GUIDELINES



Expert Panel Consensus Recommendations for Allergic Rhinitis in Patients with Asthma in India

R. Narasimhan · Sitesh Roy · Meghanadh Koralla · P. K. Thomas · M. Ilambarathi · S. Balamurugan · M. Harish ·

R. Sabarinath \cdot Gaurav Medikeri \cdot Partha Bose \cdot V. R. Pattabhiraman \cdot M. K. Rajasekar \cdot A. R. Gayathri \cdot

T. Dhanasekar · V. Nandagopal · G. Gananathan · S. K. Ravichandran · M. N. Shankar · Aniruddha Majumder ·

Shelley Shamim · Meenesh Juvekar · Vijay K. Singh · T. Mohankumar · S. Prasanna Kumar · Debraj Jash ·

Salil Bendre · Suhail Neliyathodi · Sunil Janardanan Unnithan · Archana Karadkhele 🗓

Received: August 3, 2024 / Accepted: September 16, 2024 / Published online: October 17, 2024 © The Author(s) 2024, corrected publication 2025

ABSTRACT

Allergic rhinitis and asthma are commonly coexisting conditions, significantly impacting patient health and quality of life. Despite their interrelation, diagnosing allergic rhinitis in

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41030-024-00273-z.

R. Narasimhan

Pulmonology Respiratory Medicine Specialist, Apollo Hospital, Chennai, Tamil Nadu, India

S. Roy

Dr Roy Health Solutions Clinic, Mumbai, India

M Koralla

ENT Surgeon, MAA ENT Hospital, Hyderabad, India

P. K. Thomas

MGA Healthcare, Chennai, Tamil Nadu, India

M. Ilambarathi

Igeny Daycare Center, Chennai, Tamil Nadu, India

S. Balamurugan

A.C.S Medical College & Hospital, Chennai, Tamil Nadu, India

M. Harish

Kauvery Hospital, Chennai, Tamil Nadu, India

R. Sabarinath

Sree Balaji Medical College, Chennai, Tamil Nadu, India

patients with asthma remains challenging, leading to underdiagnosis and suboptimal management. The expert consensus engaged a modified Delphi method involving 29 experts including pulmonologists, ear, nose, and throat surgeons, and allergologists. Through group discussions, consensus statements were developed regarding the epidemiology, diagnosis, and management of allergic rhinitis and asthma. Final consensus statements were formulated based on the experts' collective clinical judgment and experience. This expert consensus provides updated

G. Medikeri

Medikeri's Super Speciality ENT Center, Bangalore, Karnataka, India

P. Bose

SAANS Foundation, National Heart Institute, New Delhi, India

V. R. Pattabhiraman

Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India

M. K. Rajasekar

Balaji Medical College, Chennai, Tamil Nadu, India

A. R. Gavathri

Department of Respiratory Medicine, Apollo Hospital, Chennai, Tamil Nadu, India

T. Dhanasekar

Pulmonology department, Sri Ramachandra Medical College, Chennai, Tamil Nadu, India recommendations tailored to the Indian context, addressing the gaps in existing research and clinical practice. By promoting a systematic and evidence-based approach to diagnosis and management, this consensus aims to support clinicians in effectively identifying and treating allergic rhinitis in patients with asthma, thereby improving overall disease management and patient well-being.

Keywords: Allergic rhinitis; Asthma; Diagnosis; Management; India

Key Summary Points

Allergic rhinitis (AR) and asthma are frequently coexisting conditions that significantly impact patient health and quality of life.

The expert consensus employed a modified Delphi method involving 29 experts to develop consensus statements on the epidemiology, diagnosis, and management of AR and asthma in the Indian context.

Early diagnosis and optimal management of AR can improve asthma symptoms and reduce the burden of both upper and lower airway inflammation.

Comprehensive management strategies, including allergen avoidance, pharmacotherapy, and immunotherapy, are crucial for improving patient outcomes and quality of life in patients with AR and asthma.

INTRODUCTION

Allergic rhinitis (AR) is a prevalent comorbid condition linked with asthma. AR is characterized by inflammation of the nasal lining, resulting in symptoms such as rhinorrhoea, sneezing, nasal blockage, and itching. Asthma, however, is a chronic inflammatory disorder of the airways that manifests as recurrent episodes of wheezing, breathlessness, chest tightness, and cough, with reversible airway obstruction but persistent inflammation [1]. Over the past two decades, the prevalence of AR in India has steadily risen, particularly among older children aged 13–14 years, with a relatively smaller increase

V. Nandagopal

Institute of Lung Care & Research Hindustan Hospital, Coimbatore, India

G. Gananathan

Vijaya Group of Hospital, Vadapalani, Tamil Nadu, India

S. K. Ravichandran

Nalayini ENT Clinic, Chennai, Tamil Nadu, India

M. N. Shankar

Madras Medical College, Chennai, Tamil Nadu, India

A. Majumder

Diamond Harbour Government Medical College, ENT, Harbour, West Bengal, India

S. Shamim

Chest Department, Calcutta National Medical College, Kolkata, India

M. Juvekar

Bombay Hospital, Mumbai, Maharashtra, India

V. K. Singh

Chest and Allergy Clinic, Delhi, India

T. Mohankumar

One Care Hospital, Coimbatore, Tamil Nadu, India

S. Prasanna Kumar

Shri Ramchandra Medical Centre, Chennai, Tamil Nadu, India

D. Jash

Medical Superspeciality Hospital, Kolkata, India

D. Jash

Manipal Hospital, Salt Lake, Kolkata, India

S. Bendre

Nanavati Max Hospital, Mumbai, Maharashtra, India

S. Neliyathodi

MES Medical College, Angadipuram, Kerala, India

S. J. Unnithan

KERF Hospital, Kollam, Kerala, India

A. Karadkhele (⊠)

Medical Affairs, Sun Pharma Laboratories Limited, Mumbai, Maharashtra, India

 $e\hbox{-}mail: archana.karadkhele @sunpharma.com\\$

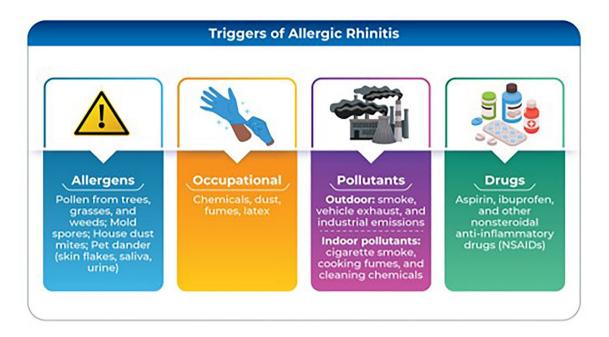


Fig. 1 Allergic and non-allergic triggers of allergic rhinitis and asthma

observed in 6- to 7-year-old children [2, 3]. The Global Burden of Disease study spanning 1990–2016 reported an estimated 37.9 million cases of asthma in India in 2016.

The Death and Disability Associated Life Years (DALY) per case of asthma in India were 2.4 times higher than the global average, and the Indian Human Development Survey (IHDS-II) reported an increase in asthma prevalence from 41.9/1000 to 54.9/1000 population [4, 5].

The strong connection between the upper and lower airways has generated significant interest. The presence of shared inflammatory mediators and the substantial effect of treating one airway on the other reinforce the idea of a unified airway disorder [1].

Optimally managing AR can alleviate symptoms of coexisting mild asthma. This involves diagnosing AR, avoiding allergens, using pharmacotherapy, and offering immunotherapy where indicated. AR management complexity mirrors its multifaceted nature [6]. In asthma, the focus is on controlling symptoms, reducing exacerbation risk, enhancing quality of life, and minimizing medication side effects. Asthma management includes patient education, trigger

avoidance, symptom monitoring, and pharmacological treatment [7, 8] (Fig. 1).

NEED OF CONSENSUS

Nasal allergy and asthma frequently coexist, with 1 in 3 patients with AR also experiencing asthma, and most patients with asthma exhibit chronic nasal symptoms. Upper airway inflammation is often overlooked by patients, leading them to develop lower airway inflammation and subsequently present with asthma symptoms. Physicians may focus solely on presenting asthma-related symptoms, resulting in the oversight of AR symptoms. Early diagnosis and optimal management of AR can improve the symptoms of coexisting asthma and reduce the burden of upper and lower airway inflammation. There is a need to develop Indian guidelines for AR management in patients with asthma. This would ensure standardized care practices and improve patient outcomes across the country. Factors like medication availability and socioeconomic disparities influence AR management in India. Based on medical history,

current symptoms, and their onset, patients with asthma should be screened for AR. There is a need to provide expert-led guidance on appropriate clinical action in screening, diagnosing, and managing AR in patients with asthma, including the role of the newer antihistamines recently being recommended and used.

METHODS

The Expert Forum Consensus Group was formed across India to address the challenges associated with better diagnosis and management of patients of AR associated with asthma, recognizing the lack of India-specific data. A steering committee of pulmonologists, ear, nose, and throat (ENT) surgeons, and allergologists guided the development of updated recommendations using the Modified Delphi Method (Fig. 2). A comprehensive literature review identified key gaps, which informed the creation of 80 questionnaires, which were framed to gather expert opinions, and voting was conducted to finalize the recommendations (Supplementary Table 1). In Phase 1 of Delphi, experts rated their agreement with each statement on a 5-point Likert scale, with consensus defined as ≥ 80% agreement. Statements lacking consensus were further discussed in an in-person meeting as part of phase 2, where non-concordant points were resolved, leading to the final consensus.

As this process did not involve experiments with human participants or animals, ethics committee approval was not required.

EXPERT OPINION

Epidemiology of AR with Asthma

Consensus:

 The panel strongly recommends screening patients with AR for asthma and vice versa, as the incidence of AR is high in asthma and vice versa.

- The panel recommends using the Global Initiative for Asthma (GINA) Symptombased screening tool or the Asthma Control Test and RHINASTHMA questionnaires as initial screening tools for asthma and AR, respectively.
- Questionnaires should be customized to the Indian context, focusing on the patient's symptoms, tailored to their understanding, and presented in their local or vernacular language.

The expert panel reached a consensus on the epidemiology of AR with asthma, as outlined in Fig. 3.

Evidence:

In a prospective study of 74 patients, it was observed that 81% presented with intermittent AR, while only 19% exhibited persistent AR. The study also revealed a slightly higher percentage of males (53.8%) compared to females (46.1%) [9].

Most patients with asthma, comprising over 80%, also have comorbid AR. Despite this high prevalence, AR is often overlooked in asthma management [10, 11]. This underscores the importance of recognizing and managing the relationship between AR and asthma to improve overall asthma outcomes (Fig. 4).

In India, the diagnosis and management of AR fall short of international guidelines due to reasons like limited allergy and immunology training among clinicians, inadequate diagnostic facilities, and expensive medications [12]. The India ARIA (Allergic Rhinitis and its Impact on Asthma) Asia Pacific Workshop Report indicates that 17–38% of patients with AR concurrently experience asthma.

Severe AR worsens asthma control, with around 60–70% of pediatric asthma cases linked to AR. A Dutch study showed that 76.2% of asthmatic kids with AR had lower Asthma Control Questionnaire scores. An Indian multicenter study utilizing the coexistence of AR and asthma questionnaire reported a high prevalence of 65.24% of concomitant AR in adult asthmatics [13].

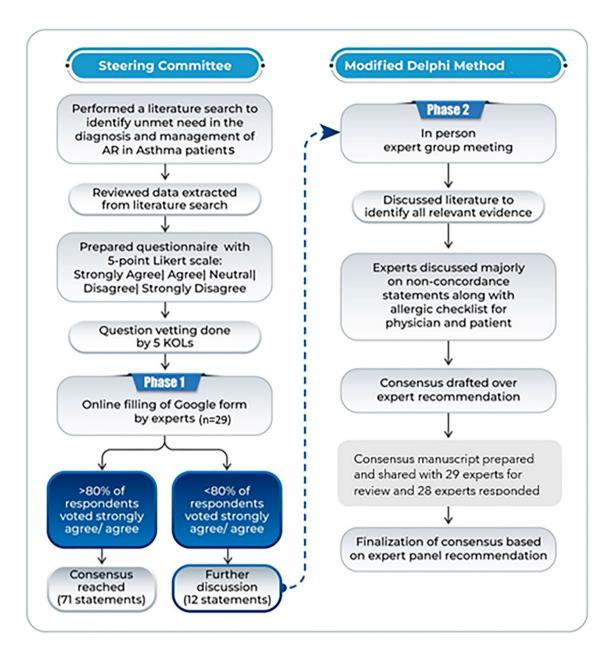


Fig. 2 Methodology of consensus

Relationship between AR and Asthma

Consensus: The Panel strongly recommends conducting a detailed history and asking specific questions to establish an association between the source of allergens, symptoms, risk factors, exposure history, and clinical correlation with disease manifestations (Fig 5).

Evidence:

The "One Airway, One Disease" idea proposes that upper airway issues may increase the risk of lower airway diseases like asthma. Allergen sensitization in the upper airway can trigger lower airway hyperreactivity, possibly contributing to asthma from early in life. AR also significantly affects children's quality of life. Integrated management of both upper and

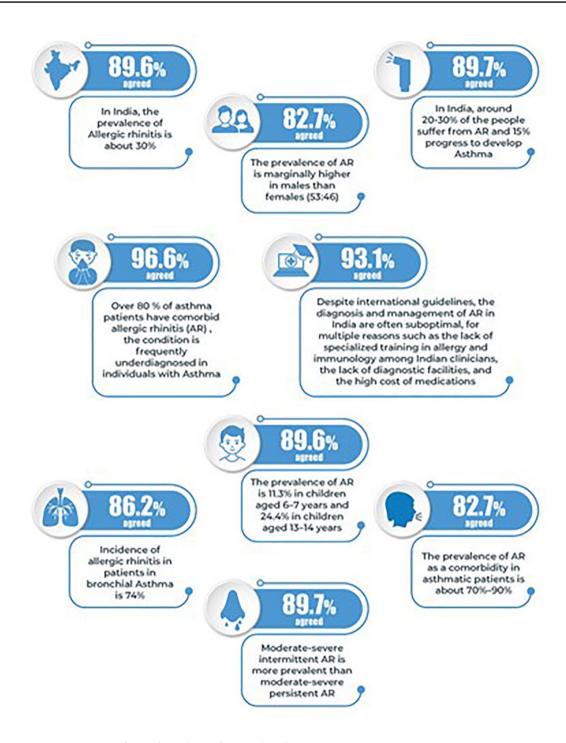


Fig. 3 Consensus statements for epidemiology of AR with asthma

lower airway diseases leads to better outcomes, emphasizing the close connection between these disorders [13] (Fig. 6).

It is a proven fact that hormones play a significant role in asthma, rhinitis, and eczema. Hyperthyroidism can worsen asthma due to

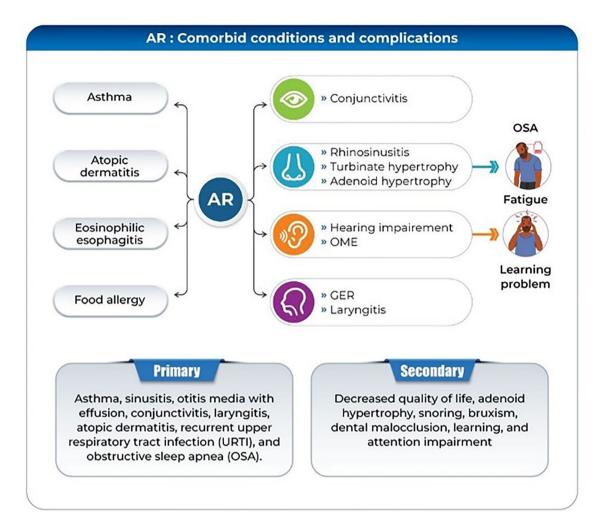


Fig. 4 Comorbid conditions and complications of AR in asthma. *OME* otitis media with effusion, *OSA* obstructive sleep apnoea, *GER* gastroesophageal reflux, *AR* allergic rhinitis, *URTI* upper respiratory tract infection

altered oxygen species, but symptoms improve when thyroid levels are normal. Screening for thyroid levels is important in asthmatics experiencing exacerbations to differentiate symptoms. Hypothyroidism may lead to milder asthma symptoms, especially in women and older individuals. Excessive iodine intake or thyroid problems should be considered in asthmatics as they can worsen symptoms or weaken the airways [14]. Patients with AR often experience a higher hypothyroidism risk, impacting mucociliary clearance and infection vulnerability. Levothyroxine treatment enhances nasal function in hypothyroid AR sufferers, with combined management proving more effective for rhinitis than treating hypothyroidism alone [15].

Early diagnosis and management of AR are vital for optimal asthma control. Only 25% of ASPAIR-India physicians use validated outcome questionnaires like ACT or ACQ. Among general physicians, it is even lower, at 16% [16]. RHINASTHMA questionnaire assessments show higher scores for patients with AR + asthma compared to AR alone, indicating a poor quality of life for those with both conditions [12].

In patients with asthma stratified by 2017 GINA grades, the association with AR was strongest in severe persistent asthma and weakest in mild persistent asthma. According to GINA grade, patients with AR with severe persistent asthma had poorer control (β for CARAT-Total score: -0.25; 95%CI: -0.31, -0.19) than

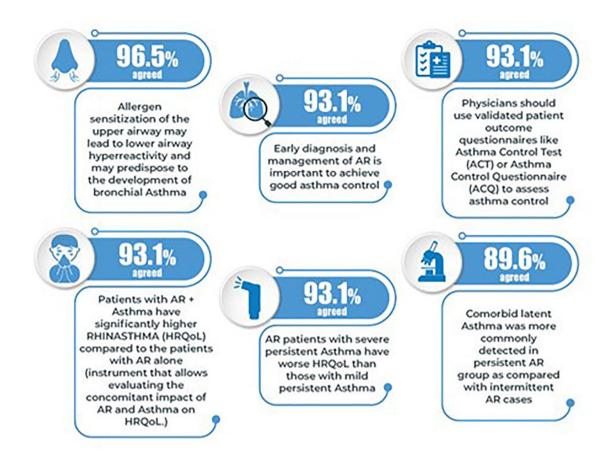


Fig. 5 Consensus statement on relationship between AR and asthma

those with mild persistent asthma (β : – 0.06; 95%CI: – 0.14, 0.03). [9]

Risk Factors

In patients with asthma, risk factors for AR include sensitization to allergens such as pollen, house dust mites, and animal dander, as well as exposure to environmental pollutants and tobacco smoke. Addressing these risk factors through allergen and irritant avoidance strategies, and appropriate asthma management is crucial in mitigating the burden of both diseases in patients and improving overall respiratory health (Fig. 7).

Evidence:

The occurrence of both AR and asthma is strongly associated with personal and family histories of atopy, with significant odds ratios of 2.53 and 1.51, respectively (both P < 0.005). Several risk factors contribute to the coexistence of AR and asthma (P < 0.005), including exposure to second-hand smoke, biomass fuel, pets and animals at home, and sensitization to allergens, such as pollens, house dust mites, and animal dander [17, 18]. In India, common aeroallergens linked to AR and asthma include house dust mites, cockroaches, pollen, and mold spores. A key study from Eastern India found that 96% of individuals with nasobronchial allergy were sensitized to house dust mites, with the most prevalent mites being Dermatophagoides pteronyssinus, D. farinae, and Blomia tropicalis at rates of 75.06%, 63.72%, and 72%, respectively. Studies from other regions of India, including Western, Northern, and Southern areas, reported slightly lower sensitization rates, though D. pteronyssinus remained a predominant allergen [19].

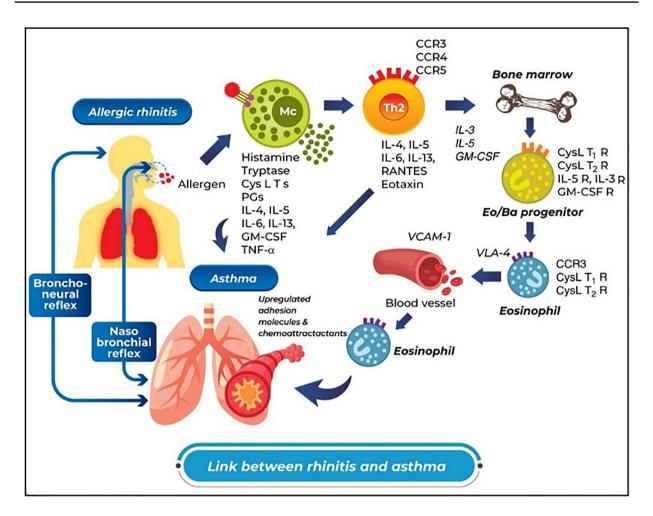


Fig. 6 Potential mechanism linking AR and asthma. *TNF-α* tumor necrosis factor-alpha, *IL* interleukin, *VLA* very late antigen, *VCAM* vascular cell adhesion molecule, *GM-CSF* granulocyte–macrophage colony-stimulating fac-

tor, *PG* prostaglandin, *RANTES* regulated on activation normal t cell expressed and secreted, *CysLT1R* cysteinyl leukotriene type 1 receptor, *CCR3* CC chemokine receptor 3

A study found that asthma and atopic dermatitis led to the highest number of non-ENT physician visits [20]. The coexistence of AR and asthma often results in treatment delays, as patients seek consultations from multiple specialists, primarily focusing on asthma treatment while overlooking associated rhinitis. AR is recognized as an etiological risk factor for both the development and severity of asthma, contributing to complications and poor asthma control. The severity of rhinitis significantly influences the development of asthma, with individuals experiencing persistent and severe rhinitis having a substantially higher risk of asthma. Given the frequent coexistence of

asthma and rhinitis, it is imperative to assess and manage AR in every patient with asthma to ensure comprehensive disease management [20] (Fig. 8).

Diagnosis.

Consensus: The Panel strongly recommends investigations for AR, which could include detailed clinical evaluation and nasal examination. Total IgE, skin prick tests, and imaging can be carried out as required. Rhinomanometry can used to distinguish structural and soft tissue causes for nasal obstruction. A normal total IgE or negative skin prick test does not always rule out atopic disease (Fig. 9).

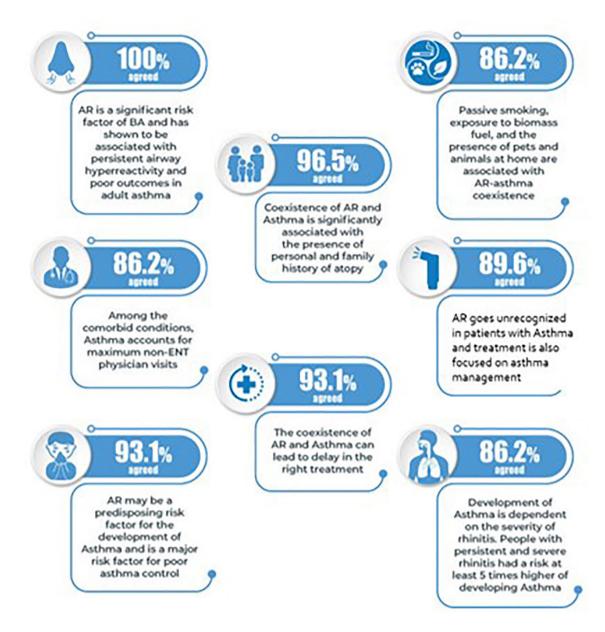


Fig. 7 Consensus statements on risk factors

Evidence:

In a study by Shah et al., symptoms of rhinitis were found in 75% of children and 80% of adults among 646 outpatient asthmatics [21].

In ASPAIR-India, 79% of physicians enquired about AR symptoms in patients with asthma at every visit, with 36% enquiring seasonally and 33% during increased symptoms. For patients with AR, 76% of physicians enquired about asthma symptoms at every visit [16].

According to the CARAS survey, 7.83% of the total study population underwent a skin prick test, showing a high prevalence of concomitant AR in Indian patients with asthma. The results underscore the need for early diagnosis and guideline-based management of AR in patients with asthma [17].

Suggested investigations for AR diagnosis by the Indian Medical Association include complete clinical evaluation, nasal examination,



Fig. 8 Environmental control measures for patient with house dust mite allergy

allergy skin prick tests, and assessment of specific IgE testing [22]. Elevated IgE levels are frequently observed in patients with atopic dermatitis, food allergies, and asthma. When serum IgE exceeds 2000 IU/ml, it is often associated with severe atopic conditions [23]. A cross-sectional study including 562 patients with asthma found higher mean serum IgE levels (554 IU/mL) compared to controls (69 IU/ mL). After immunotherapy, IgE levels decreased by 36%, confirming that total IgE levels are predictive in asthma and have a high value in assessing overall atopic status [24]. Component-resolved diagnostics or molecular allergology blood tests provide interesting insights into the risk of development of asthma in patients with AR as well as predicting the response to immunotherapy for selected patients. The international consensus statement on allergy and rhinology emphasizes assessing symptoms post-allergen exposure, as sensitization detected does not always match allergy symptoms. Rhinomanometry aids in distinguishing nasal obstruction causes between structural and soft tissue [25].

Management

Consensus: The Panel strongly recommends: Avoidance of the allergen as the first step in non-pharmacological management of AR. The

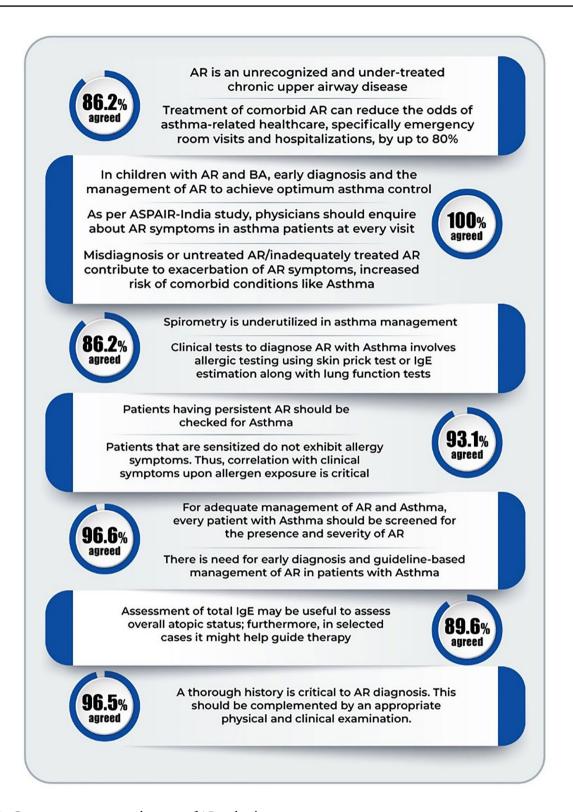


Fig. 9 Consensus statement on diagnosis of AR and asthma

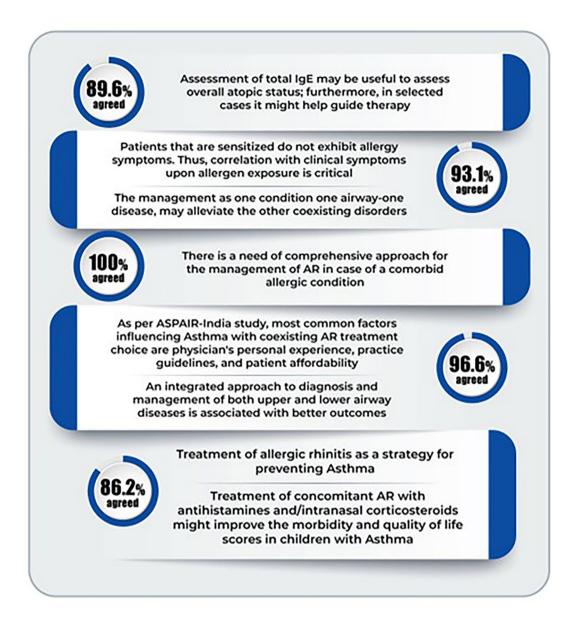


Fig. 10 Consensus statements on management of AR and asthma

Panel conditionally recommends performing pulmonary function tests (spirometry) for patients with AR exhibiting symptoms suggestive of asthma. Additionally, peak flow meters can serve as a screening tool for patients with occupational asthma to identify temporal associations of lower respiratory symptoms. This involves measuring peak expiratory flow rate readings every second hour over a 12- to 16-h period, with 6–8 readings per day, including

both during work hours and off-work periods (Fig. 10).

Evidence: A European study found that patients with both AR and asthma have lower quality of life and symptom control compared to AR alone [12]. This emphasizes the need for a comprehensive approach to managing AR in comorbid allergic conditions to reduce global disease burden. Addressing underlying inflammation in AR is crucial, with emerging strategies targeting asthma prevention [26, 27].

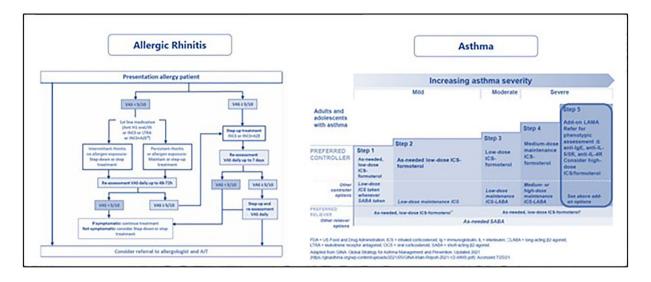


Fig. 11 Treatment algorithm for allergic rhinitis and asthma

Multiple guidelines address oral antihistamine use in AR. In 2004, the ARIA group and EAACI outlined recommendations focusing on newer-generation antihistamines over first-generation ones due to better efficacy, safety, and pharmacology. In 2020, the ARIA group released GRADE-based guidelines incorporating realworld patient-reported experiences and clinical studies. ARIA (2020) and GINA (2023) guidelines provided a detailed treatment algorithm, considering symptom severity and medication history to define the role of newer-generation antihistamines in AR management in patient with asthma. (Fig. 11).

Most often, pollution is associated synonymously with outdoor air pollution. Considering the rapid urbanization, the sources of indoor air pollution should also be screened in appropriate patients.

Intranasal Corticosteroid

Intranasal corticosteroids (INCS) is the first-line therapy for AR, effectively relieving symptoms and reducing exacerbation risk in both AR and asthma [29, 30]. In 2023, GINA recommended regular (inhaled corticosteroid) ICS treatment for adults, adolescents, and children over 5 with asthma. For children \leq 5, ICS is advised if asthma is likely or if symptoms are uncontrolled

or occur frequently [31]. Available INCS in India show minimal differences in efficacy and safety but vary in sensory perceptions [32] (Fig. 12).

Antihistamines

In the Indian market, there are several oral second-generation antihistamines available. comprised of oral tablets and capsules. These antihistamines include cetirizine dihydrochloride, levocetirizine hcl, loratadine, desloratadine, fexofenadine HCL, ebastine, rupatadine, mizolastine, bilastine, bepotastine, and ketotifen. While targeting the histamine H1 receptor, these antihistamines play a crucial role in enhancing the quality of life for patients with AR. Unlike first-generation antihistamines, which often induce sedation and other adverse effects, second-generation antihistamines, as classified by the US FDA, generally exhibit nonsedating properties. Evidence also supports the efficacy and safety of second-generation oral H1 antihistamines, especially in specific patient groups such as children [33] (Fig. 13).

Second-generation antihistamines are preferred for allergic rhinitis due to lower risks of sedation and anticholinergic effects compared to first-generation antihistamines. While loratadine and desloratadine may cause sedation at high doses, cetirizine and intranasal azelastine can cause sedation even at recommended doses.

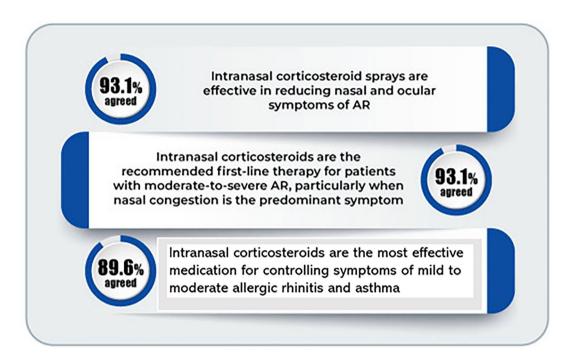


Fig. 12 Consensus statements on intranasal corticosteroid

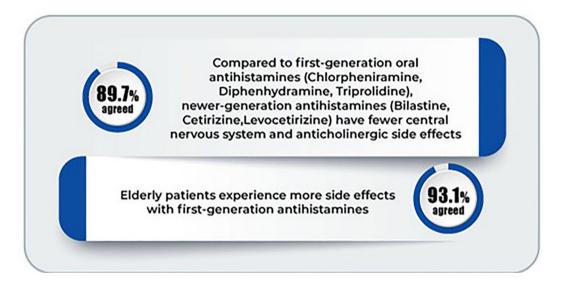


Fig. 13 Consensus statements on antihistamines

Fexofenadine does not cause sedation [34]. High-quality evidence, particularly for newer agents like bilastine and rupatadine, is growing and they are considered effective and safe for AR treatment, showing comparable efficacy and safety to other oral antihistamines [25, 35].

In clinical trials, bilastine at a single daily dose of 20 mg has demonstrated efficacy and safety, which is superior to the placebo [36]. Combining bilastine with montelukast has shown dual action on early- and late-phase allergic reactions

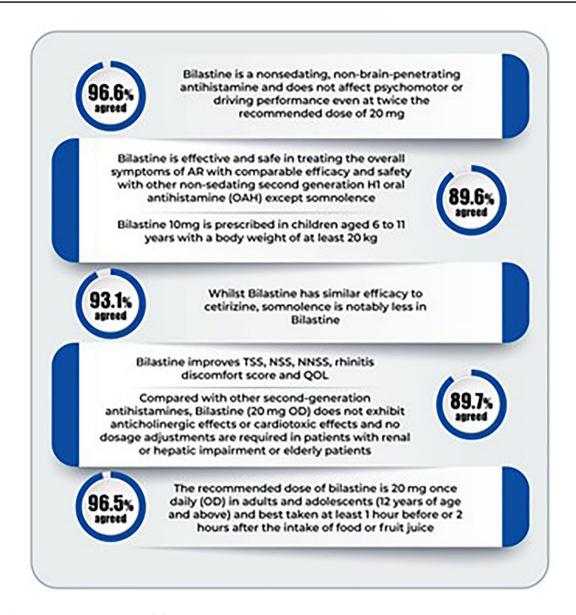


Fig. 14 Consensus statements on bilastine

in patients with AR with concomitant asthma [36, 37] (Fig. 14).

LTRA

Leukotriene receptor antagonists (LTRAs), like montelukast and zafirlukast, are crucial in managing AR and asthma. Montelukast is used for asthma prophylaxis and easing AR symptoms but is not the first line for AR. Patients prefer its once-daily oral dose for convenience and to avoid long-term corticosteroid side effects.

Zafirlukast, mainly for asthma, being used in AR off-label. Both offer promising options for treating asthma and AR together [38]. However, it is important to note that montelukast is not indicated for the treatment of bronchospasm in acute asthma attacks, including status asthmaticus. Due to the rare potential for neuropsychiatric severe adverse events, particularly suicide, a black box warning has been issued. Treatment should be discontinued upon the occurrence of any neuropsychiatric side effects [39] (Fig. 15).

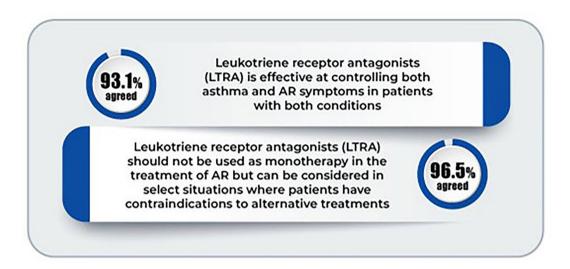


Fig. 15 Consensus statements on leukotriene receptor antagonist

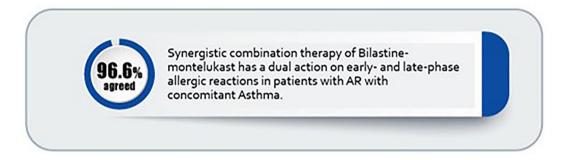


Fig. 16 Consensus statement on combination of antihistamine and LTRA

Combination of Antihistamine and LTRA

The combination therapy of antihistamines and LTRA presents a promising approach to managing AR and asthma, offering enhanced symptom relief and improved disease control. Bilastine treats allergic rhino conjunctivitis, while montelukast manages mild asthma and AR symptoms. Used together, they provide a dual-action approach, especially beneficial for patients with both conditions [37].

Montelukast and fexofenadine are commonly used to manage AR, with proven effectiveness individually. In India, a fixed-dose combination of montelukast 10 mg and fexofenadine 120 mg is available and utilized for treating AR [40]. Combinations of desloratadine, levocetrizine,

and bilastine with montelukast are also available in India. (Fig. 16).

Oral Corticosteroid

Oral corticosteroids provide dose-dependent relief for specific symptoms of AR in patients with asthma. Low doses effectively reduce nasal congestion, drainage, and eye symptoms, but have less impact on itching, rhinorrhoea, and sneezing [41]. Laursen et al. found comparable symptom relief between daily oral prednisolone for 3 weeks and a single intramuscular betamethasone injection for AR. However, daily prednisolone significantly lowered plasma cortisol levels after 3 weeks.

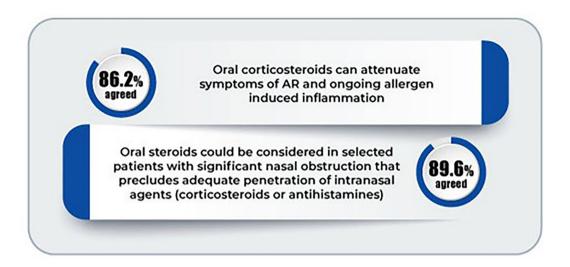


Fig. 17 Consensus statements on oral corticosteroid

Overall, short-term oral or depot steroids offer significant relief from AR symptoms and improve quality of life in asthmatic individuals, making them valuable for AR management [42] (Fig. 17).

Nasal Decongestant

Nasal congestion in AR with asthma can be managed with decongestants like phenylephrine, oxymetazoline, and pseudoephedrine, but caution is needed, especially with pseudoephedrine due to abuse potential. Side effects like sneezing and nasal dryness are common. Short-term use is advised to prevent rebound congestion. If intranasal corticosteroids are not effective, decongestants can be considered, with careful attention to individual patient factors and medical history [33, 43] (Fig. 18).

Combination Therapy

Combinational therapy may be useful for symptom control, particularly in patients with comorbid asthma, though caution is warranted due to boxed warnings limiting its use in AR without asthma [25] (Fig. 19).

Immunotherapy

For patients with seasonal and perennial AR seeking to alleviate symptoms and reduce medication use, recommendations endorse tablet or aqueous sublingual immunotherapy (SLIT). This approach not only addresses AR symptoms but also potentially lowers the risk of developing asthma or new allergen sensitization [25]. Allergen immunotherapy (AIT), particularly SLIT, stands out for its allergen specificity, immunomodulatory effects, and high safety profile, marking a significant advancement in respiratory allergy management. Tablet-formulated AIT further expands treatment options, offering efficacy, safety, and official recognition as a pharmaceutical product, signaling rapid progress in the field [44]. Subcutaneous immunotherapy also has more than 110 years of evidence in the management of AR with an excellent safety profile when performed by trained allergologists [45] (Fig. 20).

Unmet need

The coexistence of nasal allergy and asthma is well established, but there is a gap in recognizing and managing both conditions. Early identification and optimal management of AR can improve asthma symptoms. However, guidelines lack expert-led guidance on managing these

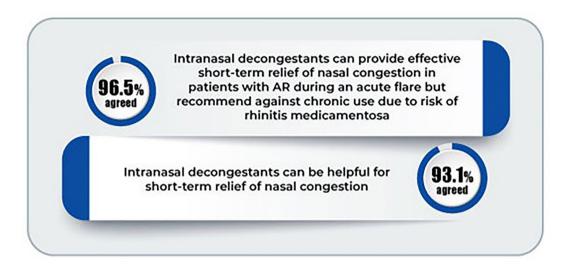


Fig. 18 Consensus statements on nasal decongestion

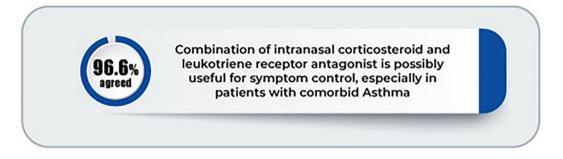


Fig. 19 Consensus statement on combination therapy

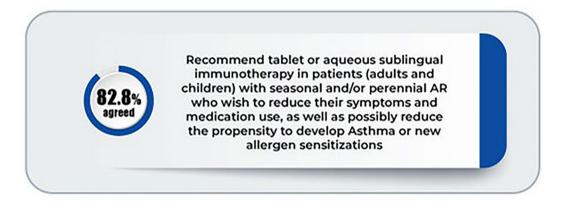


Fig. 20 Consensus statement on immunotherapy

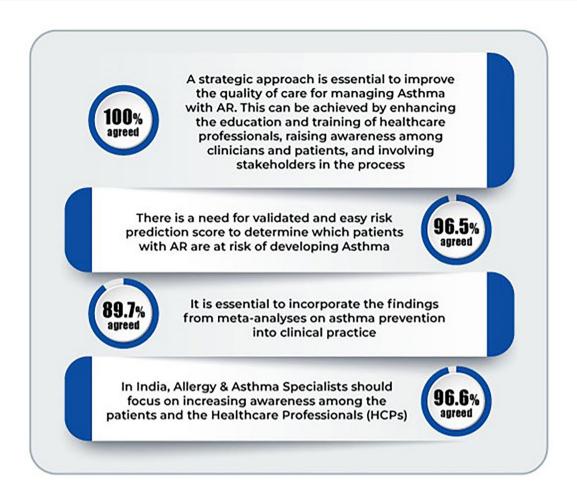


Fig. 21 Consensus statement on unmet need

conditions together. Overlooking initial upper airway symptoms in patients with asthma is common, but can affect diagnosis and treatment efficacy. Acknowledging this issue can refine approaches and enhance outcomes for patients with both conditions (Fig. 21).

Phase 2

In Phase 2, following a thorough discussion among the experts, 7 statements were modified, 5 were accepted (Table 1; Fig. 22).

LIMITATIONS

The consensus manuscript represents a comprehensive effort by a diverse group of experts in the field of AR and asthma management

in India; it is essential to acknowledge certain limitations. The extensive number of authors involved in this collaborative endeavor may have inadvertently resulted in the inability to capture every individual insight and perspective. One limitation of our discussion, as well as any similar points that may have been overlooked during voting, is the absence of specific recommendations or guidelines despite the well-known fact that hormones significantly impact asthma and rhinitis. Furthermore, the focus of the manuscript primarily on the management of AR in patients with asthma may have limited the depth of coverage on individual disease management strategies for each condition separately. Lastly, while efforts were made to ensure inclusivity and representativeness, there may still exist variations in practice

 Table 1
 Non-concordance consensus statements discussed in Phase 2

Table 1 1001 collections statements discussed in times a			
Non-concordance statement	Phase 1	Phase 2	Final statement
About 60-90% of children with BA had AR	72.4%	100%	About 60–80% of children with BA had AR
About 40–50% of patients with AR also have asthma	%6.89	100%	About 40–60% of pediatric patients with AR also have asthma
The incidence of asthma in patients with AR is 36%	75.9%	100%	The incidence of asthma in adult patients of AR is 36%
Symptoms of rhinitis are present in 75% of children and 80% of asthmatic adults	79.3%	100%	Symptoms of rhinitis are present in 80% of children and 75% of asthmatic adults
In the ASPAIR-India study,90% of physicians preferred nasal and 75% preferred ocular symptoms to diagnose AR in patients with diagnosed asthma	79.3%	100%	The majority of physicians diagnose AR based on nasal symptoms
Skin prick test should be used as a routine procedure in all age groups in order to identify the specific allergen that the patient is sensitized with	55.2%	89.7%	Skin prick test should be carried out in selected cases and should be restricted to a hospital or specialist setting
Less than 10% of the patients are sent for skin prick test	79.3%	100%	Less than 10% of the patients are sent for skin prick test
Intradermal testing may be used to determine aeroallergen sensitization in individuals suspected of having AR	72.4%	89.7%	Intradermal testing may be considered for patients with negative skin prick test and should be performed in a hospital/specialist setting
Nasal endoscopy and anterior rhinoscopy are considered as a diagnostic 75.9% adjunct in the evaluation of patients with suspected AR	75.9%	89.7%	Nasal endoscopy and anterior rhinoscopy are considered as a diagnostic adjunct in the evaluation of patients with suspected AR
Rhinomanometry is useful to improve patient selection for surgery, distinguish between structural and functional causes of nasal obstruction, diagnose nasal valve collapse, clarify conflicting symptoms and exam findings, and in nasal allergen challenges	79.3%	89.7%	Rhinomanometry should be restricted for selected cases and performed in a hospital/specialist setting
Intranasal antihistamines are superior to INCS for sneezing, itching, rhinorrhoea, and ocular symptoms	72.4%	89.7%	Intranasal corticosteroids are superior to oral antihistamines for sneezing, itching, rhinorrhoea, and ocular symptoms
Allergen-specific immunotherapy may reduce the risk of asthma development in pediatric patients with AR	79.3%	89.7%	Allergen-specific immunotherapy may reduce the risk of asthma development in pediatric patients with AR
	-		

AR allergic rhinitis, BA bronchial asthma, INCS intranasal corticosteroids

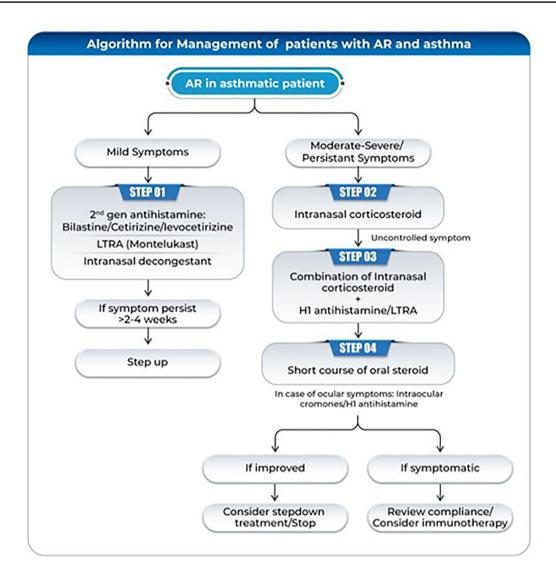


Fig. 22 Treatment algorithm for AR in patients with asthma

patterns and resource availability across different regions of India, which could impact the applicability of certain recommendations in diverse healthcare settings.

FUTURE DIRECTIONS

When prescribing antihistamines for asthma and rhinitis, clinicians should consider individual

patient characteristics, including the presence of concomitant conditions, potential drug interactions, and side effect profiles. Moreover, further research is warranted to elucidate the optimal role of antihistamines in the management of asthma and rhinitis, particularly in patients with severe disease or refractory symptoms. Emerging therapies targeting novel inflammatory pathways may also offer promising alternatives or complementary approaches in the treatment of these respiratory conditions.

CONCLUSION

The expert consensus represents a significant advancement in addressing the complexities of managing coexisting AR and asthma. By identifying and addressing gaps in both research and clinical practice, updated guidelines have been established to assist healthcare professionals. The focus on a systematic and evidence-based approach to diagnosis and management aims to enhance the recognition and treatment of AR in patients with asthma. Through the provision of improved tools and strategies, the consensus aims to raise the standard of care, leading to better disease management and improved quality of life for patients affected by these chronic respiratory conditions. To address a critical gap in clinical practice, developed a novel questionnaire specifically designed to aid Indian clinicians in diagnosing and managing AR in patients with asthma (Supplementary Fig. 1). This expertconsensus-based tool aims to standardize care and enhance patient outcomes in the Indian healthcare setting. The questionnaire, the first of its kind, represents a significant contribution by consensus group experts from India to the therapy area for better management of AR with asthma. The expert recommendation emphasizes the importance of conducting a detailed patient history and asking specific questions to establish a temporal association between symptoms, risk factors, exposure history, and clinical correlation, aiding in the identification of potential allergen sources. Key components of asthma management include patient education, minimizing exposure to triggers, monitoring for symptom or lung function changes, and pharmacologic therapy.

Antihistamines play a multifaceted role in managing asthma and rhinitis by mitigating histamine-mediated inflammatory responses. Although their effectiveness in symptom alleviation and lung function improvement varies, antihistamines remain a valuable treatment option, particularly for individuals with asthma and rhinitis. Ongoing research and clinical trials are essential for optimizing their use and

investigating innovative treatment strategies for these prevalent respiratory conditions. In addition to INCS as the primary treatment for moderate to severe symptoms, oral antihistamines, oral LTRAs, and intranasal antihistamines are used as supplementary therapies. Furthermore, immunotherapy, such as subcutaneous or sublingual immunotherapy, may be considered for patients with persistent symptoms that do not respond to conventional treatments or those seeking long-term symptom control. (see Table S1 and Figs. S1 and S2 in the electronic supplementary material for details).

ACKNOWLEDGEMENTS

Dr. K.R. Radhakrishnan was part of the investigation and voting process. He was fully aware of the study's objectives, having been provided with a detailed overview during the initial consultation phase. He was also informed that the study's results would be published, a plan he acknowledged and understood. Dr. Radhakrishnan agreed to participate and provided formal consent through a consent form, which detailed the study's objectives, his role, and the publication intentions. Additionally, his independence was verified, with Dr. Radhakrishnan confirming that he had no conflicts of interest that could influence his contribution to the study. Dr Sunaina Anand and Dr Sreeni Nair from IntelliMed Healthcare Solutions helped in data curation, writing the original draft, writingreview, and editing.

Medical Writing Assistance. IntelliMed Healthcare Solutions Pvt Ltd helped in formal analysis, software, data curation, and resources funded by Sun Pharma Laboratories Limited, India.

Author Contribution. Dr R Narasimhan: Validation, Visualization, Investigation, Writing-Review and Editing; Dr Sitesh Roy: Validation, Investigation, Visualization, Writing-Review and Editing; Dr Meghanadh Koralla: Validation, Visualization, Investigation, Writing-Review and

Editing: Dr P K Thomas: Validation, Visualization, Investigation, Writing-Review and Editing; Dr Ilambarathi.M: Visualization, Investigation, Writing-Review and Editing: Dr S Balamurugan: Validation, Visualization, Investigation, Writing-Review and Editing; Dr M, Harish: Investigation, Writing-Review and Editing; Dr Sabarinath Ravichandar: Investigation, Writing-Review and Editing; Dr Gaurav Medikeri: Validation, Investigation, Writing-Review and Editing; Dr Partha Bose: Investigation, Writing-Review and Editing; Dr V R Pattabhiraman: Investigation, Writing-Review and Editing: Dr Rajasekar M K: Investigation. Writing-Review and Editing; Dr A R Gayathri: Investigation, Writing-Review and Editing, Dr Dhanasekar T: Investigation, Writing-Review and Editing, Dr Nandagopal: Investigation, Writing-Review and Editing; Dr G Gananathan: Investigation, Writing-Review and Editing, Dr Ravichandran S K: Investigation, Writing-Review and Editing; Dr M N Shankar: Investigation, Writing-Review and Editing, Dr Aniruddha Majumder: Investigation, Writing-Review and Editing; Dr Shelley Shamim: Investigation, Writing-Review and Editing; Dr Meenesh Juvekar: Investigation, Writing-Review and Editing; Dr Vijay K Singh: Investigation, Writing-Review and Editing; Dr T Mohankumar: Investigation, Writing-Review and Editing; Dr Prasanna Kumar T: Investigation, Writing-Review and Editing; Dr Debraj Jash: Investigation, Writing-Review and Editing; Dr Salil Bendre: Investigation, Writing-Review and Editing; Dr Suhail Neliyathodi: Investigation, Writing-Review and Editing; Dr Sunil Janardanan Unnithan: Investigation, Writing-Review and Editing; Dr Archana Karadkhele: Investigation, Conceptualization, Methodology, Writing -Original draft, Writing-Review and Editing, Visualization, Supervision, Project administration, Funding acquisition. Author Agreement: All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Funding. As a therapy contribution, Sun Pharma Laboratories Limited, India, supported

advisory board meeting and journal rapid service fee.

Declarations

Conflict of interest. Dr Archana Karadkhele is an employee of Sun Pharma Laboratories Limited, India. Dr Narasimhan R, Dr Sitesh Roy, Dr Meghanadh Koralla, Dr P K, Dr Ilambarathi. M, Dr S Balamurugan, Dr M Harish, Dr Sabarinath Ravichandar, Dr Gaurav Medikeri, Dr Partha Bose, Dr V R Pattabhiraman, Dr Rajasekar M K, Dr A R Gayathri, Dr Dhanasekar T, Dr Nandagopal, Dr G Gananathan, Dr Ravichandran S K, Dr M N Shankar, Dr Aniruddha Majumder, Dr Shelley Shamim, Dr Meenesh Juvekar, Dr Vijay K Singh, Dr T Mohankumar, Dr Prasanna Kumar S, Dr Debraj Jash, Dr Salil Bendre, Dr Suhail Neliyathodi, and Dr Sunil Janardanan Unnithan declare that they have no competing interests.

Ethical approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativeco mmons.org/licenses/by-nc/4.0/.

REFERENCES

- Anas M, Shameem M, Ahmad Z. Clinicopathological, epidemiological, and immunological relationship between allergic rhinitis and bronchial asthma. Indian Journal of Allergy, Asthma and Immunology [Internet]. 2020 [cited 2023 Dec 17];34:92. https://journals.lww.com/IJAA/Fulltext/2020/34020/Clinicopathological,_epidemiological,_and.9.aspx
- 2. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998. 34 351:1225–32.
- 3. Lai CKW, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the international study of asthma and allergies in childhood (ISAAC). Thorax. 2009;64:476–83.
- 4. India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of india: the global burden of disease study 1990–2016. Lancet Glob Health. 2018;6:e1363–74.
- Kumar P, Ram U. Patterns, factors associated and morbidity burden of asthma in India. PLoS ONE. 2017;12: e0185938.
- Linton S, Burrows AG, Hossenbaccus L, Ellis AK. Future of allergic rhinitis management. Annals of Allergy, Asthma & Immunology [Internet]. 2021 [cited 2023 Dec 22];127:183–90. Available from: https://www.sciencedirect.com/science/article/pii/ S1081120621003379
- 7. Overview | Asthma: diagnosis, monitoring and chronic asthma management | Guidance | NICE [Internet]. NICE; 2017 [cited 2024 Mar 28]. Available from: https://www.nice.org.uk/guidance/ng80
- 8. 2023 GINA Main Report Global Initiative for Asthma GINA [Internet]. [cited 2024 Mar 28]. Available from: https://ginasthma.org/2023-gina-main-report/
- Monga S, Malik J, Sharma AP, Jan S, Nabi N, Bahadur S. Deranged Pulmonary Function Tests in Allergic Rhinitis in North Indian Patients. Clin Med Insights Ear Nose Throat [Internet]. 2019 [cited 2023 Dec 29];12:1179550619888856. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6859672/
- 10. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its

- Impact on Asthma (ARIA) 2008*. Allergy [Internet]. 2008 [cited 2023 Dec 29];63:8–160. Available from: https://onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1111/j.1398-9995.2007.01620.x
- 11. Egan M, Bunyavanich S. Allergic rhinitis: the "Ghost Diagnosis" in patients with asthma. Asthma Res Pract [Internet]. 2015 [cited 2023 Dec 29];1:8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142399/
- 12. Moitra S, Mahesh PA, Moitra S. Allergic rhinitis in India. Clin Exp Allergy. 2023;53:765–76.
- 13. Shanmuganathan A, Gopalakrishnan K, Ganga N. Prevalence of Coexistent Allergic Rhinitis in Schoolchildren with Bronchial Asthma and Its Association with Asthma Control. Journal of Association of Pulmonologist of Tamil Nadu [Internet]. 2022 [cited 2023 Dec 29];5:50. Available from: https://journals.lww.com/jatn/fulltext/2022/05020/prevalence_of_coexistent_allergic_rhinitis_in.2.aspx
- 14. Weare-Regales N, Chiarella SE, Cardet JC, Prakash YS, Lockey RF. Hormonal Effects on Asthma, Rhinitis, and Eczema. J Allergy Clin Immunol Pract [Internet]. 2022 [cited 2024 Apr 18];10:2066–73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9392967/
- 15. Günel C, Başak HS. Güney E [The relationship between hypothyroidism and rhinitis]. Kulak Burun Bogaz Ihtis Derg. 2010;20:163–8.
- 16. Markandeywar N, Kubal V, Khosla I, Shantakumar S, Hinds D, Kotak B, et al. Physician beliefs and management practices of coexistent Asthma-Allergic Rhinitis: Indian results from multi-country ASPAIR study. IP Indian Journal of Immunology and Respiratory Medicine [Internet]. 2021 [cited 2023 Dec 29];5:237–43. Available from: https://www.ijirm.org/article-details/12818
- 17. Jaggi V, Dalal A, Ramesh B, Tikkiwal S, Chaudhry A, Kothari N, et al. Coexistence of allergic rhinitis and asthma in Indian patients: The CARAS survey. Lung India [Internet]. 2019 [cited 2023 Dec 29];36:411–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6710977/
- 18. Saha GK. House dust mite allergy in Calcutta, India: evaluation by RAST. Ann Allergy. 1993;70:305–9.
- Krishna MT, Mahesh PA, Vedanthan P, Moitra S, Mehta V, Christopher DJ. An appraisal of allergic disorders in India and an urgent call for action. World Allergy Organ J [Internet]. 2020 [cited 2024 Jul 10];13:100446. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7398972/

- 20. Singh DrR, Vaish DrS. Epidemiological prospective study on estimating the coexistence of allergic rhinitis and asthma in adult patients. Int J Adv Res Med [Internet]. 2021 [cited 2023 Dec 29];3:529–32. Available from: https://www.medicinepaper.net/archives/2021.v3.i1.I.201
- 21. Shah A, Pawankar R. Allergic rhinitis and comorbid asthma: perspective from India ARIA Asia-pacific workshop report. Asian Pac J Allergy Immunol. 2009;27:71–7.
- 22. IMAHQ_Allergy Booklet_2.pdf [Internet]. [cited 2023 Dec 29]. Available from: https://www.ima-india.org/ima/pdfdata/IMAHQ_Allergy%20Booklet_2.pdf
- 23. Chin A, Balasubramanyam S, Davis CM. Very elevated IgE, atopy, and severe infection: a genomics-based diagnostic approach to a spectrum of diseases. Case Reports Immunol. 2021;2021:2767012.
- 24. Ahmad Al Obaidi AH, Mohamed Al Samarai AG, Yahya Al Samarai AK, Al Janabi JM. The predictive value of IgE as biomarker in asthma. J Asthma. 2008. 45: 8 654–63.
- 25. Wise SK, Damask C, Roland LT, Ebert C, Levy JM, Lin S, et al. International consensus statement on allergy and rhinology: Allergic rhinitis 2023. International Forum of Allergy & Rhinology [Internet]. 2023 [cited 2023 Dec 17];13:293–859. Available from: https://onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1002/alr.23090
- 26. Testa D, Bari DI, M, Nunziata M, Cristofaro GD, Massaro G, Marcuccio G, et al. Allergic rhinitis and asthma assessment of risk factors in pediatric patients: a systematic review. Int J Pediatr Otorhinolaryngol. 2020;129: 109759.
- 27. Morjaria JB, Caruso M, Emma R, Russo C, Polosa R. Treatment of allergic rhinitis as a strategy for preventing asthma. Curr Allergy Asthma Rep. 2018;18:23.
- Varshney J, Varshney H. Allergic Rhinitis: an Overview. Indian J Otolaryngol Head Neck Surg [Internet]. 2015 [cited 2024 Mar 28];67:143–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4460099/
- 29. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ. 1998;317:1624–9.
- 30. Vervloet D, Charpin D, Desfougeres JL. Intranasal fluticasone once daily compared with once-daily cetirizine in the treatment of seasonal allergic

- rhinitis: results of a multicentre. Double-Blind Study Clin Drug Investig. 1997;13:291–8.
- 31. Levy ML, Bacharier LB, Bateman E, Boulet L-P, Brightling C, Buhl R, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. npj Prim Care Respir Med [Internet]. 2023 [cited 2023 Dec 17];33:1–13. Available from: https://www.nature.com/articles/s41533-023-00330-1
- 32. Khanna P, Shah A. Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. Am J Rhinol. 2005;19:316–21.
- 33. Kawauchi H, Yanai K, Wang D-Y, Itahashi K, Okubo K. Antihistamines for Allergic Rhinitis Treatment from the Viewpoint of Nonsedative Properties. Int J Mol Sci [Internet]. 2019 [cited 2024 Apr 3];20:213. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6337346/
- 34. Lambert M. Practice Parameters for Managing Allergic Rhinitis. afp. 2009;80:79–85.
- 35. Linton S, Hossenbaccus L, Ellis AK. Evidence-based use of antihistamines for treatment of allergic conditions. Ann Allergy Asthma Immunol. 2023;131:412–20.
- 36. Lavorini F, Matucci A, Rossi O, Pistolesi M. Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivits and mild-to-moderate asthma. Allergy. 2020;75(4):675–7.
- 37. Jain S, Verma S, Balamurugan S, Reddy KRBK, Christopher DJ. Expert opinion on the role of bilastine and bilastine-montelukast combination in the management of allergic rhinitis: An Indian perspective. The Journal of Association of Chest Physicians [Internet]. 2023 [cited 2024 Jan 2];11:1. Available from: https://journals.lww.com/ascp/Fulltext/2023/11010/Expert_opinion_on_the_role_of_bilastine_and.1.aspx
- 38. Choi J, Azmat CE. Leukotriene Receptor Antagonists. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554445/
- 39. Zschocke A, Horak F, Eber E, Frischer T, Simma B, Stetzl W, et al. FDA warning montelukast 03 2020-Statement of the Austrian working group of pediatric pulmonology and allergology. Wien Klin Wochenschr. 2022;134(1):86–8.
- 40. Naik M, Nayak A, Khandeparkar P, Mukaddam Q. Efficacy and Safety of Montelukast Plus Fexofenadine Fixed Dose Combination in Allergic Rhinitis:

- Results of Post-Marketing Study In India. 2013 [cited 2024 Apr 16]; Available from: http://imsear.searo.who.int/handle/123456789/157539
- 41. Abdullah B, Abdul Latiff AH, Manuel AM, Mohamed Jamli F, Dalip Singh HS, Ismail IH, et al. Pharmacological Management of Allergic Rhinitis: A Consensus Statement from the Malaysian Society of Allergy and Immunology. J Asthma Allergy [Internet]. 2022 [cited 2024 Apr 15];15:983–1003. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9356736/
- 42. Laursen LC, Faurschou P, Pals H, Svendsen UG, Weeke B. Intramuscular betamethasone dipropionate vs. oral prednisolone in hay fever patients. Allergy. 1987;42(1):168–72.

- 43. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg. 2015;152:197–206.
- 44. Passalacqua G, Canonica GW, Bagnasco D. Benefit of SLIT and SCIT for allergic rhinitis and asthma. Curr Allergy Asthma Rep. 2016. https://doi.org/10. 1007/s11882-016-0666-x.
- 45. Pfaar O, Bousquet J, Durham SR, Kleine-Tebbe J, Larché M, Roberts G, et al. One hundred and ten years of Allergen Immunotherapy: A journey from empiric observation to evidence. Allergy [Internet]. 2022 [cited 2024 May 3];77:454–68. Available from: https://onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1111/all.15023