regulation treatment, with biologics effectively improving symptoms and controlling systemic immune dysregulation.

These clinical data support the transition from local treatment to systemic immune regulation treatment, with biologics effectively improving symptoms and controlling systemic immune dysregulation.[83,84] Traditional immunotherapy mainly involves subcutaneous and sublingual treatments targeting specific allergens.[85] With advances in immunology, the concept of immunotherapy has gradually shifted toward building systemic immune tolerance. AIT not only alleviates nasal symptoms but also improves the patient's long-term health by reducing systemic inflammatory responses.[86] However, the efficacy of AIT is influenced by various factors, such as individual differences, allergen types, and the timing of treatment, so future treatment trends may focus more on individualized and precision treatments.[87]

In the framework of viewing AR as a systemic immune dysregulation phenotype, clinical management should not only focus on short-term symptom control but also emphasize long-term follow-up strategies based on risk stratification. Patients can be classified into low, medium, and high-risk levels based on symptom duration, severity (eg, ARIA classification), the presence of multiorgan allergic manifestations (eg, asthma, AD, or allergic conjunctivitis), and previous acute exacerbations.[88] For medium- and high-risk patients, it is recommended to develop more intensive follow-up plans to identify disease progression and new comorbidities early. Furthermore, biological risk assessment based on

immune and inflammatory markers is essential. For example, an increase in peripheral eosinophil counts, elevated serum total IgE or specific IgE levels usually indicates active Th2-type inflammation, and such patients are more likely to have lower airway involvement or other allergic diseases.[89]

For patients with comorbid obesity, metabolic abnormalities, or cardiovascular risk factors, monitoring blood pressure, blood glucose, and blood lipids in routine follow-ups is crucial to shift from "nasal symptom management" to "comprehensive management of systemic risk factors".[90] Risk stratification also helps guide the choice of treatment intensity and intervention strategies. Low-risk patients can be treated with traditional medications, along with lifestyle and environmental exposure management, while high-risk patients, especially those with asthma or frequent acute exacerbations, should consider allergen-specific immunotherapy or biologics early on, with dynamic assessments of their impact on systemic inflammation and comorbidities during follow-up. This integrated management model allows for the treatment of AR to shift from passive control of a single organ disease to proactive prevention and intervention of a systemic disease.

Conclusion

Accumulating evidence indicates that AR should be viewed not merely as a localized nasal inflammatory disorder but as a manifestation of systemic immune dysregulation.[91] Advances in immunology, molecular biology, precision medicine, and microbiology have expanded our understanding of AR pathogenesis and systemic immune involvement. Multi-omics approaches, including transcriptomics, metabolomics, proteomics, and microbiomics, provide integrated insights into immune regulation networks and facilitate the identification of disease-associated pathways and biomarkers.[92–95] Increasing evidence also highlights the role of microbiota–immune interactions, particularly along the gut–nose–lung axis, in shaping systemic immune responses and potentially influencing disease progression and therapeutic responsiveness.[96–99] Clinically, recognition of AR as a systemic immune phenotype supports a shift from symptom-centered local treatment toward integrated risk stratification and mechanism-driven interventions, including allergen immunotherapy and targeted biologics.[100–103] Although current evidence has limitations regarding causality and heterogeneity, the systemic framework offers a more comprehensive model for understanding AR and promotes the development of personalized therapeutic strategies aimed at improving long-term outcomes and managing comorbidities.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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