

REVIEW

Advances and highlights in allergic rhinitis

Yuan Zhang^{1,2,3}  | Feng Lan²  | Luo Zhang^{1,2,3} 

¹Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China

²Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China

³Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China

Correspondence

Luo Zhang and Feng Lan, Beijing Institute of Otolaryngology, No. 17, HouGouHuTong, DongCheng District, Beijing, 100005, China.
Emails: dr.luozhang@139.com (L.Z.); fenglanent@126.com (F.L.)

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Abstract

Allergic rhinitis (AR) is a growing public health, medical and economic problem worldwide. The current review describes the major discoveries related to AR during the past 2 years, including risk factors for the prevalence of AR, the corresponding diagnostic strategy, precise underlying immunological mechanisms, and efficient therapies for AR during the ongoing global “coronavirus disease 2019” (COVID-19) pandemic. The review further attempts to highlight future research perspectives. Increasing evidence suggests that environmental exposures, climate changes, and lifestyle are important risk factors for AR. Consequently, detailed investigation of the exposome and the connection between environmental exposures and health in the future should provide better risk profiles instead of single predictors, and also help mitigate adverse health outcomes in allergic diseases. Although patients with dual AR, a newly defined AR phenotype, display perennial and seasonal allergens-related nasal symptoms, they are only allergic to seasonal allergens, indicating the importance of measuring inflammation at the local sites. Herein, we suggest that a combination of precise diagnosis in local sites and traditional diagnostic methods may enhance the precision medicine-based approach for management of AR; however, this awaits further investigations. Apart from traditional treatments, social distancing, washing hands, and disinfection are also required to better manage AR patients in the ongoing global COVID-19 pandemic. Despite recent advances in understanding the immune mechanisms underlying the effects of allergen immunotherapy (AIT), further understanding changes of cell profiles after AIT and accurately evaluate the efficacy of AIT are required.

KEYWORDS

allergen immunotherapy, allergic rhinitis, COVID-19, dual allergic rhinitis, real-world evidence

1 | INTRODUCTION

Allergic rhinitis (AR) is a global concern, particularly as the incidence of the disease has increased dramatically in recent years. In Europe, the prevalence of AR among Danish adults has progressively increased from 19% to 32% over the last three decades.¹ Similarly, in Asia the standardized prevalence of adult AR in China has increased by 6.5% over recent 6 years,² with prevalence of

self-reported pollen-induced AR (PiAR) reaching an extremely high value of 32.4% in northern grassland region of China, where high concentrations of seasonal pollen are detected.³ Three nationwide cross-sectional surveys in Japanese children, conducted between 2005 and 2015, have also shown a continuous increase in rhinoconjunctivitis.⁴ The high incidence of AR imposes a heavy burden to general well-being, and has a significant financial impact from both direct and indirect costs for management of the disease. One

recent study from the Netherlands has calculated that the total costs of AR were €4827 patient/year.⁵ Under imposition of such a heavy burden, the impact of risk factors, precise underlying immunological mechanisms, the corresponding diagnosis strategy, and efficient therapy for AR is certainly worthy of further assessment (Figure 1).

2 | CLIMATE CHANGE AND LIFESTYLE FACTORS ARE RISK FACTORS IN HIGH PREVALENCE OF AR

Environmental exposures, climate changes, and lifestyle are gradually being regarded as risk factors for AR. Increasing evidence demonstrates that air pollution increases AR prevalence, the onset and exacerbation of airborne pollen sensitized AR.^{6–11} A higher environmental composite quality index score (ECQI), which estimates both outdoor environmental and household indoor air quality, has been shown to be associated with a higher risk of asthma and allergy among children in Northeast China.¹² Changes in climatic factors (temperature, wind speed, humidity, thunderstorms, desert dust, etc.), which can prolong the pollen season and create new sources of pollen due to new invasive species,^{8,10,11,13} have recently received much attention. To this end, an earlier start of birch pollen season as well as a significant increase in the number of days with high pollen counts has been noticed in Munich, Germany, over the last three decades.¹⁴ Lifestyle factors, such as increased time spent indoors, use of antibiotics, consumption of processed foods and decreased exposure to farm animals and pets, limited exposure to environmental allergens, infectious parasitic worms, and microbes, are also regarded to be important factors that may influence the prevalence of AR.¹⁵ The hygiene hypothesis suggests that loss of symbiotic relationships with evolutionary relevant microorganisms prevents the necessary stimulus to train

the immune system to develop tolerogenic responses and is therefore proposed to be the underlying cause for allergy epidemic.¹⁶ Indeed, less frequent bathing and showering appear to be protective against aeroallergen sensitization in children without current allergy.¹⁷ Using novel tobacco products such as electronic cigarette and heated tobacco products also enhance the influence of conventional cigarette smoking on the risk of AR in adolescents.¹⁸ Dietary changes are also suggested to play a role in the increasing prevalence of allergic diseases and asthma, and children with high levels of butyrate and propionate (≥ 95 th percentile) in feces at the age of 1 year have been shown to have significantly less atopic sensitization between 3 and 6 years.^{19,20} Moreover, a recent meta-analysis of observational studies has indicated that there is a direct association between obesity or overweight and risk of AR in children.²¹ Indeed, environmental factors are the driving force behind the increasing prevalence of AR, and epigenetics in particular have provided a better insight into how pollution and other environmental factors alter gene expression. For example, North and colleagues²² showed that exposure for 3 h to grass pollen in an environmental exposure chamber led to alterations in DNA methylation in *Schlafen 12* (*SLFN12*) and *mucin 4* (*MUC4*) in peripheral blood mononuclear cells (PBMCs) of AR patients. As adolescence is often accompanied by significant changes in body mass index (BMI), a genome-wide longitudinal study in United Kingdom to assess any association between allergic sensitization and pre- and post-adolescence genome-wide DNA methylation has demonstrated that the effect of sensitization on DNA methylation at 3 CpG sites (*cg14121142*, *cg23842695*, and *cg26496795*) was strengthened at age 18 years compared to 10 years, and therefore likely to be age-related.²³ In this regard, research on the exposome should improve our understanding on the connections between environmental exposures and health, and help to mitigate adverse health outcomes by providing better risk profiles instead of single predictors in allergic diseases.^{24,25}

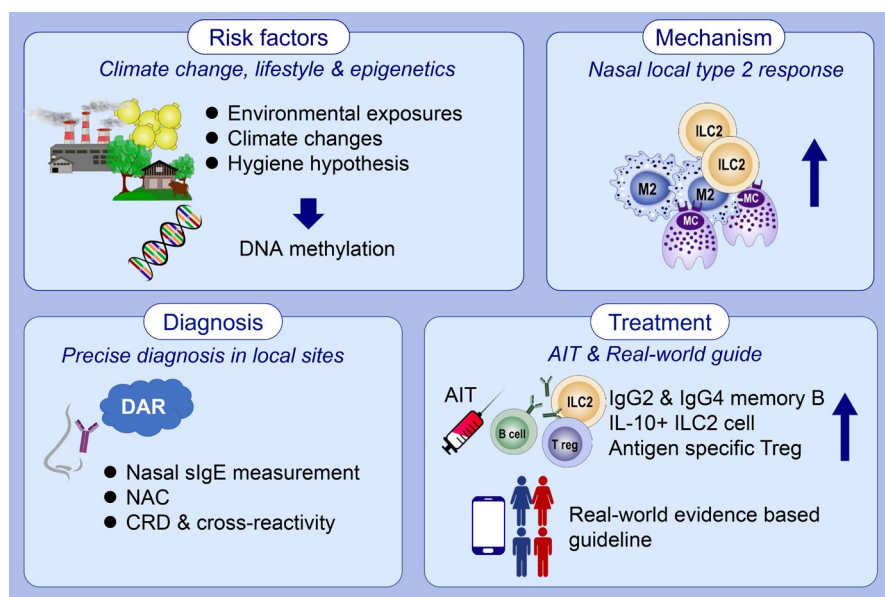


FIGURE 1 Schematic view of recent advances and highlights in risk factors, mechanisms, diagnosis, and treatment involved in allergic rhinitis. AIT, allergen immunotherapy; CRD, component-resolved diagnosis; DAR, dual allergic rhinitis; ILC2, group 2 innate lymphoid cells; M2, alternatively activated macrophage; MC, mast cell; NAC, nasal allergen challenge; and Treg, regulatory T cell

3 | NASAL LOCAL TYPE 2 RESPONSE IN AR

A new AR phenotype, termed dual AR (DAR), has first been defined in 2015. DAR patients display nasal allergen-specific reactivity to both perennial and seasonal allergens; however, these patients have perennial symptoms and positive skin prick test (SPT) to seasonal allergens only, suggesting that local inflammation might be different from peripheral inflammation in these patients.²⁶ One study in mice has recently demonstrated that intranasal application of chitosan resulted in a patchy occludin expression, which facilitated allergen passage due to impaired epithelial integrity and subsequently increased mast cell degranulation, even in the absence of allergic inflammation.²⁷ Indeed, nanovesicles released from activated mouse bone marrow-derived mast cells have been shown to amplify allergic inflammation by interaction with high-affinity immunoglobulin E receptor (FcεRI)-bound Immunoglobulin E (IgE) complexes, and facilitating vesicular endocytosis and absorption, and exacerbation of local allergic reactions.²⁸ Local CD68⁺CD206⁺ alternatively activated (M2) macrophages in inferior turbinate, as well as serum levels of M2a subsets-related markers YKL40, CCL17, CCL18, and CCL26 from HDM⁺ AR patients, have also been shown to be significantly higher than in samples from healthy controls.²⁹ Furthermore, M2a subsets have been reported to be positively correlated with AR symptom severity,²⁹ and epinephrine-treated human allergic M2a macrophages reportedly converted into a "M2b-like" phenotype, which can inhibit IgE-dependent release of inflammatory mediators from mast cells.³⁰ Beside mast cells and macrophages, the levels of group 2 innate lymphoid cells (ILC2s) have also been reported to be increased in peripheral blood of AR patients during the grass pollen season,³¹ but decreased in peripheral blood of birch-allergic AR patients following a nasal allergen challenge (NAC) outside of the local birch pollen season.³² It is possible that low dose of birch pollen pre-exposure may differentially regulate peripheral ILC2 migration before local allergen challenge. Similarly, Takeshi Shimizu, Fu Qingling, and their colleagues^{33,34} have demonstrated that ILC2s are also significantly increased in inferior turbinate tissues of patients with house dust mite (HDM)-induced AR compared to control subjects, and express prostaglandin D₂ (PGD₂) and cysteinyl leukotriene (cysLTs) receptors. Furthermore, both PGD₂ and cysLTs may activate the tissue-resident ILC2s in earlier stage,^{33,35} to produce Th2 cytokines IL-5 and IL-13 cytokines. Increasing evidences suggest that inflammation in local sites is different from that in the periphery of AR patients, and thus, further investigations are warranted to attain a better understanding of allergen-mediated cellular mechanisms at the local sites in AR patients.

4 | PRECISE DIAGNOSIS IN LOCAL SITES

AR and allergic asthma patients may profit from an earlier accurate local diagnosis before the disease is systemically detectable.³⁶ In

this respect, Gökaya and colleagues³⁷ have adopted the Immuno Solid-phase Allergen Chip (ISAC) to measure aeroallergen-specific IgE in nasal fluid, which might be the first step toward nasal molecular allergy diagnostic. The NAC has always been regarded as a useful tool for the diagnosis of AR and LAR and therefore might serve to design and monitor allergen immunotherapy.³⁸ Indeed, the safety and reproducibility of NAC in the clinical practice in both children and adults with or without asthma have been confirmed by a recent study by Eguluz-Gracia and colleagues,³⁹ who performed a retrospective evaluation of the NACs conducted in their unit from 2005 to 2017. To further accurately monitor NAC in clinic, these authors have suggested the use acoustic rhinometry (AcRh) and a decrease $\geq 24.48\%$ in nasal patency as the optimal cutoff point to confirm or otherwise nasal allergen-specific reactivity.⁴⁰ As current practice for diagnosis of almost 2/3 of all types of allergic diseases and 90% of respiratory allergies relies heavily on skin tests as the first option, an action plan has recently been set up by European Academy of Allergy and Clinical Immunology (EAACI) for availability of high-quality diagnostic allergens and to facilitate a sustainable and comprehensive service for the diagnosis and treatment of allergic diseases in Europe.⁴¹

A phenotype-/endotype-based classification approach has been recommended to lead toward the application of stratified and personalized medicine in the rhinitis field in recent years.⁴² Based on socio-demographical and clinical variables, 5 different phenotypes of AR patients have been identified by ascending hierarchical clustering analysis, and one of these phenotypes represents a high-risk factor for asthma involvement.⁴³ Six endotypes with different inflammatory patterns in tissue have also been classified in AR patients, with higher levels of eosinophil cationic protein (ECP) and leukotriene C4 (LTC4) found in patients in 3 clusters and significantly higher levels of vasoactive intestinal polypeptide (VIP) and substance P (SP) found in patients in cluster 6, which may help in delivering individualized treatment toward anti-inflammatory mediators.⁴⁴

A recent real-life and multicenter study has shown that the severity of disease is dependent on the number of recognized HDM allergen components in mono-sensitized asthmatic patients.^{45,46} Pollen food syndrome (PFS) has recently been proposed to be the result of cross-reactivity of homologous components in both pollen and food^{47,48}; particularly as many plant food allergens contain homologs to pollen allergens, extensive IgE cross-reactivity between birch and hazelnut and olive pollen and peach have been noticed in AR patients with PFS.^{47,49–51} Herein, component-resolved diagnosis (CRD) can be recommended to distinguish the primary sensitization or cross-reactivity among components, especially for patients who are polysensitized or demonstrate poor effect of immunotherapy.^{52,53}

5 | THE IMMUNE EFFECT OF ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy (AIT) is regarded as a most efficient treatment of AR patients, and thus, the usage and administration

of AIT according to the 2019 ARIA care pathways⁵⁴ should be seriously considered by clinicians managing AR patients. AIT results in profound changes in the profiles of gene and protein expression in allergen-specific T cells and protein expression in plasma cells in nasal tissues, resulting in long-lasting beneficial effects.⁵⁵ In AR patients T-B cell interactions have been shown to be bridged by CD23 expressed specifically on CD19⁺CD20⁺CD27⁺IgD⁺ switched memory B cells, and type 2 T follicular helper cells (Tfh2), rather than type Th2 cells, play a crucial role in controlling IgE production and induction of CD23 expression on switched memory B cells via IL-4.⁵⁶ Indeed, the finding that expression of CD23 is reduced on switched memory B cells in AR patients receiving AIT further confirms the central role of CD23 in T-B cell interactions in AR patients.⁵⁷ Moreover, a recent study has demonstrated that SLIT induced a rapid increase in peripheral blood IgG2⁺ and IgG4⁺ memory B cells, without any interference on the IgE⁺ memory B cells, in patients with atopic seasonal rhinoconjunctivitis,⁵⁸ which may in turn inhibit histamine release from basophils due to the induction of IgG2 by IgG2⁺ cells.⁵⁹ Additionally, as a key regulatory cell population, regulatory T cells (Tregs) are involved in the induction of immune tolerance to allergens in AIT.⁶⁰ As only IL-10⁺ Der p 1-specific Treg cells have been shown to remain at high frequency after 3 years of HDM-AIT, and decreased ILT3⁺ Treg cells are correlated with improved allergic symptoms,⁶¹ it is likely that a better understanding of the appropriate peptide-MHC multimers may lead to a better understanding of the status and different functions of antigen-specific Treg cells in AR patients receiving AIT. Interestingly, SLIT has also been shown to induce differentiation of IL-10-producing ILC2s from ILC2 precursors regulating the pathology of grass pollen-induced allergy.⁶² Unbiased systems-level gene co-expression network analysis has demonstrated that the reduction of early symptom in the early phase of SCIT is associated with initial merging of Th2-effector and IL-2/T-regulatory network modules, without major quantitative changes in gene expression.⁶³ Furthermore, as type 1 IFNs negatively control many of the downstream proinflammatory effects of Th2 cytokines, a fusion with an upregulated type 1 interferon signaling module may potentially stabilize Th2 response in the second year of SCIT.⁶³ A comprehensive longitudinal analysis of the systemic innate immune cell repertoire during the course of AIT has demonstrated a sustained decrease of group ILC2s and increase in group ILC1s after AIT, as well as a shift in monocytes from a proinflammatory (non-classical) to an anti-inflammatory (intermediate) phenotype, and up-regulation of plasmacytoid dendritic cells (pDCs) and CD141⁺ myeloid DCs in the first year of AIT.⁶⁴ However, overall evidence of the immunomodulatory properties of AIT on T cells, B cells, ILC2s, monocytes, and DCs, and the understanding of the collective effects of these immune cells in AIT are relatively scant. Thus, it is still worth exploring the maintenance of efficacy after treatment, as well as the accurate evaluation of criteria for the effectiveness of the treatment.

6 | REAL-WORLD EVIDENCE-ORIENTED GUIDELINE

Precision medicine (PM) is increasingly recognized as the way forward for optimizing AR patient care. Consequently, the major focus in patients care has shifted to face the need to improve the level of disease control, enhance patient satisfaction and increase effectiveness of preventive interventions.⁶⁵ The selection of pharmacotherapy for patients with AR depends on factors involving age, prominent symptoms and symptom severity, control of AR, patient preferences, and cost. Often, guidelines do not reflect patients' needs or real life and therefore are not followed sufficiently by the patients. As there is an increasing trend toward the use of real-world evidence and algorithms to aid patients and healthcare professionals to jointly determine treatment and its step-up or step-down strategy depending on AR control,⁶⁶ it has been suggested that the next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for AR should be developed based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence.⁶⁶ In this regard, the Mobile Airways Sentinel Network (MASK) study has demonstrated that the adherence to treatment among AR patients is generally low,⁶⁷ and that an approach for measuring retrospective daily adherence based on a mobile app such as the MASK-air app, rather than a questionnaire, represented a novel approach for analyzing assessment of AR in a real-world setting.⁶⁸ In a separate study, Valero and colleagues⁶⁹ have combined the four original ARIA items employed for classification of AR severity and disease control (ARIA-C) estimations into a single instrument to provide the basis for establishing a real-world correlation between control categories and therapeutic approaches in the future.

7 | COVID-19 AND AR

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a widespread and life-threatening coronavirus disease 2019 (COVID-19) pandemic, which has posed great challenges to world health management during the last year. Scholars all over the world have analyzed the various factors and molecular mechanisms underlying the prognosis of COVID-19 patients, and shed light that may facilitate efficient intervention and management of COVID-19 patients. It has reported that the peripheral blood eosinopenia count may be a robust indicator for diagnosis, evaluation, and monitoring of the development of COVID-19 patients.⁷⁰ Another study has expounded that eosinopenia was inversely related to various inflammatory markers and may be associated with the severity of COVID-19.⁷¹ Comparison of disease incidence, clinical features, and immunological findings between allergic and non-allergic COVID-19 patients, however, has suggested that allergy is not a risk factor for COVID-19 development, severity, and disease course.^{72,73} Consistent with this finding in Chinese patients, two studies of patients in Italy have also

demonstrated subjects with atopic status are at low risk of developing COVID-19.^{74,75} The prevalence of allergic children (30%) and asthmatic children (11.6%) is relative high in south Lombardy and Liguria, Italy; however, only two allergic children (food allergy and AR) and one child with asthma are found in 40 pediatric COVID-19 patients.⁷⁶ Yao and colleagues⁷⁷ have further demonstrated that AR co-morbidity does not alter the expression of angiotensin-converting enzyme 2 (ACE2), a key cell entry receptor for SARS-CoV-2, in AR patients and therefore might not have significant modifying effects on the development of COVID-19 in these patients. A cross-sectional study has shown that depression and reported post-traumatic stress disorder are present in individuals with allergic diseases during the COVID-19 pandemic.⁷⁸ However, a study from Wuhan, China, using a before-and-after COVID-19 infection approach has indicated that the psychological status of AR patients was not significantly influenced by the COVID-19 infection.⁷⁹ Efficient and safe COVID-19 vaccines are still under investigation.⁸⁰ Appropriate management of AR in COVID-19 infected patients also needs to be addressed urgently.^{81,82} Indeed, the EAACI has recently developed an expert consensus statement on the use of intranasal corticosteroids in AR and asthma patients infected with COVID-19, and recommended that INS should be continued at the recommended dose as stopping it would increase sneezing and lead to more spreading of the virus.⁸³ As SARS-CoV-2 is mainly transmitted via respiratory droplets and aerosols, face masks and eye protection, in addition to social distancing, washing hands, and disinfection, which have been proven to limit the spread of SARS-CoV-2, are also useful in the management of AR patients.⁸⁴ While more time outdoors and greater household ventilation are also likely to be helpful, it is worth mentioning that the use of face masks and low air pollution emissions resulting due to COVID-19 lockdowns have been proposed as having the potential benefit of decreasing symptom severity in patients with AR.^{85,86}

8 | CONCLUSION AND PERSPECTIVE

We believe that the increased prevalence of AR is influenced by climate change and lifestyle factors. To recognize different endotypes of AR in the clinic, we suggest analyzing the intrinsic value of a combination of local inflammation with traditional diagnostic methods for AR. AIT is increasingly recognized as a natural and effective therapy for AR. Nevertheless, much effort is still required to understand and accurately evaluate the efficacy of AIT in the future. Although many recommendations and consensus statements have been published on AR treatments during the COVID-19 pandemic, considering the differences in different territories, these may need to be modified accordingly to meet the local needs.

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CONFLICT OF INTEREST

All authors declare no financial or commercial conflicts of interest.

AUTHOR CONTRIBUTIONS

YZ, FL, and LZ prepared the manuscript. FL and LZ designed the study and participated in the interpretation and discussion of the review.

ORCID

Yuan Zhang  <https://orcid.org/0000-0003-1080-4267>

Feng Lan  <https://orcid.org/0000-0002-1709-5179>

Luo Zhang  <https://orcid.org/0000-0002-0910-9884>

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