Received: 9 September 2022 | Revised: 11 November 2022 | Accepted: 13 September 2022

DOI: 10.1002/alr.23090

IFAR: International Forum of Allergy & Rhinology

REVIEW ARTICLE

International consensus statement on allergy and rhinology: Allergic rhinitis – 2023

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Abstract

Background: In the 5 years that have passed since the publication of the 2018 International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR-Allergic Rhinitis 2018), the literature has expanded substantially. The ICAR-Allergic Rhinitis 2023 update presents 144 individual topics on allergic rhinitis (AR), expanded by over 40 topics from the 2018 document. Originally presented topics from 2018 have also been reviewed and updated. The executive summary highlights key evidence-based findings and recommendation from the full document.

Methods: ICAR-Allergic Rhinitis 2023 employed established evidence-based review with recommendation (EBRR) methodology to individually evaluate each topic. Stepwise iterative peer review and consensus was performed for each topic. The final document was then collated and includes the results of this work.

Results: ICAR-Allergic Rhinitis 2023 includes 10 major content areas and 144 individual topics related to AR. For a substantial proportion of topics included, an aggregate grade of evidence is presented, which is determined by collating the levels of evidence for each available study identified in the literature. For topics in which a diagnostic or therapeutic intervention is considered, a recommendation summary is presented, which considers the aggregate grade of evidence, benefit, harm, and cost.

Conclusion: The ICAR-Allergic Rhinitis 2023 update provides a comprehensive evaluation of AR and the currently available evidence. It is this evidence

that contributes to our current knowledge base and recommendations for patient evaluation and treatment.

KEYWORDS

allergen extract, allergen immunotherapy, allergy, allergic rhinitis, antihistamine, asthma, atopic dermatitis, avoidance, biologic, cockroach, conjunctivitis, consensus, corticosteroid, cough, cromolyn, decongestant, eosinophilic esophagitis, environment, epicutaneous, immunotherapy, epidemiology, evidence-based medicine, food allergy, house dust mite, IgE, immunoglobulin E, immunotherapy, inhalant allergy, leukotriene, microbiome, occupational rhinitis, omalizumab, pediatric, perennial, pet dander, pollen, probiotic, rhinitis, rhinosinusitis, saline, seasonal, sensitization, sinusitis, socioeconomic, specific IgE, subcutaneous immunotherapy, sublingual immunotherapy, systematic review, rhinitis, total IgE, transcutaneous immunotherapy, validated survey

I | EXECUTIVE SUMMARY

I.A | Introduction

The International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis 2023 (ICAR-Allergic Rhinitis 2023) was developed as an update to the original ICAR-Allergic Rhinitis 2018[1] document. The goal of this document is to summarize and critically review the best evidence related to allergic rhinitis (AR). Through a systematic approach including literature review, semi-blinded stepwise iterative review process, and consensus and oversight by associate editors, all steps of document development have been rigorous and of high quality.

ICAR-Allergic Rhinitis 2023 is not intended to be a clinical practice guideline, meta-analysis, or expert panel report. The ICAR authors have carefully reviewed all relevant literature and determined the strength of the available evidence. Based upon this evidence, where applicable, recommendations are made for various diagnostic and treatment options in the realm of AR. A secondary goal of this document is to identify updates in the field as compared to the previous ICAR-Allergic Rhinitis 2018 document and highlight advances in our understanding of AR, as well as its diagnosis and treatment. Through this in-depth investigation, we are also able to identify areas in which further work is needed.

Since the publication of ICAR-Allergic Rhinitis 2018, there are numerous new high-level publications in various aspects of AR. There have been updates in levels of evidence and recommendations. These findings, along with a comparison to the ICAR-Allergic Rhinitis 2018 available publications, and levels of evidence, are shown in the tables in this executive summary. Still, several important areas of future investigation remain.

I.B | Methods

In the ICAR-Allergic Rhinitis 2023 update, there were a total of 144 individual topics assigned to 87 primary authors. A multidisciplinary group of expert authors from around the world, often with a notable publication record in the field, were invited to contribute to both authorship and iterative peer review aspects of the ICAR process. Topics were assigned as literature reviews, evidence-based reviews without recommendations, or evidence-based reviews with recommendations, depending on the available literature, strength of evidence, and type of intervention. Topics that had sufficient evidence to substantiate clinical recommendations were assigned as evidence-based reviews with recommendations, based on the work of Rudmik and Smith.[2]

For each section, authors were instructed to perform systematic reviews, which included the Ovid MEDLINE, EMBASE, and Cochrane Review databases, and generally followed PRISMA guidelines (Preferred Reporting for Systematic Reviews and Meta-Analyses).[3] Included studies were presented in table format, indicating the level of evidence. Systematic reviews, meta-analyses, and randomized controlled trials were noted as providing the highest levels of evidence. An aggregate grade of evidence was determined for each topic, and an evidence-based recommendation was made considering benefit, harm, and cost for each topic, where appropriate.[4]

Each section then underwent a stepwise review in a semi-blinded fashion by two additional experts. Consensus was reached after each stage in the iterative review process. The review process was overseen by an associate editor to ensure adherence to the ICAR methodology and assist in resolution of any concerns. Following completion of all topics, the individual sections were collated into major content areas (e.g., Evaluation and Diagnosis,

Management, Associated Conditions) and each major content area was reviewed by three to five associate editors. The final ICAR-Allergic Rhinitis 2023 document was then compiled and reviewed by all authors for consensus.

The ICAR process aims to be systematic, consistent, and thorough; however, certain limitations exist. The literature search for each topic was performed by the individual invited author for that topic. This has the potential to introduce some variability in search results despite detailed literature search instructions. Also, for some topics, there is extensive high-quality literature available. This may allow an aggregate grade of evidence to be delineated without listing every published study on that topic. In these cases, an exhaustive list of lower-level studies may not be provided in the evidence tables.

I.C | Results

I.C.1 | Definitions, classification, and differential diagnosis

AR is primarily driven by an immunoglobulin E (IgE)-mediated type 1 hypersensitivity response, due to an allergen exposure. Classically, seasonal AR was thought to be associated with outdoor allergens and perennial AR with indoor year-round exposure to allergens. However, climate change and polysensitization may make these classifications challenging. Intermittent AR is defined as symptoms for less than 4 days per week or less than four consecutive weeks. Persistent AR is defined as symptoms for more than 4 days per week for at least 1 month. Sensitization to allergens may be identified on skin or in vitro testing which assesses the presence of allergen-specific IgE (sIgE). However, many people that are sensitized do not exhibit allergy symptoms, so correlation with clinical symptoms upon allergen exposure is critical. Classic AR symptoms include sneezing, rhinorrhea, and nasal congestion/obstruction. These symptoms are non-specific, and the differential diagnosis of AR is broad. Section V of the ICAR-Allergic Rhinitis 2023 document explores AR definition, classification, and differential diagnosis (Table I.C.1).

TABLE I.C.1 Definition and differential diagnosis of allergic rhinitis

Definition of allergic rhinitis	Allergic rhinitis is an immunoglobulin E (IgE)-mediated, type 1 hypersensitivity response of the nasal mucosal membranes, resulting from allergen exposure in a sensitized individual.[5]
Differential diagnosis of allergic rhinitis	• Drug-induced rhinitis • Rhinitis medicamentosa • Occupational rhinitis • Chemical rhinitis • Smoke-induced rhinitis • Infectious rhinitis • Rhinitis of pregnancy • Hormonally induced rhinitis • Food and alcohol induced rhinitis • Non-allergic rhinitis with eosinophilia syndrome • Non-allergic rhinopathy and vasomotor rhinitis • Age-related rhinitis (i.e., elderly) • Empty nose syndrome • Atrophic rhinitis • Autoimmune, granulomatous, and vasculitic rhinitis • Rhinosinusitis • Non-rhinitis conditions (e.g., anatomical obstruction, neoplastic, cerebrospinal fluid rhinorrhea, foreign body, cystic fibrosis, primary ciliary dyskinesia, gastroesophageal reflux)

I.C.2 | Pathophysiology and mechanisms

Shortly after IgE receptor stimulation, mast cells secrete proteins due to stimulated gene transcription. Multiple cytokines and chemokines are released, which recruit inflammatory cells such as eosinophils, basophils, neutrophils, macrophages, and T cells.

Various inflammatory processes occur at different stages of AR. These processes are driven by the type 2 immune response. Considering the pathophysiology of AR, the ICAR-Allergic Rhinitis 2023 document explores local and systemic IgE-mediated inflammation, cellular infiltrates, cytokines and soluble mediators, neural mechanisms, histologic and epithelial changes, epithelial barrier alterations, association with vitamin D, alterations in nitric oxide and the microbiome, as well as the unified airway concept. Section VI of the ICAR-Allergic Rhinitis 2023 document discusses AR pathophysiology and mechanisms.

I.C.3 | Epidemiology

The prevalence of AR has been reported from 5% to 50% worldwide. Prevalence reporting is dependent on the method of diagnosis and age of participants studied, which may explain some of the variability in reported AR prevalence. There have been increased attempts to provide more uniformity in the terminology and diagnostic criteria for AR. The available literature suggests that AR had been previously increasing across the globe. While recent evidence indicates this upward trend may have leveled

TABLE I.C.4.-1 Risk factors for the development of allergic rhinitis – comparison between 2018 and 2023

Risk factor or exposure	Year	Number of listed studies	Aggregate grade of evidence	Interpretation
Genetics	2023	9	C	Multiple genes, variants, and their complex interactions contribute to the development of AR.
	2018	5	C	
Mites: in utero or early exposure	2023	7	C	Data inconclusive.
	2018	6	C	
Pollen: in utero or early exposure	2023	2	C	Data inconclusive.
	2018	2	C	
Animal dander: in utero or early exposure	2023	46	C	Data inconclusive.
	2018	39	C	
Fungal allergens: in utero or early exposure	2023	15	C	Data inconclusive.
	2018	13	C	
Restricted diet: in utero and early childhood	2023	18	A	Maternal diet restriction while child is in utero is not a contributing factor to the development of AR. Food allergy during childhood is a risk factor for AR.
	2018	5	A	
Pollution	2023	15	C	Data inconclusive.
	2018	14	C	
Tobacco smoke	2023	6[a]	C	Most studies did not identify a correlation between tobacco smoke and AR.
	2018	7	C	
Socioeconomic status	2023	17	C	Most available studies suggest that higher SES is associated with increased risk of AR.
	2018	10	C	

Abbreviations: AR, allergic rhinitis; SES, socioeconomic status.

[a]Studies included in systematic reviews were not separately listed in tables.

TABLE I.C.4.-2 Protective factors for the development of allergic rhinitis – comparison of 2018 and 2023

Risk factor or exposure	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Breastfeeding	2023	7	C	Recommendation	Recommendation due to various positive effects, and possible protective effects for AR.
	2018	2	C	Option	
Pet exposure	2023	5[a]	C	Option	Conflicting evidence. Early pet exposure, especially dog exposure in non-allergic families early in childhood, may be protective.
	2018	6	C	No recommendation	
Microbial diversity ("Hygiene Hypothesis")	2023	21	B	–	There is some evidence of the protective effect of the hygiene hypothesis on AR.
	2018	15	B	–	

Abbreviations: AR, allergic rhinitis.

[a]Studies included in systematic reviews were not separately listed in tables.

off, notable geographic differences exist. The rate of AR typically increases with age until young adulthood. The effects of geographic influences on epidemiology of AR and the role of climate change are active areas of research. Section VII of the ICAR-Allergic Rhinitis 2023 document reviews the epidemiology of AR.

I.C.4 | Risk factors and protective factors for the development of allergic rhinitis

Several risk factors for the development of AR have been investigated. There is conflicting data for many of these potential risk factors, and this area of work remains a topic

TABLE I.C.5 Allergic rhinitis disease burden – comparison between 2018 and 2023

Burden of AR	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Effect on quality of life	2023	56	B	Recommendation	Treatment of AR is recommended to improve QOL.
	2018	33	B	Recommendation	
Effect on sleep	2023	63	B	Recommendation	Treatment of AR is recommended to improve sleep.
	2018	46	B	Recommendation	

Abbreviations: AR, allergic rhinitis; QOL, quality of life.

of active investigation. Section VIII of the ICAR-Allergic Rhinitis 2023 document explores risk factors and potential protective factors for the development of AR (Tables I.C.4.-1 and I.C.4.-2).

Breastfeeding

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study)
Benefit: Benefits on general health of infant and possible protection against AR, especially in young children.
Harm: None.
Cost: Low.
Benefits-harm assessment: Slight preponderance of benefit over harm for protection against AR. Large preponderance of benefit over harm for breastfeeding for all infants, unless there is a contraindication. The benefit of breastfeeding for all infants inextricably influences this recommendation.
Value judgments: Evidence suggests that breastfeeding may reduce the risk of AR without harm.
Policy level: Recommendation for breastfeeding due to various positive effects on general health and possible protective effects on AR.
Intervention: Breastfeeding for at least 4–6 months should be encouraged unless contraindicated.

Childhood exposure to pets

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 2 studies, level 4: 2 studies)
Benefit: Exposure to pets at birth and in the first year of life has potential benefits of decreasing risk of AR.
Harm: Pet keeping in childhood could have a negative effect, especially in Asians.
Cost: Various.
Benefits-harm assessment: Difficulty distinguishing between benefits and harm.
Value judgments: There is conflicting evidence that childhood pet exposure prevents the development of AR.
Policy level: Option.
Intervention: Recommendation to expose or avoid pets for the prevention of AR in children cannot be provided based on current evidence.

I.C.5 | Disease burden

ICAR-Allergic Rhinitis 2023 reviewed the disease burden of AR as it relates to quality of life (QOL) and sleep disturbance. Several new studies have been added in each of these categories since ICAR-Allergic Rhinitis 2018. AR also has substantial impact at a societal level, which may be quantified in direct and indirect costs, absenteeism or presenteeism, and other measures. Individual and societal burdens of AR are significant and addressed further in the full ICAR-Allergic Rhinitis 2023 document (Table I.C.5).

Disease burden – quality of life

Aggregate grade of evidence: B (Level 1: 6 studies, level 2: 35 studies, level 3: 15 studies)
Benefit: Successful treatment of AR leads to improved overall and disease specific QOL.
Harm: Depending on the specific treatments for AR, there are variable levels of harm.
Cost: Treatments for AR have variable costs.
Benefits-harm assessment: The benefits of treating patients with AR to improve QOL likely outweigh risks of treatment.
Value judgments: Validated measures of QOL should be utilized in future studies of treatments for AR.
Policy level: Recommendation.
Intervention: Validated measures of QOL should be utilized in future studies of treatments for AR.

Disease burden – sleep disturbance

Aggregate grade of evidence: B (Level 2: 5 studies, level 3: 8 studies, level 4: 50 studies)
Benefit: AR negatively impacts sleep quality. Successful management of AR leads to decreased sleep disturbance in adults and children.

Harm: Medical management of AR is generally low risk and medications have low side-effect profiles. allergen immunotherapy (AIT) is associated with rare serious adverse events.
Cost: Associated costs consist of the direct costs of allergy testing and medical management, and indirect cost of increased time and effort for AIT.
Benefits-harm assessment: The benefits of treating patients with AR may outweigh any associated risks.
Value judgments: In patients with AR, the successful control of symptoms with medical management or AIT can lead to important improvements in sleep disturbance. The level of available evidence is stronger for the adult population compared with the pediatric population.
Policy level: Treatment of AR to improve sleep disturbance – Recommended in adults. Option in children.
Intervention: Intranasal corticosteroids (INCS), oral antihistamines, montelukast, and AIT are appropriate options, when medically indicated, to improve sleep disturbance in patients with AR.

I.C.6 | Evaluation and diagnosis

A thorough history is critical to AR diagnosis. This should be complemented by an appropriate physical examination, and nasal endoscopy may also be considered. Various diagnostic testing modalities may also be employed to solidify a diagnosis of AR or when considering an alternate etiology for the patient's symptoms. A summary of various diagnostic modalities for AR is presented in Table I.C.6.

The section that follows includes the recommendation summaries for AR diagnostic modalities considered in the ICAR-Allergic Rhinitis 2023 document.

Patient history

Aggregate grade of evidence: D (Level 4: 5 studies, level 5: 7 guidelines or expert recommendations)
Benefit: Improves accuracy of diagnosis, avoid unnecessary referrals, testing, or treatment.
Harm: Potential misdiagnosis or inappropriate treatment.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Using history to make a presumptive diagnosis of AR is reasonable and would not delay treatment initiation. History should be combined with physical examination, which may not be possible in some scenarios such as telemedicine. Confirmation with diagnostic testing is required for progression to AIT or targeted avoidance therapy, or desirable with inadequate response to treatment.
Policy level: Recommendation.
Intervention: Despite low level evidence specifically addressing this area, history is essential in the diagnosis of AR.

Physical examination

Aggregate grade of evidence: D (Level 4: 2 studies, level 5: 6 guidelines)
Benefit: Possible improved diagnosis of AR with physical examination findings, along with evaluation and/or exclusion of alternative diagnoses.
Harm: Possible patient discomfort from routine examination, not inclusive of endoscopy.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm, potential misdiagnosis, and inappropriate treatment if used in isolation.
Value judgments: Telemedicine is a safe and useful tool in pandemic conditions but does limit what can be gleaned from physical examination. Without the use of nasal endoscopy, it is possible some physical examination findings may be missed.
Policy level: Recommendation.
Intervention: When possible, physical examination should be performed with appropriate personal protective equipment to aid in the diagnosis of AR and exclusion of other conditions. When combined with patient history, it increases diagnostic accuracy and may exclude alternative causes of symptoms.

Nasal endoscopy

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 1 study, level 4: 7 studies)
Benefit: Possible improved diagnosis with visualization of middle or inferior turbinate edema, pale/bluish discoloration, or isolated central compartment polypoid changes and/or edema, which have been associated with AR.
Harm: Possible patient discomfort.
Cost: Moderate equipment and processing costs, as well as procedural charges.
Benefits-harm assessment: Balance of benefit and harm.

Value judgments: Nasal endoscopy may increase diagnostic sensitivity among children and adults with AR.
Policy level: Option.
Intervention: Nasal endoscopy may be considered as a diagnostic adjunct in the evaluation of patients with suspected AR.

Radiologic studies

Aggregate grade of evidence: D (level 3: 1 study, level 4: 7 studies)
Benefit: Some radiologic findings, particularly those associated with central compartment edema/polyposis, may alert the clinician to the possibility of an associated allergic etiology.
Harm: Unnecessary radiation exposure, unnecessary cost.
Cost: High equipment and processing costs. Additional costs for interpretation of studies by radiologist.
Benefits-harm assessment: Preponderance of harm over benefit.
Value judgments: Long-term risks of ionizing radiation outweigh potential benefit.
Policy level: Recommendation against.
Intervention: Routine use of imaging is not recommended for the diagnosis of AR.

Use of validated subjective instruments and patient-reported outcome measures

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 2 studies, level 3: 5 studies, level 4: 13 studies)
Benefit: Validated surveys offer a simple point-of-care option for screening and tracking symptoms, QOL, and control of allergic disease.
Harm: Minimal. Time to complete survey. Potential risk of misdiagnosis when based on survey data alone.
Cost: No financial burden to patients. Some fees associated with validated tests used for clinical research.
Benefits-harm assessment: Preponderance of benefit over harm. Risk of misdiagnosis leading to unnecessary additional testing. Likewise, there is a risk that false negative responses may lead to delay in testing and further management.
Value judgments: Validated surveys may be used as a screening tool and primary or secondary outcome measure.
Policy level: Recommendation.
Intervention: Validated surveys may be used to screen for AR, follow treatment outcomes and as a primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathological scenarios.

Skin prick testing

Aggregate grade of evidence: B (Level 1: 1 study, level 3: 2 studies, level 4: 7 studies, level 5: 2 studies)
Benefit: Confirm AR diagnosis and direct appropriate pharmacologic therapy, initiation of AIT, as well as avoidance measures.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. See Table II.C. in full ICAR document.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Patients can benefit from identification of their specific sensitivities. Skin prick testing (SPT) is a quick and relatively comfortable way to test several antigens with accuracy similar to other available methods of testing.
Policy level: Recommendation.
Intervention: Regular use of the same SPT device type will allow clinicians to familiarize themselves with it and interpretation of results may therefore be more consistent. The use of standardized allergen extracts can further improve consistency of interpretation.

Skin intradermal testing

Aggregate grade of evidence: C (Level 3: 7 studies, level 4: 13 studies)
Benefit: May improve identification of allergic sensitization in patients with low-level skin sensitivity or with non-standardized allergens.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. See Table II.C. in full ICAR document.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Benefit over harm when used as a stand-alone diagnostic test, when used to confirm the results of SPT, and as a quantitative diagnostic test.
Value judgments: Intradermal skin tests may not perform as well as SPT in most clinical situations.

Policy level: Option for using intradermal testing as a stand-alone diagnostic test for individuals with suspected AR. Option for using intradermal testing as a confirmatory test following negative SPT for non-standardized allergens.
Intervention: Intradermal testing may be used to determine aeroallergen sensitization in individuals suspected of having AR.

Blended skin testing techniques

Aggregate grade of evidence: D (Level 4: 7 studies)
Benefit: Ability to establish an endpoint in less time than intradermal dilutional testing, potential to determine allergen sensitization after negative SPT.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. Additional time and discomfort versus SPT alone. See Table II.C. in full ICAR document.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: While AIT can be based off SPT results alone, endpoint-based immunotherapy may have possible benefits of decreased time to therapeutic dosage.
Policy level: Option.
Intervention: Blended skin testing techniques, such as modified quantitative testing, are methods that can be used to determine a starting point for AIT or confirm allergic sensitization.

Issues that may affect the performance and interpretation of skin tests – medications:

- *H_1 antihistamines – Aggregate grade of evidence*: A (Level 2: 3 studies, level 3: 3 studies, level 4: 1 study). Should be discontinued 2–7 days prior to testing.
- *H_2 antihistamines – Aggregate grade of evidence*: A (Level 2: 2 studies, level 3: 1 study, level 4: 1 study). Ranitidine may suppress skin wheal-ing response, leading to false negative results. Should be discontinued 2 days prior to testing.
- *Topical antihistamines – Aggregate grade of evidence*: Unable to determine from one level 2 study. Should be discontinued 2 days prior to testing.
- *Anti-IgE (omalizumab) – Aggregate grade of evidence*: A (Level 2: 1 study, level 3: 1 study). Results in negative allergy skin test results. May suppress skin whealing response for 4–6 months.
- *Leukotriene modifying agents – Aggregate grade of evidence*: A (Level 2: 2 studies, level 3: 1 study). May be continued during testing.
- *Tricyclic antidepressants – Aggregate grade of evidence*: B (Level 2: 1 study, level 4: 1 study). Antidepressants with antihistaminic properties suppress allergy skin test responses. Should be discontinued 7–14 days prior to testing.
- *Topical (cutaneous) corticosteroids – Aggregate grade of evidence*: A (Level 2: 3 studies, level 3: 1 study). Skin tests should not be placed at sites of chronic topical steroid treatment.
- *Systemic corticosteroids – Aggregate grade of evidence*: C (Level 2: 1 study, level 3: 1 study, level 4: 2 studies; conflicting results). Systemic corticosteroid treatment does not significantly impair skin test responses.
- *Selective serotonin reuptake inhibitors – Aggregate grade of evidence*: C (Level 3: 1 study, level 4: 1 study). Selective serotonin reuptake inhibitors do not suppress allergy skin test responses.
- *Benzodiazepines – Aggregate grade of evidence*: C (Level 4: 2 studies). May suppress skin test responses. Should be discontinued 7 days prior to testing.
- *Topical calcineurin inhibitors (tacrolimus, picrolimus) – Aggregate grade of evidence*: C (Level 2: 2 studies; conflicting results). Conflicting results regarding skin test suppression.

Issues that may affect the performance and interpretation of skin tests – skin conditions: Common sense dictates that allergy skin tests should not be performed at sites of active dermatitis, but clinical studies to investigate this phenomenon are lacking. There are insufficient studies published on this topic, and an Aggregate Grade of Evidence could not be assigned.

Serum total immunoglobulin E

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 11 studies)
Benefit: Possibility to suspect allergy or atopy in a wide screening.
Harm: Cost of test, undergoing of venipuncture, low level does not exclude AR.
Cost: Low, dependent on country and local healthcare environment.

Benefits-harm assessment: Slight preponderance of benefit over harm. In addition, the ratio of total to allergen-specific IgE (sIgE) may be useful to interpret the real value of sIgE production and predict treatment outcomes with AIT.
Value judgments: The evidence does not support routine use.
Policy level: Option.
Intervention: Assessment of total IgE may be useful to assess overall atopic status; furthermore, in selected cases it might help guide therapy (i.e., predict outcome of AIT).

Serum allergen-specific immunoglobulin E

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 2 studies, level 3: 6 studies, level 4: 6 studies, level 5: 1 study)
Benefit: Confirms diagnosis and directs appropriate pharmacological therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance, directs AIT.
Harm: Adverse events from testing including discomfort from blood draw, inaccurate test results, false positive test results, misinterpreted test results.
Cost: Moderate cost of testing.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Patients can benefit from identification of their specific sensitivities. Further, in some patients who cannot undergo SPT, serum sIgE testing is a safe and effective alternative.
Policy level: Recommendation.
Intervention: Serum sIgE testing may be used in patients who cannot undergo allergy skin testing. The use of highly purified allergen or recombinants can increase the sensitivity, specificity, and diagnostic accuracy of sIgE tests. Rigorous proficiency testing on the part of laboratories may also improve accuracy.

Nasal allergen-specific immunoglobulin E

Aggregate grade of evidence: C (Level 1: 1 study, level 2: 21 studies, level 3: 3 studies, level 4: 11 studies)
Benefit: Patients with non-allergic rhinitis found to have nasal sIgE may have local AR and could benefit from avoidance or AIT.
Harm: Measurement of nasal sIgE is minimally invasive. No significant adverse effects have been reported. Possible discomfort from sample collection.
Cost: Associated costs include the direct costs of testing and indirect cost of increased time and effort for performing nasal sIgE diagnostic test.
Benefits-harm assessment: The benefits of identifying patients with an allergic component to their rhinitis may outweigh associated risks.
Value judgments: In patients with non-allergic rhinitis who also have risk factors for atopic disease and have inadequate response to pharmacotherapy, testing for nasal sIgE may be helpful in confirming a diagnosis of local AR and allowing for treatment with AIT. There is no consensus for levels of nasal sIgE that indicate sensitivity.
Policy level: Option.
Intervention: Measurement of nasal sIgE is an option in patients with non-allergic rhinitis suspected of having local AR to support this diagnosis and guide AIT if pharmacologic therapies are inadequate. Consensus for levels of nasal sIgE indicating AR need to be established.

Basophil activation test

Aggregate grade of evidence: C (Level 2: 5 studies, level 3: 13 studies, level 4: 1 study)
Benefit: May help diagnose AR in specific cases where common approaches are not possible or show conflicting results.
Harm: Discomfort of venipuncture.
Cost: Moderate cost of performing the test, plus venipuncture. Depending on the local situation and availability.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: The evidence does not support routine use for the diagnosis of AR or for following AIT response.
Policy level: Option.
Intervention: Application of basophil activation test in specific situations where other diagnostic procedures for AR are not possible or conflicting. Potentially useful for monitoring AIT if other methods fail or show conflicting results.

Component resolved diagnostic testing

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 2 studies, level 4: 11 studies, level 5: 1 study)
Benefit: Reliable. May help in identification and selection of suitable allergens for AIT, as well as possibly improving safety of AIT.
Harm: Discomfort of venipuncture.
Cost: Moderate cost of testing, minimal cost of venipuncture; depends on local availability.

Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Molecular diagnosis may be a useful tool for assessment of AR in some scenarios, especially in polysensitized patients.
Policy level: Option.
Intervention: Component resolved diagnostic testing is an option for diagnosis of AR by specialists.

Nasal provocation testing

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 7 studies)
Benefit: May assist in confirming diagnosis of AR in specific cases when immunological tests are unavailable or unreliable. Nasal provocation testing is crucial in diagnosing occupational rhinitis and local AR.
Harm: Not necessary if first- and second-line tests are indicative for AR diagnosis.
Cost: Depending on the local situation and availability of equipment and staff, costs may be high.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: The evidence does not support routine use for diagnosis of AR, but provocation testing is useful for diagnosis of occupational rhinitis and local AR.
Policy level: Option for diagnosis of AR when skin or in vitro tests are equivocal or unreliable. Recommendation for diagnosis of local AR and occupational rhinitis.
Intervention: Application of nasal provocation testing is useful in local AR and to confirm occupational rhinitis.

Nasal cytology

Aggregate grade of evidence: C (Level 1: 1 study, level 3: 3 studies, level 4: 3 studies)
Benefit: Low costs and low invasiveness. Could help to detect eosinophils in non-allergic rhinitis and to diagnose a mixed rhinitis.
Harm: Nasal cytology is minimally invasive and minimal adverse effects have been reported.
Cost: Associated costs include the direct cost of nasal cytology and indirect cost of increased time and effort for performing nasal cytology.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: The evidence does not support routine clinical use.
Policy level: Option.
Intervention: Nasal cytology could help in cases of non-allergic rhinitis to suspect local AR or in cases of AR to diagnose a mixed rhinitis. It could be considered an option in cases of negative SPT and/or serum sIgE to evaluate the presence of mucosal eosinophils and consideration of local AR or type 2 inflammation. The cut-off values for determining non-allergic rhinitis with eosinophilia syndrome (NARES) are not yet clear.

Nasal histology

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 7 studies, level 4: 2 studies)
Benefit: May assist in evaluation of tissue eosinophilia and expression of mediators. May be useful in clinical research.
Harm: Small risk of complications (e.g., bleeding, infection).
Cost: Associated costs consist of the direct cost of nasal histology and indirect cost of increased time and effort for performing nasal histology.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: The evidence does not support routine clinical use.
Policy level: Recommendation against.
Intervention: Nasal histology may be helpful in clinical research or selected cases (e.g., evaluation of tissue eosinophils during surgery). Recommendation against in routine clinical practice for AR evaluation due to invasive nature of obtaining a specimen.

Rhinomanometry

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 2 studies, level 3: 5 studies, level 4: 4 studies, level 5: 6 studies)
Benefit: 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, use as a medicolegal tool and in nasal allergen challenges. Four-phase rhinomanometry correlates with subjective scores.
Harm: Low. Rhinomanometry has limited effectiveness in patients with complete nasal obstruction or septal perforation. The equipment is not portable and therefore requires a clinic visit and trained staff. The procedure may be considered time consuming.
Cost: High.

Benefits-harm assessment: Benefits outweigh harm.
Value judgments: For some patients, it may be important to avoid unnecessary costs in the diagnosis of AR; therefore, this procedure is less preferred.
Policy level: Option.
Intervention: Rhinomanometry is useful in distinguishing between structural and soft tissue causes of obstruction, when history and examination findings are not congruent, as well as a research tool. Better with individual nasal cavity assessment and four-phase rhinomanometry.

Acoustic rhinometry

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 5 studies, level 4: 3 studies, level 5: 2 studies)
Benefit: Improves patient selection for surgery, helps distinguish between structural and functional causes of nasal obstruction, evaluates a response in nasal allergen challenges, and functions as a medicolegal tool to demonstrate objective evidence of effectiveness of an intervention.
Harm: Low. Equipment is not portable therefore, requires a clinic visit and trained staff. Time-consuming. Leakage into sinuses may provide inaccurate results and lead to inappropriate treatment.
Cost: High.
Benefits-harm assessment: Benefits outweigh harm as harm is low.
Value judgments: For some patients, it may be important to avoid unnecessary cost in the diagnosis of AR, and thus acoustic rhinometry is less preferred.
Policy level: Option.
Intervention: Acoustic rhinometry is most useful in research setting as opposed to as a clinical diagnostic tool.

Peak nasal inspiratory flow

Aggregate grade of evidence: B (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study, level 5: 1 study)
Benefit: Can improve patient selection for surgery, can evaluate a response in nasal allergen challenges, and can be used as a medicolegal tool to demonstrate objective evidence of effectiveness of an intervention.
Harm: Low. Risk of missing valve collapse and septal deviation as causes of obstruction.
Cost: Low.
Benefits-harm assessment: Benefits likely to outweigh harm as harm is low.
Value judgments: Relies on patient effort and does not assess individual nasal cavities. Unable to evaluate nasal valve collapse.
Policy level: Option.
Intervention: Use in conjunction with patient reported outcome measures to improve utility.

Nitric oxide measurements

Aggregate grade of evidence:
- Fractional exhaled nitric oxide (FeNO): D (Level 4: 7 studies)
- Nasal nitric oxide (nNO): C (Level 2: 2 studies, level 4: 6 studies)

Benefit: Possible benefit in differentiation of allergic and non-allergic rhinitis through non-invasive testing. Possible benefit in monitoring treatment response.
Harm: No studies have shown harm with either exam.
Cost:
- FeNO: Relatively high. FeNO analyzers are approximately $7000–10,000 US, but testing is covered by some insurance plans.
- nNO: High. Chemiluminescence NO analyzers are approximately $30,000–50,000 US, and clinical testing is not covered by insurance in the US.

Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: There is inconsistent evidence in the ability of FeNO or nNO to differentiate adults and children with AR and non-allergic rhinitis. Most studies were of low evidence or small impact. There is no agreed upon cut-off value when performing FeNO or nNO for the diagnosis of AR.
Policy level:
- FeNO: Recommend against for routine diagnosis of AR.
- nNO: Recommend against for routine diagnosis of AR.

Intervention: History and physical, diagnostic skin testing, or sIgE testing should be the first-line evaluation of AR. FeNO or nasal NO testing may provide additional diagnostic information if necessary but should not be routinely employed for AR diagnosis.

TABLE I.C.6 Diagnostic modalities for evaluation of allergic rhinitis – comparison between 2018 and 2023

Diagnostic modality	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Clinical examination (history and physical)	2023	20	D	Recommendation	While there is low level evidence, guideline documents support the recommendation of combined history and physical.
	2018	9	D	Recommendation	
Nasal endoscopy	2023	10	C	Option	Nasal endoscopy may be considered a diagnostic adjunct.
	2018	5	D	Option	
Radiologic imaging	2023	8	D	Recommend against	Radiologic imaging is not recommended for the diagnosis of AR.
	2018	0	n/a	Recommend against	
Use of validated survey instruments	2023	22	B	Recommendation	Validated survey instruments can be used to screen for AR, follow treatment outcomes, and as an outcome measure for clinical trials.
	2018	10	A	Strong recommendation	
Skin prick testing	2023	12	B	Recommendation	Skin prick testing is recommended for AR diagnosis.
	2018	8	B	Recommendation	
Skin intradermal testing	2023	20	C	Option	Option for intradermal testing as a stand-alone test or confirmatory test.
	2018	17	B	Option	
Blended skin testing techniques	2023	7	D	Option	Modified quantitative testing is a technique that may be used to determine a safe starting dose for AIT.
	2018	5	D	Option	
Serum total IgE	2023	15	C	Option	Serum total IgE is an option to assess atopic status and guide therapy.
	2018	15	C	Option	
Serum allergen-specific IgE	2023	16	B	Recommendation	Serum sIgE testing is recommended for allergy testing.
	2018	7	B	Recommendation	
Correlation between skin and in vitro testing	2023	19	B	–	Studies differ regarding the concordance of various allergy testing methods.
	2018	19	B	–	
Nasal sIgE	2023	36	C	Option	Nasal sIgE is an option in patients with suspected AR.
	2018	24	C	Option	
Basophil activation test	2023	19	C	Option	BAT may be used for diagnosis when first-line tests are discordant, and for monitoring response to AIT.
	2018	12	B	Option	
Component resolved diagnostic testing	2023	18	C	Option	May improve selection of allergens for AIT, especially in polysensitized patients.
	2018	n/a	n/a	n/a	
Nasal provocation testing	2023	8	C	Option	Option for diagnostic testing for AR. Recommended for diagnosis of occupational rhinitis and local AR.
	2018	4	C	n/a	

(Continues)

TABLE I.C.6 (Continued)

Diagnostic modality	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Nasal cytology	2023	7	C	Option	May be considered with negative allergy testing results to assess for eosinophil levels.
	2018	4	C	n/a	
Nasal histology	2023	10	B	Recommend against	Nasal histology is used for research on the pathophysiology of AR but is not recommended for routine clinical use.
	2018	11	B	n/a	
Rhinomanometry	2023	19	B	Option	Option for use in AR diagnosis.
	2018	n/a	n/a	n/a	
Acoustic rhinometry	2023	11	C	Option	Acoustic rhinometry is most useful in a research setting.
	2018	n/a	n/a	n/a	
Peak nasal inspiratory flow	2023	8	B	Option	May be used with PROMs to improve utility.
	2018	n/a	n/a	n/a	
FeNO	2023	7	D	Recommend against	Should not be used routinely for the diagnosis of AR.
	2018	n/a	n/a	n/a	
nNO	2023	8	C	Recommend against	Should not be used routinely for the diagnosis of AR.
	2018	n/a	n/a	n/a	

Abbreviations: AR, allergic rhinitis; AIT, allergen immunotherapy; IgE, immunoglobulin E; sIgE, allergen-specific immunoglobulin E; BAT, basophil activation test; n/a, not applicable (not considered in ICAR-Allergic Rhinitis 2018 document); PROM, patient reported outcome measure; FeNO, fractional exhaled nitric oxide; nNO, nasal nitric oxide.

TABLE I.C.7.a Avoidance measures and environmental controls for the treatment of allergic rhinitis – comparison between 2018 and 2023

Allergen or exposure	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
House dust mite	2023	14	B	Option	Acaricides used independently or with other EC measures are an option for the treatment of AR.
	2018	12	B	Option	
Cockroach	2023	12	B	Option	Combination of physical measures and education is an option for AR management.
	2018	11	B	Option	
Pets	2023	5	C	Option	Pet avoidance and EC strategies are an option for AR related to pets, especially in patients with diagnosed Fel d 1 sensitivity.
	2018	3	B	Option	
Rodents	2023	15	C	Option	Avoidance likely improves allergen exposure, option depending on circumstance (occupational).
	2018	n/a	n/a	n/a	
Pollen	2023	4	B	Option	Pollen avoidance is well tolerated and low cost.
	2018	3	B	Option	
Occupational	2023	5	C	Recommendation	Patients should avoid exposure to allergens in their occupational setting.
	2018	n/a	n/a	n/a	

Abbreviations: AR, allergic rhinitis; EC, environmental control; n/a, not applicable (not considered in ICAR-Allergic Rhinitis 2018 document)

I.C.7 | Management

I.C.7.a | *Avoidance measures and environmental controls*

Allergen avoidance is generally low risk and may provide some benefit in controlling AR symptoms. Both physical interventions and chemical applications may reduce allergen load in the environment, although assessment of the effects of these interventions on control of AR symptoms is lacking in some studies. ICAR-Allergic Rhinitis 2023 evaluated allergen avoidance and environmental control measures for house dust mite, cockroach, pets, rodents, pollen, and occupational allergens. Section XI.A of the ICAR-Allergic Rhinitis 2023 document summarizes studies of avoidance measures and environmental controls employed for the treatment of AR (Table I.C.7.a).

The section that follows includes recommendation summaries for allergen avoidance and environmental controls that are included in the ICAR-Allergic Rhinitis 2023 document.

Avoidance – house dust mite (HDM)

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 12 studies)
Benefit: Potential improvement in AR symptoms and QOL with reduced concentration of environmental HDM antigens.
Harm: None.
Cost: Low to moderate. However, cost-effectiveness was not evaluated.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: There is supporting evidence for the use of acaricides in reducing HDM concentration in children who have AR coexistent with asthma. In adults and children without concomitant asthma, the use of acaricides with/without bedroom-based control programs for reducing HDM concentration are promising, but further, high-quality studies are needed to evaluate clinical outcomes.
Policy level: Option.
Intervention: Acaricides used independently or alongside environmental control measures, such as air filtration devices, could be considered as options in the management AR.

Avoidance – cockroach

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 8 studies, level 3: 2 studies, level 4: 1 study)
Benefit: Reduction in cockroach count but allergen concentrations (Bla g 1 and Bla g 2) often above acceptable levels for clinical benefits. No studies included clinical endpoints related to AR.
Harm: None noted.
Cost: Direct costs include multiple treatment applications or multi-interventional approaches. Indirect costs include potential time off work for interventions in home and substantial labor of cleaning measures to eradicate allergens.
Benefits-harm assessment: Balance of benefits and harms since lack of clear clinical benefits.
Value judgments: Control of cockroach populations especially in densely populated multi-family dwellings is important to control cockroach allergen levels.
Policy level: Option.
Intervention: Combination of physical measures (e.g., insecticide bait traps, house cleaning) and education-based methods seem to have the greatest efficacy. Additional research on single intervention approaches is needed with cost analysis, as well as investigation of clinical outcomes related to AR.

Avoidance – pets

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 2 studies, level 4: 1 study)
Benefit: Decreased environmental allergen exposure with possible reduction in symptoms and secondary prevention of asthma.
Harm: Emotional distress caused by removal of household pets. Financial and time costs of potentially ineffective intervention.
Cost: Low to moderate.
Benefits-harm assessment: Equivocal.
Value judgments: While several studies have demonstrated an association between environmental controls and reductions in environmental antigens, only a single, multi-modality randomized controlled trial has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity. The secondary prevention and treatment of asthma in sensitized individuals must also be considered.
Policy level: Option.
Intervention: Pet avoidance and environmental control strategies, particularly multi-modality environmental controls among patients with diagnosed Fel d 1 sensitivity, may be presented as an option for the treatment of AR.

Avoidance – rodents

Aggregate grade of evidence: C (Level 2: 5 studies, level 3: 5 studies, level 4: 4 studies, level 5: 1 study)
Benefit: Reduces rodent allergen levels (specifically mouse allergen) but no information on AR outcomes.
Harm: Reduction in patient QOL due to removal of pet rodent to whom patient is emotionally attached. Change in job position or role if primary rodent exposure is work-related.
Cost: Direct costs include the cost of interventions such as extermination and mitigating causal factors or loss of income if a job change occurs. Indirect costs include time off work for pest control appointments.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Careful patient selection based on exposure history. Heterogeneity of integrated pest management protocols makes quantification of benefit difficult.
Policy level: Option.
Intervention: Avoidance likely improves rodent-specific allergen exposure, especially when the interaction can be eliminated such as when it is work-related or with a pet rodent. Integrated pest management should be considered in select patients, such as pediatric inner-city patients that suffer from asthma and are mouse sensitized.

Avoidance – pollen

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 3 studies)
Benefit: Decreased symptoms and medication use with potential for improved QOL.
Harm: Interventions may vary in cost and efficacy of each may be inadequately defined.
Cost: Generally low monetary cost depending on strategy.
Benefits-harm assessment: Equivocal, most interventions with lower harm but not well-defined benefits.
Value judgments: Most pollen avoidance measures are based on clinical and expert opinion although trial-based evidence is available for some interventions.
Policy level: Option.
Intervention: Pollen avoidance strategies are generally well tolerated and lower cost, non-medication-based interventions that may have benefit with minimal harm to the patient, but further randomized controlled trials with larger populations would be needed to better characterize efficacy.

Avoidance – occupational

Aggregate grade of evidence: C (Level 3: 5 studies)
Benefit: Decreased allergen exposure may lead to reduction in symptoms, improvement in QOL, and possible reduced likelihood of developing occupational asthma.
Harm: Potential for socioeconomic harm with loss of wages or requiring changes in occupation.
Cost: Individually may vary if avoidance results in loss of income; for employers, potentially high cost depending on interventions or environmental controls required.
Benefits-harm assessment: Where possible from a patient-centered perspective, in occupational rhinitis complete avoidance is likely beneficial in improving health quality compared to ongoing exposures.
Value judgments: Based primarily on observational studies, allergen avoidance or decreasing exposure is recommended for all patients but can be nuanced depending on the resulting socioeconomic impact.
Policy level: Recommendation.
Intervention: Patients should be counseled to avoid or decrease exposure to inciting agents in occupational respiratory disease.

I.C.7.b | *Pharmacotherapy and procedural options*

Pharmacologic treatments are frequently employed to control AR symptoms. Depending on the specific therapy and geographic region, these may be available by prescription or over-the-counter. The evidence for pharmacologic options for AR has been reviewed (Table I.C.7.b).

The section that follows includes recommendation summaries for pharmacotherapies and procedural interventions that are included in the ICAR-Allergic Rhinitis 2023 document. A standard listing of side effect and adverse effects of most AR management options may be found in Table II.C. within the full ICAR-Allergic Rhinitis 2023 document.

Oral H_1 antihistamines

Aggregate grade of evidence: A (Level 1: 19 studies, level 4: 5 studies)
Benefit: Reduction in symptoms of AR.

Harm: Compared to first-generation oral antihistamines, newer-generation antihistamines have fewer central nervous system and anticholinergic side effects. The side effects of first-generation antihistamines can be more pronounced in the elderly. See Table II.C. in full ICAR document.
Cost: Inexpensive. Given their improved side effect profile, newer-generation oral antihistamines also have lower indirect costs than first generation oral H_1 antihistamines.
Benefits-harm assessment: The benefits outweigh harm for use of newer-generation H_1 oral antihistamines for AR.
Value judgments: First-generation oral antihistamines are not recommended for the treatment of AR because of their central nervous system and anticholinergic side effects.
Policy level: Strong recommendation for the use of newer-generation oral antihistamines for AR.
Intervention: Newer-generation oral antihistamines can be considered in the treatment of AR.

Oral H_2 antihistamines

Aggregate grade of evidence: B (Level 2: 7 studies)
Benefit: Decreased objective nasal resistance, and improved symptom control in 4 studies when used in combination with H_1 antagonists.
Harm: Drug–drug interaction (p450 inhibition, inhibited gastric secretion, and absorption).
Cost: Increased cost associated with H_2 antagonist over H_1 antagonist alone.
Benefits-harm assessment: Unclear benefit and possible harm.
Value judgments: No studies evaluating efficacy of H_2 antihistamines in context of INCS. There were 2 studies that showed no benefit for H_2 antagonist when used alone or as an additive to H_1 antagonist therapy.
Policy level: No recommendation. Available evidence does not adequately address the benefit of H_2 antihistamines in AR.
Intervention: Addition of an oral H_2 antagonist to an oral H_1 antagonist may improve symptom control in AR, but data is limited.

Intranasal antihistamines

Aggregate grade of evidence: A (Level 2: 44 studies)
Benefit: Rapid onset; more effective for nasal congestion than oral antihistamines; more effective for ocular symptoms than INCS; consistent reduction in symptoms and improvement in QOL in randomized controlled trials compared to placebo.
Harm: Patient tolerance, typically related to taste aversion; less effective for congestion than INCS. See Table II.C. in full ICAR document.
Cost: Low to moderate financial burden; available as prescription or nonprescription product.
Benefits-harm assessment: Preponderance of benefit over harm. Intranasal antihistamine as monotherapy is consistently more effective than placebo. Most studies show intranasal antihistamines superior to INCS for sneezing, itching, rhinorrhea, and ocular symptoms. Adverse effects are minor and infrequent. Generic prescription and over-the-counter formulations now available.
Value judgments: Extensive high-level evidence comparing intranasal antihistamine monotherapy to active and placebo controls demonstrates overall effectiveness and safety.
Policy level: Strong recommendation.
Intervention: Intranasal antihistamines may be used as first- or second-line therapy in the treatment of AR.

Oral corticosteroids

Aggregate grade of evidence: B (Level 2: 6 studies, level 3: 1 study, level 4: 3 studies)
Benefit: Oral corticosteroids can attenuate symptoms of AR and ongoing allergen induced inflammation.
Harm: Oral corticosteroids have multiple potential adverse effects, including hypothalamic-pituitary axis suppression. Prolonged use may lead to growth retardation in pediatric populations. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: The risks of oral corticosteroids outweigh the benefits, given similar symptomatic improvement observed with the use of safer INCS.
Value judgments: In the presence of effective symptom control using INCS, the risk of adverse effects from using oral corticosteroids for AR outweighs potential benefits.
Policy level: Strong recommendation against routine use.
Intervention: Although not recommended for routine use in AR, certain clinical scenarios may warrant the use of short courses of systemic corticosteroids, following a discussion of the risks and benefits with the patient. For example, oral

steroids could be considered in select patients with significant nasal obstruction that precludes adequate penetration of intranasal agents (corticosteroids or antihistamines). In these cases, a short course of systemic corticosteroids may improve congestion and facilitate access of topical medications. No evidence supports this suggestion, and thus careful clinical judgment and risk discussion are advocated.

Intranasal corticosteroid sprays

Aggregate grade of evidence: A (Level 1: 18 studies, level 2: 29 studies, level 3: 3 studies)
Benefit: INCS sprays are effective in reducing nasal and ocular symptoms of AR. Studies have demonstrated superior efficacy compared to oral antihistamines and leukotriene receptor antagonists (LTRAs).
Harm: INCS sprays have undesirable local adverse effects, such as epistaxis, with increased frequency compared to placebo in prolonged administration studies. There are no apparent negative effects on the hypothalamic-pituitary axis. There might be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: The benefits of using INCS sprays outweigh the risks when used to treat seasonal or perennial AR.
Value judgments: INCS sprays are first line therapy for the treatment of AR by virtue of their superior efficacy in controlling nasal symptoms. Subjects with seasonal AR should start prophylactic treatment with INCS sprays several days before the pollen season with an evaluation of the patient's response a few weeks after initiation, including a nasal exam to evaluate for local irritation or mechanical trauma. Children receiving INCS sprays should be on the lowest effective dose to avoid negative growth effects.
Policy level: Strong recommendation.
Intervention: The demonstrated efficacy of INCS sprays, as well as their superiority over other agents, make them first-line therapy in the treatment of AR.

Intranasal corticosteroids: non-traditional application

Aggregate grade of evidence: B (Level 2: 4 studies, level 3: 1 study)
Benefit: Nebulized steroids or those used via irrigation show some benefit in the treatment of AR in limited studies. Furthermore, steroids inhaled or exhaled through the nose in patients with asthma and rhinitis also show some benefit for rhinitis. Nasal steroid drops are not approved for treatment of rhinitis but are used in certain countries.
Harm: Nasal steroid drops have significant systemic side effects. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: The risks of using corticosteroid nasal drops for AR outweigh the benefits. Limited evidence suggests that nasal steroid irrigations for rhinitis lead to significant improvement of symptoms. Scarce evidence does not support routine recommendation for this route of therapy.
Value judgments: In the presence of effective symptom control using traditional spray administration for INCS, there is no solid data to support other routes of administration.
Policy level: Recommendation against routine use.
Intervention: There is some evidence that inhaled steroids, when exhaled through the nose might improve AR symptoms. Similar benefit is seen when steroids are inhaled by first passing through the nose. These routes might be useful in patients with both rhinitis and asthma.

Injectable corticosteroids

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 11 studies, level 4: 2 studies)
Benefit: Injectable corticosteroids improved symptoms of AR in clinical studies.
Harm: Injectable corticosteroids have known undesirable adverse effects on the hypothalamic-pituitary axis, growth, osteoporosis, glycemic control, and other systemic adverse effects, for varied periods of time after injection. Intraturbinate corticosteroids have a small but potentially serious risk of ocular side effects including decline or loss of vision. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: In routine management of AR, the risk of serious adverse effects outweighs the demonstrated clinical benefit.
Value judgments: Injectable corticosteroids are effective for the treatment of AR. However, given the risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of effective alternatives (e.g., INCS sprays),

injectable corticosteroids are not recommended for the routine treatment of AR.
Policy level: Recommendation against.
Intervention: None.

Oral decongestants

Aggregate grade of evidence: A (Level 2: 12 studies)
Benefit: Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.
Harm: Oral decongestants have known undesirable adverse effects. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Balance of benefit and harm for pseudoephedrine. Possible harm for phenylephrine.
Value judgments: Little evidence for benefit in controlling symptoms other than nasal congestion.
Policy level: Strong recommendation against for routine use in AR. In certain cases, combination therapy with an oral antihistamine may be beneficial to alleviate severe nasal congestion in short courses.
Intervention: Although not recommended for routine use in AR, pseudoephedrine can be effective in reducing nasal congestion in patients with AR; however, it should only be used as short-term/rescue therapy after a discussion of the risks and benefits with the patient (comorbidities) and consideration of alternative intranasal therapy options.

Intranasal decongestants

Aggregate grade of evidence: B (Level 2: 10 studies, level 3: 2 studies) Limitation – only 3 studies included subjects with AR.
Benefit: Reduction in symptoms of nasal congestion/blockage and corresponding objective markers with intranasal decongestants compared to placebo.
Harm: Side effects include nasal discomfort/burning, dependency, dryness, hypertension, anxiety, and tremors. Potential for rebound congestion with long-term use. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Harm likely outweighs benefit if used long-term, with adverse effects appearing as early as 3 days.
Value judgments: Intranasal decongestants can be helpful for short-term relief of nasal congestion.
Policy level: Option for short-term use.
Intervention: Intranasal decongestants can provide effective short-term relief of nasal congestion in patients with AR during an acute flare but recommend against chronic use due to risk of rhinitis medicamentosa.

Leukotriene receptor antagonists (LTRA)

Aggregate grade of evidence: A (Level 1: 13 studies; level 2: 21 studies)
Benefit: Consistent reduction in symptoms and improvement in QOL compared to placebo.
Harm: United States Food and Drug Administration (FDA) boxed warning regarding neuropsychiatric side effects, including suicidal ideation. Consistently inferior compared to INCS at symptom reduction and improvement in QOL. Equivalent or inferior effect compared to oral antihistamines in symptom reduction and improvement of QOL. See Table II.C. in full ICAR document.
Cost: Moderate.
Benefits-harm assessment: LTRAs are effective as monotherapy compared to placebo. However, there is a consistently inferior or equivalent effect to other, less expensive agents used as monotherapy. The FDA boxed warning is associated with LTRAs as well.
Value judgments: LTRAs are more effective than placebo at controlling both asthma and AR symptoms in patients with both conditions. However, in the light of significant concerns over its safety profile and the availability of effective alternatives such as INCS and oral antihistamines, evidence is lacking to recommend LTRAs as monotherapy in the management of AR.
Policy level: Recommendation against LTRAs as first-line monotherapy for patients with AR. Option for LTRA as monotherapy in patients with contraindications to other preferred treatments.
Intervention: LTRAs should not be used as monotherapy in the treatment of AR but can be considered in select situations where patients have contraindications to alternative treatments.

Intranasal cromolyn

Aggregate grade of evidence: A (Level 2: 25 studies)
Benefit: Disodium cromoglycate (DSCG) is effective in reducing sneezing, rhinorrhea, and nasal congestion.
Harm: Rare local side effects.
Cost: Low.

Benefits-harm assessment: Preponderance of mild to moderate benefit over harm. Less effective than INCS and intranasal antihistamines.
Value judgments: DSCG is useful for preventative short-term use in adult patients, children (2 years and older), and pregnant patients with known exposure risks.
Policy level: Recommendation as a second-line treatment in AR.
Intervention: DSCG may be used as a second-line treatment for AR in patients who fail INCS or intranasal antihistamines, or for short-term preventative benefit prior to allergen exposures.

Intranasal anticholinergics (ipratropium bromide (IPB))

Aggregate grade of evidence: A (Level 2: 10 studies, level 3: 2 studies)
Benefit: Reduction of rhinorrhea with topical anticholinergics.
Harm: Care should be taken to avoid overdosage leading to systemic side effects. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Preponderance of benefit over harm in AR patients with rhinorrhea.
Value judgments: Benefits limited to controlling rhinorrhea. Can be used as add on treatment for AR patients with persistent rhinorrhea despite first-line medical management.
Policy level: Option.
Intervention: IPB nasal spray may be used as an adjunct medication to INCS in AR patients with persistent rhinorrhea.

Biologic therapies

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 8 studies, level 3: 2 studies)
Benefit: Omalizumab treatment resulted in improvement of symptoms, rescue medication, and QOL as a monotherapy. Dupilumab data is less robust and needs further investigation.
Harm: Local reaction at injection site and risk of anaphylaxis.
Cost: High.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Biologic therapies show promise as a treatment option for AR; however, no biologic therapies have been approved by the US FDA for this indication.
Policy level: Option based upon published evidence, although not currently approved for this indication.
Intervention: Monoclonal antibody (biologic) therapies are not currently approved for the treatment of AR.

Intranasal saline

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 17 studies)
Benefit: Improved nasal symptoms and QOL, reduction in oral antihistamine use, and improved mucociliary clearance. Well-tolerated with excellent safety profile.
Harm: Nasal irritation, sneezing, cough, and ear fullness. See Table II.C. in full ICAR document.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Nasal saline can and should be used as a first line treatment in patients with AR, either alone or combined with other pharmacologic treatments as evidence supports an additive effect. Hypertonic saline may be more effective in children. Data is otherwise inconclusive on optimal salinity, buffering, and frequency and volume of administration.
Policy level: Strong recommendation.
Intervention: Nasal saline is strongly recommended as part of the treatment strategy for AR.

Probiotics

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 5 studies)
Benefit: Improved nasal/ocular symptoms or QOL in most studies.
Harm: Mild gastrointestinal side effects.
Cost: Low.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Minimal harm associated with probiotics. Heterogeneity across studies makes magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific recommendations for treatment.
Policy level: Option.
Intervention: Consider adjuvant use of probiotics for patients with symptomatic seasonal or perennial AR.

Combination oral antihistamine and oral decongestant

Aggregate grade of evidence: A (Level 2: 30 studies)
Benefit: Improved nasal congestion and total symptom scores with combination oral antihistamine-oral decongestants.
Harm: Oral decongestants can cause adverse events in patients with cardiac conditions, hypertension, or benign prostatic hypertrophy and are not indicated in patients under age 12 or pregnant patients. Oral antihistamines are not indicated in patients under 2 years of age, and caution should be exercised in patients aged 2–5 years old. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Combination oral antihistamine-oral decongestant medications carry relatively low risks of adverse events when used as needed for episodic AR symptoms in well-selected patients. Risk may be higher if used daily or in patients with certain comorbidities. There is not a preponderance of benefit or harm when used appropriately as a treatment option.
Value judgments: Oral antihistamine-oral decongestants may be an effective option for acute AR symptoms such as nasal congestion and sneezing. Caution should be exercised with long-term use.
Policy level: Option for episodic or acute AR symptoms.
Intervention: Combination oral antihistamine-oral decongestant medications may provide effective relief of nasal symptoms of AR on an episodic basis. Caution should be exercised in chronic or long-term use as the adverse effect profile of oral decongestants is greater for chronic use.

Combination oral antihistamine and intranasal corticosteroid

Aggregate grade of evidence: A (Level 1: 1 study, level 2: 12 studies)
Benefit: The addition of oral antihistamine to INCS has not consistently demonstrated a benefit over INCS alone for symptoms of AR.
Harm: Oral antihistamines generally not recommended in patients under 2 years old, and attention to dosing is necessary in patients 2–12 years old. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Benefit likely outweighs potential harms in patients with significant nasal congestion symptoms in addition to symptoms such as sneezing and ocular itching. Addition of an INCS may be limited benefit versus potential harm in patients without significant nasal congestion symptoms.
Value judgments: Adding oral antihistamine to INCS spray has not been demonstrated to confer additional benefit over INCS spray alone. INCS improves congestion with or without oral antihistamine.
Policy level: Option.
Intervention: Current evidence is mixed to support antihistamines as an additive therapy to INCS, as several randomized trials have not demonstrated a benefit over INCS alone for symptoms of AR.

Combination oral antihistamine and leukotriene receptor antagonist

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 13 studies)
Benefit: Combination oral antihistamine-LTRA was superior in symptom reduction and QOL improvement versus placebo and versus either agent as monotherapy.
Harm: FDA boxed warning due to risks of mental health side effects limiting use for AR. See Table II.C. in full ICAR document.
Cost: Generic montelukast added to generic loratadine or cetirizine is more expensive per month than generic fluticasone furoate nasal sprays, according to National Average Drug Acquisition Cost data provided by the Centers for Medicare and Medicaid Services.
Benefits-harm assessment: Combination LTRA and oral antihistamine is superior to placebo, and superior to either agent as monotherapy. However, there is an inferior effect versus INCS, which is also less costly. In addition, there is a boxed warning associated with montelukast.
Value judgments: Combination therapy of LTRA and oral antihistamines is effective, but in light of concerns over the safety profile of montelukast, and the availability of effective alternatives such as INCS, evidence is lacking to recommend combination therapy in the management of AR.
Policy level: Recommendation against as first line therapy.
Intervention: Combination LTRA and oral antihistamines should not be used as first line therapy for AR but can be considered in patients with contraindications to other alternatives. This combination should be used judiciously after carefully weighing potential risks and benefits.

Combination intranasal corticosteroid and intranasal antihistamine

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 18 studies, level 4: 3 studies)
Benefit: Rapid onset; more effective for relief of multiple symptoms than either INCS or intranasal antihistamine alone.
Harm: Patient tolerance, especially due to taste. See Table II.C. in full ICAR document.
Cost: Moderate financial burden for combined formulation. Concurrent use of individual intranasal antihistamine and corticosteroid sprays is likely a more economical option.
Benefits-harm assessment: Preponderance of benefit over harm. Combination therapy with intranasal antihistamine and INCS is consistently more effective than placebo or monotherapy. Low risk of non-serious adverse effects.
Value judgments: High-level evidence demonstrates that combination spray therapy with INCS plus intranasal antihistamine is more effective than monotherapy or placebo, as well as more effective than combination of INCS plus oral antihistamine. The increased financial cost and need for prescription limit the value of combination therapy as a routine first-line treatment for AR. When a combined formulation is financially prohibitive, the concurrent use of two separate formulations (antihistamine and corticosteroid) is an alternative option.
Policy level: Strong recommendation for the treatment of AR when monotherapy fails to control symptoms.
Intervention: Combination therapy with INCS and intranasal antihistamine may be used as second-line therapy in the treatment of AR when initial monotherapy with either INCS or antihistamine does not provide adequate control.

Combination intranasal corticosteroid and leukotriene receptor antagonist

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 8 studies)
Benefit: Some studies demonstrate improvement of symptoms and QOL with combination therapy. One meta-analysis did not show benefit with the exception of ocular itching.
Harm: Boxed warning due to risks of serious neuropsychiatric events for LTRA limiting use for AR. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Boxed warning for AR limits use. If comorbid asthma and AR, treatment is an option with consideration of mental health risks.
Value judgments: Possibly useful for symptom control, especially in patients with comorbid asthma, however, boxed warning limits use in AR without asthma.
Policy level: Option as combination therapy if comorbid asthma present and mental health risks are considered. Not recommended for AR alone.
Intervention: Consider use in patients with AR and asthma, after weighing therapeutic benefits against risks of mental health adverse effects.

Combination intranasal corticosteroid and intranasal decongestant

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 5 studies, level 3: 1 study)
Benefit: Some evidence in randomized studies of benefit from addition of intranasal decongestant to INCS therapy in refractory AR patients. The evidence regarding the magnitude of effect is unclear, and a meta-analysis that tried to estimate this effect was significantly limited by study heterogeneity and low sample size (two trials).
Harm: See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Balance of benefit and harm with current evidence base.
Value judgments: While combination therapy of intranasal decongestant and INCS is superior to INCS therapy alone with low risk of tachyphylaxis in patients with refractory AR, the magnitude of effect is still unclear. There may be a role in patients with AR refractory to INCS and intranasal antihistamine combination therapy prior to consideration of surgery or in patients uninterested in surgery.
Policy level: Option.
Intervention: Short-term combination therapy with INCS and intranasal decongestant may be considered in patients with AR refractory to combination therapy with INCS and intranasal antihistamine prior to consideration of inferior turbinate reduction or in patients declining surgery.

Combination intranasal corticosteroid and intranasal ipratropium bromide

Aggregate grade of evidence: Unable to determine based on one study. (Level 2: 1 study)
Benefit: Reduction of rhinorrhea in INCS-treatment-refractory AR.
Harm: Usually no systemic anticholinergic activity if administered intranasally in the recommended doses. See Table II.C. in full ICAR document.
Cost: Low.
Benefits-harm assessment: Benefit for combined INCS and IPB therapy in patients with treatment refractory AR and the main symptom of rhinorrhea.
Value judgments: No evidence for benefit in controlling symptoms other than rhinorrhea. Evidence is limited, but results are encouraging for patients with persistent rhinorrhea.
Policy level: Option.
Intervention: Combining IPB with beclomethasone dipropionate can be more effective than either agent alone for the treatment of rhinorrhea in refractory AR in children and adults. Although multiple consensus guidelines have recommended, and there is evidence to support this recommendation, it is important to note that there has only been one randomized controlled trial (RCT) to study the efficacy of combined INCS and IPB therapy compared to either agent alone, and this study was performed in a combined population of patients with AR and non-allergic rhinitis.

Acupuncture

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 1 study)
Benefit: Improvement of QOL and symptoms. Fairly well tolerated with no systemic adverse effects.
Harm: Needle sticks associated with minor adverse events including skin irritation, erythema, subcutaneous hemorrhage, pruritus, numbness, fainting, and headache. Electroacupuncture can interfere with pacemakers and other implantable devices. Caution is recommended in pregnant patients as some acupoints can theoretically induce labor. Need for multiple treatments and possible ongoing treatment to maintain any benefit gained. Relatively long treatment period.
Cost: Moderate-high. Cost and time associated with acupuncture treatment; multiple treatments required.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: The evidence is generally supportive of acupuncture. Acupuncture may be appropriate for some patients to consider as an adjunct/alternative therapy.
Policy level: Option.
Intervention: In patients who are interested in avoiding medications, acupuncture can be suggested as a possible therapeutic adjunct.

Honey

Aggregate grade of evidence: D (Level 2: 3 studies, conflicting evidence)
Benefit: Unclear as studies have shown differing results and include different preparations of honey in the trials. Local honey may be able to modulate symptoms and decrease need for antihistamines.
Harm: Potential compliance issues with patients not tolerating the level of sweetness. Potential risk of allergic reaction and rarely anaphylaxis. Caution should be exercised in in pre-diabetics and diabetics for concern of elevated blood glucose levels.
Cost: Cost of honey and associated healthcare costs with increased consumption.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: More studies are required before honey intake can be widely recommended.
Policy level: No recommendation.
Intervention: None.

Herbal therapies

Aggregate grade of evidence: Uncertain.
Benefit: Unclear, but some herbs may be able to provide symptomatic relief.
Harm: Some herbs are associated with mild side effects. Also, the safety, quality, and standardization of herbal remedies and supplements are unclear.
Cost: Cost of herbal supplements.
Benefits-harm assessment: Unknown.
Value judgments: There is a lack of sufficient evidence to recommend the use of herbal supplements in AR.
Policy level: No recommendation.
Intervention: None.

Septoplasty/septorhinoplasty

Aggregate grade of evidence: C (Level 3: 1 study, level 4: 3 studies, level 5: 11 studies)
Benefit: Improved postoperative symptoms and nasal airway.
Harm: Risk of complications (e.g., septal hematoma or perforation, nasal dryness, cerebrospinal fluid leak, epistaxis, unfavorable aesthetic change); persistent obstruction.
Cost: Surgical/procedural costs, time off from work.
Benefits-harm assessment: Potential benefit must be weighed against low risk of harm and cost of procedure.
Value judgments: Properly selected patients with septal deviation impacting their nasal patency can experience improved nasal obstruction symptoms.
Policy level: Option for those with obstructive septal deviation.
Intervention: Septoplasty/septorhinoplasty may be considered in AR patients that have failed medical management and who have anatomic, obstructive features that may benefit from this intervention.

Inferior turbinate (IT) surgery

Aggregate grade of evidence: B (Level 1: 4 studies, level 2: 13 studies, level 3: 18 studies, level 4: 50 studies)
Benefit: Improvement in rhinitis symptoms including nasal breathing, congestion, sneezing, and itching. Improved nasal cavity area via objective measures, as well as increased QOL via subjective measures.
Harm: Risk of complications (e.g., swelling, crusting, empty nose syndrome, epistaxis).
Cost: Surgical/procedural costs, potential time off from work.
Benefits-harm assessment: Potential benefit outweighs low risk of harm.
Value judgments: Current evidence suggests that patients with AR who suffer from IT hypertrophy will likely experience improvement in symptoms, nasal patency, and QOL.
Policy level: Recommendation in patients with medically refractory nasal obstruction.
Intervention: In AR patients with IT hypertrophy that have failed medical management, IT reduction is a safe and effective treatment to reduce symptoms and improve nasal function. More studies are warranted to directly compare IT surgery methods (e.g., radiofrequency ablation, laser-assisted, microdebrider-assisted) for the most efficacious and long-lasting outcome.

Vidian neurectomy, posterior nasal neurectomy

Aggregate grade of evidence: B (Level 2: 3 studies, level 3: 5 studies, level 4: 7 studies, level 5: 2 studies)
Benefit: Improvement in rhinorrhea.
Harm: Risk of complications (e.g., dry eye and decreased lacrimation, numbness in lip/palate, nasal dryness, damage to other nerves).
Cost: Surgical/procedural costs, potential time off from work.
Benefits-harm assessment: Potential benefit must be balanced with low risk of harm but consider that long-term results may be limited.
Value judgments: Patients may experience an improvement in symptoms.
Policy level: Option.
Intervention: Vidian neurectomy or posterior nasal neurectomy may be considered in AR patients that have failed medical management, particularly for rhinorrhea.

Cryotherapy/radiofrequency ablation of posterior nasal nerve

Aggregate grade of evidence: C (Level 3: 2 studies, level 4: 4 studies, level 5: 5 studies)
Benefit: Improvement in rhinorrhea.
Harm: Risk of complications (e.g., epistaxis, temporary facial pain and swelling, headaches), limited long-term results.
Cost: Surgical/procedural costs, cost of device, potential time off from work.
Benefits-harm assessment: Potential benefit must be balanced with low risk of harm, especially considering limited long-term results.
Value judgments: Patients may experience an improvement in symptoms.
Policy level: Option.
Intervention: Cryoablation and radiofrequency ablation of the posterior nasal nerve may be considered in AR patients that have failed medical management, particularly for rhinorrhea.

I.C.7.c | *Allergen immunotherapy*

Unlike allergen avoidance, environmental controls, and pharmacotherapy, AIT has the benefit of initiating and sustaining immunologic alterations. Following AIT, which involves scheduled administration of allergen extracts at effective doses for a specified time frame, controlled

TABLE I.C.7.b Pharmacotherapy options for the treatment of allergic rhinitis – comparison between 2018 and 2023

Medication	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Oral H_1 antihistamines	2023	24	A	Strong recommendation	Newer-generation oral H_1 antihistamines are strongly recommended for AR treatment.
	2018	21	A	Strong recommendation	
Oral H_2 antihistamines	2023	7	B	No recommendation	Insufficient data.
	2018	6	B	No recommendation	
Intranasal antihistamines	2023	44	A	Recommendation	Intranasal antihistamines should be used as first- or second-line therapy for the treatment of AR.
	2018	44	A	Recommendation	
Oral corticosteroids	2023	10	B	Strong recommendation against	Strongly recommend against use of oral steroids for routine AR care.
	2018	9	B	Recommend against	
Injectable corticosteroids	2023	14	B	Recommend against	Systemic or intraturbinate corticosteroid injections are not recommended for routine AR treatment.
	2018	13	B	Recommend against	
Intranasal corticosteroid spray	2023	50	A	Strong recommendation	INCS should be used as first-line therapy in the treatment of AR.
	2018	53	A	Strong recommendation	
Intranasal corticosteroids, non-traditional application	2023	5	B	Recommend against	No evidence for non-traditional delivery application of intranasal steroids for AR.
	2018	n/a	n/a	n/a	
Oral decongestants	2023	12	A	Strong recommendation against	Not recommended for routine treatment AR. Short-term use of combination oral H_1 antihistamine and oral decongestant may be considered.
	2018	9	B	Option – pseudoephedrine; recommend against – phenylephrine	
Topical intranasal decongestants	2023	12	B	Option	Option for short-term topical decongestant use.
	2018	4	B	Option	
Leukotriene receptor antagonists	2023	34	A	Recommend against	LTRAs should not be used as monotherapy in the routine treatment of AR.
	2018	31	A	Recommend against	
Cromolyn (DSCG)	2023	25	A	Recommended as a second-line treatment	DSCG may be considered as a second-line treatment for AR.
	2018	22	A	Option	
Intranasal anticholinergic (IPB)	2023	12	A	Option	IPB nasal spray may be considered as an adjunct to INCS in perennial AR patients with persistent rhinorrhea.
	2018	14	B	Option	
Biologics	2023	12	A	Option	Option based on published evidence. However, omalizumab is not approved by the US FDA for the treatment of AR alone.
	2018	6	A	No indication	

(Continues)

TABLE I.C.7.b (Continued)

Medication	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Nasal saline	2023	21	A	Strong recommendation	Nasal saline is strongly recommended as part of the treatment strategy for AR.
	2018	12	A	Strong recommendation	
Probiotics	2023	9[a]	A	Option	Consider adjuvant use of probiotics for AR treatment.
	2018	28	A	Option	
Combination oral antihistamine and oral decongestant	2023	30	A	Option	Option for acute exacerbations with a primary symptom of nasal congestion.
	2018	21	A	Option	
Combination oral antihistamine and INCS	2023	13	A	Option	Current data is mixed.
	2018	5	B	Option	
Combination oral antihistamine and LTRA	2023	17	A	Recommend against	Recommendation against as first line therapy.
	2018	13	A	Option	
Combination INCS and intranasal antihistamine	2023	23	A	Strong recommendation	Strong recommendation for combination therapy when monotherapy fails to control AR symptoms.
	2018	12	A	Strong recommendation	
Combination INCS and LTRA	2023	9	B	Option	Option as combination therapy if comorbid asthma present and mental health risks are considered
	2018	n/a	n/a	n/a	
Combination INCS and intranasal decongestant	2023	7	B	Option	Option for short-term therapy.
	2018	n/a	n/a	n/a	
Combination INCS and intranasal ipratropium	2023	1	–	Option	Limited evidence to support this recommendation.
	2018	n/a	n/a	n/a	
Acupuncture	2023	5	A	Option	Acupuncture may be suggested as a possible therapeutic adjunct to other therapy.
	2018	2	B	Option	
Honey	2023	3	B	No recommendation	Studies inconclusive.
	2018	3	B	No recommendation	
Herbal therapies	2023	–	–	No recommendation	Insufficient evidence to recommend herbal remedies.
	2018	–	–	No recommendation	

Abbreviations: AR, allergic rhinitis; DSCG, disodium cromoglycate; FDA, Food and Drug Administration; INCS, intranasal corticosteroids; IPB, ipratropium bromide; LTRA, leukotriene receptor antagonists; n/a, not applicable (not considered in ICAR-Allergic Rhinitis 2018 document); US, United States.

[a]Studies included in systematic reviews were not separately listed in tables

TABLE I.C.7.c Allergen immunotherapy for the treatment of allergic rhinitis – comparison between 2018 and 2023

AIT method	Year	Number of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Subcutaneous immunotherapy (SCIT)	2023	77	A	Strong recommendation	Strong recommendation for SCIT as compared to no therapy. Option for SCIT over SLIT.
	2018	8	A	Strong recommendation	
Rush SCIT	2023	20	B	Option	Option for rush SCIT in the appropriate patient.
	2018	n/a	n/a	n/a	
Cluster SCIT	2023	15	B	Option	Option for cluster SCIT with premedication strongly considered.
	2018	n/a	n/a	n/a	
Sublingual immunotherapy (SLIT)	2023	30	A	Strong recommendation[a]	Strong recommendation for SLIT in patients unable to obtain adequate relief from pharmacotherapy.
	2018	25	A	Strong recommendation	
SLIT tablets	2023	15	A	Strong recommendation	The evidence supports a strong recommendation for SLIT tablets for refractory AR.
	2018	n/a	n/a	n/a	
Aqueous SLIT	2023	13	B	Recommendation	Aqueous SLIT recommended for refractory AR.
	2018	n/a	n/a	n/a	
Trans/epicutaneous immunotherapy	2023	5	B	Recommend against	Trans/epicutaneous immunotherapy is currently not recommended for AR treatment.
	2018	4	B	Recommend against	
Intralymphatic immunotherapy (ILIT)	2023	16	A	Option	ILIT may be a viable option for AR treatment, currently under investigation.
	2018	7	B	Option	
Combination SCIT and biologic therapy	2023	5	B	Option	Anti-IgE may be beneficial as a premedication prior to induction of cluster or rush SCIT protocols.
	2018	4	B	Option	

Abbreviations: AR, allergic rhinitis; ICAR, International Consensus Statement on Allergy and Rhinology; ILIT, intralymphatic immunotherapy; n/a, not applicable (not considered in ICAR-Allergic Rhinitis 2018 document); SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

[a]Specific recommendations for various SLIT preparations in full ICAR document.

trials demonstrate reduction in allergy symptoms and medication use.

The AIT portion of ICAR-Allergic Rhinitis 2023 discusses AIT candidacy, benefits, and contraindications. Allergen units and standardization are addressed, along with allergen extract adjuvants and modified allergen extracts. Overall, there is high level evidence supporting the use of AIT for AR (Table I.C.7.c).

Conventional subcutaneous immunotherapy (SCIT)

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 46 studies, level 3: 29 studies)

Benefit: SCIT reduces symptom and medication use, as demonstrated in multiple high-quality studies.

Harm: Risks of SCIT include frequent local reactions and rare systemic reactions, which may be severe and potentially fatal if not managed appropriately. This risk must be discussed with patients prior to initiation of therapy.

Cost: SCIT is cost-effective, with some studies demonstrating value that dominates the alternative strategy with improved health outcomes at lower cost. Direct and indirect costs of AIT vary based on the third-party payer, the office/region, co-payment responsibilities, and travel/opportunity related costs in being able to adhere to the frequency of office visits required.

Benefits-harm assessment: For patients with symptoms lasting longer than a few weeks per year and for those who cannot obtain adequate relief

with symptomatic treatment or who prefer an immunomodulation option, benefits of SCIT outweigh harm. The potential benefit of secondary disease-modifying effects, especially in children and adolescents, should be considered.

Value judgments: A patient preference-sensitive approach to therapy is needed. Comparatively, the potential for harm and burden associated with medications are significantly lower, although the potential for benefit is also lower (with no potential for any disease-modifying effect or long-term benefit) as medications do not induce immunomodulation. Logistical issues surrounding time commitment involved with AIT may be prohibitive for some patients. The strength of evidence for SCIT efficacy, along with the benefit relative to cost, would support coverage by third party payers.

Policy level: Strong recommendation for SCIT as a patient preference-sensitive option for the treatment of AR.

Strong recommendation for SCIT over no therapy for the treatment of AR.

Option for SCIT over sublingual immunotherapy (SLIT) for the treatment of AR.

Intervention: SCIT is an appropriate treatment consideration for patients who have not obtained adequate relief with symptomatic therapy or who prefer this therapy as a primary management option, require prolonged weeks of treatment during the year, and/or wish to start treatment for the benefit of the potential secondary disease-modifying effects of SCIT.

Rush subcutaneous immunotherapy

Aggregate grade of evidence: B (Level 2: 12 studies, level 3: 4 studies, level 4: 4 studies)

Benefit: Accelerates the time to reach therapeutic dosing which may improve compliance, lead to earlier clinical benefit, and be more convenient for the patient. Improvement of symptoms and decreased need for rescue medication.

Harm: Higher rates of local and systemic reactions with rush SCIT protocols compared to conventional and cluster SCIT. Inconvenience of visits to a medical facility to receive injections.

Cost: Direct costs may be similar or slightly less compared to conventional SCIT, which includes cost of extract preparation and injection visits. Indirect costs are improved due to the reduced number of appointment visits, which reduces work and school absenteeism.

Benefits-harm assessment: Balance of benefit and harm.

Value judgments: Careful patient selection and shared decision making would reduce risks. Heterogeneity of protocols, extract types, and dosing across studies makes quantification of risk difficult.

Policy level: Option.

Intervention: Aeroallergen rush SCIT is an option for AR in appropriately selected patients that do not have adequate control of their symptoms with symptomatic therapies. If available at practice location, the use of depigmented-polymerized allergen extracts for rush SCIT has a better safety profile compared with standard extracts.

Cluster subcutaneous immunotherapy

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 12 studies, level 4: 2 studies)

Benefit: Accelerates the time to reach therapeutic dosing which may improve compliance, lead to earlier clinical benefit, and be more convenient for the patient. Improvement of symptoms and decreased need for rescue medication. Similar safety profile compared to conventional SCIT.

Harm: Minimal harm with occasional, but mild, local adverse events and rare systemic adverse events when premedication is used. Inconvenience of visits to a medical facility to receive injections.

Cost: Direct costs may be similar, slightly more, or slightly less compared to conventional SCIT, depending on how the practicing provider bills for the services. This includes cost of extract preparation, injection visits, and possibly rapid desensitization codes. Indirect costs are lower due to the reduced number of appointment visits, which reduces work and school absenteeism.

Benefits-harm assessment: Preponderance of benefit over harm for patients that cannot achieve adequate relief with symptomatic management. Balance of benefit and harm compared to conventional SCIT but in slight favor of cluster SCIT due to convenience.

Value judgments: Careful patient selection and shared decision making would reduce risks. Heterogeneity of protocols, extract types, and dosing across studies makes risk quantification difficult.

Policy level: Option.

Intervention: Cluster SCIT can be safely implemented in clinical practice and offered to those patients eligible for SCIT that may prefer this

protocol compared to conventional build-up protocols due to convenience. Premedication should be strongly considered.

Sublingual immunotherapy (SLIT): general considerations

Aggregate grade of evidence: A (Level 1: 17 studies, level 2: 12 studies, level 4: 1 study)
Due to heterogeneity of SLIT study reporting, it is difficult to separate out overall versus aqueous SLIT versus tablet SLIT.
Benefit: SLIT improves patient symptom scores, even as add-on treatment with rescue medication. SLIT reduces medication use. The effect of SLIT lasts for at least 2 years after a 3-year course of therapy. In AR patients, there is some evidence that SLIT reduces the frequency of onset of asthma and the development of new sensitizations up to 2 years after treatment termination. Benefit is generally higher than with single-drug pharmacotherapy; however, it may be less than with SCIT (low quality evidence).
Harm: Minimal harm with very frequent, but mild local adverse events, and very rare systemic adverse events. SLIT seems to be safer than SCIT.
Cost: Intermediate. SLIT becomes cost-effective compared to pharmacotherapy after several years of administration. Total costs seem to be lower than with SCIT.
Benefits-harm assessment: Benefit of treatment over placebo is small but tangible and occurs in addition to improvement with medication. There is a lasting effect at least 2 years off treatment. Minimal harm with SLIT, greater risk for SCIT.
Value judgments: SLIT improved patient symptoms with low risk for adverse events.
Policy level: Strong recommendation for the use of SLIT grass pollen tablet, ragweed tablet, HDM tablet, and tree pollen aqueous solution. Recommendation for SLIT for *Alternaria* allergy. Option for SLIT for animal allergy. Recommendation for dual-therapy SLIT in bi-allergic patients.
Intervention: Recommend tablet or aqueous SLIT in patients (adults and children) with seasonal and/or perennial AR who wish to reduce their symptoms and medication use, as well as possibly reduce the propensity to develop asthma or new allergen sensitizations.

Sublingual immunotherapy tablets

Aggregate grade of evidence: A (Level 1: 11 studies, level 2: 4 studies)
Benefit: Improvement of symptoms, rescue medication, and QOL.
Harm: Local reaction at oral administration site and low risk of anaphylaxis.
Cost: Intermediate. More expensive than standard pharmacotherapy, but persistent benefit may result in cost-saving in the long-term.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Useful for patients with severe or refractory symptoms of AR.
Policy level: Strong recommendation.
Intervention: SLIT tablets are recommended for patients with severe or refractory AR. Epinephrine auto-injector is recommended in the FDA labeling for approved tablets due to the rare but serious risk of anaphylaxis. Tablets for select antigens are available in various countries.

Aqueous sublingual immunotherapy

Aggregate grade of evidence: B (Level 1: 7 studies, level 2: 5 studies, level 4: 1 study)
Benefit: Aqueous SLIT improves patient symptom scores and decreases rescue medication use. There is some indication of less benefit from aqueous versus tablet SLIT, but the lack of standardized dosing across multiple trials does not allow for adequate comparison.
Harm: Common mild to moderate local adverse events. Very rare cases of systemic adverse events. No reported cases of life-threatening reactions
Cost: Intermediate. More expensive than standard pharmacotherapy, but there are indications of lasting benefit and cost-saving in the long-term.
Benefits-harm assessment: Appreciable benefit in patient symptoms and minimal harm.
Value judgments: Aqueous SLIT improves patient symptoms and rescue medication usage with minimal risk of serious adverse events but common local mild adverse events. Single allergen therapy has been extensively tested. Multiallergen AIT requires future studies to validate its use.
Policy level: Recommendation.
Intervention: High-dose aqueous SLIT is recommended for those patients who wish to reduce their symptoms and rescue medication use.

Epicutaneous/transcutaneous immunotherapy

Aggregate grade of evidence: B (Level 2: 5 studies)
Benefit: Epicutaneous AIT to grass pollen resulted in limited and variable improvement in symptoms,

medication use, and allergen provocation tests in patients with AR or conjunctivitis.
Harm: Epicutaneous AIT resulted in systemic and local reactions, with a relative risk of 4.65 and 2.29, respectively. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous AIT.
Cost: Unknown.
Benefits-harm assessment: There is limited and inconsistent data on benefit of the treatment, while there is a concerning rate of adverse effects. Three out of 4 studies on this topic were published by the same investigators from 2009 to 2015.
Value judgments: Epicutaneous AIT could offer a potential alternative to SCIT and SLIT, but further research is needed.
Policy level: Recommendation against.
Intervention: While epicutaneous AIT may potentially have a future clinical application in the treatment of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a significant rate of adverse reactions. Given the above and the availability of alternative treatments, epicutaneous AIT is not recommended at this time.

Intralymphatic immunotherapy

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 11 studies, level 4: 3 studies)
Benefit: Shorter treatment period, decreased number of injections, smaller amount of allergen, lower risk of adverse events versus SCIT.
Harm: Local reaction at injection site and risk of anaphylaxis.
Cost: Cost savings due to shorter treatment duration and fewer injections. Additional cost for training required.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Apparent short-term favorable effect, but long-term effect is lacking.
Policy level: Option.
Intervention: More studies are essential to establish the long-term effects of ILIT.

Combination subcutaneous immunotherapy and biologics

Aggregate grade of evidence: B (Level 2: 5 studies)
Benefit: Improved safety of accelerated cluster and rush SCIT protocols, with decreased symptom and rescue medication scores among a carefully selected population.
Harm: Financial cost and low risk of anaphylactic reactions to omalizumab.
Cost: Moderate to high.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Combination therapy increases the safety of SCIT, with decreased systemic reactions following cluster and rush protocols. Associated treatment costs must be considered. While two high-quality RCTs have demonstrated improved symptom control with combination therapy over SCIT or anti-IgE alone, not all patients will require this approach. Rather, an individualized approach to patient management must be considered, with evaluation of alternative causes for persistent symptoms, such as unidentified allergen sensitivity. Also, the studies did not compare optimal medical treatment of AR (INCS, antihistamine, allergen avoidance measures) to combination therapy versus SCIT alone. The current evidence does not support the utilization of combination therapy for all patients failing to benefit from SCIT alone.
Policy level: Option.
Intervention: Current evidence supports that anti-IgE may be beneficial as a premedication prior to induction of cluster or rush SCIT protocols, and combination therapy may be advantageous as an option for carefully selected patients with persistent symptomatic AR following AIT. However, at the time of this writing, biologic therapies are not approved by the US FDA for AR alone. An individualized approach to patient management must be considered.

I.C.8 | Pediatric considerations

The pediatric section is a new addition for ICAR-Allergic Rhinitis 2023 and encompasses several literature reviews. AR takes a few years to develop in children. A family history of AR, atopy, or asthma is important to discuss as children may be at an increased risk of developing AR or other allergic diseases. The "allergic march," described as a specific sequence of atopic disorders, should be considered in children with clinical suspicion. Diagnosis may be challenging in the pediatric population, and some diagnostic clues include chapped lips from mouth breathing, fatigue, irritability, poor appetite, and attention issues.

TABLE I.C.9 Allergic rhinitis associated conditions – comparison between 2018 and 2023

Condition	Year	Number of listed studies	Aggregate grade of evidence	Interpretation
Asthma – association with rhinitis	2023	17	B	Asthma is associated with AR and non-allergic rhinitis, due to the "unified airway" concept.
	2018	7	C	
Asthma – rhinitis as a risk factor	2023	22	C	AR and non-allergic rhinitis are risk factors for developing asthma.
	2018	13	C	
Asthma – benefit of pharmacologic treatment for AR on asthma	2023	28	A	See Section XIII.A.4. for specific recommendations.
	2018	–	–	
Asthma – benefit of biologics for AR on asthma	2023	2	B	Omalizumab improves comorbid asthma.
	2018	n/a	n/a	
Asthma – benefit of AIT for AR on asthma	2023	13	A	Both SCIT and SLIT improve comorbid asthma.
	2018	n/a	n/a	
Chronic rhinosinusitis without nasal polyps	2023	10	D	Conflicting evidence for/against an association.
	2018	10	D	
Chronic rhinosinusitis with nasal polyps	2023	21	D	Conflicting evidence for/against an association.
	2018	21	D	
Allergic fungal rhinosinusitis (AFRS)	2023	15	C	Conflicting evidence, but allergy is thought to play an important role in AFRS.
	2018	n/a	n/a	
Central compartment atopic disease (CCAD)	2023	13	C	Conflicting evidence, but early studies generally support an association between AR and CCAD.
	2018	n/a	n/a	
Aspirin exacerbated respiratory disease (AERD)	2023	6	C	High rate of concomitant atopy in AERD, however majority of AERD symptoms likely unrelated to AR.
	2018	n/a	n/a	
Conjunctivitis	2023	12	C	Conjunctivitis is a frequently occurring comorbidity of AR, especially in children.
	2018	7	C	
Atopic dermatitis	2023	31	C	There is evidence for an association between AR and atopic dermatitis.
	2018	20	C	
Pollen food allergy syndrome (PFAS)	2023	17	C	There is evidence for a link between pollen allergy and PFAS. Currently AIT is not recommended for the sole purpose of ımproved food tolerance.
	2018	12	B	
Anaphylactic food allergy	2023	20	C	Evidence for AIT treatment for food allergies; see full ICAR section for details.
	2018	n/a	n/a	
Adenoid hypertrophy	2023	13	C	Conflicting evidence for/against an association.
	2018	11	C	
Otologic conditions – Eustachian tube dysfunction	2023	16	C	There is a causal role for AR in the development of Eustachian tube dysfunction.
	2018	7	C	
Otologic conditions – otitis media	2023	36	C	Relationship between AR and otitis media is unclear; however, allergy treatment has not been effective in resolving middle ear effusion.
	2018	16	C	
Otologic conditions – Meniere's disease	2023	12	C	Possible association between Meniere's disease and AR; needs more rigorous investigation.
	2018	8	C	
Cough	2023	18	C	Conflicting evidence. Treatment of AR may improve associated cough.
	2018	9	C	

(Continues)

TABLE I.C.9 (Continued)

Condition	Year	Number of listed studies	Aggregate grade of evidence	Interpretation
Laryngeal disease	2023	23	C	There is increasing evidence for an association between AR and laryngeal disease.
	2018	18	C	
Eosinophilic esophagitis	2023	35	C	Limited observational data suggests a potential association between aeroallergens and pathogenesis of eosinophilic esophagitis.
	2018	13	C	
Sleep disturbance and OSA	2023	16[a]	B	Sleep disturbance is associated with AR. Treatment of AR can improve sleep quality.
	2018	20	B	

Abbreviations: AERD, aspirin exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; AIT, allergen immunotherapy; AR, allergic rhinitis; CCAD, central compartment atopic disease; OSA, obstructive sleep apnea; PFAS, pollen food allergy syndrome; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

[a]Studies included in systematic reviews were not separately listed in tables.

TABLE I.C.12 Summary of knowledge gaps and future research needs in allergic rhinitis, based on the work in ICAR-Allergic Rhinitis 2023

Major content area	Knowledge gaps and future research needs
Epidemiology and risk factors	• Improved understanding of the incidence of AR based on geographic location • Evaluation of climate change effects on incidence and severity of AR • Improved understanding of the relationship between genetics and environmental factors in the development of AR • High quality longitudinal studies evaluating risk factors for development of AR
Evaluation and diagnosis	• Increased understanding of hyposmia as a symptom of AR or a marker if its severity • Further evaluation and validation of nasal sIgE testing for AR diagnosis • Further work evaluating the use of novel AR testing techniques, such as BAT and mast cell activation testing, provocation testing, and objective measures of nasal air flow • Improvement of low-cost diagnostic tools
Pediatrics	• Improved treatment options for young children • Improved interpretation of skin testing results in young children • Optimizing treatment strategies for children who are polysensitized • Further work developing allergen immunotherapy delivery routes appropriate and safe for children
Management	• Continued investigation of combination therapy options, including topical therapies • Studies of comparative effectiveness and cost-effectiveness for AR treatments • Further work directly comparing SCIT to SLIT in large-scale RCTs • Standardization of rush and cluster SCIT protocols for aeroallergen immunotherapy
Associated conditions	• Improved understanding of treatment effects of AR on specific comorbid CRSwNP subtypes/endotypes • Continued work to determine the relationship of AR to ear disease • Investigation of treatment effect of AR on cough
COVID-19	• Improved understanding of the aerosolization risk during nasal endoscopy • Improved understanding of the risks of AR treatment, including allergen immunotherapy, during COVID infection • A deeper understanding of the long-term effects of COVID on allergic diseases and their development

Abbreviations: AR, allergic rhinitis; COVID, coronavirus disease 2019; BAT, basophil activation test; CRSwNP, chronic rhinosinusitis with nasal polyps; SCIT, subcutaneous immunotherapy; sIgE, allergen-specific immunoglobulin E; SLIT, sublingual immunotherapy.

Physical exam findings include posterior pharyngeal cobblestoning, clear nasal drainage, and enlarged/boggy inferior turbinates, "allergic" or "adenoid" facies, the allergic salute, allergic crease, allergic shiners, or Dennie–Morgan lines. The diagnosis of AR in children should be based on both clinical history and testing. SPT is generally accepted as the preferred method of testing in children. Treatment options for children under age 2 are limited. For older children, treatment options are similar to the adult population. AIT is also an option for children with persistent symptoms. AIT may reduce the risk of asthma development in pediatric patients with AR.

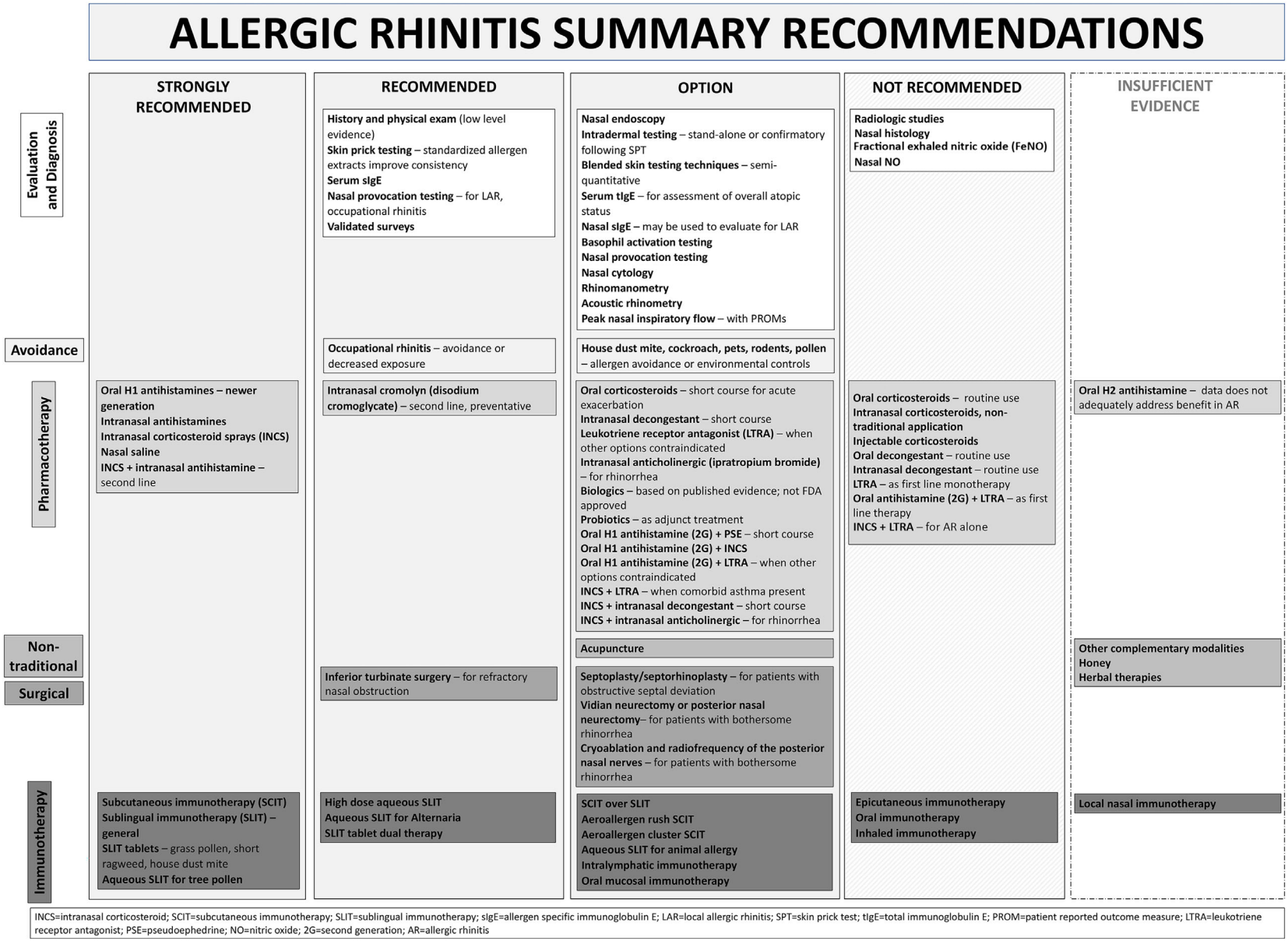

FIGURE I.C.11 Allergic Rhinitis Summary Recommendations

I.C.9 | Associated conditions

There is evidence for the association of several comorbid conditions with AR, which are listed in Table I.C.9. Several additional conditions have been added since ICAR-Allergic Rhinitis 2018.

I.C.10 | Special section on COVID-19

Coronavirus disease 2019 (COVID-19) case rates have changed practice strategies. AR has not been identified as a risk factor for severe COVID-19. However, there have been challenges with overlapping symptoms of AR and COVID-19. Telemedicine visits have been helpful for initial evaluation; however, many diagnostic techniques for AR require face-to-face encounters. Recommendations have continued to evolve during the pandemic. Standard therapies for AR were not shown to increase the risk of severe COVID-19. Additionally, anti-IgE therapy has not increased susceptibility or severity of COVID-19 infection.

I.C.11 | Summary figure for allergic rhinitis diagnosis and management

See Figure I.C.11 for summary diagnosis and management options for AR, based upon current evidence.

I.C.12 | Knowledge gaps

Evidence in the realm of AR continues to grow at a steady pace. We have seen substantial progress in many aspects of the AR literature in recent years. However, several knowledge gaps remain. Table I.C.12. lists knowledge gaps and future research needs that have been identified as a result of the work in ICAR-Allergic Rhinitis 2023.

I.D | Discussion

In the executive summary for ICAR-Allergic Rhinitis 2023, we highlight the current evidence levels and recommendations (where applicable) for AR diagnosis, management, and associated conditions. Over 40 new topics have been added to this evidence-based assessment since the initial ICAR-Allergic Rhinitis 2018 publication. In many individual topic areas, numerous additional studies were identified and evaluated. In certain cases, the recommendation level changed. While these advances in our current literature are exciting, there are several knowledge gaps that remain – and there is still work to be done to further our understanding of various aspects of AR pathophysiology, epidemiology, disease burden, diagnosis, management, and associated conditions.

I.E | Lay summary

The International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis 2023

ICAR-Allergic Rhinitis 2023 contains the most complete and up-to-date information on how allergic rhinitis develops, how medical teams can identify it, how it may be treated, and other conditions that can be seen with allergic rhinitis. The document has been written and reviewed by a large group of medical and research experts from around the world. ICAR-Allergic Rhinitis 2023 may be used by medical providers who treat allergic rhinitis.

What is allergic rhinitis?
Allergic rhinitis is a reaction that occurs from substances that we breathe in from the environment. Patients often have drainage and blockage from their nose, along with sneezing and itching. While there are many possible causes of these symptoms, allergic rhinitis is due to a specific trigger in the environment that the body is sensitive to. Allergic rhinitis may be associated with other diseases, such as asthma, sleep problems, sinus and ear problems, cough, and more.

How common is allergic rhinitis?
Allergic rhinitis is a common problem. Depending on the specific research study and the location where the study is done, allergic rhinitis has been reported in 5%–50% of the population. It is more common in children.

How severe is allergic rhinitis?
Allergic rhinitis can affect quality of life. It may also interrupt sleep. Allergic rhinitis medicines, other treatments, and medical visits cost money directly. There are added costs related to missing work or school – or not functioning as well at work. Research suggests that treating allergic rhinitis helps improve overall quality of life and sleep.

How is allergic rhinitis treated?
People may avoid their allergic triggers if they are aware of the specific things that they react to – and if these things can be easily avoided. Using different types of medications can also help control allergic symptoms. Immunotherapy, such as allergy shots or drops/tablets under the tongue, introduces the known allergen to the body in small amounts at first. Over time, the body will not react to the allergen. There are also some procedures and surgeries that can decrease drainage from the nose or improve breathing through the nose.

What disorders are associated with allergic rhinitis?
Asthma, atopic dermatitis (a condition of the skin), eye symptoms, food allergies, and sleep problems are all associated with allergic rhinitis. Some studies report that certain ear issues and sinus problems may be related to allergic rhinitis, although more studies should be done to understand these better.

II | TABLE OF CONTENTS AND NAVIGATING THROUGH THE DOCUMENT

II.A | Detailed table of contents

II.B | List of abbreviations

AAO-HNSF	American Academy of Otolaryngology-Head and Neck Surgery Foundation
AAP	American Academy of Pediatrics
AC	allergic conjunctivitis
ACC	allergen challenge chamber
ACEI	angiotensin converting enzyme inhibitors
AD	atopic dermatitis
AERD	aspirin-exacerbated respiratory disease
AFRS	allergic fungal rhinosinusitis
AH	adenoid hypertrophy
AHI	apnea-hypopnea index
AIDS	acquired immunodeficiency syndrome
AIT	allergen-specific immunotherapy
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
AP	activator protein
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ARS	acute rhinosinusitis
ASHMI	Anti-Asthma Simplified Herbal Medicine Intervention
ATH	adenotonsillar hypertrophy
AU	allergy units
BAT	basophil activation test
BAU	biologic allergy units
cAMP	cyclic adenosine monophosphate
CBER	Center for Biologics Evaluation and Research
CC	central compartment
CCAD	central compartment atopic disease
CCL5	C-C chemokine ligand-5
CD	cluster of differentiation
CDC	Centers for Disease Control
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related protein
CI	confidence interval
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVID	coronavirus disease
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CPT	conjunctival provocation test
CRD	component-resolved diagnostics
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps

CS	combined score
CSF	cerebrospinal fluid
CT	computed tomography
DAMP	damage-associated molecular pattern
DSCG	disodium cromoglycate
dsDNA	double stranded DNA
EAACI	European Academy of Allergy and Clinical Immunology
EBRR	evidence-based review with recommendations
ECHRS	European Community Respiratory Health Survey
ECP	eosinophil cationic protein
EEC	environmental exposure chamber
EGPA	eosinophilic granulomatosis with polyangiitis
EGR	early growth response
ELISA	enzyme-linked immunosorbent assay
eNOS	endothelial nitric oxide synthase
ENS	empty nose syndrome
EoE	eosinophilic esophagitis
ET	Eustachian tube
ETD	Eustachian tube dysfunction
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FITC	fluorescein isothiocyanate
FOXP3	forkhead-box P3
GA^2LEN	Global Allergy and Asthma European Network
GATA	GATA binding protein
GINA	Global Initiative for Asthma
GITRL	glucocorticoid-induced TNF receptor ligand
GM-CSF	granulocyte-macrophage colony stimulating factor
GPA	granulomatosis with polyangiitis
GWAS	genome-wide association studies
HDM	house dust mite
HEPA	high-efficiency particulate air [filtration]
HIV	human immunodeficiency virus
HMGB-1	high mobility group box-1
HMW	high molecular weight
HNS	head and neck surgery
HSP	heat shock protein
ICAM	intercellular adhesion molecule
ICAR	International Consensus Statement on Allergy and Rhinology
ICD	International Classification of Disease
IDT	intradermal dilutional testing
IFN	interferon
Ig	immunoglobulin
IgE	immunoglobulin E
IL	interleukin
ILC	innate lymphoid cell
ILIT	intralymphatic immunotherapy
IMAP	inferior meatus augmentation procedure
INCS	intranasal corticosteroid
INDC	intranasal decongestant
iNOS	inducible nitric oxide synthase
IPB	ipratropium bromide
ISAAC	International Studies of Asthma and Allergies in Childhood
IT	inferior turbinate
ITAM	immunoreceptor tyrosine-based activation motif
KNHANES	South Korean National Health and Nutrition Examination Survey
LAR	local allergic rhinitis
LMW	low molecular weight
LOE	level of evidence
LPR	laryngopharyngeal reflux
LSR	lipolysis-stimulated lipoprotein receptor
LTRA	leukotriene receptor antagonist
MBP	major basic protein
MCP	monocyte chemoattractant protein
MD	molecular diagnostics
MEE	middle ear effusion
MMP	matrix metalloproteinase
MQT	modified quantitative testing
mRQLQ	mini-Rhinoconjunctivitis Quality of Life Questionnaire
MT	middle turbinate
NARES	non-allergic rhinitis with eosinophilia syndrome
NC	nasal cytology
NF	nuclear factor
NFAT	nuclear factor of activated T cells
NGF	neural growth factor
NH	nasal histology
NHANES	National Health and Nutrition Examination Survey
NK	natural killer
nNO	nasal nitric oxide
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
NOSE	Nasal Obstruction Symptom Evaluation
NPT	nasal provocation test
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OAS	oral allergy syndrome
OME	otitis media with effusion
OMIT	oral mucosal immunotherapy
OR	odds ratio
OSA	obstructive sleep apnea

PAMD@	precision allergy molecular diagnostic applications
PAMP	pathogen-associated molecular pattern
PDE	phosphodiesterase
PEF	peak expiratory flow
PFAS	pollen food allergy syndrome
PFT	pulmonary function test
PG	prostaglandin
PM	particulate matter
PNEF	peak nasal expiratory flow
PNIF	peak nasal inspiratory flow
PNN	posterior nasal nerve
PO	per os (by mouth)
ppb	parts per billion
ppm	parts per million
PPV	positive predictive value
4PR	four-phase rhinomanometry
PROM	patient reported outcome measure
PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PSG	polysomnogram
QALY	quality adjusted life year
QID	four times daily
QOL	quality of life
RANTES	regulated upon activation, normal T cell expressed and presumably secreted
RAP	Respiratory Allergy Prediction
RAPP	RhinAsthma Patient Perspectives
RARS	recurrent acute rhinosinusitis
RAST	radio allegro-sorbent test
RCT	randomized controlled trial
RDI	respiratory disturbance index
REM	rapid eye movement
RMS	rescue medication score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RR	relative risk
RSDI	Rhinosinusitis Disability Index
RTSS	Rhinitis Total Symptom Score
SARS-CoV-2	virus that causes COVID-19
SCIT	subcutaneous immunotherapy
SDB	sleep disordered breathing
SES	socioeconomic status
sIgE	allergen-specific immunoglobulin E
sIgG	allergen-specific immunoglobulin G
SLIT	sublingual immunotherapy
SMA	smooth muscle actin
SMD	standardized mean difference
SNHL	sensorineural hearing loss
SNOT	SinoNasal Outcome Test
SNP	single nucleotide polymorphism
SPT	skin prick test
SRMA	systematic review and meta-analysis
STAT	signal transducer and activator of transcription
TARC	thymus and activation-regulated chemokine
TCM	Traditional Chinese Medicine
TGF	transforming growth factor
Th	T helper
tIgE	total immunoglobulin E
TJ	tight junction
TL1A	tumor necrosis factor-like cytokine 1A
TLR	toll-like receptor
TNF	tumor necrosis factor
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TPRV	transient receptor potential vanilloid
Treg	T regulatory cell
TRP	transient receptor potential
TSLP	thymic stromal lymphopoietin
TSS	total symptom score
UK	United Kingdom
US	Unites States
VAS	visual analog scale
VCAM	vascular cell adhesion molecule
VCOS	validated clinical outcome survey
VD3	vitamin D
VDR	vitamin D receptor
VHI	voice handicap index
WAO	World Allergy Organization
WHO	World Health Organization
ZO	zonula occludens

II.C | Possible adverse effects of common allergic rhinitis treatments

Various aspects of the International Consensus Statement on Allergy and Rhinology (ICAR): Allergic Rhinitis (ICAR-Allergic Rhinitis) 2023 document include possible side effects or treatment risks of interventions under consideration. In order to standardize listing of these potential side effects and treatment risks within the document text and recommendation summaries, Table II.C. defines known and typical side effects and adverse effects for commonly utilized treatment modalities that should be considered when determining policy level recommendations. Table II.C. may not include all possible risks of listed interventions.

III | INTRODUCTION

The original ICAR-Allergic Rhinitis 2018 document was developed to summarize and critically review the best

TABLE II.C Possible side effects and adverse effects of common allergic rhinitis diagnostic modalities and treatments[a]

Intervention	Possible side effects and adverse effects
Allergy skin testing	Discomfort, pruritis, prolonged skin reaction, systemic reaction (e.g., hives, wheezing), anaphylaxis, inaccurate test results, misinterpreted test results
Nasal saline	Nasal irritation, sneezing, cough *For high volume nasal irrigations*: ear fullness, irrigation fluid transmission to middle ear
Systemic/oral corticosteroids	Increased appetite, weight gain, fluid retention, gastritis, sleep disturbance, restlessness, anxiety, depression, aggressiveness, psychosis, adrenal suppression, cataracts, glaucoma, hair/skin changes, easy bruising, acne, delayed wound healing, muscle weakness, change in body fat distribution, immunosuppression, hypertension, hyperglycemia/diabetes, osteopenia, osteoporosis, avascular necrosis of the hip, kidney stones
Intranasal corticosteroids	Discomfort/burning, epistaxis, dryness, crusting, foul taste, headache, sore throat
Oral decongestants	Irritability, anxiety, restlessness, sleep disturbance, hypertension, tachycardia, heart palpitations, drug–drug interactions, tremors *In young children*: tachycardia, seizures, loss of consciousness, death
Intranasal decongestants	Discomfort/burning, dependency, dryness, increased congestion, rhinitis medicamentosa, hypertension, anxiety, tremors
Oral H_1 antihistamines	Drowsiness, headache, dry mucous membranes, restlessness, anxiety, insomnia, tachyphylaxis, urinary retention
Intranasal H_1 antihistamines	Discomfort/burning, drowsiness, dizziness, epistaxis, dryness, crusting, foul taste, headache, sore throat, sneezing, nausea
Intranasal ipratropium	Nasal dryness/irritation, epistaxis, headache, dry mouth, sore throat, taste change, nausea, diarrhea, constipation, stomach cramps, anxiety, blurry vision, body aches, chills, cough, difficulty breathing, ear congestion
Leukotriene antagonists	Behavior/mood alterations, agitation, depression, irritability, hallucinations, tremor, suicidal thoughts and behavior *For zileuton*: hepatotoxicity
Subcutaneous allergen immunotherapy	Redness/swelling at injection site, large local injection site reactions, sneezing, cough, throat swelling, wheezing, chest tightness, nausea, dizziness, anaphylaxis
Sublingual allergen immunotherapy	Lip/mouth/tongue irritation, mouth swelling, eye swelling/itching/redness, nausea, vomiting, stomach cramps, diarrhea, nasal congestion/itching, sneezing, increased mucus production, wheezing, cough, hives, skin itching, anaphylaxis

[a]May not include all possible risks of listed interventions

available evidence for allergic rhinitis (AR), including major content areas of epidemiology, risk factors, diagnosis, management, conditions associated with AR, and others. Since the publication of ICAR-Allergic Rhinitis 2018, the AR literature has continued to grow. We previously reported that there were 8212 publications related to AR between 2010 and the final writing of ICAR-Allergic Rhinitis 2018.[1] Between 2018 and June 2022, 5803 additional AR publications have been logged in PubMed. The methodology, results, evidence levels, and quality of scientific publications vary widely, and it can be challenging to distill important findings from such a large body of work. ICAR-Allergic Rhinitis 2023 aims to evaluate and summarize the AR evidence for each topic in a succinct format to provide the clinician, researcher, or medical professional with a reference document that contains useful, relevant information. Given the recent expansion of the AR literature, an update of the original ICAR-Allergic Rhinitis 2018 document was deemed appropriate.

When evaluating a scientific publication, it is important to critically assess the study methods and presentation of results, as these contribute to the evidence levels and ultimate recommendations for patient care. ICAR-Allergic Rhinitis 2023 aims to incorporate new high-level evidence into an updated document and utilizes this evidence, along with assessment of benefit, harm, and cost to determine recommendations for AR diagnostic and management strategies, where appropriate. ICAR-Allergic Rhinitis 2023 follows previously developed methodology that has produced multiple evidence-based reviews with recommendations (EBRR)[2] in the *International Forum of Allergy and Rhinology*, as well as several ICAR documents, including those covering topics of AR, rhinosinusitis, endoscopic skull base surgery, and olfaction.[1,6–9]

ICAR-Allergic Rhinitis 2023 was created by conducting systematic literature searches on 144 individual AR topics, by 87 primary authors and 40 additional consultant authors. Over 40 new topics have been added for this

ICAR-Allergic Rhinitis update, and the number of cited references has expanded by over 1400. Like previous ICAR documents, structured grading of evidence was performed, recommendations were created where appropriate, and each section underwent stepwise semi-blinded iterative review (blinded for initial peer review then un-blinded to reach consensus). Finally, a panel of editors critiqued each major content area, and the collated manuscript was circulated to all authors for review. The EBRR and ICAR methodology appears to be effective and robust and continues to be used regularly in evaluation of the rhinology and allergy literature.

Throughout the ICAR-Allergic Rhinitis 2023 document, it is evident that many AR topics have grown in literature citations compared to 2018. This may be noted by a simple increase in the number of publications; however, the reader will also recognize that many topic areas contain new systematic reviews and meta-analyses (SRMA) that have been published since ICAR-Allergic Rhinitis 2018. This is an exciting development, as SRMAs represent the highest level of evidence and, when performed with robust methodology, collate the available evidence into a single report that should be easily understood by the reader. Still, while some areas of AR have very strong evidence, others are lacking in high-level evidence.

It is important to recognize the limitations of ICAR-Allergic Rhinitis 2023. Recommendations in this document are based on the available evidence. Each recommendation is only as strong as the evidence that supports it and the population/sample included in the studies. Practicing evidence-based medicine takes into account the available evidence, along with clinical expertise and the patient's values and expectations.[10] ICAR-Allergic Rhinitis 2023 presents evidence-based recommendations, but it is not a manual, flowchart, or algorithm for care of an individual AR patient. The clinician should continue to evaluate and treat each AR patient individually, using an evidence-based foundation combined with clinical acumen/expertise and consideration of patient values and principles. Recommendations in ICAR-Allergic Rhinitis 2023, as in previous ICAR documents, do not define the standard of care or medical necessity, nor do they dictate the care of individual patients.

Through the ICAR-Allergic Rhinitis 2023 process, several gaps in knowledge have been identified and may encourage further research in AR. Additionally, some evidence grades have changed since 2018, and we anticipate that we will continue to see evidence grow and evolve in the future. Ultimately, improved patient outcomes should result as we continue to evaluate the growing body of AR literature.

IV | METHODS

IV.A | Topic development

The methods of ICAR-Allergic Rhinitis 2023 largely follow previous ICAR documents,[1,6,7] with utmost reliance on published evidence and minimal influence of expert opinion and other biases. The 2011 EBRR method described by Rudmik and Smith[2] is the foundation of ICAR and aims to evaluate existing literature on each AR topic, grade the evidence, and provide literature-based recommendations where appropriate.

To complete ICAR-Allergic Rhinitis 2023, the subject of AR was initially divided into 144 individual topics, representing 41 additional topics compared to ICAR-Allergic Rhinitis 2018. A primary author who is a recognized expert in allergy, rhinology, or the designated topic was assigned to evaluate each topic. Authors were initially selected via online literature searches for each ICAR-Allergic Rhinitis 2023 topic. Authors of high-quality publications in each topic area were invited as ICAR contributors. Other invited authors included experts in the EBRR process, experts in education on specific AR topic areas, and those with knowledge of the systematic review process. The invited primary author was able to choose a secondary/consultant author for each section if desired.

Certain topics, such as those providing background or definitions, were assigned as literature reviews without evidence grades or recommendations. Some topics were not appropriate for clinical recommendations and were assigned as evidence-based reviews without recommendations (EBRs). Topics that had evidence to inform clinical recommendations were assigned as EBRRs. For topics included in ICAR-Allergic Rhinitis 2018, the author was instructed to perform a new literature search and include updated evidence since the previous ICAR-Allergic Rhinitis document as well as any other relevant studies previously published. Aggregate grades of evidence and recommendations summaries were updated accordingly.

Creation of the content for each individual AR topic area began with a literature search. Authors received instructions to perform a systematic review of the literature for each topic area based upon Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standardized guidelines.[3] Ovid MEDLINE (1947-2021), EMBASE (1974-2021), and Cochrane Review databases were included. The search began by identifying any previously published systematic reviews or guidelines pertaining to the assigned topic. Since clinical recommendations are best supported by high quality evidence, the search

TABLE IV.A.-1 Levels of evidence[11]

Level	Diagnosis	Therapy/prevention, etiology
1	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Systematic review of randomized trials or *n*-of-1 trials
2	Individual cross-sectional studies with consistently applied reference standard and blinding	Randomized trial or observational study with dramatic effect
3	Cohort study or control arm of randomized trial[a]	Non-randomized controlled cohort/follow-up study[b]
4	Case series or case–control studies, or poor-quality prognostic cohort study[b]	Case series, case–control studies, or historically controlled studies[b]
5	n/a	Mechanism-based reasoning

[a]Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size or if a significant dose–response relationship is demonstrated.
[b]As always, a systematic review is generally better than an individual study.

TABLE IV.A.-2 Aggregate grade of evidence[4]

Grade	Research quality
A	Well-designed RCTs
B	RCTs with minor limitations Overwhelming consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion Case reports Reasoning from first principles

Abbreviation: RCT, randomized controlled trial.

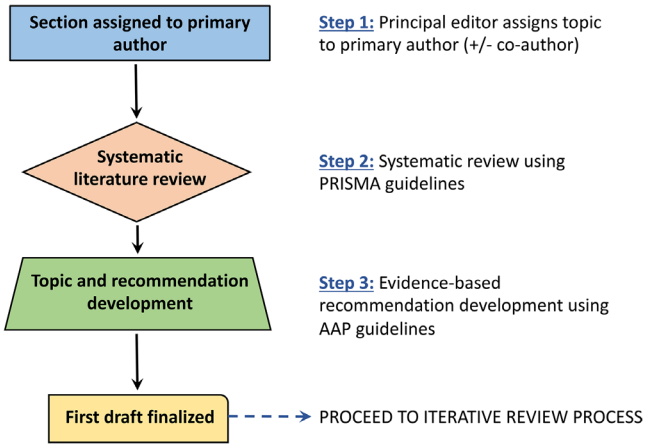

FIGURE IV.A Topic development (Stage 1). Abbreviations: AAP, American Academy of Pediatrics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

focused on identifying randomized controlled trials (RCT) and meta-analyses of RCTs to provide the highest level of evidence (LOE). Reference lists of all identified studies were examined to ensure all relevant studies were captured. If the authors felt that a non-English study should be included in the review, it was instructed that the paper be appropriately translated to minimize the risk of missing important data during the development of recommendations.[3]

To optimize transparency of the evidence, all included studies in EBR and EBRR topic sections are presented in a standardized table format and the quality of each study was evaluated to receive a level based on the Oxford LOEs (level 1–5, Table IV.A.-1).[11] Adjustments were made to the LOE due the quality of each study based on accepted standards, with specific changes often highlighted in the text or evidence tables.[12] At the completion of the systematic review and research quality evaluation for each EBR or EBRR topic, an aggregate grade of evidence (A–D) was produced for the topic based on the guidelines from the American Academy of Pediatrics (AAP) Steering Committee on Quality Improvement and Management[4] (Table IV.A.-2). For AR topics that addressed a diagnostic or therapeutic intervention and contained evidence to appropriately support formulation of a recommendation, the AAP guidelines for recommendation development were followed, thus completing the EBRR process[4] (Table IV.A.-3). Each evidence-based recommendation was formulated with consideration of the aggregate grade of evidence, benefit, harm, and cost. A summary of the EBRR topic development process is provided in Figure IV.A.

It is important to note that assignment of LOE for each publication is not always straightforward. In some instances, individual studies do not fit neatly into one of the Oxford LOE categories. Also, Oxford LOE grading has changed over time, adding complexity to the evidence grading when undertaking updates such as this one. This becomes even more difficult when evaluating certain documents that employ advanced systematic evidence searches to formulate guidelines, practice parameters, position papers, and recommendation documents (e.g., Clinical Practice Guidelines, ICAR statements, European Position Statements on Sinusitis). In these instances, even methodological experts may disagree on evidence levels – some seeing the document as a systematic review

TABLE IV.A.-3 American Academy of Pediatrics defined strategy for recommendation development[4]

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCTs	Strong recommendation	Option	Strong recommendation against
B. RCTs with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation		
C. Observational studies (case–control and cohort design)			Recommendation against
D. Expert opinion, case reports, reasoning from first principles	Option	No recommendation	

Abbreviation: RCT, randomized controlled trial.

with a high evidence level, while others would assign a lower LOE typical of a consensus statement, guideline, or expert opinion. Furthermore, these documents often contain multiple subsections that vary in the amount and quality of available evidence. Therefore, when these types of documents are included in individual topic areas, the assigned LOEs may differ.

Throughout the ICAR-Allergic Rhinitis process, when a single publication was cited in multiple sections with differing LOEs initially assigned, this was returned to the authors/reviewers of each section for collective discussion. In some circumstances, the discussion resulted in the group deciding to revise the LOE to a consistent assignment across sections. In other cases, the groups supported their initial LOE assignment with appropriate reasoning – and the original LOE assignments remained. Therefore, the reader may notice occasional fluctuation in LOE assignment throughout the ICAR document.

IV.B | Iterative review

Following the development of the initial topic text and any associated evidence tables, evidence grades, and recommendations, each section underwent a two-stage online iterative review process using two independent reviewers that were initially blinded to the author's identity (Figure IV.B.). The purpose of the individual AR topic iterative review process was to evaluate the completeness of the identified literature and ensure any EBRR recommendations were appropriate. The content of the first draft from each topic section was reviewed by the first reviewer in a blinded fashion. The process was then unblinded, and necessary changes were agreed upon and incorporated by the initial author and this first reviewer – arriving at a consensus for the first stage. The revised topic section was subsequently reviewed by a second reviewer in a blinded fashion. Following the second review, the process was again unblinded. Initial topic authors and both assigned reviewers agreed upon necessary changes before each section was considered finalized and appropriate to proceed into the final ICAR statement stage.

IV.C | ICAR-Allergic Rhinitis statement development

After the content of each of topic was reviewed and consensus reached amongst the initial author and two iterative reviewers, the principal editor (S.K.W.) compiled associated topics into major content areas. The first draft of each major content area (i.e., Evaluation and Diagnosis, Pharmacotherapy, Immunotherapy, etc.) then underwent additional reviews for consistency and flow by a group of three to five ICAR associate editors. Finally, the full draft of ICAR-Allergic Rhinitis 2023 was compiled and circulated to all authors. The final ICAR-Allergic Rhinitis 2023 manuscript was produced when all authors agreed upon the literature and final recommendations (Figure IV.C).

IV.D | Limitations of methods and data presentation

It is important to note that each topic author individually performed the literature search for his/her assigned topic. Therefore, search results may contain some inherent variability despite specific and detailed search instructions. Furthermore, while aiming to be as comprehensive as possible, this document may not present every study published on every topic. For certain topics, the literature is extensive and only high-quality studies or systematic reviews are listed. If the aggregate evidence on a topic reached a high evidence grade with only high-level studies, an exhaustive list of lower-level studies (or all studies ever performed) is not provided.

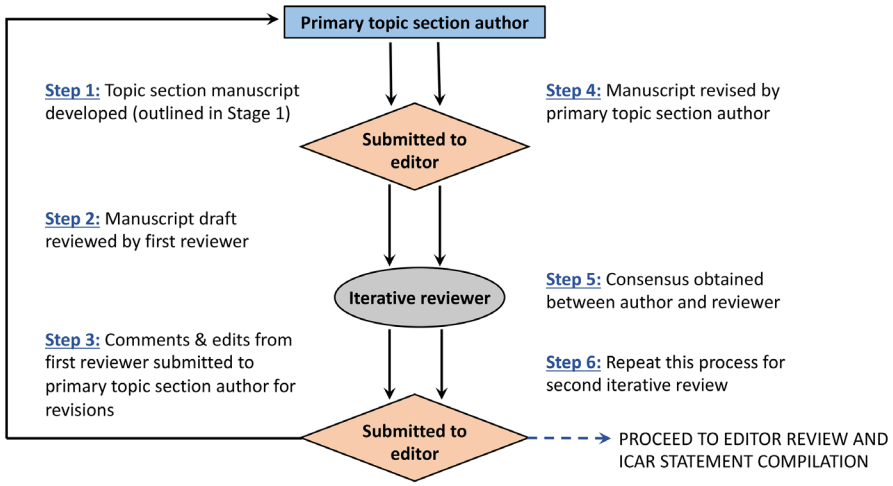

FIGURE IV.B Topic iterative review process (Stage 2)

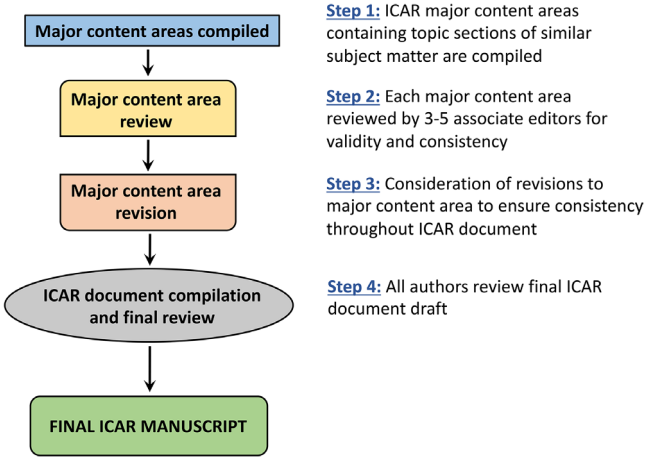

FIGURE IV.C ICAR-Allergic Rhinitis 2023 statement development (Stage 3). Abbreviation: ICAR, International Consensus Statement on Allergy and Rhinology

V | DEFINITIONS, CLASSIFICATION, AND DIFFERENTIAL DIAGNOSIS OF ALLERGIC RHINITIS

V.A | General definition and classification

V.A.1 | Definition, classification, and severity of allergic rhinitis

AR is an immunoglobulin E (IgE)-mediated, type 1 hypersensitivity response of the nasal mucosal membranes, resulting from allergen exposure in a sensitized individual.[5] Symptomatically, it is characterized by anterior or posterior rhinorrhea, nasal congestion/blockage, nasal pruritis, and sneezing.[13] AR is widely prevalent and can result in significant physical sequelae and recurrent or persistent morbidities.[5] Additionally, it is strongly associated with asthma, supporting the unified airway theory which postulates that upper and lower airway inflammation share common pathophysiologic mechanisms.[14] (See Section VI.K. Unified Airway for additional information on this topic.)

The prevalence of AR ranges from approximately 5%–50% worldwide, with the highest incidence in the pediatric population.[15] While this range of AR prevalence is wide, it is important to recognize that published studies may vary in their definition of AR and some may define AR as sensitization to allergens. (See Section VII. Epidemiology of Allergic Rhinitis for additional information on this topic.) AR is essentially absent in infants and typically develops in school age children. Since sensitization takes years to develop, it is unlikely to manifest before 2 years of age. This is likely secondary to the rapidly evolving immune system inherent in a child's early development. AR often results from an overactive response of T helper (Th)-2 lymphocytes and initiation of a systemic IgE-driven reaction, which can dominate a child's immune system until completely mature.

In the atopic individual, exposure to allergens may prompt allergen-specific IgE (sIgE) production. Subsequent exposure triggers both early and late-stage reactions, leading to the clinical manifestations of AR. The early-stage reaction typically occurs within minutes after re-introduction of the sensitized allergen, producing a rapid onset of nasal itching, congestion, and rhinorrhea.[16] The late-stage reaction often occurs during the 4- to 8-h period after allergen re-introduction and results in congestion, hyposmia, increased anterior and posterior rhinorrhea, and nasal hyper-responsiveness. (See Section VI. Pathophysiology and Mechanisms of Allergic Rhinitis for additional information on this topic.)

Allergic Rhinitis and its Impact on Asthma (ARIA) proposals have categorized AR by presumed cause and the timing during which it occurs. Classically, this has been categorized as seasonal AR (i.e., hay fever) and perennial AR. *Seasonal AR* is typically associated with outdoor allergens, such as pollens, and usually occurs during seasons with high pollen counts.[5] *Perennial AR* is typically associated with indoor allergens, such as house dust mites (HDM), insects, and animal dander, and has been considered to occur consistently throughout the year.[5] Mold exposure may occur indoors or outdoors depending on the specific environmental situation.

Of note, the classification of seasonal versus perennial AR can potentially be in conflict. For example, seasonal AR may persist for longer periods secondary to the effects of climate change, with resultant prolonged elevations in pollen counts. Seasonal AR may also continue across multiple seasons secondary to polysensitization. Furthermore, manifestations of perennial allergy may not occur throughout the entire year. This is particularly the case for patients allergic to HDM, who may demonstrate mild or moderate/severe intermittent AR.[17–20]

Because of the priming effect on the nasal mucosa introduced by low levels of pollen exposure,[21–26] and minimal but persistent nasal inflammation in patients with "symptom-free rhinitis,"[19,27,28] symptoms may not occur entirely in conjunction with allergen exposure. This may result in non-specific exacerbations. Additionally, air pollution may also contribute to variations in allergen sensitivity, resulting in fluctuating symptom severity depending on location/air quality.[29] (See Section VIII.B.3. Risk Factors for Allergic Rhinitis – Pollution for additional information on this topic.)

Subsequently, ARIA proposed a new method of classification based on the length and persistence of symptoms.[30] *Intermittent AR* is characterized by symptoms for less than 4 days per week or less than four consecutive weeks. *Persistent AR* is characterized by symptoms occurring more than 4 days per week for at least four consecutive weeks.[31] Additionally, it was demonstrated that the previous categories of seasonal and perennial AR cannot be used along with the new classification of intermittent/persistent AR, as they do not represent the same stratification of the disease state. As such, intermittent AR and persistent AR are not synonymous with seasonal and perennial classifications.[32–35]

The ARIA guidelines have likewise proposed another stratification of severity (mild and moderate-severe) with respect to these disabilities.[18] AR can result in problematic symptoms, including sleep disturbance; impairment of daily, leisure, or sport activities; impairment of school or work; or troublesome symptoms. AR is considered mild if none of these occur. If one or more of these symptoms exist, AR is classified as moderate–severe.

V.A.2 | Sensitization versus clinical allergy

Atopic diseases comprise of a range of linked conditions presenting as multiple heterogeneous clinical phenotypes ranging from single organ to multi-system disease.[36,37] Currently used taxonomy is largely organ-based and does not fully take into account the mechanisms leading to symptoms.[38] For example, the 2016 Melbourne epidemic thunderstorm asthma event saw a dramatic increase in asthma-related hospitalizations and 10 deaths over a 30-h period.[39] Interestingly, most patients hospitalized with severe asthma attack did not have a diagnosis of asthma. They did have a diagnosis of AR[40] and allergen-specific immunotherapy (AIT) appeared to offer protection.[41] It can be postulated that these patients suffered from a single IgE-driven condition with a clear pathophysiological mechanism, for which there are available biomarkers (e.g., sIgE) and mechanism-based treatment (e.g., AIT).[42]

Although patients with AR and allergic asthma are by definition sensitized, many individuals with allergic sensitization do not have symptoms of allergic disease,[43] and in a proportion of patients with AR and allergic asthma, sensitization is not related to the presence or severity of symptoms.[38] Furthermore, the reliability of skin testing depends greatly on allergen extracts and methods used.[44] Thus, clinicians face a problem that sensitization on standard allergy tests does not prove that symptoms are caused by allergy. Some subtypes of allergic sensitization are benign and not associated with clinical symptoms, while others are pathologic and lead to a spectrum of disease from single-organ disease to allergic multi-morbidity.[42] (See Sections XI.D.11.a.ii. Multi-allergen Immunotherapy and XI.D.11.b.ii. Polysensitization and for additional information on this topic.)

Better ways of differentiating clinically significant sensitization are needed. Quantification of sensitization through standard diagnostic tests (i.e., sIgE titer, size of skin test wheal) can increase the specificity, both in terms of diagnostic accuracy and the capacity to predict the persistence of symptoms.[45–48] However, the problem of false-positive test results remains.[48] Currently, nasal allergen challenges is the most accurate way to confirm clinical allergy. Recent studies show that this is highly sensitive and specific, with negative and positive predictive values greater than 90%.[49,50] It can also be helpful in the diagnosis of local nasal allergy, which may otherwise be missed on skin testing or in vitro testing methods. However, in most

healthcare systems, this procedure is restricted to centers with specialist expertise.

We can now assess sensitization in greater detail using component-resolved diagnostics (CRD), which measures sIgE to multiple allergenic molecules and may be more informative than standard tests.[51–55] Recent novel analyses of CRD data demonstrated that the pattern of interaction between allergen component-specific IgEs predicts asthma[56] and that networks of interactions between sIgE to multiple components are predictors of asthma severity across the lifespan.[57] These findings offer clues about mechanisms contributing to presence and severity of allergic airway disease and suggest that it may be possible to develop biomarkers/prediction tools based on CRD to help in diagnosis,[56] severity assessment,[57] prediction of future risk,[52] and ultimately, the prediction of response to treatment.[58]

V.B | Differential diagnosis

V.B.1 | Drug induced rhinitis

Rhinitis secondary to systemic medications can be classified into local inflammatory, neurogenic, and idiopathic types.[59–61] The local inflammatory type occurs when usage of a drug causes a direct change in inflammatory mediators within the nasal mucosa. The neurogenic type occurs after use of a drug that systemically modulates neural stimulation, leading to downstream changes in the nasal mucosa. The idiopathic classification is applied when a well-defined mechanism has not been elucidated. Rhinitis medicamentosa and hormone-induced rhinitis are discussed in later sections (Table V.B.1).

Local inflammatory type. Systemic ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) in specific patients can cause respiratory symptoms and may be associated with nasal polyposis and asthma due to abnormal arachidonic acid metabolism.[62] NSAIDs inhibit cyclooxygenase (COX)-1, leading to decreased prostaglandin (PG) E2 and increased leukotriene production due to an imbalance toward the lipoxygenase pathway. Reduction in PGE2, and increased leukotriene C4, D4, and E4 production contributes to eosinophilic and mast cell inflammation within the upper and lower respiratory tracts.[59,63–65]

Neurogenic type. Neurogenic-type non-allergic rhinitis is caused by drug-induced modulation of the autonomic nervous system. Antihypertensives and vasodilators are among the many classes of drugs that cause neurogenic drug-induced non-allergic rhinitis. Other nonspecific drugs, such as psychotropics and immunosuppressants, have unknown direct mechanisms and are categorized as idiopathic type, but can also cause neuromodulatory effects. Modulation of the autonomic nervous system leads to downstream changes in the nasal mucosa, blood vessels, and secretory glands.[66]

Alpha- and beta-adrenergic modulators. Alpha- and β-adrenergic receptor modulators are indicated for various cardiovascular and respiratory diseases. The nasal mucosa is replete with sympathetic and parasympathetic end-units that influence nasal physiology during systemic drug use. Alpha- and β-adrenergic antagonists, and presynaptic α-agonists cause decreased sympathetic tone and unopposed parasympathetic stimulation producing mucosal engorgement, nasal congestion, and rhinorrhea.[67–69]

Phosphodiesterase inhibitors. Phosphodiesterease (PDE) inhibitors prevent enzymatic breakdown of cyclic nucleotides. This inhibition has diverse effects including smooth muscle relaxation, vasodilation, and bronchodilation, making PDE inhibitors useful for numerous disease processes. PDE-3 and PDE-5 inhibitors are commonly used to treat intermittent claudication, heart failure, pulmonary hypertension, lower urinary tract symptoms, and erectile dysfunction.[70,71] PDE-3 and nonselective PDE inhibitors inhibit cyclic adenosine monophosate (cAMP) hydrolysis, which ultimately prevents platelet aggregation and encourages vasodilation with increased extremity blood flow. PDE-5-specific inhibitors encourage smooth muscle relaxation through inhibition of nitric oxide (NO)-generated cyclic guanosine monophosphate (cGMP), causing vasodilation of the corpus cavernosum and pulmonary vasculature as well as changes in the lower urinary tract. NO/cyclic nucleotide mediated vasodilation occurs in the nasal mucosa causing nasal mucosal engorgement and edema[72–76] (Table V.B.1).

Angiotensin converting enzyme inhibitors. Angiotensin converting enzyme inhibitors (ACEI) inhibit the conversion of angiotensin I to angiotensin II in the lungs and are commonly used for cardiac and renal diseases. ACEI upregulate the formation of bradykinin, an inflammatory peptide that causes vasodilation and smooth muscle contraction.[77] Bradykinin B1 and B2 receptors have been demonstrated in nasal mucosa,[78] and bradykinin application to nasal mucosa has resulted in increased sneezing.[74,79] In addition to cough, rhinorrhea and nasal obstruction have been associated with ACEI.[77]

Illicit drug use. The nose provides a unique portal for illicit drug use due to well vascularized and easily accessible nasal mucosa. Applying a crushed solid, liquid, or aerosolized form of a drug to the nasal cavity avoids invasive intravascular or intramuscular administration. For some drugs, nasal administration increases bioavailability and shortens time to onset when compared to oral ingestion.[80,81] In contrast to oral agents, intranasal administration bypasses portal filtration.

TABLE V.B.1 Drug-induced rhinitis medication list[59,61,73]

Local inflammatory type			NSAIDs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, naproxen, piroxicam, sulindac) Aspirin Ketolorac (if administered via nasolacrimal duct)
Neurogenic type	**α- and β-adrenergic receptor modulators**	α-antagonists	Alfuzosin (α-1) Doxazosin (α-1) Indoramin (α-1) Phentolamine (α-1, α-2) Prazosin (α-1) Silodosin (α-1) Tamulosin (α-1)
		Presynaptic α-2 agonists	Clonidine Guanfacine Methyldopa Piribedil
		β-antagonists	Atenolol (β-1) Bisoprolol (β-1) Carvedilol (β-1, β-2, α-1) Labetolol (β-1, β-2, α-1) Metoprolol (β-1) Pindolol (β-1, β-2) Propranolol (β-1, β-2)
		Presynaptic depletion of norepinephrine stores	Guanethidine
	Phosphodiesterase inhibitors	Phosphodiesterase-3 specific	Amrinone Anagrelide Cilostazol Dipyridamole Milrinone
		Phosphodiesterase-5 specific	Avanafil Sildenafil Tadalafil Vardenafil
		Non-selective phosphodiesterase	Pentoxifylline Theophylline
	Angiotensin converting enzyme inhibitor		Benazepril Captopril Enalapril Lisinopril Quinapril Ramipril
Idiopathic type		Psychotropics	Alprazolam Amitriptyline Chlorpromazine Mianserin Reserpine Risperidone Thioridazine
		Immunomodulators	Cyclosporine
		Hormones	Estrogen Oral contraceptives
		Antihypertensives	Amiloride Chlorothiazide Hydralazine Hydrochlorothiazide
		Other	Gabapentin Gingko biloba

Cocaine is most commonly associated with nasal illicit drug use and exerts its effect by modulating dopamine transporters to inhibit synaptic reuptake, increasing dopamine for post-synaptic stimulation.[82] After application to nasal mucosa, cocaine is quickly metabolized by native mucosal esterases into its bioactive metabolite, which then passively diffuses across the nasal mucosa and the olfactory bulb, leading to elevated systemic and brain concentrations resulting in a psychotropic euphoria.[83] Cocaine-induced rhinitis is a result of vasoconstrictive events, which can be followed by rebound nasal mucosal edema and mucus production, similar to rhinitis medicamentosa.[84–87] In the repeat user, vasoconstriction, direct trauma compounded by anesthetic effects, and/or injury secondary to contaminants may result in tissue necrosis.[88–91] Similarly, prescription narcotics, antidepressants, anticholinergics, and psychostimulants can be abused by intranasal administration.[78,92] Tissue necrosis has also been associated with intranasal opioid and acetaminophen abuse.[93–95] Possible mechanisms of injury include hyperosmotic conditions, vasculitic-like inflammation, or direct injury secondary to talc.[95,96]

Drug-induced rhinitis is a subtype of non-allergic rhinitis that can cause mucosal edema, vasodilation, and inflammatory mediator production. Vasoconstriction and mucosal injury often accompany illicit drug use. Drug-induced rhinitis differs from AR as it is not allergen-induced nor dependent on IgE mechanisms, although symptomatology may be similar.

V.B.2 | Rhinitis medicamentosa

Rhinitis medicamentosa is a drug-induced rhinitis resulting from prolonged topical intranasal decongestant (INDC) use.[31,97] Topical INDCs are readily available without a prescription and often lack appropriate warnings of prolonged use, potentially resulting in overuse and dependence. Although no consensus diagnostic criteria exist, rhinitis medicamentosa was originally associated with the triad of prolonged INDC use, persistent nasal obstruction, and rebound swelling of the nasal mucosa.[97] Patients present with nasal congestion, often lack rhinorrhea or sneezing, and may note reduced efficacy, or tachyphylaxis, with further use of INDCs.[87,98,99] Physical examination is variable, but often reveals nasal mucosal edema, erythema, and hyperemia (Table V.B.2).

Nasal anatomy and physiology. Vasculature within the nasal mucosa consists of resistance vessels (arterioles), whose sympathetic innervation is predominated by α-2 adrenergic receptors, and capacitance vessels (venous sinusoids), that are innervated by α-1 and α-2 receptors.

TABLE V.B.2 Intranasal decongestants associated with rhinitis medicamentosa[31,97]

Class	Active drug	Examples of OTC products in the United States containing this medication
Sympathomimetic amines	Phenylephrine	Neo-synephrine Vicks Sinex Ephrine nasal drops
	Pseudoephedrine	
	Ephedrine	
Imidazoline derivatives	Oxymetazoline	Afrin Sudafed nasal decongestant Mucinex Sinus-Max Zicam extreme congestion relief
	Xylometazoline	Otrivine and otrivin nasal spray
	Naphazoline	Privine nasal spray

Abbreviation: OTC, over-the-counter.

Stimulation of these receptors results in vasoconstriction with resultant decongestion due to decreased blood flow and increased sinusoid emptying.[97,100] The two classes of nasal decongestants are imidazolines and sympathomimetic amines. Imidazolines are α-2 receptor agonists, while sympathomimetic amines encourage presynaptic norepinephrine release. Norepinephrine stimulates α-adrenergic receptors and weakly stimulates β-adrenergic receptors. Both medication classes have a rapid onset, are potent, and are long-acting.[97,101]

The exact pathophysiologic mechanism causing rhinitis medicamentosa is unclear, although several hypotheses exist: (1) chronic vasoconstriction causes recurrent nasal tissue hypoxia and ischemia, which may cause interstitial edema; (2) changes in endothelial permeability may result in increased edema; and (3) continuous INDC use may decrease endogenous norepinephrine and downregulate α-receptors, through negative neural feedback, causing decreased adrenergic responsiveness.[86,87,97,100–102] Inflammatory cells, local inflammatory mediators, uninhibited parasympathetic stimulation, and increased mucin production also contribute to symptomatology.

Histologic changes within the mucosa after prolonged INDC use include ciliary damage and ciliary loss, epithelial cell injury, epithelial metaplasia and hyperplasia, dilated intercellular spaces, goblet cell hyperplasia, and edema.[103–105] Benzalkonium chloride, an antimicrobial preservative used in many nasal sprays, has been implicated in the mechanism of rhinitis medicamentosa. Stud-

ies have demonstrated that benzalkonium chloride is toxic to nasal epithelium and induces mucosal edema, propagating rhinitis medicamentosa, although the data are inconclusive.[106–110] Neither duration, nor cumulative dose of INDC needed to initiate rhinitis medicamentosa is known. Rebound congestion has developed after 3 to 10 days of medication use,[87,104] but may not occur until after 30 days.[111,112] Other studies have demonstrated a lack of rebound congestion after 8 weeks of continuous use.[111–114] Furthermore, doubling the dose of intranasal imidazoline did not increase the extent of rebound edema.[111] Although inconclusive, studies suggest that INDC use should be discontinued after 3 days to avoid rebound congestion.[98,115,116]

Treatment of rhinitis medicamentosa. Despite the lack of formal treatment guidelines for rhinitis medicamentosa, discontinuation of INDCs is paramount. Patients should be educated regarding common over-the-counter products containing decongestants as labeling may be inadequate. Various treatments have been trialed including nasal cromolyn, nasal saline spray, oral/intranasal antihistamines, turbinate steroid injections, and oral/intranasal corticosteroids.[98,100,117–122] Intranasal corticosteroids (INCS) are the most common treatment for rhinitis medicamentosa. Many initiate INCSs while weaning INDCs.[101,105,120–123] Often there is an underlying undiagnosed rhinitis and/or anatomic issue that initiated decongestant use, and this should be addressed to relieve the drive to use INDCs. For refractory cases, oral steroids and inferior turbinate (IT) reduction have been considered.[122]

Rhinitis medicamentosa is typically associated with repeated exposure to INDCs, with increasing symptoms when the medication is withheld. In contrast, AR is classically associated with an allergic trigger with similar symptoms increasing upon allergen exposure and is dependent upon IgE-mediated inflammation. It is possible that both may coexist, and a careful history should be obtained regarding these triggers to obtain an accurate diagnosis and provide appropriate treatment.

V.B.3 | Occupational rhinitis

Occupational rhinitis is an inflammatory disease of the nose, characterized by intermittent or persistent symptoms of nasal congestion, sneezing, rhinorrhea, itching, and/or variable nasal airflow obstruction due to causes and conditions attributable to a particular work environment.[124,125] While many social activities or hobbies can result in overlapping symptoms, stimuli that are encountered outside the workplace are not considered occupationally related.[126]

The pathophysiological mechanisms of occupational rhinitis are the same as other forms of chronic rhinitis although symptoms may be intimately tied to work exposure.[1,124,126] Occupational rhinitis may be classified as allergic, resulting from an immunological exposure to a sensitizing high molecular weight protein (HMW > 5 kDa) or non-allergic, mediated by non-immunological low molecular weight chemical irritant (LMW < 5 kDa).[127,128] Non-allergic occupational rhinitis is sometimes subdivided into annoyance (e.g., perfumes), irritant-induced (e.g., formaldehyde or smoke), or corrosive rhinitis (e.g., ammonia or acids), the latter of which may include permanent inflammation of the nasal mucosa, ulcerations, and perforation of the nasal septum.[1,124]

Cross sectional studies of various workers show a wide range of occupational rhinitis prevalence rates (3%–87%),[124,126,129] although rates are higher for HMW agents compared to lower for LMW agents.[126] Occupations and commonly implicated agents are reported in Table V.B.3.[130–135] Pre-existing AR or allergic asthma, baseline total IgE >150 kIU/L, or occupations with frequent exposure to animals have been shown to be risk factors for occupational rhinitis.[136,137]

Occupational rhinitis tends to be three times more prevalent than occupational asthma,[129] but the two disorders are often associated (up to 92% of cases).[126] In most cases, work-related nasal symptoms develop 5–6 months before the onset of bronchial symptoms.[124,138] Consequently, occupational rhinitis may be considered a marker of the likelihood of developing occupational asthma. Previous practice parameters and consensus documents suggest that workers in certain high-risk occupations be periodically monitored by survey and/or skin prick testing (SPT) so that risk mitigation strategies can reduce sensitization, and potentially limit progression of occupational rhinitis or the development of occupational asthma.[1,139,140]

The clinical presentation of occupational rhinitis does not differ from those of non-occupational chronic rhinitis. Diagnostic assessment must include a thorough clinical and occupational history, aimed to investigate the type of symptoms and work-related temporality, and to collect information on specific occupational exposures. Documentation of noxious compounds in the workplace should include examination of available Material Safety Data Sheets.[124] The presence of a latency period between beginning of occupational exposure and symptom onset (months or even years) suggests an immunologic mechanism. This contrasts to non-allergic irritant occupational rhinitis which may occur immediately upon first exposure.

Nasal endoscopy, assessing nasal patency, inflammation, and secretions minimize patient misclassification.[1,141,142] Sensitization to a suspected HMW agent by SPT may be preferred over serum sIgE assessment

TABLE V.B.3 High risk occupations and causal agents for occupational rhinitis[130–135]

Agents	Occupation
Allergic agents (high molecular weight)	
Cereal flours	Bakers, food industry
Laboratory animals (rat, mouse, monkey)	Laboratory workers
Latex	Health care workers
Animal-derived allergens (horse, cat, dog), plant allergens, molds	Farmers, veterinarians
Shellfish, bony fish	Seafood workers
Biological enzymes	Pharmaceutical and detergent industries
Non-allergic agents (low molecular weight)	
Persulfates	Hairdressers
Wood dust	Carpentry, furniture making
Drugs	Pharmaceutics, health care workers
Cigarette smoke	Various occupations
Formaldehyde	Construction, morticians, hairdressers, agriculture
Exhaust pollutants	Highway workers, mechanics
Benzene or toluene	Painters
Capsaicin	Hot pepper workers
Talc	Cosmetic industry
Ammonia, bleach or acids (corrosive)	Cleaners, chemical factory workers
Perfumes (annoyance)	Department stores or hairdressers

as skin testing has been reported to be more sensitive and specific in various reports.[143–146] However, the reliability of sIgE testing depends on the equipment, materials, and technique employed; therefore, a standardized approach and validated extracts are required, which are often not available especially for LMW agents.[44,126,146–148] A truly definitive diagnosis can only be established by objective demonstration of the causal relationship between rhinitis and the work environment through nasal provocation test (NPT) with the suspected agent(s). However, irritant triggers, LMW agents, and delayed type reactions are often not easily identified by NPT[49,124,146,149,150] (Figure V.B.3). Validated clinical assessment tools such as the Total Nasal Symptom Score (TNSS) or and/or sneeze counts administered pre-and-post exposure may aid in quantifying the severity of the response. At some institutions, rhinomanometry is also available to obtain additional quantitative data.

If NPT is negative, further evaluation of work-related changes in nasal parameters at the workplace is recommended, especially in the presence of a highly suggestive clinical history.[151] When possible, a formal site visit may allow the technician to directly observe the workplace environment, symptomatology, and Material Safety Data Sheets, and suggest specific workplace modifications. Due to the strict relationships between upper and lower airways, spirometry and exhaled NO assessment should be performed in patients with occupational rhinitis.[1,126]

The primary treatment of allergic occupational rhinitis is avoidance or reduction of culprit exposures.[126] Pharmacologic treatment does not differ from that of non-occupational rhinitis, although medications alone may be insufficient given the intensity and frequency of many workplace exposures.[152] In allergic occupational rhinitis due to HMW sensitizers, AIT may be considered when validated extracts are available.[153] However, AIT may have limitations in those individuals with continued high workplace exposure; therefore, simultaneous mitigation and avoidance strategies are essential.

Occupational rhinitis has both medical and socioeconomic implications,[154] and may be the cause of leaving work.[155] Since occupational rhinitis is acknowledged as a risk factor for the development of occupational asthma, the prevention and early identification of occupational rhinitis of exposed workers may provide an excellent opportunity to prevent the development of occupational asthma.[156] (See Section XI.A.6. Allergen Avoidance – Occupational for additional information on this topic.)

V.B.4 | Chemical rhinitis

As exposure to environmental chemicals and pollutants increases in daily life, patients may present with rhinitis symptoms that do not necessarily fall within a traditional allergic profile. Chemicals may cause sensory irritation which can include congestion, sneezing, rhinorrhea, nasal discomfort, post-nasal drainage, headache, olfactory function, and epistaxis. This is often associated with lower airway symptoms and conjunctival irritation.[126] The differential diagnosis of chemical rhinitis is broad, including occupational rhinitis, but not all chemical rhinitis is occupational. Typically, the differential should include causes of both AR and non-allergic rhinitis, as well as mixed rhinitis, recurrent acute rhinosinusitis (RARS), and chronic rhinosinusitis (CRS).

Exposures at home and work are important elements to obtain in the history. There are many chemicals with which specific occupations are closely associated, and household chemicals may play a role as well. Volatile

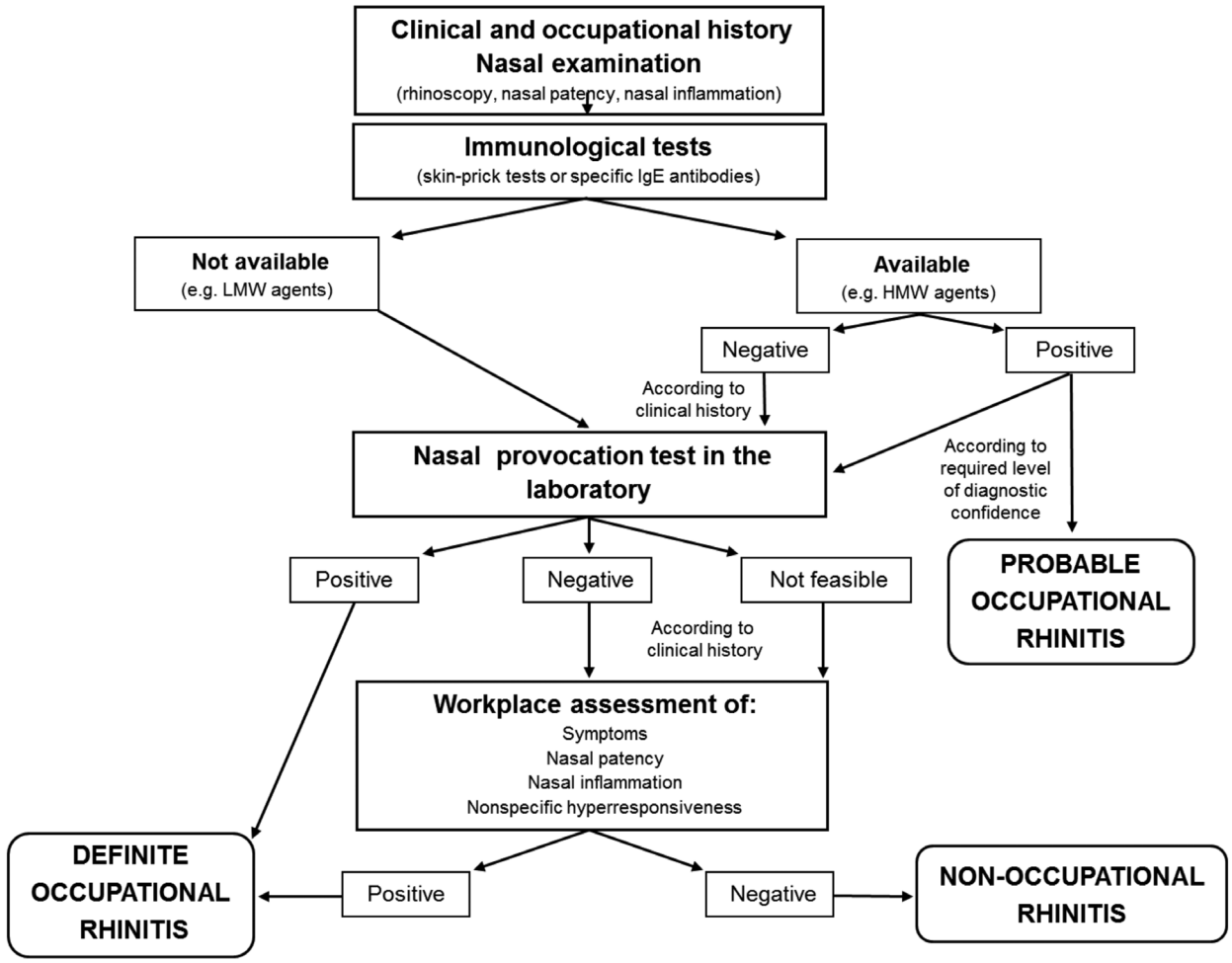

FIGURE V.B.3 Diagnostic algorithm for occupational rhinitis

organic compounds such as benzene, toluene, and the secondary production of formaldehyde can be found in cleaning products, furniture, plastics, flooring and can cause barrier dysfunction and inflammation in both the upper and lower airway.[134,157,158] Larger chemical particles greater than 10 μm in diameter are generally deposited in the upper airway and agents such as ammonia, formaldehyde, nitrogen dioxide, or sulfur dioxide among others may readily disrupt the epithelial barrier.[124]

In general, inquiring about exposure to vapors, fumes, smoke, and dust can be helpful to determine if a patient has an element of chemical rhinitis. These responses are typically non-IgE-mediated by a reflex response which is often termed neurogenic inflammation.[159] A subset of these individuals involved in single exposure incidents may develop persistent and chronic symptoms. This phenomenon has been described as reactive upper airways dysfunction syndrome when only rhinitis symptoms are present, and reactive airways dysfunction syndrome when asthma-like symptoms are present.[160,161]

Chemicals known to cause respiratory inflammation and in some cases, allergic sensitization include diisocyanates, acid anhydrides, some platinum salts, reactive dyes, and many cleaning products that are used in hospitals and in the pandemic era including glutaraldehyde, quaternary ammonium compounds, and chloramine.[134,162–164] There is still debate concerning the exact mechanism behind sensitization to these chemicals. However, smaller chemical compounds must associate with larger protein molecules in order to induce an immune response. As a result, evaluation of sensitization through skin testing and/or evaluation of sIgE can be helpful and in the future, immunoassays based on cellular responses may serve as better biomarkers of exposure to chemicals.[165,166]

V.B.5 | Smoke induced rhinitis

Tobacco smoke exposure is associated with chronic rhinitis and CRS.[167–169] Other smoke exposure sources besides conventional cigarettes, cigars, and pipes include electronic cigarettes, vaping, and cannabis. Although there is limited research on these other methods of smoke

exposure, initial studies support that there may be an increased risk of rhinitis with some of these products and these exposures should be considered in the differential diagnosis.[170,171] Symptoms common to both AR and smoke-induced rhinitis include rhinorrhea and congestion, but smoke-induced rhinitis is not driven by IgE-mediated hypersensitivity which tends to also exhibit sneezing on exposure to a specific allergen.[172–175]

Symptoms of rhinitis are provoked by exposure to the chemicals in smoke and can correlate with serum cotinine levels in patients using tobacco.[174] Furthermore, smoking in combination with occupational irritants are additive risk factors for nasal symptoms and may be independent of allergic sensitization.[175] Although smoke-induced rhinitis does not require allergen sensitization, there has been at least one report of potential allergenic compounds in smoke.[176] Interestingly, active smokers show elevated total serum IgE, although they exhibit a lower skin test reactivity to specific allergens compared to non-smokers despite well documented increased rates of lower respiratory disorders such as asthma, cough, sputum production, and wheezing.[177] This may be due in part to the fact that tobacco smoke exposure results in decreased mucociliary clearance.[178]

One of the mechanisms to explain nasal irritation resulting from smoke exposure may be related to capsaicin-sensitive neurons in the nasal mucosa.[179] This neurogenic type of nasal inflammation is mediated by neuropeptides such as substance P, neurokinin A, and calcitonin gene-related peptide (CGRP). These mediators are released by sensory nerve fibers in the nose and result in vasodilation, edema, and inflammation.[180]

Patients who are reactive to tobacco exposure are identified by both subjective (congestion, rhinorrhea, sneezing) and an objective response (increased nasal resistance) to controlled challenge with tobacco smoke. In a prospective study, patients were defined as demonstrating reactivity if nasal resistance increased by more than 35% by acoustic rhinometry in response to tobacco smoke; patients with less than 5% increase in nasal resistance were defined as nonreactive.[178] Congestive responses have been demonstrated on challenge with both brief and prolonged exposure to tobacco smoke. In individuals who report a history of smoke induced rhinitis, only *brief* smoke exposure (45 parts per million [ppm] for 15 min) leads to increased nasal resistance as measured by posterior rhinometry (although there were no significant increases in histamine levels noted).[181] However, *prolonged* exposure to moderate levels of smoke (15 ppm for 2 h) induced a congestive response lasting for an hour or longer in both individuals with and without a history of smoke-induced rhinitis.[178] While objective response may be short lived, patients reported symptoms lasting hours to days following exposure. Since significant symptom overlap exists, a thorough history and allergy testing can help further differentiate smoke-induced rhinitis from other types of rhinitis.

V.B.6 | Infectious rhinitis

Infectious rhinitis is a very common diagnosis in general practice. Differences in onset and pathogenic cause lead to various pathophysiologies and forms. Common conditions in general practice are acute viral and bacterial rhinitis. Nasal symptoms include clear or discolored nasal discharge, nasal obstruction, postnasal drip, cough, and facial pressure depending on the etiology. These symptoms may also be present in non-infectious rhinitis; most commonly AR. This diagnostic distinction is important to avoid inappropriate treatment and diagnostic procedures. Distinctive clinical characteristics suggestive of AR are sneezing, nasal or ocular itching, the presence of an obvious allergic trigger, and the presence of recurrent seasonal-related symptoms – these symptoms are less frequent in infectious rhinitis.[31,182]

Rhinitis symptoms are the result of nasal mucosa and/or sinus inflammation. The mucosa of the nose and sinuses are contiguous. Thus, the clinical presentations of rhinitis and rhinosinusitis are overlapping, and it is difficult to differentiate between them. Infectious rhinitis or rhinosinusitis are classified by duration and pathogenic cause into subtypes including acute viral (common cold), post-viral, and bacterial.[183] (See Sections V.B.15. Differential Diagnosis - Rhinosinusitis and XIII.B. Associated Conditions - Rhinosinusitis for additional information on this topic.)

Acute viral rhinitis, or the common cold, is responsible for most acute infectious rhinitis, especially in children.[31] The incidence of acute viral rhinosinusitis is expected to be as high as 98%.[184,185] Common organisms are rhinovirus, adenovirus, influenza virus, and parainfluenza virus.[120] Viral rhinitis is a self-limited illness and only requires supportive treatment. Most symptoms resolve by day five; nasal discharge and cough may last longer.[186] Prolonged symptoms of more than 2 weeks duration suggest a non-infectious etiology or post-viral rhinosinusitis.

The relationship between viral infection and AR has been studied. The upregulation of intercellular adhesion molecule (ICAM)-1, which is the major human receptor of rhinovirus, was shown in patients with underlying allergic disease.[187–189] The increased expression of ICAM-1 was demonstrated in both upper and lower allergic airway diseases compared with healthy controls.[190–192] This enhances the susceptibility of airway epithelial cells to viral infection.

In some cases, viral rhinitis episodes are secondarily infected by bacterial organisms such as *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catharralis*.[184,185] This occurs in 0.5%–2.0% of all viral infections.[183,184] Clinical presentation distinguishing viral from bacterial rhinitis/rhinosinusitis is often impossible.[193–196] Inappropriate prescribing of antibiotics and diagnostic tools is often secondary to misdiagnosis of the symptoms and signs of viral and bacterial origin with up to 60% starting a course of antibiotics at first symptom presentation.[197–199]

The possibility of bacterial infection increases if there is deterioration in symptoms after day 5.[186] Predicting criteria for bacterial infection have been suggested using clinical characteristics, the pattern of symptoms, and laboratory reports.[183,200,201] However, the maximum sensitivity and specificity only reach 69% and 81%, respectively, among various criteria.[199,202] Additionally, a collection of factors contribute to developing an infection of bacterial origin. These factors include dental infection or procedure, previous sinus surgery/nasogastric tube insertion/nasal packing, underlying immunodeficiency, structural nasal problems, and evidence of underlying nasal mucosa edema such as AR.[186]

V.B.7 | Rhinitis of pregnancy and hormonally induced rhinitis

Rhinitis of pregnancy. Pregnancy-induced rhinitis describes nasal symptoms that occur during pregnancy, are independent of other etiologies for rhinitis, and remit after delivery.[203–205] Symptoms include rhinorrhea, sneezing, hyposmia, and nasal itching.[206] In a multicenter study of 599 previously asymptomatic women, prevalence of rhinitis of pregnancy was 22%.[207] A history of AR and smoking increase risk for its development.[203–205]

Quantifying the impact of pregnancy-induced rhinitis has been done objectively and subjectively. Acoustic rhinometry, rhinomanometry, peak nasal airflow measurements, and saccharin testing confirm that changes to nasal airway patency occur.[205,206,208] Electron microscopy demonstrates glandular hyperactivity, increased phagocytotic activity, and increased amounts of acid mucopolysaccharides in the ground substance.[209] Studies using validated patient reported outcome measures (PROMs) (e.g., Nasal Obstruction Symptom Evaluation [NOSE] scale, Rhinitis Quality of Life Questionnaire [RQLQ])[208,210] confirm the subjective component of pregnancy-induced rhinitis.[205,206,208]

The precise pathophysiology of pregnancy-induced rhinitis remains unknown.[206,211,212] Estrogen, progesterone, and placental growth hormonal have all been implicated.[203–205,208] Increased expression of histamine receptors secondary to β-estradiol and progesterone in nasal epithelial and endothelial cells has been demonstrated and is proposed as a potential mechanism of nasal hyperreactivity in pregnancy-induced rhinitis.[213] Additionally, serum levels of placental growth hormone were significantly higher in patients with pregnancy-induced rhinitis throughout their pregnancy.[214]

Pregnancy-induced rhinitis has been implicated in potential risks for the mother and fetus.[203,204,212] Mouth breathing from pregnancy-induced rhinitis bypasses the benefits of nasal breathing, including preparation of inspired air for the lungs and NO release from the maxillary sinuses, which reduces pulmonary vascular resistance and contributes to increased pulmonary oxygenation.[204,212] Additionally, maternal sleep disruption, when severe, can be associated with snoring and obstructive sleep apnea (OSA) and may contribute to increased risk for pre-eclampsia and maternal hypertension.[215] Intrauterine growth retardation and decreased Apgar scores are also possible.[203,215]

Treatment is conservative and relies on education. Reassurance regarding the temporary nature of pregnancy-induced rhinitis is beneficial. Regular use of nasal saline lavage is safe and provides symptomatic relief.[182,211,212] Counseling against the routine use of oral and topical decongestants is critical due to the risk for congenital gastroschisis, pyloric stenosis, endocardial cushion defects, renal anomalies, and limb defects. These risks are greater in the first trimester, but caution should be maintained throughout the pregnancy.[182,211,212] INCS are generally considered safe for use during pregnancy; however, triamcinolone is associated with congenital respiratory defects.[182] A treatment option under investigation is topical hyaluronate, which facilitates mucociliary clearance and hydration. In a 2019 pilot study of pregnancy-induced rhinitis, sodium hyaluronate use decreased snoring, mucosa congestion, and nasal secretions and had no adverse events.[216] More studies are needed before recommending its routine use during pregnancy.

Hormonally-induced rhinitis. Cytological changes and cell turnover of the nasal epithelium during the phases of the menstrual cycle have been demonstrated. In general, estrogens are thought to cause nasal vascular engorgement, resulting in obstruction and rhinorrhea. As with pregnancy-induced rhinitis, the mechanism of these changes remains unclear.[182,217–219] The expression of histamine H_1-receptors within the nasal epithelium and microvascular endothelial cells are increased in response to β-estradiol and progesterone. These hormones may also induce eosinophil migration and/or degranulation.[217]

Rhinitis can also occur in patients with endocrine pathologies. Hypothyroidism can cause hypertrophy of

mucous glands, increased submucosal connective tissue, and resultant nasal obstruction and rhinorrhea.[217,218,220] These patients may also have prolonged mucociliary clearance time.[221] Rhinitis with sinonasal mucosal hypertrophy and polyp formation can also be seen in acromegaly, though it is unclear if elevated serum levels of growth hormone are the cause.[222]

V.B.8 | Food and alcohol induced rhinitis

Food-induced rhinitis. Gustatory rhinitis is characterized by watery, unilateral, and/or bilateral rhinorrhea within a few minutes after the ingestion of food, usually hot and spicy foods such as tabasco sauce, hot chili peppers, horseradish, red cayenne or black pepper, and other foods that contain capsaicin. The rhinorrhea lasts as long as the food is ingested.[182,223–226] Gustatory rhinitis can be confused with IgE-mediated food allergy, but there is no sneezing, pruritus, or facial pain and the time course of the rhinorrhea is self-limited.[223] There is also no associated disturbance of smell or taste.[227] Gustatory rhinitis occurs more often in patients with AR and patients who have a history of smoking, but not those with asthma or food allergies.[225]

The pathophysiology has been confirmed through pharmacologic observations and immunohistology studies to occur through a neural reflex arc initiated upon the stimulation of afferent sensory nerves. This leads to the stimulation of the parasympathetic efferent nerve supply to the submucosal glands in the nasal mucosa.[224,226] It is additionally possible that interactions between the sympathetic and parasympathetic nervous system could lead to uninhibited activity of the parasympathetic system with resultant rhinorrhea.[226] For example, the chemical capsaicin is known to cause gustatory rhinitis. The capsaicin receptor is a transient receptor potential vanilloid subtype 1 (TRPV1) receptor and exists in neuronal as well as non-neuronal cells along the nasal mucosa and oral epithelium.[228] A direct effect on goblet cell secretion may be triggered when capsaicin is ingested.[227] A well-known culprit of gustatory rhinitis is chili peppers, which contain capsaicin.[227] A variety of other foods are associated with gustatory rhinitis including horseradish, wasabi, black pepper, hot mustard, and vinegar.[225,226]

Treatment of gustatory rhinitis is avoidance of the inciting food. Topical anticholinergic medications such as ipratropium bromide (IPB) are used when avoidance is impractical.[224,226,227] The use of topical capsaicin and resection of the posterior nasal nerve (PNN) have been proposed as a last resort for intractable gustatory rhinitis.[227,229]

Alcohol-induced rhinitis. Exacerbation of respiratory symptoms after ingestion of alcohol occurs in approximately 3%–4% of the general population. Among the nasal symptoms that occur, blockage is the most common and may be accompanied by rhinorrhea, sneezing and lower airway symptoms. This is reportedly more common in patients with AR, asthma, chronic obstructive pulmonary disease (COPD), and emphysema.[230] Up to 75% of aspirin-exacerbated respiratory disease (AERD) patients suffer exacerbations of respiratory symptoms when they consume alcohol.[231–233] Symptom exacerbations occur relatively soon after alcohol ingestion, are often associated with the ingestion of small volumes, and seem to correlate with peak blood alcohol levels.[233] Such symptoms can arise regardless of the type of alcohol ingested.[230,232] These reactions to alcohol consumption are more prevalent in chronic rhinosinusitis with nasal polyp (CRSwNP) patients who suffer with severe and recurrent disease and are related to the severity of upper airway inflammation.[233]

In AERD patients, the severity of aspirin-induced respiratory symptoms is positively correlated with the severity of alcohol-induced reactions.[233] Exacerbations of respiratory symptoms in response to alcohol have been shown to be decreased after aspirin-desensitization in patients with AERD.[231] Patients with AERD have elevated baseline cysteinyl leukotriene levels, which are proposed to mediate the upper and lower airway reactions to aspirin.[231,232] Cardet et al.[232] propose that cysteinyl leukotrienes mediate the response to alcohol in these patients as well, though the pathway for such a mechanism is unknown.

High alcohol consumption is observationally and genetically associated with high serum IgE levels, though not with allergic disease. Two possible mechanisms have been proposed as the etiology for this observation: (1) alcohol changes the balance of the Th1 and Th2 responses toward a Th2 immune response with a direct effect on B cells, or (2) alcohol induces increased uptake of endotoxins from the gut resulting in elevated IgE levels.[234]

V.B.9 | Eosinophilic rhinitis and non-allergic rhinitis with eosinophilia syndrome (NARES)

Non-allergic rhinitis with eosinophilia syndrome (NARES) is a clinical disorder comprising symptoms consistent with perennial AR in which there is an absence of atopy but presence of local eosinophilia found on nasal cytology.[235] The pathophysiology of NARES is not well understood, but a key component involves chronic local eosinophilic, self-perpetuating inflammation, with non-specific histamine release. It is one of the most common type of inflammatory non-allergic rhinitis that was first described by Jacobs and colleagues in 1981.[236]

NARES patients report symptoms that are similar to those of perennial AR: nasal congestion, profuse

aqueous rhinorrhea, sneezing, and nasal and ocular pruritis. A prominent feature of NARES is olfactory dysfunction. NARES patients demonstrate significantly higher thresholds on olfactory testing than seasonal and perennial AR patients.[237] NARES is diagnosed by obtaining a careful history, findings on physical exam, not unlike those found in perennial AR patients (pale, boggy turbinates), and negative skin or in vitro allergy testing. Cytologic examination in NARES reveals the presence of prominent eosinophilia, usually 10%–20% on nasal smear, with a diagnostic criterion of 25% or more eosinophils.[235,238] In addition, nasal biopsies from these patients commonly show increased numbers of mast cells with prominent degranulation.[239,240]

Research has supported the role of chronic inflammation in the development of NARES. Though there is still a lack of understanding as to the exact pathophysiology, studies have shown an increased transendothelial migration of eosinophils in nasal lavage fluid, which are attracted and activated by chemokines and cytokines.[241,242] Specifically, NARES is characterized by elevated nasal fluid levels of tryptase (which is also seen in perennial AR) and eosinophilic cationic protein.[243] Elevated levels of interleukin (IL)-1β, IL-17, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and RANTES (regulated upon activation, normal T cell expressed and presumably secreted) in nasal fluid were found in NARES compared to controls.[244,245]

A correlation between the concentration of RANTES with nasal symptoms and eosinophil counts in perennial AR patients has been shown.[246] However, levels of MCP-1 and RANTES were significantly higher in the nasal fluid of NARES compared to perennial AR subjects. Elevation of these cytokines correlated with the ratio of nasal symptom scores/percentage of eosinophils in NARES patients, where nasal symptoms of nasal obstruction, rhinorrhea, hyposmia, sneezing, and itching were each measured using a 3-point scale.[246] Several studies from European cohorts have found a lack of nasal mucosal IgE in NARES patients.[247,248] More recent studies of Chinese cohorts of NARES patients have found increased expression of Charcot-Leyden crystals which correlated with severity of symptoms and degree of eosinophilia.[249] Elevated cysteine protease inhibitor cystatin SN was also observed with greater loss of sense of smell.[250] Neuropeptide mediated eosinophil chemotaxis, including substance P, CGRP, and cholecystokinin octapeptide, has also been described as a contributing factor to the symptomatology in NARES patients.[251]

NARES may occur in isolation, but it can be associated with (and may be a precursor for) AERD.[235] NARES has also been identified as a risk factor for the induction or exacerbation of OSA[252] and has been associated with increased tendency for lower airway hyperresponsiveness.[253]

The treatment of non-allergic rhinitis centers on its underlying cause. NARES is primarily treated with INCS, which decrease neutrophil and eosinophil chemotaxis, reduce mast cell and basophil mediator release, and result in decreased mucosal edema and local inflammation.[254,255] A combined analysis of three double-blind, randomized, prospective, placebo-controlled studies of 983 patients (309 of whom were classified as NARES) demonstrated a positive treatment effect using INCS with improvement in symptoms of nasal obstruction, postnasal drip, and rhinorrhea.[256] Additionally, the intranasal antihistamine azelastine and leukotriene receptor antagonists (LTRA) have been shown to reduce symptoms of rhinitis, including postnasal drainage, sneezing, rhinorrhea, and congestion.[152,257–259]

V.B.10 | Non-allergic rhinopathy

Non-allergic rhinopathy/rhinitis is a chronic rhinitis made by a diagnosis of exclusion of other etiological factors. These include CRSwNP, NARES, AERD, infectious rhinitis, anatomical abnormalities, rhinitis medicamentosa, drug side effects, cerebrospinal fluid (CSF) rhinorrhea, and rhinitis of pregnancy. Clinical characteristics of non-allergic rhinopathy/rhinitis include primary symptoms of nasal congestion and rhinorrhea, postnasal drip in the absence of acid reflux, throat clearing, cough, Eustachian tube dysfunction (ETD), sneezing, hyposmia, and facial pressure/headache.[67] These symptoms may be perennial, persistent, or seasonal, and are typically elicited by defined triggers, such as cold air, climate changes (e.g., temperature, humidity, barometric pressure), strong smells, tobacco smoke, changes in sexual hormone levels, environmental pollutants, physical exercise, and alcohol. Notably, the lack of a defined trigger does not preclude the diagnosis of non-allergic rhinopathy.

The prevalence of non-allergic rhinopathy, the second most common form of rhinitis, is between 7% and 9.6% in the adult population in the United States (US) and Europe.[34,60] Vasomotor rhinitis is the most common cause of non-allergic rhinitis, and is found in 71% of cases.[260–262] Non-allergic rhinopathy occurs with a female-to-male ratio of 2:1 to 3:1[67] and is typically seen after the age of 20.[263] It is defined by the absence of an IgE-mediated immune response.[152] The term "non-allergic rhinopathy" has been suggested to replace vasomotor rhinitis, as allergic inflammation is absent in the pathogenesis, although vasomotor

causes may not account for the entirety of non-allergic rhinopathy/rhinitis cases.

The nasal mucosa of patients with non-allergic rhinopathy displays erythema and clear rhinorrhea. Allergy testing can be used to differentiate between non-allergic rhinopathy and AR. Vasomotor rhinitis, the most common subtype of non-allergic rhinopathy, has been linked to autonomic dysfunction and has been attributed to an imbalance between the parasympathetic and sympathetic systems.[264]

Local allergic rhinitis (LAR) is a distinct rhinitis that presents with features in between AR and non-allergic rhinopathy.[265] Patients with LAR demonstrate entopy or local IgE production in the nasal mucosa but lack skin test positivity. Individuals with LAR suffer from typical allergic symptoms upon allergen exposure but display a lack of systemic IgE sensitization. Local provocation is necessary to definitively exclude this diagnosis.[265,266] The prevalence of LAR among non-allergic rhinopathy has been reported to be 26.5%.[267] (See Section VI.A.3. Local IgE Production for additional information on this topic.) Additional forms of non-allergic rhinopathy include food-induced rhinorrhea and age-related rhinitis. (See Section V.B.8. Food and Alcohol Induced Rhinitis and Section V.B.11. Age-related Rhinitis for additional information on this topic.)

Neurosensory abnormalities are thought to play an important role the development of non-allergic rhinopathy.[67] In previous evaluation of central responses to olfactory stimuli, subjects with non-allergic rhinopathy underwent functional magnetic resonance imaging following exposure to different odors (vanilla and hickory smoke). Findings included increased blood flow to the olfactory cortex, leading to the hypothesis of an altered neurologic response.[268,269]

Medical management of non-allergic rhinopathy includes topical nasal sprays that have variable responses which have been used alone or in combination: INCS,[256,270] topical azelastine,[271] and IPB.[272] In addition adjunctive treatments include nasal saline sprays or lavage, especially with tenacious post nasal drip.[264]

For severely symptomatic patients refractory to medical therapy, surgical approaches targeting the vidian nerve and its branches have been shown to result in symptom control.[229,273] These include botulinum toxin injections which result in temporary symptom improvement, endoscopic vidian neurectomy, endoscopic posterior nasal neurectomy, and cryoablation of the posterior nasal nerve. Posterior nasal neurectomy is purported to result in lower rates of dry eye complications than vidian neurectomy.[274] Recent studies show that office based cryotherapy can achieve improvement in rhinorrhea and congestion for up to 1 year.[275,276]

V.B.11 | Age-related rhinitis

As the percentage of the adult population aged 65 years and older continues to increase, so does the prevalence of diseases associated with aging. Specific to rhinologic disease, the physiological process of aging results in neural, hormonal, mucosal, and histologic alterations that cause morphological and functional changes in the nasal cavity.[277,278] This, in turn, can result in symptoms of rhinorrhea, nasal congestion, postnasal drip, dry nose, intranasal crusting, and decreased olfaction in the elderly population.[279,280]

Rhinorrhea. A questionnaire distributed to a cohort of adults in Pittsburgh demonstrated that 33% of the younger age group respondents (n = 76, mean age 19 years) regularly reported clear anterior nasal drainage as compared to 74% of the older age group respondents (n = 82, mean age 86 years).[281] It is known that autonomic function declines with age as $\alpha-$ and $\beta-$receptors become less sensitive. Therefore, an imbalance of this system with decreased sympathetic tone and unopposed parasympathetic stimulation could result in a rise in glandular activity in the nasal cavity, leading to increased nasal drainage.[281–284] This mechanism is similar to the process classically termed "vasomotor rhinitis," where the autonomic response to certain stimulants causes the nasal mucosal blood vessels to dilate and the mucus glands to become overactive, resulting in hypersecretion and excessive drainage.[285] Vasomotor rhinitis is the most common type of non-allergic rhinopathy/rhinitis, and the highest prevalence of non-allergic rhinopathy is seen in the elderly,[260,280,286,287] supporting an autonomic nervous system mechanism as the physiologic reason for increased rhinorrhea in this population.

Nasal obstruction and congestion. Other changes that occur in the aging nose include thicker mucus secondary to a decrease in body water content,[288–290] loss of nasal cartilage elasticity and tip support,[278,280,290] mucus stasis secondary to a less effective mucociliary clearance system,[280,289,291] and age-related central nervous system changes that affect the physiologic nasal cycle,[288,292] all of which can result in nasal obstruction/congestion.

Nasal dryness and intranasal crusting. Nasal dryness and intranasal crusting in the elderly often occurs due to decreases in mucosal blood flow and an increase in epithelial degeneration.[293] This, in turn, results in intranasal volume increase due to nasal mucosal atrophy.[279] Schrodter et al.[294] evaluated nasal mucosa samples from the middle turbinate (MT) of 40 healthy subjects 5–75 years old, and found an age-related increase in atrophic epithelium (only seen in patients over 40 years) with thickened basement membranes. Nasal crusting may also occur due to

a decrease in intranasal temperature and humidity in the aging nose.[280]

Allergic rhinitis. The worldwide growth of both the aging population and allergic disease has caused an increase in the prevalence of AR in the elderly,[278] with the prevalence estimated to be around 5%–10%.[290,295] However, epidemiologic data is overall lacking and AR in the elderly population is likely under-diagnosed and under-treated. Although there is symptomatic overlap between age-related rhinitis and AR in the elderly, AR is a type I hypersensitivity IgE-mediated reaction,[296,297] whereas age-related rhinitis is more similar to vasomotor or non-allergic rhinopathy/rhinitis in that allergens do not play a role in the aforementioned physiologic changes of the aging nose. AR in the elderly should be treated similarly to AR in the younger population, with INCS, oral and topical antihistamines,[290,298] and AIT.[299] For age-related/non-allergic rhinitis rhinorrhea, saline lavage and topical anticholinergics may be therapeutic.[277] However, both conditions can be concomitantly present in the elderly population, presenting as a "mixed rhinitis," and should be considered in elderly patients who are refractory to typical medical management for a singular disease.

V.B.12 | Atrophic rhinitis

Atrophic rhinitis is a chronic disease of the nose presenting with symptoms of nasal dryness and crusting, persistent fetid odor, recurrent epistaxis, and nasal obstruction.[300,301] It is characterized by progressive atrophy of the nasal mucosa and bone, leading to anatomically wider nasal airways, albeit many patients paradoxically complain about the symptom of nasal obstruction. Upon removing crusts, the nasal cavity appears enlarged, with significant atrophy of the nasal turbinates. Atrophic rhinitis can be classified into primary or if occurring as a sequela of a causative factor, secondary.[302] Both primary and secondary atrophic rhinitis are significantly different in their clinical presentation and underlying pathophysiology compared to AR.[182]

The prevalence of primary atrophic rhinitis varies across regions worldwide, with a higher prevalence in tropical countries such as India or Thailand compared to Europe or the US.[303–307] It is also more commonly found in young to middle-aged adults, with a predominance of females.[303] Primary atrophic rhinitis has also been linked to environmental and socioeconomic factors. For example, it has been more commonly found in industrial workers, those with lower socioeconomic status (SES), and those in rural areas.[303] While there are no universally accepted guidelines for diagnosing primary atrophic rhinitis, it usually consists of a structured medical history and physical examination, including nasal endoscopy.[306,308]

The differentiation with secondary atrophic rhinitis includes the exclusion of potential causative etiologies related to secondary atrophic rhinitis, such as excessive nasal surgery, chronic granulomatous infections (e.g., tuberculosis, syphilis, leprosy), autoimmune/inflammatory disorders (e.g., granulomatosis with polyangiitis [GPA] or sarcoidosis), and excessive drug use (nasal sprays and cocaine).[309] Studies in the US on atrophic rhinitis patients revealed that secondary atrophic rhinitis accounted for more than 80% of atrophic rhinitis cases and was most commonly found in middle-aged adults.[304] Compared to the diagnosis of primary atrophic rhinitis, which mainly consists of excluding potential causative etiologies related to secondary atrophic rhinitis, a complete medical history to evaluate for causative factors represents the most correctly step for correctly diagnosing secondary atrophic rhinitis.[300]

To work up atrophic rhinitis, accurate and comprehensive medical history is important. Nasal endoscopy, cultures, and histopathology can also help clarify the diagnosis. Ly et al.[310] identified seven key symptoms that can be used to establish the diagnosis of atrophic rhinitis: purulence, nasal obstruction, history of nasal/sinus surgeries (at least two), crusting, recurrent epistaxis, smell loss, and chronic inflammatory disease of the upper airway. While more symptoms are associated with a higher sensitivity to diagnose atrophic rhinitis, the authors proposed that the presence of at least two symptoms (excluding nasal obstruction) enhances the sensitivity and specificity to 95% and 77%, respectively, to support the diagnosis of atrophic rhinitis.[310] Endoscopic findings usually include nasal crusting and enlarged lateral sidewalls.[304]

The underlying etiology and pathophysiology of primary atrophic rhinitis are still unknown, although persistent bacterial infection is commonly believed to be the causative agent. Microbiological cultures from the middle meatus can aid in the diagnosis.[311] The most common bacteria found in affected individuals is *Klebsiella ozaenae*,[303,304,312,313] albeit many other bacteria such as *Staphylococcus aureus* or *Pseudomonas aeruginosa* have also been isolated from nasal cultures.[303,306] Histopathological changes in both primary and secondary atrophic rhinitis may include partial or total squamous metaplasia, granulation tissue, atrophy, reduction of the seromucous glands, and vascular changes (e.g., reduced vascularity, dilated blood vessels, and in some cases endarteritis).[309] Interestingly, there have also been case reports which suggest primary atrophic rhinitis may have a genetic inheritance pattern.[314]

V.B.13 | Empty nose syndrome

Empty nose syndrome (ENS) is a rare and complex acquired upper airway disease. "ENS" was coined nearly three decades ago to describe the "empty" or "wide open" nasal cavity examination and imaging in patients following turbinoplasty with excess loss of turbinate tissue or contour.[304,315–319] Clinically, it is characterized by a spectrum of debilitating symptoms like nasal burning, dryness, and crusting, accompanied by symptoms quite unique to ENS like severe suffocation, paradoxical sensation of nasal obstruction, or excessive nasal airflow (i.e., "nose feels too open").[304,320,321]

ENS is linked to several IT reduction approaches, such as total turbinectomy, IT trimming, and radiofrequency ablation.[321,322] Presentation can be immediate or delayed, secondary to over-aggressive IT reduction or suboptimal post-surgical healing and scarring, respectively.[316,323,324] While ENS is mostly associated with inferior turbinoplasty (ENS-IT), ENS from MT tissue loss (ENS-MT) has been reported.[317]

The physiologic basis for perceiving reduced and/or unpleasant nasal breathing may be related to altered signaling through trigeminal sensory receptors, specifically TRPM8. Resultant aberrant thermosensation and neurosensory deprivation manifest as muted airflow sensation.[325–330] Damage to, and/or delayed recovery of, the trigeminal sensory nerve has also been implicated in the development of ENS in a minority of patients.[331] Additionally, objective shifts in nasal airflow support a novel "aberrant airflow" hypothesis.[332–334] Computational fluid dynamics modeling of nasal airflow demonstrates abnormally high velocity airflow to the middle meatus and dampened airflow vectors to the inferior meatus in ENS.

There has been welcome progress in the diagnosis and treatment of ENS in the past decade. In addition to a history of nasal surgery and abnormally expansive unilateral/bilateral nasal airway with concomitant IT tissue loss, thickened central nasal septum mucosa has been shown to be present in longstanding ENS.[323] The validated patient reported outcome measure Empty Nose Syndrome 6-item Questionnaire (ENS6Q) can be used to quantify the severity of six cardinal ENS symptoms on a 5-point Likert scale. A score ≥11 indicates ENS.[320] Placement of a cotton plug in the inferior meatus to simulate turbinate bulk (the cotton test) has been validated as an office-based tool to assess/alleviate ENS symptoms.[335] A positive blinded cotton test both confirms the ENS diagnosis and informs candidacy for possible treatment interventions.[335]

ENS has historically been a challenging disease to effectively treat due to debilitating nasal symptoms and, in a minority of patients, concerning psychiatric overtones.[336–340] Past therapies were confined to reducing the daily burden of ENS symptoms via nasal maintenance strategies including moisturizers and emollients, increasing nasal airflow (supplemental oxygen, CPAP [continuous positive airway pressure] use), and psychiatric interventions like cognitive behavioral therapy.[341,342]

Current published interventions focus on restoring tissue volume to the truncated ITs or the adjacent inferior meatus. Submucosal injection of slow-resorbing gel fillers can be trialed for the effect of "transient turbinate augmentation" lasting 1–3 months.[343] A wide variety of biomaterials – including acellular dermis, implants, and xenografts – have been published as bulking options to sites of inferior meatus and IT tissue loss.[344–349] Importantly, a procedure originally reported by Houser,[318] now termed the inferior meatus augmentation procedure (IMAP), where missing turbinate contour is replaced with fashioned rounded rib grafts placed in the anterolateral nasal airway, has accumulated strong evidence for effectively treating ENS.[350] IMAP has yielded statistically significant short[351] and long[352] term reductions in the ENS6Q and the Sinonasal Outcome Test (SNOT)-22. Mechanistically, comparing computational fluid dynamics airflow modeling pre/post-surgery, the cotton test and IMAP procedures both normalize disordered vectors of ENS airflow,[353] highlighting a novel function of the turbinates in guiding and/or enhancing nasal airflow. Future ENS research will determine anatomic versus physiologic prognostic factors to identify "at risk" subpopulations for developing ENS[336,337] and design more nuanced airflow metrics for upper airway function in health and disease.

V.B.14 | Autoimmune, granulomatous, and vasculitic rhinitis

Differential diagnosis. Vasculitic, granulomatous, and autoimmune diseases may cause non-specific sinonasal symptoms (e.g., nasal obstruction, rhinorrhea, facial pain, and loss of smell) often mimicking AR. Therefore, broadening the differential diagnosis to consider systemic etiologies when evaluating these sinonasal symptoms is crucial. Crusting, recurrent epistaxis, or negative skin and/or blood allergy tests are among the signs that should heighten one's suspicion of alternative systemic diseases.[354,355]

Granulomatosis with polyangiitis (GPA). This is an uncommon disease with highest prevalence amongst people of Northern European descent, with men and women equally affected and incidence peaking in the seventh decade of life.[356] It is a chronic, relapsing, and idiopathic disease characterized by necrotizing and granulomatous inflammation affecting predominantly small to medium

sized blood vessels.[357] Potential triggers include *Staphylococcus aureus* as well as other infectious, environmental, chemical, or pharmacologic agents.

Sinonasal manifestations (e.g., nasal obstruction, crusting, epistaxis, anosmia, cacosmia, and paranasal sinus inflammation) are the presenting symptoms of GPA in about 73% of patients.[358] Recurrent serous otitis, mastoiditis causing hearing loss, and lower respiratory tract symptoms (e.g., cough, breathlessness, stridor, wheeze) occur in 80%–90% of patients.[354,359] Additionally, renal (75% of patients), ocular (50% of patients), and systemic manifestations (e.g., fever, arthritis, weight loss) are also possible.[360]

Diagnosis is often dependent on a multidisciplinary approach and based on a combination of suggestive local and systemic clinical manifestations, positive ANCA (anti-neutrophil cytoplasmic antibody) serology, and histological evidence of necrotizing vasculitis or glomerulonephritis by a positive organ biopsy (skin, lung, or kidney).[361,362]

Before the introduction of effective therapy, GPA was a potentially life-threatening disease. Treatment includes corticosteroids and immunosuppressive agents to induce remission. Cyclophosphamide and rituximab are often used for induction and maintenance. Patients can be transitioned to other immunosuppressive agents (e.g., azathioprine, mycophenolate, or methotrexate) with fewer potential side effects when disease remission is obtained.[363]

Eosinophilic granulomatosis with polyangiitis (EGPA). EGPA (formerly Churg–Strauss syndrome) is a small-vessel vasculitis. Defining features include eosinophil-rich, necrotizing granulomatous inflammation involving the respiratory tract. It is associated with asthma, eosinophilia, and CRSwNP. It is a rare disease with a prevalence of 10–15 people per million in Europe and appears in patients 40–60 years old.[364] EGPA has different triggers and frequently progresses through three stages gradually appearing over years. An initial phase with rhinitis (75%), asthma, and CRSwNP is often followed by peripheral eosinophilia and additional organ involvement, and finally diffuse clinical manifestations secondary to small vessel vasculitis.[365] Diagnosis should be suspected in patients with asthma, increased peripheral-blood eosinophil count (>10%) and pulmonary infiltrates.[365] CRSwNP is present in approximately 50% of patients. Nasal crusting, purulent, or bloody discharge can be present, but is less common than in GPA.[366] Treatment includes high doses of corticosteroids with rituximab in specific cases. Mepolizumab, an anti-IL-5 antibody, has shown efficacy in the eosinophilic inflammation and was approved for the treatment of EGPA in 2017 by the Food and Drug Administration (FDA).[355,367]

Sarcoidosis. This is chronic multisystem disorder characterized by bilateral hilar lymphadenopathy and pulmonary infiltrates. Ocular and skin lesions are more common in young and middle-aged adults.[368] Sinonasal involvement occurs in 1%–4% of cases and symptoms are non-specific: chronic crusting (70%–90%), nasal obstruction (80%–90%), anosmia (70%), and epistaxis (2%).[355,357,369] Aggressive non-caseating granulomas can cause hard or soft palate erosions as well as a saddle-nose deformity. Intranasal findings include erythematous, edematous, and friable mucosa, as well as submucosal yellow nodules (representative of intramucosal granulomas).[370] Diagnosis is usually made by a lung (transbronchial), skin, minor salivary gland, or lymph node biopsy.[368]

Sinonasal sarcoidosis treatment depends on its location, extension, and severity going from topical to systemic therapy (when nasal obstruction is severe). Endoscopic sinus surgery can be effective when medical treatment has failed, particularly in cases of sinus drainage blockage. Sinus surgery improves quality of life (QOL) but does not eradicate the disease nor prevent recurrence.[371] Biological therapy with anti-TNF agents has improved the therapeutic options in refractory organ-threatening sarcoidosis.[371]

Systemic lupus erythematosus. This is an autoimmune disease that predominantly affects women (10:1) with an incidence of 5.6 per 100,000 people.[372] Oral, nasal (nasal skin or vestibule), and pharyngeal mucosal lesions are seen in 9%–18% of cases.[357,372] Diagnosis requires a detailed medical history, physical examination, and laboratory tests (ANA [antinuclear antibody] or anti-dsDNA [double stranded DNA]).[354,373]

Therapy with corticosteroids, immunomodulators (e.g., prasterone, vitamin D, hydroxychloroquine), or immunosuppressants (e.g., azathioprine, cyclophosphamide, mycophenolate) is used for symptom control. Belimumab, an anti-BAFF (B cell activating factor) monoclonal antibody, is the only therapy currently utilized for extrarenal disease due to its modest effect on lupus activity.[374] Anifrolumab, an IFN-type 1 monoclonal antibody, has substantial evidence in effectively and safely treating moderate to severe active lupus.[375]

V.B.15 | Rhinosinusitis

The symptoms of AR may overlap with those of rhinosinusitis.[7,376] Rhinosinusitis is a broad term that includes the diagnosis of acute rhinosinusitis (ARS), RARS, and CRS. Symptomatically, these conditions are characterized by nasal obstruction, nasal congestion, facial pressure or pain, anterior or posterior nasal discharge, and anosmia/hyposmia.[7,183] AR and rhinos-

inusitis have several overlapping symptoms, namely rhinorrhea and nasal congestion, which can make it challenging to differentiate these conditions.[7,377,378] It is important to differentiate between AR and rhinosinusitis to ensure the correct diagnosis and subsequent treatment.

ARS is defined as the sudden onset of sinonasal symptoms outlined above with associated sinonasal inflammation that lasts less than 4 weeks – it may be viral or bacterial in nature.[7,183,184,201,379] In ARS, nasal discharge is often unilateral and purulent.[183,201] Associated facial pressure and pain is described as moderate to severe.[201] Viral ARS is typically present for less than 10 days, whereas a longer duration of illness suggests bacterial ARS.[183,201] Progressive worsening over a short period of time (i.e., 5 days) is also suggestive of bacterial ARS.[183,201] RARS is defined as at least four episodes of ARS per year.[183,201,379,380] CRS is an inflammatory condition of the sinonasal cavity, defined as sinonasal inflammation persisting for more than 12 weeks with at least two of the sinonasal symptoms outlined above.[7,183,184,201,379] In addition, patients must have objective evidence of sinonasal inflammation on either nasal endoscopy (polyps, edema, mucopurulent rhinorrhea) or on computed tomography (CT) scan of the sinuses.[183,184,201,379]

Comparatively, AR is characterized by nasal obstruction, nasal congestion, clear watery rhinorrhea (anterior or posterior), and allergic symptoms such as nasal itching, sneezing, and allergic conjunctivitis.[377,378] AR is not typically associated with purulent or unilateral nasal discharge. Moderate to severe facial pain is also atypical and may indicate an episode of ARS or an acute exacerbation of CRS.[7,183,201] AR symptoms are variable in duration and tend to have daily and/or local environmental fluctuations.[7,183,201] As a result, AR symptoms have been classified by duration (intermittent vs. persistent) and severity. AR symptoms, in general, present for at least 1 h on most days; however, patients may have symptom-free intervals.[377,378] AR symptoms are also exacerbated by exposure to allergens in a time-dependent fashion.[377] The early reaction occurs immediately after exposure, lasting approximately 30 min (sneezing, nasal/ocular itching, rhinorrhea), while the late reaction occurs up to 6 h after exposure (nasal obstruction and congestion).[377] Superimposed late reactions from multiple exposures may blunt the manifestation of acute phase symptoms and make the diagnosis of AR less obvious.

When attempting to determine whether a patient has AR, ARS, RARS, or CRS, it is important to elicit the onset and duration of symptoms. A history of allergic symptoms or allergen exposure-related symptoms is more consistent with AR.[377,378] The development of acute, unilateral, moderate to severe symptoms, and nasal purulence may be consistent with ARS or RARS.[7,183,201] A prolonged duration of symptoms (greater than 12 weeks) as well as presence of smell loss, which is not as common in AR, should raise suspicion for CRS and prompt further investigation.[7,183,201] Of note, these conditions are not mutually exclusive. It is possible to have concurrent AR and rhinosinusitis, and this should be considered when patient symptomatology or response to treatment does not fit a single diagnosis.[7,183,376] (See Section XIII.B. Associated Conditions – Chronic Rhinosinusitis for additional information on this topic.) Careful consideration of these symptoms and environmental triggers may help guide clinicians to the correct diagnoses.

V.B.16 | Non-rhinitis conditions

There are a variety of non-rhinitis conditions which can be included in the differential diagnosis of AR. In general, non-rhinitis conditions can be differentiated from AR based on a thorough history and physical exam, with an emphasis on laterality, timing, and associated symptoms (Table V.B.16).

Anatomical conditions, such as septal deviation, turbinate hypertrophy, or nasal valve collapse, overlap symptomatically with AR largely by causing nasal obstruction.[381] Septal deviations often have an asymmetry in airflow, with one side being more obstructed than the other.[382–384] Nasal valve collapse is often associated with obstruction on inspiration or during exercise.[381,382,385] Some congenital anatomical abnormalities such as piriform aperture stenosis or choanal atresia also cause nasal obstruction, which typically results in lifelong symptoms, which may or may not be identified in childhood.[386] The majority of these structural conditions should be evident on a physical examination including nasal endoscopy.

Sinonasal neoplasms often present with nasal obstruction.[387] The differential for sinonasal masses is extensive, including papillomas, hemangiomas, encephaloceles, osseous lesions, congenital masses, carcinomas, melanomas, and lymphomas.[381,384,387–389] Sinonasal neoplasms are typically associated with unilateral nasal obstruction, but they can cause bilateral obstruction if they grow larger or if they block the nasopharynx.[387] When sinonasal neoplasms cause unilateral nasal obstruction, they can also be associated with unilateral rhinorrhea, which is more likely to be thick or mucopurulent.[387] Rarely, neoplasms can erode through the skull base and cause CSF rhinorrhea, discussed below.[390,391] The onset of symptoms in sinonasal neoplasms usually spans weeks to months with a progressive worsening of symptoms.[387] Associated symptoms including epistaxis, hypoesthesia, visual changes, epiphora,

TABLE V.B.16 Allergic rhinitis differential diagnosis: non-rhinitis conditions

Category	Examples	Potential differentiating symptoms
Anatomical	Septal deviation Turbinate hypertrophy Nasal valve collapse Piriform aperture stenosis Choanal atresia	Asymmetric airflow Obstruction on inspiration or during exercise
Masses and neoplastic conditions	Papillomas Hemangiomas Encephaloceles Osseous lesions (osteoma, fibrous dysplasia, ossifying fibroma) Congenital masses (dermoid, dacryocystocele) Carcinomas Melanomas Lymphomas	Unilateral nasal obstruction Unilateral rhinorrhea Mucopurulent rhinorrhea Progressive worsening of symptoms Epistaxis Hypoesthesia Visual changes Epiphora Trismus Dental changes
Other	Cerebrospinal fluid Retained foreign bodies Rhinolithiasis Primary ciliary dyskinesia Cystic fibrosis Gastroesophageal reflux disease Laryngopharyngeal reflux disease	Unilateral rhinorrhea Positional rhinorrhea Purulent nasal drainage Systemic organ dysfunction Retrosternal burning Globus Dysphagia

trismus, or dental changes should raise the clinical suspicion for a nasal mass versus AR.[387,392,393] These symptoms would be highly atypical for AR and would warrant a careful physical exam, endoscopy, and sinonasal imaging, which can localize the sinonasal lesion if present.[387]

There are a variety of other less common non-rhinitis conditions to consider in the evaluation of AR. CSF rhinorrhea is associated with episodes of thin, watery rhinorrhea, much like AR.[394] Unlike AR, CSF rhinorrhea is most commonly unilateral and often reproducible with positional maneuvers.[394] While many CSF leaks are spontaneous, a history of significant head trauma or previous sinonasal surgery preceding the onset of symptoms should raise suspicion for a CSF leak over AR.[289,395] Retained foreign bodies or rhinolithiasis can also cause nasal obstruction and rhinorrhea, though these are usually associated with unilateral symptoms and purulent nasal drainage.[289,396,397] Disorders which affect mucociliary clearance, including primary ciliary dyskinesia or cystic fibrosis, can also lead to nasal obstruction and rhinorrhea.[398,399] These persistent rhinitis symptoms without allergic variation, with viscous secretions and systemic organ dysfunction are not consistent with AR and should raise suspicion for alternative diagnoses.[382,398]

There is increasing evidence suggesting an association between reflux disease and sinonasal symptoms.[400] Reflux disease (gastroesophageal, laryngopharyngeal) has been associated with nasal congestion and postnasal drip.[401,402] Congestion and inflammation of the nasal mucosa may result from acidic content directly affecting the mucosa or from esophageal-nasal reflexes triggered by the vagal nerve.[400,402] Reflux symptoms may warrant treatment but whether this improves sinonasal symptoms or not is unclear.[400]

While many of these non-rhinitis conditions have symptoms that overlap with AR, a careful assessment of the laterality, timing, and associated symptoms can help differentiate these conditions from AR. Similarly, a careful physical examination and nasal endoscopy will aid in identifying the correct diagnosis. A high degree of clinical suspicion will help clinicians accurately diagnose AR versus alternative diagnoses.

VI | PATHOPHYSIOLOGY AND MECHANISMS

VI.A | IgE-mediated allergic rhinitis

VI.A.1 | IgE/IgE-receptor cascade

In the last several years, much has been learned about the immunologic cascade that follows antigen cross-linking of IgE bound to cellular receptors. Three different IgE receptors have been described. The type I high-affinity IgE receptor (FcεRI) is found on mast cells and basophils through which it mediates cellular degranulation and cytokine production.[403] It is also found on dendritic cells and macrophages where it mediates the internalization of IgE-bound antigens for processing and presentation, and facilitates production of cytokines promoting the Th2 immune response.[403] The low affinity cluster of differentiation (CD)23/FcεRII receptor is found on macrophages and epithelial cells and mediates the uptake of IgE-antigen complexes.[404] FcεRIII is expressed by B cells and regulates IgE production and facilitates antigen processing and presentation.[405] This section will focus on the cascade that follows activation of the high-affinity receptor FcεRI.

FcεRI consists of an α chain which is a transmembrane protein that binds the IgE FC portion, a β chain which is a receptor-stabilizing and signal-amplifying subunit with four transmembrane domains, and disulfide-linked

dimeric γ chains which act as signal-triggering subunits.[406] Secreted IgE binds to FcεRI on mast cells or basophils. When an antigen binds or cross-links two IgE/FcεRI complexes, activation of mast cells and basophils is triggered and degranulation occurs causing the release of histamine, tryptase, cysteinyl leukotrienes, and platelet activating factors among others.[405,407] This process is known as the early allergic response and is associated with vasodilation, edema, and bronchoconstriction.[405,407]

Within the β and γ subunits of the FcεRI receptor is the immunoreceptor tyrosine-based activation motif (ITAM). Following receptor stimulation, ITAM on the β and γ subunits undergo phosphorylation by Src family protein tyrosine kinases and recruitment of another tyrosine kinase Syk.[408] Through conformational changes and tyrosine phosphorylation, Syk is activated.[409] Syk is critical for most activation events within the mast cell which lead to degranulation as well as the de novo synthesis and production of chemokines, cytokines, and lipid mediators.[410,411]

Within a few hours of IgE receptor stimulation by IgE cross-linking, activated mast cells secrete a large amount of newly synthesized proteins, a result of de novo gene transcription prompted by receptor stimulation.[412,413] Following stimulation of the FcεRI receptor, human mast cells have been demonstrated to upregulate 260 genes and downregulate 84 genes for up to 2 h.[414] The upregulated genes include gene sets encoding cell surface molecules, cytokines/chemokines, signaling molecules, transcription factors, proteases, and other enzymes.[406] The downregulated genes include gene sets involved in signal transduction, apoptosis, cell proliferation, and genes encoding receptors.[415]

Cross-linking of the FcεRI receptors by antigen-bound IgE leads to the activation of several transcription factors. These signal dependent transcription factors including signal transducer and activator of transcription (STAT)-5, nuclear factor of activated T cells (NFAT), activator protein (AP)-1, nuclear factor (NF)-κB, and early growth response (EGR)-2 function in FcεR1 upregulated gene expression.[416] Ultimately, this complex process of de novo gene transcription and upregulation/downregulation of genes results in the production and release of cytokines and chemokines.[417] This includes IL-3, IL-4, IL-5, IL-13, C-C chemokine ligand-5 (CCL5), and granulocyte-macrophage colony stimulating factor (GM-CSF).[418–420] The effect of these cytokines and chemokines is the recruitment of inflammatory cells including eosinophils, basophils, neutrophils, macrophages, and T cells.[418–420] This is referred to as the late allergic response characterized by airway inflammation, hyperresponsiveness, airway remodeling, and mucus hypersecretion.[407]

VI.A.2 | Systemic mechanisms and manifestations of allergic rhinitis

Allergic diseases such as asthma, atopic dermatitis (AD), and AR share a common inflammatory pathway involving the adaptive immune system mediated by sIgE. The adaptive immune system can generally be categorized into Th1, Th2, and Th17 responses, named after the Th cells that orchestrate the corresponding immune responses. The Th1 response provides defense against intracellular pathogens, and has IFN-γ as its canonical cytokine.[421] The Th17 response also provides defense against pathogens, such as bacteria and fungi, and is characterized by neutrophilic inflammation and its canonical cytokine, IL-17. The Th2 response provides defense against parasites and is marked by the expression of IL-4, IL-5, and IL-13.[421,422] These ILs represent integral mediators responsible for driving IgE- and eosinophil-associated inflammation that often characterizes atopic disease.[421] Type 2 innate lymphoid cells (ILC2s) are a newly characterized group of effector cells of the innate immune response that also have the capacity to produce large quantities of the type 2 cytokines, especially IL-4, IL-5, and IL-13, playing a critical early role in the initiation of Th2 responses to aeroallergens during allergic inflammation.[423–425]

In AR, aeroallergens are inhaled onto the nasal mucosa. When mucosal epithelial integrity is disrupted, epithelial cells release alarmins and other damage-associated molecular patterns (DAMPs).[426,427] These mediators possess pro-inflammatory properties and have been shown to assist in initiating and maintaining a Th2 immune response.[428,429] For example, thymic stromal lymphopoietin (TSLP) is an important alarmin which can promote the recruitment of inflammatory cells (i.e., eosinophils, basophils, and mast cells) and the maturation of dendritic cells into Th2-promoting subtypes, further enhancing Th2 polarization.[430–433] It is theorized that in AR, this pathway is similarly activated and there are aeroallergens (e.g., dust mite allergens), that directly compromise the mucosa through protease activity or by activating pattern recognition receptors of which the toll-like receptor (TLR) family is the most well-known.[434]

On first exposure to an allergen, dendritic cells in the nasal mucosa process the allergen and then migrate to present it on MHC class II to naive helper T (Th0) cells in secondary lymphoid organs.[422] Once exposed to antigen/allergen in the appropriate costimulatory environment, Th0 cells become activated and differentiate into allergen-specific Th2 cells. Th2 differentiation requires costimulation via the interaction of CD28 on T cells with CD80 and CD86 on antigen presenting cells and the presence of IL-4.[435,436] IL-4 binds STAT-6 on Th0 cells which

activates the master switch GATA-3 (GATA-binding protein 3).[430] As a result, Th2 cells release cytokines such as IL-4, IL-5, and IL-13 which activate B cells and initiate IgE class switching.[422,434] Class switching occurs via upregulation of ε-germline gene transcription and clonal expansion, as well as the interaction between surface CD40 ligand on T cells with surface CD40 on B cells. This process allows B cells to differentiate into plasma cells that produce sIgE.[435] The end result is the creation of a pool of memory Th2 and B cells.[434] sIgE is released into circulation and binds to high-affinity FcεRI IgE receptors on the surface of effector cells such as mast cells and basophils.[434] During IgE-mediated reactions, prostaglandin D2 (PGD2) which is mainly synthesized by mast cells has recently been shown to exert an important role in recruitment and activation of ILC2s, in addition to leukotrienes, and innate cytokines.[437,438] Crosslinking of IgE on the surface of these effector cells causes degranulation and the release of inflammatory mediators such as histamine and leukotrienes, resulting in classic symptoms of AR.

AR has traditionally been thought of as resulting from an immune response leading to systemic IgE production.[439,440] The classic example of systemic reactivity in AR is the cutaneous reaction elicited during traditional skin testing.[441] The concept of LAR is discussed in the section that follows.

VI.A.3 | Local IgE production

When systemic allergen sensitization is present, sIgE is detected via serum in vitro testing or allergy skin testing. However, systemic allergy testing methods do not provide direct information regarding the target-organ immunological response.[265,442–444] Studies in recent decades support the concept of local IgE production. LAR is characterized by allergic nasal symptoms in patients with negative systemic allergy testing. However, in these patients, positive NPT and/or detection of nasal sIgE and/or positive basophil activation test (BAT) demonstrate a localized allergic response.[265,443,445–449]

Local IgE production has been demonstrated in patients with AR[450–453] and LAR.[454–463] In LAR, sIgE in nasal secretions has been confirmed after natural exposure,[455,456] after controlled exposure to aeroallergens by NPT,[456,458–460,464] and also during periods of non-exposure to aeroallergens.[455,456] It is theorized that in LAR individuals, sIgE produced at the mucosal level can be enough to sensitize nasal effector cells, but not to reach skin mast cells or to be detected in the free state in serum.[465]

The immunopathology of local sIgE production in LAR is not completely understood. Flow cytometry of nasal lavage confirms a nasal IgE-mediated inflammatory response in LAR patients, with increased eosinophils, basophils, mast cells, CD3+ and CD4+ T cells, and local sIgE, along with characteristic pro-inflammatory mediators such as tryptase and eosinophil cationic protein (ECP) during natural exposure to aeroallergens.[444,454–466]

NPT studies to assess potential mechanisms of local sIgE production have revealed characteristic immediate/early and late phases of the allergic response in LAR. In these patients, nasal mucosal reaction to administered allergen is immediate and occurs mostly by stimulation of IgE-coated mast cells and basophils. This results in the secretion of tryptase, histamine, cys-leukotriene, and PGD2, which then stimulate the local sensory nerve and vascular receptors in nasal mucosa. Mast cells secrete chemotactic agents and platelet activating factor, contributing to the development of inflammation with local production of sIgE and eosinophil activation.[462] As a result, serum IL-5 levels increase and IL-5 is transported into the pulmonary circulation, causing increased exhaled NO and bronchial hyperreactivity.[461,463] Finally, in a study by Campo et al.,[467] following NPT with nOle e 1 (the most significant allergen of *Olea europea*), 83% of LAR *O. europaea* sensitized subjects responded. Further, ECP levels in nasal lavage significantly increased after NPT in LAR patients indicating that secretion of ECP following NPT could potentially act as a confirmatory biomarker.

Additional studies have shown that sIgE produced in the nasal mucosa of patients with LAR sensitized to HDM and pollens has the capability of binding to the FcεRI high-affinity receptor on basophils.[450,468] Furthermore, the sIgE-related mechanism of basophil activation in LAR has been demonstrated by performing BAT with wortmannin pretreatment, showing reversal of positive results when wortmannin was added to the assay.[468] These findings suggest that after local IgE production, basophils might be the first target cells for sIgE produced in the target organ transported from the site of inflammation (nasal mucosa) to the general circulation.[469]

Studies report LAR prevalence is approximately 26% in Mediterranean countries (Portugal, Spain, Italy and Greece)[470] and 7%-10% in Asian countries (China and Korea).[150,471,472] LAR may affect approximately 47% of children previously classified as non-allergic rhinitis.[444,464,466,473,474] Exposure to environmental factors such as temperature, humidity and pollution are associated with higher incidence of LAR.[466,475] There is a low rate of conversion (~3%) to systemic detection of allergen sensitivity, development of asthma, and worsening clinical progression is rarely seen.[239,448,475–477]

VI.B | Non-IgE-mediated inflammation in allergic rhinitis

AR is thought of as mainly an IgE-driven response.[478] Nonetheless, our awareness and comprehension of the important contributions of the nasal innate immune response to the pathogenesis of AR has grown immensely in recent years.[479]

The pathophysiological mechanisms of inflammatory airway diseases are associated with large biological networks involving the environment and the host.[480] The nasal epithelium first encounters aeroallergens in the host. Disruption of epithelial barrier function by proteolytic mechanisms, lipid-binding activity, and interactions with polysaccharides and polysaccharide molecular recognition systems of allergens may allow allergen to penetrate into local tissues, perpetuating chronic and ongoing inflammatory processes.[481,482] This may also occur with irritants like chlorine[483] and air pollution.[484] Epithelial barrier dysfunction has been shown to contribute to the development of inflammatory diseases including AR.[485] However, additional research is needed to determine the extent to which primary (genetic) versus secondary (inflammatory) mechanisms drive barrier dysfunction.[486] (see Section VI.G. Epithelial Barrier Alterations for additional information on this topic.)

Epithelial cells act as a physical barrier toward inhaled allergens and actively contribute to airway inflammation by detecting and responding to environmental factors. Nasal epithelial cells bear TLR pattern recognition receptors.[480,487,488] Exposure of the nasal epithelium to molecules such as allergens and pathogens results in stimulation of TLRs and the production of alarmins: IL-25, IL-33, and TSLP, which in turn activate dendritic cells, T cells, and type 2 ILCs. ILCs are key players in the pathogenesis of Th2 type diseases like AR, CRSwNP, and asthma.[489–491] Three major subsets have been defined based on their phenotype and functional similarities to Th1 (ILC1), Th2 (ILC2), and Th17 (ILC3) cells. The release of the cytokines IL-25, IL-33, and TSLP by epithelial cells directly activate ILC2s, then they produce the prototypical type 2 cytokines IL-5 and IL-13.[492]

Allergen challenge in AR subjects induces increased numbers of peripheral blood ILC2s[493,494] and results in and influx of ILC2 in the nasal mucosa.[495] Pre-treatment with INCS attenuates allergen-induced increases in ILC2s in the nasal mucosa of AR patients.[496] ILC2s also contribute to epithelial barrier leakiness through IL-13.[497] Treatment with anti-IL13 has shown significant reduction of AR symptoms,[498] pointing to the important role of the innate immune system in the development of symptoms and signs of disease. AIT reduces ILC2's and increases IL-10-producing ILCs in the peripheral blood of AR patients.[499] Moreover, the frequency of IL-10-producing ILCs correlated with improvement in clinical parameters. More novel therapies directed toward the innate immune system are in development for treatment of AR.[480]

VI.C | Cellular inflammatory infiltrates

Various types of inflammation are involved at different AR stages, including sensitization, exacerbations, remodeling, and remission. Different mediators orchestrate a type 2 immune response.[500] Most commonly a type 2 inflammatory environment is observed with Th2 cells, M2 macrophages, eosinophils, and type 2 ILCs playing important roles.[501] Other patterns with mixed type 2 and type 3, or even type 1 may arise depending on the allergen protease activity and the microbial and inorganic environments.[502,503] As it is virtually impossible to define one inflammatory pattern, endotyping in AR seems highly important to drive personalized medicine.[504]

Cellular interactions are important, including the role of a defective barrier and the release of epithelial alarmins. IL-33 acts on Type 2 ILCs and promotes mast cell degranulation through inhibition of autophagy.[505] In the induction of a type 2 response, IL-25 acts on Th2 cells and ILC2s while TSLP mainly activates dendritic cells.[500]

Allergen-specific CD4+ T cells regulate multiple facets of allergen-specific responses: IgE production in B cells, regulation of eosinophilia by IL-5, and enhancement of type 2 inflammation by IL-9. Antigen-presenting cells, such as dendritic cells, are increased in frequency, higher in maturation markers CD40,[506] and loaded with sIgE contributing to atopy, while elimination of dendritic cells suppresses AR.[507] Dendritic cells are crucial in the initiation of a Th2 response, while basophils will merely amplify it.[508] Myeloic dendritic cells may activate ILC2s and plasmacytoid dendritic cells play important roles in AR through IL-2 and IL-6 pathway alterations.[509]

Innate and effector mechanisms affect allergic disease.[510] A skew toward Th2 with GATA-3 overexpression are hallmark findings in AR mucosa.[511,512] Tissue γ/δ-T cells and CD4+ memory T cells are increased.[513] Different type 2 cytokines orchestrate the production of sIgE, eosinophilia, mucus, tissue migration of Th2 cells, and regulation of tight junctions (TJ) and barrier integrity.[500,514–517]

Distinct phenotypes of regulatory T cells (Treg) subsets include CD4+CD25+ Forkhead-box P3 (FOXP3)+ Tregs and type 1 Tregs.[518–520] Allergen-specific Tregs suppress other T cells, IgE, eosinophils, and dendritic cell maturation to control AR development. They increase in the mucosa after AIT correlating with clinical remission.[521–523] The ratio between effector and regulatory cell types

determines whether an allergic response is triggered. Regulatory B cells and Th17 cells may play important roles in intolerance and AR.[524,525] Increased levels of CD4+ T cells were identified in AR patients' blood with reduced CXCR3 expression.[526]

ILCs, introduced and described in prior sections, lack rearranged antigen receptor or lineage markers. In addition to their contribution to type 2 inflammation, ILC1s increase in local sinonasal infections and ILC3s increase in remodeling. ILC2s closely interact with epithelial cells and others leading to a type 2 favoring cytokine environment.[527] They particularly open epithelial barriers and make the tissues prone to environmental insults.

IgE-producing B cells reside in the lymphoid follicles of the Waldeyer's ring where antibodies are transferred to the mucosa.[528] However, B cells and plasma cells also produce IgE locally which is becoming a hallmark finding of AR.[529] In AR, numbers of circulating memory B cells were found to be increased.[530]

Major basic protein (MBP)-positive and activated eosinophils can increase locally during the pollen season. This increase is not observed in the T lymphocyte subsets, neutrophils, and macrophages. Yet, mast cells seem to infiltrate the mucosa and the submucosal layer similarly to eosinophils.[531]

Both mast cell and basophil granulocyte degranulation are relevant components of the early and late phases of a type I hypersensitivity reaction after an allergen is encountered and crosslinking of IgE occurs.[532,533] Basophils accumulate within 1 h after allergen provocation in the lamina propria.[534]

Adhesion molecules are upregulated and chemoattractants facilitate the influx of inflammatory cells during the late phase.[535] This allows for further accumulation of cells promoting remodeling with upregulation of matrix metalloproteinases and angiogenic factors.[536]

VI.D | Cytokine network and soluble mediators

The pathophysiology of AR involves IgE-mediated inflammation which is a type 2 immune response. IgE crosslinking results in mast cell activation and release of inflammatory cytokines such as IL-4, IL-5, IL-6, IL-13, IL-25, and IL-33 as well as preformed bioactive mediators and newly formed mediators including histamine, leukotrienes, prostaglandins, and kinins. These cytokines regulate the allergic inflammatory cascade through induction of IgE synthesis, upregulation of IgE production, and production of other cytokines and chemokines from epithelial cells which results in the mucosal recruitment of inflammatory cells.[537–539] Numerous cell types act as sources for type 2 cytokines including T cells, nasal epithelial cells, ILC2s, mast cells, and eosinophils.

Nasal epithelial cells secrete inflammatory cytokines including TSLP, IL-25, and IL-33.[540] TSLP is a critical upstream cytokine for ILC2s, mast cells, dendritic cells, T cells, and basophils.[541–543] IL-25, IL-33, and TSLP secreted by epithelial cells act on surrounding cells resulting in the release of IL-4, IL-5, and IL-13 which recruit additional inflammatory cells leading to a type 2 response.[544] Nasal epithelial cells are also a source for IL-1, IL-6, IL-8, and TNF-α, and through these signals, play a role in the migration and activation of eosinophils, basophils, and Th2 cells.[545]

ILC2s are tissue resident cells that can be stimulated to secrete IL-4, IL-5, and IL-13 by the alarmins TSLP, IL-25, and IL-33 (which are secreted by epithelial cells or myeloid dendritic cells) via the IL-33/ST2 pathway.[509,544,546] Survival factors or co-stimulators including IL-2, IL-4, IL-7, IL-9, TNF-like cytokine 1A (TL1A), and glucocorticoid-induced TNF receptor ligand (GITRL) serve to maintain basic functionality of ILC2s.[501] Both TL1A and GITRL are responsible for ILC2 proliferation and the release of type 2 cytokines from these cells.[547] IL-2, IL-7, and IL-9 are regulatory factors necessary for the development, maintenance, and survival of ILC2s.[547] IL-2 activates ILC2s and induces them to secrete IL-9, which is also critical for maintaining the activity and survival of ICL2s.[489,548,549]

Airway mast cells are a source of type 2 cytokines, proinflammatory cytokines, chemokines, and TSLP.[537,550–552] IL-13 from mast cells plays a role in mast cell-induced local IgE synthesis by B cells, which in turn upregulate FcεRI expression on mast cells.[553] Along with IL-4 and IL-13, TNF-α, a proinflammatory cytokine produced by mast cells, enhances the production of thymus and activation-regulated chemokine (TARC), TSLP, and eotaxin from epithelial cells.[538] This suggests a crucial interplay between mast cells and epithelial cells in promoting and regulating the allergic inflammatory cascade.

Both mast cells and epithelial cells directly produce or upregulate eosinophil chemoattractants including eotaxin, macrophage/monocyte chemotactic protein 4, RANTES, and cysteinyl leukotrienes.[554–556] Eosinophils are a key factor in type 2 inflammation and are regulated by IL-4, IL-5, and IL-13. These cells are also a major source of inflammatory cytokines including macrophage migration inhibitory factor, eosinophil peroxidase, and nerve growth factor.[557,558]

Finally, Th17 cells may play an important role in AR. The major cytokine of Th17 cells is IL-17. Six isoforms of IL-17 exist denoted as IL-17a to IL-17f.[559] Currently, it is understood that IL-17a and IL-17f play roles in allergic-type inflammation.[559] Studies have shown that the production of IL-1, IL-6, IL-8, matrix metalloproteinases, and TNF-α

can be induced via IL-17 receptors on different cell types.[525] A recent systematic review by Hofmann et al.[525] evaluated 10 studies looking at IL-17 levels in either serum or nasal fluid in patients with AR. In all studies, elevated IL-17 levels in either serum or nasal fluid were observed in patients with AR compared to controls. These findings could indicate that Th17 cells and associated type 3 inflammation play a role in the pathophysiology of AR, but the exact role remains unclear.

VI.E | Neural mechanisms

The pathophysiology of AR is heavily influenced by sensory neurons, axonal reflexes, and neurotransmitters.[560] The trigeminal sensory, sympathetic, and parasympathetic nervous systems work in concert to form a protective barrier in the upper airway mucosa and regulate epithelial, glandular, and vascular processes.[561] Branches of the trigeminal nerve innervate blood vessels and mucous membranes in the nasal cavity. The trigeminal nerve has nociceptive Aδ and C fibers that are stimulated by physical and chemical ligands as well as products of allergic reactions.[562] Inflammatory mediators (e.g., bradykinin, histamine, acetylcholine, and capsaicin) are capable of activating sensory neurons in the trigeminal nerve, largely through TRP ion channels.[563–566] Through repeated depolarization, lasting changes develop in TRP channels as demonstrated for the TRP cation channel subfamily V member 1 (TRPV1) and subfamily A member 1 (TRPA1). This leads to hyperexcitability of neurons in AR patients through changes in stimulation threshold and membrane potentials.[565,567] Studies investigating treatment with intranasal capsaicin, the prototypic ligand for TRPV1, have demonstrated significant improvement in nasal congestion, sinus pressure, pain, and headache within 5 min after administration in patients with non-allergic and mixed rhinitis but not clearly in AR.[568] Furthermore, treatment with azelastine nose spray, approved by the FDA for treatment of AR and non-allergic rhinitis, has been shown to downregulate TRP receptors.[563,564]

Depolarization of these nociceptive channels on sensory nerves leads to the release of neuropeptides including substance P, CGRP, and neurokinin-A.[564] Substance P receptors are located on nasal epithelium, glands, and arterial and venous vessels, and sinusoidal vessels, which leads to glandular secretion, increased vessel permeability, edema, vasodilation, and further activation of inflammatory cells.[562,566,567] Substance P has been recognized as a short acting vasodilator while CGRP is a long-acting arterial vasodilator found in increased concentrations in AR patients compared to controls.[567,569,570] Substance P and CGRP also activate mast cells to release more inflammatory mediators, such as histamine, that further propagate the hypersensitivity reaction.[565] Neurokinin A, a tachykinin that acts similarly to substance P, causes increased vascular permeability, vasodilation, bronchial smooth muscle contraction, mucus secretion, mast cell degranulation, as well as leukocyte chemotaxis and activation.[562,564,567] Understanding these biologic pathways has led to investigation of novel therapies including bradykinin antagonists and TRP receptor calcium ion channel blockers.[567]

Parasympathetic and sympathetic nerves also play a central role in the neural response to allergens. Acetylcholine and vasoactive intestinal peptide are released during the parasympathetic response leading to mucous cell secretion, vasodilation, and epithelial cell activation via muscarinic receptors found on the nasal epithelium, submucosal glands, and blood vessels.[566,567] Sympathetic nerves respond to neurokinin Y leading to vasoconstriction and nasal decongestion.[567] A widely accepted mechanism of non-allergic rhinitis has been an imbalance between the sympathetic and parasympathetic response leading to parasympathetic overactivity and manifests as nasal congestion, rhinorrhea, and postnasal drainage.[571]

The neuropeptides previously discussed are significantly increased in nasal lavage of AR patients compared to controls.[569,572] Upregulation of these inflammatory mediators and neuropeptides leads to peripheral sensitization of nerve fibers which can subsequently cause central sensitization or a lowered threshold for a given stimulus.[569] Neural growth factor (NGF) is a neurotrophin that leads to survival and growth of neurons that express an NGF receptor. Sources of NGF, such as mast cells and eosinophils, are chronically activated in AR patients and may account in part for the nasal hyper-responsiveness, increased sensory nerve concentration, and increase in neuropeptides that further propagate this inflammatory response.[572–575] Unfortunately, clinical trials investigating neuropeptide and TRP antagonists in seasonal AR have been unsuccessful this far.[576–578]

VI.F | Histologic and epithelial changes

The nasal mucosa warms, conditions, and humidifies air entering the respiratory tract. It is also the first line of defense against pathogens, through both the innate and acquired immunity.[579–581] The structure of the nasal mucosa is well adapted to carry out these roles. The normal sinonasal epithelium forms a physical barrier, comprised of pseudostratified columnar ciliated and non-ciliated cells, goblet cells and basal cells. The epithelial cells are linked by apical junctional complexes.[516] At the superior nasal septum and superior turbinate, olfactory epithelium

is also present, which consists of bipolar olfactory receptor neurons, sustentacular (supporting) cells, basal cells, and Bowman glands.[582] Overlying the sinonasal epithelium is a mucus blanket, which consists of water, mucin glycoproteins, and antimicrobial peptides such as lactoferrin, lysozyme, and defensins.[583] The mucus blanket forms a double layer, consisting of an inner serous (sol or periciliary) layer and an outer viscous (gel) layer. The basement membrane separates the epithelium from the submucosa or lamina propria.

In the presence of conditions that impair mucosal integrity, the epithelium releases alarmins and other DAMPs or pathogen-associated molecular patterns (PAMPs) that initiate repair mechanisms and induce protective inflammation.[434,584] The epithelial inflammatory response to allergens is a key feature of AR. The histological characteristics of airway inflammation are commonly goblet cell hyperplasia, mucus hypersecretion, basal membrane thickening, and airway smooth muscle hyperplasia.[585] This inflammatory response translates into mucosal edema, increased mucosal secretions and hyperresponsiveness common in AR. Allergens (e.g., *Alternaria* and HDM) are shown to enhance the chemical mediator production from nasal epithelial cells, and these allergens may induce not only a type 2 inflammatory response but also other, for example, type 1, inflammatory responses in the nasal mucosa.[586] Nasal epithelial cells of AR patients showed increased expression of pro-inflammatory and IL-1 family cytokines at baseline and under stimulation, which could contribute to a micromilieu which is favorable for type 2 of inflammation.[587] Whether robust type 2 inflammation contributes to the development of airway remodeling in AR remains controversial. One study demonstrated that after repeated nasal allergen challenge, no differences were observed in epithelial integrity, reticular basement membrane thickness, glandular area, expression of markers of activation of airway remodeling including α-smooth muscle actin (SMA), heat shock protein (HSP-47), extracellular matrix (matrix metalloproteinase [MMP]-7, MMP-9, and TIMP [metallopeptidase inhibitor]-1), angiogenesis, and lymphangiogenesis for AR patients compared with healthy controls.[588]

The nasal lavage samples from patients with ongoing grass pollen AR showed distinct gene expression profiles and functional gene pathways which reflect their anatomical and functional origins.[589] Mucin production, regulated by the mucin genes MUC5AC and MUC5B in particular, is upregulated by allergens.[590] Goblet cell hyperplasia in allergic airway inflammation is partially due to high expression of CD44v3, a surface marker for intermediate progenitor cells from basal cells.[591] AR may be associated with increased epithelial permeability or defective epithelial barriers as a result of decreased expression of the TJ proteins occludin and zonula occludens (ZO)-1.[485] Impairment of ZO proteins are observed in AR patients and dysfunction of ZOs allows allergens to pass into the subepithelium.[592] This may also be mediated by various factors such as histone deacetylase activity[593] and deficiency of the MUC1 gene.[594] Some allergens, such as Der p 1 in HDM, have protease activity and can directly compromise the epithelial barrier.[427] Dysfunction of the epithelial barrier and allergen entry into the submucosa may trigger the inflammatory cascade observed in AR. (see Section VI.G. Epithelial Barrier Alterations for additional information on this topic.)

VI.G | Epithelial barrier alterations

The epithelial barrier consists of different layers that defend against airborne pollutants, allergens, and pathogens, while maintaining homeostasis within the subepithelial compartment. Over 40 years ago, epithelial barrier leakiness was described in AR.[595] A defective epithelial barrier may facilitate allergens and pathogens entering the mucosa, thus perpetuating inflammation.

Within the supra-epithelial layer different proteins and peptides (including mucins) are found, mainly protecting against pathogens, but also against allergens. Furthermore, a large part of the nasal microbiome is found within this layer. However, improperly cleared bacteria and fungi may lead to colonization and activation of the adaptive immune system, accentuating the cycle of inflammation. Proinflammatory cytokines produced during allergic inflammation, in particular IL-13, are known to affect mucin expression (i.e., MUC5AC), leading to viscous secretions and impairment of mucociliary clearance.[596] Microbial derived short chain fatty acids also impact the epithelial barrier. Sodium butyrate leads to blocking of histone deacetylase, restoring defective TJs.[597] Synthetic histone deacetylase inhibitors show strong antiallergic effects in a HDM-sensitized mouse model.[593]

The epithelium itself creates the main barrier. Intercellular junctions are prerequisites of an intact barrier. TJs, adherens junctions, (hemi-)desmosomes, and gap junctions with their connecting proteins are the main determinants of an intact epithelial barrier. They also polarize the epithelium into an apical and basolateral compartment. TJs are defective in both AR and rhinosinusitis patients.[485,514] Disruption of different parts of the TJs in AR has been demonstrated microscopically and in functional analyses comparing diseased mucosa with healthy controls. Type 2 cytokines like IL-4 and IL-13 can disrupt the epithelial barrier leading to leakiness as shown by fluorescently labeled small molecule (fluorescein isothiocyanate [FITC])-dextran assays. Pollen peptidases and Der

TABLE VI.G Dysregulative processes affecting the epithelial barrier in allergic rhinitis

Reference	Mediator	Affected protein	Function	Type of dysregulation
Steelant et al.[600]	IL-4	Occludin	TJ protein	Downregulation
Steelant et al.[600]	IL-4	ZO-1	Adaptor protein	Downregulation
Steelant et al.[600]	IL-13	Occludin	TJ protein	Downregulation
Steelant et al.[600]	IL-13	ZO-1	Adaptor protein	Downregulation
Wang et al.[597] Steelant et al.[593] Wawrzyniak et al.[606]	HDAC	Occludin Claudin-4, -7 ZO-1	TJ protein	Increased in AR Decrease in TJ
Ohwada et al.[601]	HMGB-1	Angulin1/LSR	TJ protein	Downregulation
Steelant et al.[600]	Nasal secretions from AR patients	Unknown	Unknown	TER decrease
Henriquez et al.[599]	HDM	Claudin-1 JAM-A	TJ protein	Downregulation
Runswick et al.[598]	Pollen	Occludin ZO-1 Claudin-1	TJ protein	Disruption
Steelant et al.[600]	Histamine	Unknown	Unknown	TER decrease
Fukuoka et al.[602]	Particulate matter 2.5	ZO-1	TJ protein	Downregulation
Nur Husna et al.[607]	Second-hand smoke	Claudin-7 Occludin	TJ protein	Downregulation
Kamekura et al.[603]	TSLP	Claudin-1,4,7 Occludin	TJ protein	Upregulation

Abbreviations: AR, allergic rhinitis; HDAC, histone deacetylase; HDM, house dust mite; HMGB-1, high mobility group box-1; IL, interleukin; JAM, junction adhesion molecule; LSR, lipolysis-stimulated lipoprotein receptor; TJ, tight junction; TSLP, thymic stromal lymphopoietin; ZO, zonula occludens.

p 1 were shown to actively disrupt the epithelial barrier specifically at the level of TJs.[598,599] Interestingly, fluticasone treatment of air–liquid interfaces in IL-4 exposed primary nasal epithelial cells could restore TJs even in the absence of inflammatory cells. INCS are also effective ex vivo in restoring the barrier in HDM-sensitive AR patients' derived mucosa (Table VI.G).

AR derived nasal secretions and histamine are strong disruptors of the epithelial barrier function.[600] Very recently, high mobility group box-1 (HMGB1), which is increased by transforming growth factor (TGF)-β1 in AR, was shown to disrupt the epithelial barrier by decreasing angulin-1/LSR (lipolysis-stimulated lipoprotein receptor) in vitro in human nasal epithelial cell cultures.[601] Even particulate matter (PM)-2.5, a very fine particle found in air pollution, affects the epithelial barrier in an AR mouse model by reducing ZO-1 expression.[602] TSLP seems to play an important role in AR; interestingly it increases TJ proteins thus preserving the epithelial barrier.[603] Finally, epithelial to mesenchymal transition has been shown to occur in type 2 CRS affecting the barrier function of the epithelium.[604] Similar findings are expected to occur in AR.[605]

There are several features of the epithelial barrier that seem impaired in AR and can contribute to the cycle of inflammation at different levels of the epithelium. This may contribute to the recently observed increase in allergies worldwide.[605] The cause and consequence of a defective epithelial barrier in AR remains open for additional research.

VI.H | Vitamin D

Vitamin D (VD3) circulates in its inactive form (25-VD3) and is converted to its active form (1,25-VD3) by 1-α hydroxylase. VD3 is obtained from two distinct sources, diet and ultraviolet-mediated synthesis in the epidermal layer of the skin.[608] In the skin, ultraviolet rays promote biochemical reactions converting 25-VD3 to 1,25-VD3. The liver and kidneys also play important roles in 1,25-VD3 synthesis. The active form of VD3 binds to vitamin D receptors (VDR), ultimately modulating gene transcription and expression.[609] VDRs are present in several organ systems including bone, skin, intestines, kidneys, brain, eyes, heart, pancreas, and immune cells.[610] VD3 is an important immune mediator influencing T cell activation, cytokine production, and B lymphocyte inhibition. VD3's role in AR has been a focus of investigation and the discovery of VDR on immune cells has led to research

aiming to elucidate the immunomodulatory action of 1,25-VD3.

Many immune cells, including macrophages and dendritic cells, are capable of synthesizing 1,25-VD3 potentially shaping adaptive immune responses.[608] While conflicting data exists, most studies suggest that type 1 inflammatory cytokines (e.g., IFN-γ, IL-2, TNF-α, IL-12) are suppressed by exposure to 1,25-VD3 while type 2 cytokines are upregulated.[611] The impact of VD3 on the Th1/Th2 balance has been a focus of research as it may potentially explain, in part, the role of VD3 in allergic diseases. In recent studies Th17 and Treg cells have been implicated in the development of AR as well, and among the various T cells, elevated VDR expression is found on differentiated Th17 cells.[612–614]

Increasing numbers of epidemiological studies have linked VD3 levels with allergic disorders, especially asthma. Recent systematic reviews have demonstrated some support for VD3 in reducing asthma exacerbations, but further well-designed studies are required.[615,616] This has led to more recent investigations into the relationship between VD3 and AR.

Clinical studies investigating an association between VD3 and AR are conflicting. A recent clinical study investigating the relationship between VD3 levels and allergen sensitization to 59 aeroallergens in adults demonstrated no significant association after controlling for confounders (sex, age, and winter season).[617] A separate cross-sectional study looking at a pediatric population (<16 years old) found a high prevalence of vitamin D deficiency in children with asthma and AR.[618] A recent systematic review investigating VD3 levels in AR found that prior VD3 levels were not predictive of developing AR, but lower VD3 levels were associated with higher AR prevalence in children.[619] The precise relationship between VD3 and AR, however, is still a subject of investigation.

Similarly, the data on VD3 supplementation for AR is inconclusive. Multiple RCTs looking specifically at children with AR have demonstrated symptom improvement following VD3 supplementation.[620,621] However, a recent systematic review concluded that there is insufficient evidence to support VD3 supplementation for AR prevention.[619] Given the widespread prevalence of VD3 deficiency and its impact upon a spectrum of health aspects, physicians should consider evaluating VD3 levels, especially in children.

In summary, VD3 has critical immunomodulatory effects and has been implicated in other allergic disease processes such as asthma. There appears to be a stronger association between VD3 and AR in the pediatric population and assessing VD3 levels is a low-risk intervention that may provide useful information in the management of AR, as well as other aspects of health. Further research is needed to elucidate the relationship between AR and VD3.

VI.I | Nitric oxide

The nose and paranasal sinuses are a major site of intrinsic NO production in human airways, and AR is characterized by increased release of NO.[622–627] NO plays several important roles in the maintenance of physiological homeostasis and regulation of airway inflammation[628,629] through the expression of three isoforms: neuronal NO synthase (nNOS), endothelial NO synthase (eNOS), and inducible NO synthase (iNOS).[630]

NO is a key molecular player in the primary host defense and its cytotoxic effects are essential to prevent pathogen infection.[631–634] However, the bacteriostatic or bactericidal effects of NO may be species-specific.[635] Recent studies demonstrate that bactericidal activities could elicit bitter taste receptor-activated downstream responses, enhancing the production of NO.[636–638] NO has also shown antiviral effects against DNA and RNA viruses, including SARS-CoV-2, by partially inhibiting virus replication.[639–641] Moreover, NO is an important modulator of epithelial ciliary beating – important for the clearance of pathogens – through activation of the sGC-GMPc-PKG pathway.[642–645] Based on these findings, NO plays a protective role against a variety of microbial infections[631,646–650] and has been considered an important mediator in pathophysiological events underlying inflammatory airway responses.[651,652]

NO also causes disruption of Treg cell-mediated tolerance. Accordingly, NO derived from iNOS and eNOS affects the differentiation of helper T cells and the effector functions of T lymphocytes.[653,654] The function of T cell mediated immunity can be regulated by endogenous NO at various concentrations.[655–657] NO secreted by activated dendritic cells plays a complicated role in restricting T cell activity, by inducing dendritic cell stimulatory capacity on T cells.[658–663] Therefore, NO might have potential impact in the regulation of inflammatory responses through its interaction with Treg cells.

NO further links innate and adaptive immunity, regulates the adaptive immune response,[664–668] and is believed to participate in both type 1 and type 2 immune responses, which may depend on the concentration of NO. Type 1 inflammation is triggered by low NO concentrations and inhibited by high concentrations,[669–671] whereas type 2 cell proliferation can be induced by higher NO concentrations.[655,672–675] Moreover, NO is involved in T cell differentiation at the transcriptional level, and high levels of NO may activate Th2 transcription factors, upregulating IL-4-mediated Th2 cell differentiation.[669,670] In this sense, NO is a key molecule in maintaining the Th1/Th2 balance that regulates the evolution of airway inflammation.

NO is also presumably involved in the regulation of various signaling pathways related to transcription factor

activation and gene expression, as well as posttranslational regulation. NF-κB is a key mediator regulated by NO in the airway epithelial inflammatory response, which is either increased or decreased after NO exposure, dependent on the NO concentration and the time of exposure.[676] NO increases IL-8 expression in airway epithelial cells, which may be important to initiate an inflammatory response in the airway epithelium.[677,678] In addition, the IL-33–ST2 axis is believed to control Th2 and Th17 immune responses in allergic airway diseases,[679] and the balance between oxidative stress and antioxidant responses plays a key role in controlling IL-33 release in airway epithelium.[680]

Therefore, expression of NO and NOS in innate and adaptive immune cells reveals new functions and modes of NO action. These are particularly notable in the control and escape of microbes, T lymphocyte differentiation, interaction with NO reaction partners, and regulation of NOS by micromilieu factors, micro RNAs, and "unexpected" cytokines. However, we only understand the "tip of the iceberg" regarding NO and its role in nasal mucosal physiopathology. (See Section X.G. Evaluation and Diagnosis – Exhaled Nitric Oxide for additional information on this topic.)

VI.J | Microbiome

Humans are colonized by an estimated 100 trillion microorganisms.[681] The aggregate of these microorganisms that live on or within human tissue and fluids is termed the human microbiome. The microbiome is extraordinarily diverse – both within an individual at various anatomic sites and between individuals.[682–685] With modern technology we can use culture-independent high throughput sequencing techniques to gain insight into the composition of the microbiome among organs and individuals to try and understand its role in health and disease.

ICAR-Allergic Rhinitis 2018 presented a number of studies that linked the gut microbiome to the development of allergic disease, specifically in children.[686–691] However, differing methodologies, sample sizes, and culture techniques used in each study made it difficult to interpret results and draw conclusions.[1] In the years since then, the role of the microbiome in the development of AR has been further investigated.

In an analysis of gut microbial composition of adults with AR compared to healthy controls, Watts et al.[692] concluded that the AR cohort had reduced overall microbial diversity, with more abundant *Bacteroidetes* and decreased *Firmicutes* phyla. Similar results were reported by Zhou et al.[693] in a smaller patient series and by Hua et al.[694] in an evaluation of the association of the gut microbiome and self-reported allergy utilizing data from the American Gut Project. The *Firmicutes* phyla is associated with butyrate production, which is an important regulator of the intestinal barrier via TJ modulation. It is hypothesized that decreased butyrate may lead to increased pro-inflammatory molecular activity in the submucosa.[692] In a mouse model studying the effect of intranasal sodium butyrate in AR, Wang et al.[597] demonstrate that nasal mucosal epithelial morphology improved and levels of pro-inflammatory markers corrected, supporting this proposed mechanism.

Although the gut is the most well studied microbiome, the nasal microbiome may also influence pathologic states, including allergic inflammation.[695] In a study comparing the nasal microbiome of patients with AR, CRS, and a control group, Gan et al.[696] did not find a significant difference in microorganism richness or diversity between the groups. Similarly, in a study evaluating the role of AIT on the nasal microbiome of patients with AR, Bender et al.[697] showed no difference in the nasal microbial richness between patients with AR and controls, although they did conclude that AR patients have more similar microbiomes to each other than to controls. Gan et al.[696] identified an association between *Spirochaetae* and AR, a higher abundance of *Pseudomonas* and *Peptostreptococcaceae* in AR, and lower abundance of *Lactobacillus* in AR. These findings may suggest a possible role of microbial dysbiosis as the pathogenesis of local mucosal inflammation. However, a mechanism for this is not yet elucidated and the validation of these results remains uncertain.

Interestingly, the differentially detected microorganism species in the adult population studied by Watts et al.[692] were not always consistent with those found in reports that included children.[698] The reason for this is unclear. Nonetheless, the microbes present in infancy cannot be extrapolated to adults. However, there is evidence that altered DNA methylation patterns in upper airway mucosal cells during infancy contributes to the development of AR into childhood.[699] Longitudinal studies to understand shifts in the microbiome of AR patients over time will be required.

While it seems apparent that microbiome biodiversity is associated with microbiome fitness and alterations are associated with disease states, including AR, there are studies that contradict this assertion.[700] Specific mechanisms of the microbe–host relationship are not well understood. Future research should provide a more complete understanding of the dynamic human microbiome during all ages and at all anatomic sites and its impact on AR. (See Section VIII.C.3. Hygiene Hypothesis and Section XI.B.9. Management – Probiotics for additional information on this topic.)

VI.K | Unified airway

The upper and lower airways are linked anatomically, histologically, and immunologically to form a united airway system.[701] Inflammation in either the upper or lower airway influences the other, giving rise to the concept of united airway disease.[701,702] As the development of biological treatments options progresses, understanding the unified airway system has been recently underscored.[703,704]

The upper and lower airways share several histological features, such as in the mucosa, which is composed of columnar pseudo-stratified epithelium and ciliated cells on a basement membrane. Likewise, the submucosa of both airway portions consists of mucus glands, fibroblasts, and inflammatory cells. Differences in histology lie in the absence of smooth muscles in the upper airways, while the lower airways lack extensive sub-epithelial capillaries, arterial systems, and venous cavernous sinusoids, all of which are instrumental in oxygen exchange.

In the allergy realm, the concept of unified airway disease has arisen with the observation that upper and lower airway allergic diseases often coexist.[705] Indeed, evidence has uncovered the association between AR and asthma, as well as between CRS and asthma.[705–707] Moreover, both AR and non-allergic rhinitis have been suggested to be risk factors for asthma onset and asthma persistence, while CRSwNP has been suggested to share a common pathogenic mechanism.[701] Interestingly, both AR and asthma have similar hyperreactivity, further solidifying the concept a unified response between the upper and lower airways.[708–710]

Similarities between the upper and lower airways extend to endotypes, such as in type 2 immune responses. Type 2 inflammation is a prominent endotype in allergic diseases and can involve Th2 cells, type 2 B cells, IL-4 producing natural killer (NK)/T cells, basophils, eosinophils, mast cells, ILC2, IL-4, IL-5, IL-13, IL-25, IL-31, IL-33.[478,492,711–713] In general, the type 2 profile in AR and asthma is related to a good response to corticosteroids.[714] However, systemic corticosteroids carry serious adverse effects and side effects which generally outweigh the benefits especially in the upper airways.[715,716] Alternative type 2 inflammation-targeted treatments include anti-IgE antibodies, anti-IL5 (mepolizumab), and anti-IL4/13 (dupulimab), which have been used to treat asthma – a lower airway disease – with greater efficacy.[703] These drugs have also been shown to be effective in the treatment of upper airway disease such as CRSwNP, due to the similarities in endotype response between upper and lower airway inflammatory diseases.[717,718]

Shared characteristics between the upper and lower airways extend from acquired immune response to the role of innate immunity like epithelial barrier function and innate lymphoid cells.[719–723] (See Section VI.B. Non-IgE-mediated Inflammation in Allergic Rhinitis for additional information on this topic.) Mechanisms proposed for the interaction between upper and lower airway dysfunction include altered breathing patterns, nasal-bronchial reflex, and uptake of inflammatory mediators in the systemic circulation.[724] Most convincingly, AR may result in nasal blockage and the preference for oral breathing, which is associated with asthma.[725] Additionally, small molecules such as molds and cat dander – which may pass through the upper airway into the lower airway – are associated with an increased risk for asthma; larger molecules such as tree and grass pollen are primarily associated with upper airway symptoms.[726] The evidence supporting other hypotheses are weak. Although a clear relationship exists between postnasal drip and cough, the relationship between nasal secretions and its contact with bronchial mucosa remains unclear, since radio-labeled allergen deposited in the upper airway it is not detected in the lower airway.[727] Instead, stimulation of pharyngolaryngeal receptors has been suggested as the more likely cause of a postnasal drip-related cough.[726] Likewise, evidence supporting nasal-bronchial reflex as an important contributor to the unified airways is lacking. Nasal allergen challenge could be blocked with a vasoconstrictor but not with lidocaine, and the lower airway responses after allergen challenge were generally more delayed than would be expected following a nasal-bronchial reflex.[726]

Allergen provocation studies have provided a greater understanding of the nasal-bronchial interaction in allergic airway disease. In patients with AR, segmental bronchial provocation, as well as nasal provocation, induced allergic inflammation in both the nasal and bronchial mucosa.[728–730] Presumably, absorption of inflammatory mediators (e.g., IL-5 and eotaxin) from sites of inflammation into the systemic circulation results in the release of eosinophils, basophils, and their progenitor cells from the bone marrow.[731] The systemic allergic response is further characterized by increased expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and E-selectin, on nasal and bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue.[730] Increases in CD34+ cells capable of eosinophil differentiation, as well as other circulatory mediators (IL-5, eotaxin, and cysteinyl leukotrienes), are associated with impaired lung function parameters and enhanced mucosal inflammation in asthmatic patients[731] and can be inhibited by local corticosteroids in rhinitis patients.[732] Supporting evidence suggests that treatment with biologics against type 2 inflammation has been shown to be effective in both asthma and eosinophilic

upper airway disease.[703,733] Overall, these studies demonstrate that AR is not a local disease but that the entire respiratory tract is involved, even in the absence of clinical asthma. Systemic factors, such as the number of blood eosinophils and atopy severity, are indicative of a more extensive airway disease.

VII | EPIDEMIOLOGY OF ALLERGIC RHINITIS

VII.A | Epidemiology of allergic rhinitis in adults

To assist in concretely defining the prevalence of AR in adults, recent literature has attempted to provide more uniformity in the terminology and diagnostic criteria used to identify it. The International Study of Asthma and Allergies in Childhood (ISAAC), ARIA, the European Community Respiratory Health Survey (ECHRS), and International Classification of Diseases (ICD) have recognized and adopted a more standardized definition and methodology for diagnosing AR in a given population.[152,734,735] As such, there has been more consistency in the response data obtained from study subjects and clarity in the criteria used in identifying AR. Nonetheless, the prevalence estimates of AR still differ widely across studies, with an approximate range of 5%–50%.[736,737]

As noted in ICAR-Allergic Rhinitis 2018,[1] differing AR definitions affect prevalence estimates. Incidence of physician-diagnosed AR, which entails the precondition of being diagnosed or informed of AR affliction, potentially underestimates AR, as reflected in the South Korean National Health and Nutrition Examination Survey (KNHANES) data from 2008 to 2012 (35.02% according to questionnaire responses and ARIA guidelines; 14.89% when "diagnosed with AR by a medical doctor").[738] Likewise, the inclusion of at least one allergen test reaction (e.g., positive reaction to SPT) resulted in a lower prevalence estimates for AR in a Danish study in 2010 (AR, 39.0%; AR with SPT reaction, 25.9%), a Chinese study in 2018 (AR, 32.4%; AR with SPT reaction, 18.5%), and KNHANES data from 2008 to 2012 (current AR, 35.02%; AR based on allergy tests: 17.56%).[738–740] Identification of AR according to ICD codes from databases generally yielded lower estimates for AR (German AOK Saxony database study, 6.2%).[741] Conversely, estimates for lifetime AR were slightly higher than that of current AR, which was often defined as occurring within 12 months; this was observed in the Tromsø Study Fit Future 2, an expansion of the Tromsø Study (current AR, 26.0%; ever AR, 28.9%).[742–744]

Additionally, age ranges of given study samples may also capture subjects at different stages of the putative atopic march.[745] KNHANES identified a falling AR prevalence from 21.1% in 20- to 29-year-olds, to 5.4% in over 60-year-olds.[746] Considering all age ranges, AR prevalence in a Swedish study of 18- to 65-year-olds was 24%, and 27.2% in an Iranian study of 20- to 65-year-olds.[747,748] Although time of year and study location may potentially affect the presence of allergens and manifestations of AR, this discrepancy can often be obviated by including the temporal range of any time "in the last 12 months."

Notably, studies spanning longer periods of time have noted changes in the prevalence of AR. A Finnish study of conscripts' medical data identified a 100-fold-increase in AR prevalence from 1966 to 1993, and reached an approximate plateau around 10.7% in 2017.[749] Similarly, in Italy, prevalence of AR increased from 16.2% in 1985–1988, to 20.2% in 1991–1993, to 37.4% in 2009–2011[750] another study comprising randomly selected ECRHS subjects estimated that prevalence for AR changed from 19.7% in 1990–1994, to 23.1% in 1999–2001, to 24.7% in 2010–2012, with an overall change of 5.1%.[751] In contrast, in Brazil the prevalence of ever having hay fever in adults decreased from 52.0% in 2011 to 43.3% in 2018.[737]

Overall, the AR prevalence in Asia ranges approximately 5%–35%, depending on the method of diagnosis. In Europe, the most recent estimates put AR prevalence at around 25%. Variations in the prevalence were likely due to differences in participants' age, and thus the corresponding stage of the atopic march. Regardless, considering the data available, the worldwide prevalence of AR likely ranges between 5% and 50%.

VII.B | Epidemiology of allergic rhinitis in children

Several studies have attempted to describe the incidence and prevalence of AR in the pediatric population. AR symptoms have been shown to manifest in children as young as 12 months of age.[752] A separate study of 1850, 18-month-olds found AR-like symptoms and biological evidence of atopy, giving an AR prevalence estimate of 9.1%.[753] Kulig et al.,[754] however, performed a multi-center longitudinal study in 587 children from birth to 7 years of age in Germany and posited that two periods of seasonal allergen exposure are typically required to develop clinically significant AR. In their cohort, no children were diagnosed with seasonal AR by age 1. The remission rate of AR in children is relatively low, cited as occurring at a rate of 12% by one study performed in 2024 children from ages 4 to 8 years old.[755]

Most studies regarding AR prevalence in children are cross-sectional in design, of which the Phase 1 and Phase 3 ISAAC remain among the largest undertaken to date.

Therein, patient-reported symptom questionnaires were administered to hundreds of thousands of children comprising two age groups (6–7-year-olds and 13–14-year-olds) in 98 countries.[756–759] The average prevalence of AR across all centers was 8.5% for 6–7-year-olds and 14.6% in 13–14-year-olds.[756] In the 6–7-year age group, the lowest current symptom prevalence was observed in the Indian subcontinent (4.2%) and the highest in Latin America (12.7%). In the 13–14-year age group, the lowest prevalence was in Northern and Eastern Europe (9.2%), and the highest regional prevalence rates were recorded in Africa (18%) and Latin America (17.3%). Several follow-up studies of similar design have been performed on smaller scales in several countries across the world. For instance, such survey-based epidemiologic studies have been performed in children from Costa Rica (42.6% prevalence), Japan (18.7% in 6–8-year-olds, 26.7% in 13–15-year-olds), United Arab Emirates (46.5% in 6–7-year-olds, 51.3% in 13–14-year-olds), Nigeria (19.4% in 6–17-year-olds), Brazil (range of 45.3%–35.4% in children over 10 years of age), and Ecuador (48% in 3–5-year-olds).[760–765] These studies also indicate an overall increase in AR prevalence with age into young adulthood. Recent Chinese studies have estimated an AR prevalence averaging 28.6% in 6–12-year-olds in Wuhan and 28.9% in 5–18-year-olds in Zhongshan.[766,767]

The regional variations in reported AR prevalence highlight some limitations in questionnaire-based, "open" studies of AR prevalence.[768] Many of these studies might be over- or underestimating prevalence of AR because of disparities in responder education and researcher definitions of AR.[769] Also, one must consider differences accounted for by measuring point prevalence and lifetime prevalence of AR. Pols et al.[770] investigated AR prevalence by using physician-diagnosed and treated atopic disease in a primary care database consisting of 478,076 children and found the peak point-prevalence of AR to be 5.7% at 18 years. The lifetime cumulative incidence in this study was much higher at 16%–22.5%. A separate study conducted by Kurukulaaratchy et al.[771] in the Isle of Wight birth cohort (1456 participants) performed SPT to define AR and observed prevalence from 5.4% at 4 years to 27.3% at 18 years. In a separate longitudinal study comprising 5471 children from birth to 10 years, de Jong et al.[772] estimated a prevalence of allergic sensitization to be 32.2% when using skin testing results and 12.4% when using physician diagnosis.

Taken together, the available evidence indicates that the prevalence of AR in children increases with age into young adulthood. Moreover, the prevalence of AR has previously been reported to be increasing across the globe. It should be noted, however, that recently published data indicate that this trend of increasing AR prevalence may not persist into the future, although substantial geographic differences exist.[773] The underlying factors that determine prevalence are complex, multifactorial, and reviewed in detail in the sections that follow.

VII.C | Geographic variation and effect of climate on prevalence of allergic rhinitis

The prevalence of AR varies significantly based on geographic location. However, other factors such as population density (urban vs. rural) can further alter AR rates within the same locale. One important challenge in meaningfully comparing AR rates between locations is the variability created by differences in study subject recruitment and method of diagnosing AR. For example, Bauchau and Durham,[17] who diagnosed patients via serological IgE testing after a positive telephone screen, reported that Belgium had an AR prevalence of 28.5% (the highest of the European countries he evaluated). On the other hand, Bousquet et al.,[774] who skin tested randomly sampled subjects, reported a rate in Belgium of 16.4%, one of the lowest of 15 countries examined.

Given the difficulty in standardizing AR prevalence studies across different locations, there have been major international efforts to examine national prevalence rates of AR using standardized methods (i.e., ECRHS and ISAAC). These studies show marked geographic variation with a higher prevalence of AR in "English speaking" countries (i.e., United Kingdom [UK], Australia, New Zealand), a higher rate in Western Europe than in Eastern Europe, and a higher prevalence in countries with higher rates of asthma and sensitization to seasonal allergens.[775,776] However, these studies have evaluated national rates from only one or a few centers within each country, and substantial intra-country variation may occur. For example, the prevalence of AR varies from 9.6% to 23.9% in 18 major cities in China.[777]

Geographic variation in AR prevalence may also be impacted by climate change, which has an association with lengthening pollen seasons, increasing pollen counts, and broadening/altering the typical vegetative species for a location.[778] Climate change has been estimated to be associated with increased seasonal pollen exposures, and as a result, sensitizations are anticipated to more than double in the next few decades, particularly in colder climates that previously were spared from higher rates of seasonal AR.[779] Additionally, this increased environmental exposure has been shown to be associated with an increased risk of AR as well as patient symptoms of atopic nasal diseases.[780,781]

When assessing geographic variations associated with AR, differentiating between seasonal and perennial AR is also an important consideration not examined in the ECRHS or ISAAC studies. Smaller studies over more

limited geographic regions which have examined perennial AR suggest increased sensitivity rates in urban settings and colder climates.[782–785] Li et al.[783] theorized that urban dwellers participate in more indoor activities compared to their rural counterparts, amplifying their exposure to dust mites and possibly leading to increased sensitization to these perennial allergens. Additionally, some reports suggest exposure to urban pollutants may be associated with increased AR in children.[782]

Latitude plays a more questionable role with regards to perennial AR. For example, the prevalence of persistent AR was found to be higher in both Northern Europe and Northern China compared to their southern counterparts.[17,783] This may occur because those in colder climates spend more time indoors, increasing their exposure to dust mites and other perennial allergens. However, it has also been reported that peak months for AR outpatient visits were the same in most regions of China, regardless of the latitude.[786] Latitude may also an important determinant of seasonal AR. Allergenic plants are often characteristic for certain locations and the pollen concentrations of various species depend on the climate of a specific region.[778]

Overall, improved knowledge of the geographic influences, seasonal variations, and the role of climate change on AR prevalence is important in that it allows patients to anticipate and better self-manage their symptoms through avoidance techniques and preemptive use of pharmacologic therapies.[781,787]

VIII | RISK FACTORS AND PROTECTIVE FACTORS FOR ALLERGIC RHINITIS

VIII.A | Genetics

Hereditary factors play a role in both AR and non-allergic rhinitis with presence of disease in family members being the strongest risk factor.[788] Studies on twins have shown that genetic factors account for up to 70%–80% of interindividual variability in susceptibility to development of AR.[789,790] However, no single gene or polymorphism can account entirely for the hereditary effect. Many genes, along with their respective variants and complex interactions, contribute to disease initiation, persistence, and severity. In this section, the current literature on the genetics of AR is reviewed, with a focus on recent large-scale genome-wide association studies (GWASs) and evidence for shared genetics between allergic diseases. In addition, gene–environment interaction effects and epigenetics studies are briefly covered.

1 | Single nucleotide polymorphisms (SNPs) associated with allergic rhinitis

Genome-wide association studies. GWASs, with their unbiased approach that includes hundreds of thousands of common variants, have successfully identified important genes for complex diseases over the past decade (https://www.ebi.ac.uk/gwas/). Thirty-four GWASs involving AR (or seasonal AR/hay fever) have been published up to November 2021, of which nine (one exome-sequencing project) reported genome-wide significant hits (Table VIII.A). SNPs in *LRRC32* (leucine-rich repeat-containing protein 32) have been strongly associated with AR in five of the GWASs,[791–795] as well as with asthma,[792,796] eczema,[793,797] and other allergy-related comorbidities.[791,796,798] LRRC32 is known to regulate T cell proliferation, cytokine secretion, and TGF-β activation.[799] These associations support the concept of shared genetic mechanisms for AR and other allergy-related diseases. This concept is further supported by a GWAS on self-reported cat, dust mite, and pollen sensitization (as well as AR), which revealed 16 shared susceptibility loci with strong association ($p < 5 \times 10^{-8}$; *TLR*-locus top hit).[792] Strong overlap between top loci for sensitization and self-reported allergies also are found in two of the larger GWASs.[792,800] In a recent GWAS specifically designed to evaluate pleiotropy between asthma, eczema, and hay fever, a total number of 136 SNPs were identified at the genome-wide significant level (including 73 novel at the time), of which only six SNPs showed evidence for disease-specific effects.[801] In a follow-up study, additional novel loci for comorbid allergic disease were identified by applying a gene-based test of association.[802] The only larger exome-sequencing study published to date identified rare variants in *IL33*, a well-known gene associated with other types airway inflammation, including asthma.[803]

As expected, larger studies with better power allow for improved ability to accurately detect novel loci and potentially novel AR-related disease mechanisms. Recently, very large GWASs were able to confirm many of the previously identified susceptibility loci for AR, with top hits *HLA-DQB1/DQA1*, *IL1RL1*, *TLR1/10*, *WDR36*, and *LRRC32*.[794,795] A recent multi-institutional study comprising over 50,000 cases of AR identified the novel loci *IL7R*, which encodes the receptor for IL-7 (and TSLP) involved in immunoregulation, and *CXCR5*, a chemokine receptor involved in B cell migration.[795]

Candidate gene studies. The candidate gene approach for selecting disease-relevant genes is based on known molecular biology or gene function relevant to disease pathophysiology. Such studies in AR have identified several

TABLE VIII.A Key findings from genome-wide association studies on allergic rhinitis or hay fever

Author	Year	Study design	Sample size	Ethnicity	Top SNPs for AR	*p*-value	Nearby gene(s)	Protein function	LOE
Andiappan et al.[823]	2011	Nested case–control with replication	1132 AR cases 997 controls	Chinese	1) rs811930 2) rs505101	1) 7.3E-05 2) 1.3E-04	1) *MRPL4* 2) *BCAP (PIK3AP1)*	1) Protein synthesis within the mitochondrion 2) Protein tyrosine kinase	3
Ramasamy et al.[793]	2011	Meta-analysis of four cohorts	3933 AR cases 8965 controls	European ancestry	1) rs2155219 2) rs17513503 3) rs1044573	1) 3.8E-08 2) 7.4E-07 3) 9.7E-07	1) *LRRC32* or *C11orf30* 2)*TMEM232* or *SLCA25A46* 3) *ENTPD6*	1) LRRC32: T cell regulation, TGF-β activity. C11orf30: regulation of viral immunity and interferon pathways 2) Transmembrane protein 3) Catabolism of extracellular nucleotides	3
Hinds et al.[792]	2013	Private company data (23andMe)	46,646 total (look-up association for AR of GWAS top hits for self-reported allergy)	>97% European ancestry	1) rs1438673 2) rs2101521 3) rs10189629	1) 3.7E-19 2) 6.0E-17 3) 9.9E-15	1) *WDR36* 2) *TLR1-TLR6 - TLR10* 3) *IL1RL2 -IL1RL1*	1) Cellular processes and T cell activation 2) Pathogen recognition and activation of innate immunity 3) Pro-inflammatory effects, T helper cell function	3
Ferreira et al.[791]	2014	Meta-analysis of four cohorts/datasets	16,513 hay fever cases 17,256 controls	European ancestry	1) rs4833095 2) rs2155219 3 rs10197862	1) 4E-12 2) 7E-10 3) 2E-09	1) *TLR1* 2) *LRRC32* or *C11orf30* 3) *IL1RL1*	1) Pathogen recognition and activation of innate immunity 2) See above 3) Pro-inflammatory effects, T helper cell function	3

(Continues)

TABLE VIII.A (Continued)

Author	Year	Study design	Sample size	Ethnicity	Top SNPs for AR	*p*-value	Nearby gene(s)	Protein function	LOE
Bunyavanich et al.[824]	2014	Meta-analysis of seven cohorts	2712 AR cases 2921 controls	European ancestry, Latino (L), African American	1) rs17133587 2) rs6583203 3) rs7780001	1) 4.5E-09 (L) 2) 1.4E-08 (L) 3) 2.0E-08 (all groups)	1) *AKR1E2* 2) *DLG1* 3) *FERD3L*	1) NAD(P)H-dependent oxido-reduction 2) Scaffolding protein involved in cell metabolism 3) Transcription factor	3
Waage et al.[795]	2018	Meta-analyses	59,762 AR cases 152,358 controls	European ancestry	Top 5 SNPs in previously known loci (21 in total): 1) rs34004019 2) rs950881 3) rs5743618 4) rs1438673 5) rs7936323 Top 5 SNPs in novel loci (20 in total): 1) rs7717955 2) rs63406760 3) rs28361986 4) rs2070902 5) rs1504215	Known loci: 1) 1.00 × 10–30 2) 1.74 × 10–30 3) 4.38 × 10–27 4) 3.15 × 10–26 5) 6.53 × 10–24 Novel loci: 1) 3.78 × 10–32 2) 2.54 × 10–24 3) 2.32 × 10–23 4) 6.19 × 10–19 5) 1.54 × 10–18	Known loci: 1) *HLA-DQB1, HLA-DQA1* 2) *IL1RL1* 3) *TLR1, TLR10* 4) *CAMK4, WDR36* 5) *LRRC32, C11orf30* Novel loci: 1) *CAPSL, IL7R* 2) *CDK2AP1, C12orf65* 3) *CXCR5, DDX6* 4) *AL590714.1, FCER1G* 5) *BACH2, GJA10*	Known loci: 1) Antigen presentation 2) See above 3) See above 4) See above 5) See above Novel loci: 1) CAPSL: Calcium ion binding involved in adipogenesis, IL7R: Receptor for IL-7 (and TSLP); immunoregulation 2) CDK2AP1: cell-cycle kinase inhibitor 3) CXCR5: Involved in B-cell migration, DDX6: Involved in RNA metabolism 4) FCER1G: Component of the high-affinity IgE receptor 5) BACH2: Transcriptional regulator, GJA10: Gap junction protein	3

(Continues)

TABLE VIII.A (Continued)

Author	Year	Study design	Sample size	Ethnicity	Top SNPs for AR	*p*-value	Nearby gene(s)	Protein function	LOE
Johansson et al.[794]	2019	UK biobank	18,915 hay fever cases 327,630 controls	European ancestry	Top 5 SNPs in previously known loci (27 in total): 1) rs11236797 2) rs7728912 3) rs66819621 4) rs72823641 5) rs7744020 Novel locus (1 in total): 1) rs12920150	Known loci: 1) 4.97E-32 2) 4.50E-26 3) 2.20E-25 4) 2.35E-25 5) 3.80E-25 Novel locus: 1) $1.02 \times 10{-}9$	Known loci: 1) *LRRC32, EMSY* 2) *WDR36* 3) *TLR1* 4) *IL1RL1 IL18R1* 5) *HLA-DQB1* Novel locus: 1) *CBLN1*	Known loci: 1) See above 2) See above 3) See above 4) See above 5) See above Novel locus: 1) Synaptic activity	3
Sakaue et al.[825]	2021	Japan biobank	18,593 seasonal AR (pollinosis) 153,666 ctrls	Japanese	1) rs3213749 2) rs1050538 3) rs1140310 4) rs10519067	1) 4.35E-09 2) 3.08E-13 3) 8.21E-13 4) 3.67E-08	1) *CD207* 2) *HLA-B* 3) *HLA-DQB1* 4) *RORA*	1) Antigen presentation 2) Antigen presentation 3) See above 4) Key regulator of embryonic development, cellular differentiation	3
Backman et al.[803]	2021	UK Biobank (exome sequencing project)	73,313 seasonal AR cases 280,381 controls	European ancestry	9:6255967:G:C	9.52E-27	*IL33*	Maturation and activation of immune cells, including Th2 cells.	3

Abbreviations: AR, allergic rhinitis; GWAS, genome-wide association study; IL, interleukin; LOE, level of evidence; SNP, single nucleotide polymorphism; TGF, transforming growth factor; Th2, T helper 2; TSLP, thymic stromal lymphopoietin; UK, United Kingdom.

well-replicated genes, as summarized previously.[804–806] Notably, results from many candidate gene studies often overlap with GWASs results. For example, SNPs in genes involved in antigen presentation (e.g., *HLA-DQA1*), pathogen recognition (e.g., *TLR2,7,8*), IL signaling, and pro-inflammatory signaling (e.g., *IL13*, *IL18*, *TSLP*) have been highlighted.[804–810] However, many of the candidate gene study findings have not been well-replicated across studies and populations.[811,812] This could be due to lack of power from small sample sizes, inconsistent phenotype definition, or lack of true disease association.

2 | Gene-environment interactions and epigenetic effects

Epigenetic mechanisms, defined as changes in phenotype or gene expression caused by mechanisms (e.g., methylation) other than changes in the underlying DNA sequence, have been proposed to constitute a link between genetic and environmental factors. Recent studies show that DNA methylation in children is very strongly influenced by well-known risk factors for allergic diseases, such as tobacco smoking/maternal smoking during pregnancy,[813] air pollution exposure,[814] and length of pregnancy.[815] However, it is not currently known if these methylation changes are part of a causal pathway in the development of AR (and asthma), or if these epigenetic biomarkers are simply markers of exposure. Still, several studies have convincingly linked methylation profiles to AR[816–818] and IgE-related outcomes.[819,820] Recently, methylation signatures in nasal epithelial brushes were shown to be strongly associated with AR (and also asthma).[821] Also, epigenetic studies have highlighted shared molecular mechanisms underlying asthma, eczema and AR pathophysiology.[822]

In summary, a family history of AR remains one of the strongest risk factors for disease development, and strong associations with genes involved in antigen presentation (e.g., *HLA* genes), T cell activation (e.g., *LRRC32*), and innate immunity (e.g., *TLRs*) have been identified. Shared genetic mechanisms for AR and other allergy-related diseases clearly exist. These novel findings lend insight into mechanisms underlying the pathogenesis of AR, as well as comorbid atopic conditions, and may aid drug discovery efforts for novel disease targets. With increasing evidence for the role of epigenetics in AR, future research should also focus on investigating mechanisms, thereby providing a functional explanation for the link between genetics variants, environmental exposures, and disease development.

Risk factors – genetics

Aggregate grade of evidence: C (Level 3: 8 GWASs and 1 exome sequencing study. Candidate gene studies not assessed regarding grade of evidence, Table VIII.A).

VIII.B | Risk factors

VIII.B.1 | Inhalant allergens – in utero and early childhood exposure

VIII.B.1.a | *Mites*

While there have not been any major new studies published on this topic since 2016, three older prospective birth cohorts (not included in ICAR-Allergic Rhinitis 2018[1]) concur with the conclusion that there is no established association of early mite exposure and the development of AR.[826–828] Studies showing that early life dust mite exposure results in early sensitization (e.g., positive skin tests without symptoms) and AR later in childhood are often limited in that they fail to measure and account for dust mite allergen concentrations in the home.[829] Likewise, other studies implement dust mite reduction interventions without pre and post dust mite allergen measurements and/or combine environmental changes with dietary changes[830–832] (Table VIII.B.1.a).

It has been suggested that the effect of dust mite exposure on sensitization may follow a bell-shaped dose response curve, with both very low and very high exposure being protective.[833–837] Exposure levels that are less than 2 mg dust mite allergen/gram of house dust may be a "safe" level for atopic children for primary allergic disease prevention.[838,839] The risk of allergic disease in childhood may also depend upon mono- versus polysensitization at age 1 or 2.[840]

Risk factors – in utero and early childhood exposure to mites

Aggregate grade of evidence: C (Level 3: 7 studies, Table VIII.B.1.a)

VIII.B.1.b | *Pollen*

Since ICAR-Allergic Rhinitis 2018,[1] no new studies were identified that addressed the impact of early pollen exposure on the development of AR; furthermore, the two previous studies were inconclusive.[780,843] While very few

TABLE VIII.B.1.a Evidence table – risk factors for development of allergic rhinitis: in utero and early childhood exposure to dust mites

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Schoos et al.[841]	2016	3	Prospective birth cohort	399 children (7–13 years old) from COPSAC study	Der p 1 in bed dust sample at 1 year Der f 1 in bed dust sample at 1 year	Der p 1: no association with AR at 13 years (OR 0.96; 95% CI 0.88–1.05) Der f 1: borderline association with AR at 13 years (OR 0.89; 95% CI 0.79–1.0, $p = 0.05$)
Illi et al.[842]	2014	3	Prospective birth cohort	513 children (5 years old) from PAULA study	Dust mite allergen exposure at 3 months (measured as allergen levels in the living room floor and in the mother's or child's mattress)	No association with current AR (OR not reported)
Gehring et al.[828]	2012	3	Prospective birth cohort	416 children of atopic mothers (8 years old) from PIAMA study	Der p 1 and Der f 1 exposure at 3 months (measured as levels in child's mattress)	No association with AR at 8 years (OR presented in graphic format only)
Toelle et al.[826]	2010	3	Prospective birth cohort	450 children (8 years old) from Childhood Asthma Prevention Study	Dust mite exposure 0–5 years (measured as allergen levels in child's bed)	No association with AR at age 8 (OR not reported; absolute risk reduction −4.5; 95% CI −12.9–4.0)
Marinho et al.[46]	2007	3	Whole-population birth cohort	815 children (5 years old) from MAAS study	Der p exposure at 0–5 years (measured as allergen levels recovered from child's bed, child's bedroom floor, parental bed, and lounge floor)	No association at age 5 on multivariate analysis and no difference in atopic versus nonatopic CRC In univariate analysis there was protective factor for current CRC (OR 0.81; 95% CI 0.68–0.98)
Marks et al.[827]	2006	3	Prospective birth cohort	516 children (5 years old) from Childhood Asthma Prevention Study	Dust mite exposure at 0–5 years (measured as allergen levels recovered from child's bed)	No association with AR at age 8 (RR 1.08; 95% CI 0.88–1.33)
Kulig et al.[754]	2000	3	Prospective birth cohort	587 children (7 years old) from MAAS study	Mite (Der p 1, Der f 1) exposure at 0–18 months (measured as allergen levels obtained from carpet dust samples)	No association with seasonal AR (OR not reported)

Abbreviations: AR, allergic rhinitis; CI, confidence interval; COPSAC, Copenhagen Prospective Study on Asthma in Childhood; CRC, chronic rhinitis conjunctivitis; LOE, level of evidence; MAAS, Manchester Asthma and Allergy Study; OR, odds ratio; PAULA, Perinatal Asthma and Environment Long-term Allergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; RR, relative risk.

[a]ORs are unadjusted and reported with 95% CI.

TABLE VIII.B.1.b Evidence table – risk factors for the development of allergic rhinitis: in utero and early childhood exposure to pollen

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Erbas et al.[780]	2013	3	Prospective birth cohort	620 children (6–7 years old) from MACS RCT (with at least 1 first-degree family member with a history of eczema, asthma, hay fever, severe food allergy)	Pollen exposure[b] during infancy (0–3 months)	Risk factor for hay fever (OR 1.14; 95% CI 1.001–1.29)
Kihlstrom et al.[843]	2002	4	Cross-sectional	583 children with atopic heredity (4–5 years old)	High-dose exposure to birch pollen at 0–3 months High-dose exposure to birch pollen at 1 year	Exposure at 0–3 months: no association with allergic rhinoconjunctivitis (OR 1.0; 95% CI 0.6–1.8) Exposure at 1 year: no association with allergic rhinoconjunctivitis (OR 1.3; 95% CI 0.8–2.2)

Abbreviations: CI, confidence interval; LOE, level of evidence; MACS, Melbourne Atopy Cohort Study; OR, odds ratio; RCT, randomized controlled trial.
[a]ORs are adjusted and reported with 95% CI.
[b]Defined as birth "inside" or "outside" the pollen season and by measuring daily 24-h average pollen concentrations for grass and others (which include trees, weeds, and herbs).

studies longitudinally track pollen counts and the subsequent development of AR, several studies have demonstrated that the development of pollen sensitization in early life is associated with AR in later childhood.[844,845] In fact, following initial pollen sensitization in children, there is a progressive increase in both the level and number of pollen sensitizations.[846] While seasonal AR symptoms are rare before age 3, between 3 and 12 years, the percentage of new cases increases at a rate of approximately 2% per year.[844,847,848] With the environmental changes associated with global warming, such as increased length of pollination season, we are starting to see higher rates of pollen sensitization in young children which will likely lead to increased AR in adolescence and adulthood[849] (Table VIII.B.1.b).

Focusing on early life sensitization rather than pollen exposure may be a more productive research pathway. Sensitization to one or more allergenic molecules (e.g., Phl p 1) at age 4 has been shown to be a better predictor of AR at age 16, then a positive test to Timothy extract.[850] Likewise, higher levels of Bet v 1 or finding multiple pathogenesis-related class 10 allergens at age 4 helped to predict AR to birch in adolescence.[851] With the difficulty of conducting longitudinal pollen studies and the inability to control the year-to-year variation in pollen counts or the young child's level of exposure, the use of CRD in early childhood may prove to be the best tool for predicting pollen-induced AR in adolescence and adulthood.

Risk factors – in utero and early childhood exposure to pollen

Aggregate grade of evidence: C (Level 3: 1 study, level 4: 1 study; Table VIII.B.1.b)

VIII.B.1.c | *Animal dander*

Since the ICAR-Allergic Rhinitis 2018,[1] high quality studies have found that early life exposure to animal dander may be protective from the development of AR,[852–854] while two lower quality studies concluded that it was a risk factor.[855,856] A 2020 systematic review and pooled analysis of five cohort studies found a protective effect for early life exposure to cats and dogs.[852] Two additional prospective birth cohorts found a similar protective effect.[853,854] Animal exposure during the first 2 years of life offers the best possibility for protection.[840,853,854,857] However, when reviewing all the major studies published since 2000 one finds that the majority of studies find early life animal dander exposure to be either a risk factor or unassociated with

the development of AR. One possibility for this disparity is that lower quality studies were unable to account for all the confounding factors (e.g., atopic family history; community prevalence of pets; pet gender and breed; number of household pets; exposure to other indoor allergens, irritants, microorganisms; and child's microbiome).[858] A combination of factors, such as the addition of probiotics to the child's diet, may enhance the protective effect of early animal dander exposure.[859] At this time, it is not possible to make evidence-based recommendations regarding early life animal exposure (Table VIII.B.1.c).

Risk factors – in utero and early childhood exposure to pets

Aggregate grade of evidence: C (Level 3: 18 studies, level 4: 28 studies*; Table VIII.B.1.c)
*Level 3 studies are listed in table; level 4 studies are referenced.

VIII.B.1.d | *Fungal allergens*

Further supporting the ICAR-Allergic Rhinitis 2018[1] conclusions, all newly reviewed studies, many having a higher evidence level, concluded that early life exposure to fungal allergens or dampness is a risk factor for AR.[889–891] Unfortunately, existing studies have not been able to establish a dose–response relationship for mold exposure and the subsequent development of AR nor have they been able to define a threshold below which no effect of mold exposure on the health of the general or high-risk population would be expected.[892,893] It may be that the presence of fungal diversity alone or in combination with microbial diversity could play an even greater role than levels of indoor mold.[892] The role of outdoor fungal spores, which can vary widely by geographical location, has rarely been considered. While most studies adjust for demographic characteristics, the co-exposure levels or symptoms produced by other allergens (e.g., HDM, pollen, pet dander) are rarely studied. Consistent results from well-designed longitudinal studies are needed before one can determine the causal effect of early life exposure to fungal components on the future development of AR (Table VIII.B.1.d).

Risk factors – in utero and early childhood exposure to fungal allergens or dampness

Aggregate grade of evidence: C (Level 3: 3 studies, level 4: 12 studies; Table VIII.B.1.d)

Summary for the effect of inhalant allergens (in utero and early childhood exposure) as a risk factor for the development of AR. The impact of early inhalant allergen exposure (HDM, pollen, animal dander, fungal allergens) on the development of AR remains ambiguous. Early life allergen exposures identified as significant risk factors for AR at age 6 are often found to be insignificant by age 12 or later. Despite several in-depth reviews and a growing body of literature,[852,892,900,901] no definitive conclusions may be drawn regarding risk-benefit of early inhalant allergen exposure, and further research is welcomed to address this unmet need.

VIII.B.2 | Food allergens

Historically, there has been concern that highly allergenic foods in the maternal as well as the infant's diet would lead to the development of food allergy and subsequently to other atopic diseases, such as AR. Since ICAR-Allergic Rhinitis 2018,[1] six publications have looked at the effect of early introduction of specific foods (e.g., fish and peanut) and diverse foods into the infant's diet and the subsequent development of AR.[902–907] Older publications (not part of ICAR-Allergic Rhinitis 2018) have looked at the effect of fish and tree nuts in the maternal diet[908–910] and early introduction of specific or diverse foods into the infant's diet[911–914] (Table VIII.B.2).

A maternal diet that avoids or strictly limits highly allergenic foods, for example, cow's milk, egg, peanut, and fish has not been shown to reduce the risk of AR.[909,915–917] However, a maternal diet high in oily fish or tree nuts has been reported to reduce the risk of AR.[908,918]

Early sensitization to food has been linked to the development of AR in childhood.[754,919,920] A meta-analysis of high-risk infants found that food sensitization at age less than 24 months increased the risk of AR during childhood.[919] In a prospective birth cohort, food allergy at 4–10 years old, however, had no association with AR at age 18 or 26; whereas food sensitization (independent of symptoms) increased the risk of AR at both age 18 and 26.[904] Additional cohort studies have found that food sensitization at age less than 24 months, especially when combined with inhalant sensitization, increases the risk of AR in childhood.[920–924]

Multiple studies have evaluated the effect of early introduction of highly allergenic foods into the infant's diet. In a prospective RCT, cow's milk, egg, and peanut were avoided during the last trimester of pregnancy and during lactation and infants avoided milk, egg, peanut, and fish for 1, 2, 3, and 3 years respectively. By age 7, the food avoidance group had no reduced rates of AR.[915] In an open label RCT, there was no association of avoiding or consuming peanuts from 4 to 11 months on the risk of developing AR at age 5 years.[903]

TABLE VIII.B.1.c Evidence table – risk factors for the development of allergic rhinitis: in utero and early childhood exposure to animal dander

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Early exposure to animal dander as a protective factor for AR (Level 3 studies listed. Level 4 studies referenced.[860–865])						
Gao et al.[852]	2020	3	Systematic review and pooled analysis of 5 cohort studies	Not provided (see individual studies)	Exposure to dogs or cats in early life (0–5 years for 4 studies) or anytime (1 study)	Cat exposure has a protective effect for AR (RR 0.60; 95% CI 0.33–0.86) Dog exposure has a protective effect for AR (RR 0.68; 95% CI 0.44–0.90)
Ojwang et al.[853]	2020	3	Prospective birth cohort	3782 children (5 years old)	Exposure at home to cats or dog or visit to building housing farm animals during first year of life	Dogs: protective factor for AR (OR 0.72; 95% CI 0.53–0.97) Exposure to cats and farm animals non-significant
Al-Tamprouri et al.[854]	2019	3	Prospective birth cohort	834 children (13 years old)	Exposure at home to cats or dogs during 1st year of life	Cats; protective factor for AR (aOR 0.40; 95% CI 0.21–0.28, $p = 0.007$) Dogs; non-significant (aOR 0.82; 95% CI 0.47–1.45, $p = 0.503$)
Lodge et al.[1006]	2012	3	Prospective birth cohort	620 children (12 years old) with a family history of allergic diseases	Exposure to cats or dogs at birth	Borderline protective factor for hay fever (OR 0.7; 95% CI 0.5–1.02) Stronger protective effects if children of non-sensitized fathers (OR cats alone 0.3; 95% CI 0.2–0.8); (OR cats or dogs 0.4; 95% CI 0.2–0.8)
Alm et al.[857]	2011	3	Prospective birth cohort	4465 children (4–5 years old); 246 children with current AR	Exposure to cats at 1 year	Protective factor for AR (unadjusted OR 0.5; 95% CI 0.4–0.8; not significant in multivariate analysis)
Lampi et al.[866]	2011	3	Prospective birth cohort	5509 adults (31 years old)	Exposure to farm animals (cows, pigs, sheep, poultry, minks) Exposure to cats or dogs at age less than 7 years old	Farm animals: borderline protective factor for AR ever (OR 0.9; 95% CI, 0.7-1.03) Cats & dogs: borderline protective factor for AR (OR 0.8; 95% CI 0.7–0.96); (OR dog 0.9; 95% CI 0.8–1.01)
Perzanowski et al.[867b]	2008	3	Birth cohort	257 children (5 years old) from African American or Dominican mothers	Cat ownership (up to age of health outcomes)	Protective factor for AR at 5 years old (OR 0.4; 95% CI 0.2–0.9)

(Continues)

TABLE VIII.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Nafstad et al.[868b]	2001	3	Birth cohort	2531 children (4 years old)	Exposure to cats at birth Exposure to dogs at birth	Cats: borderline protective factor for AR (OR 0.5; 95% CI 0.2–1.4) Dogs: minimal protective factor for AR (OR 0.8; 95% CI 0.4–1.6)
Early exposure to animal dander as a risk factor for AR. (All studies level 4 and are referenced.[855,856,865,869–877])						
Early exposure to animal dander is not associated with AR (Level 3 studies listed. Level 4 studies referenced.[869,871,873,878–884])						
Schoos et al.[841]	2016	3	Prospective birth cohort	399 children (13 years old) from COPSAC study	Prenatal (3rd trimester of pregnancy) and perinatal (at 1 year) cat exposure, and Fel d 1 in dust samples (at 1 year) Prenatal (at 3rd trimester of pregnancy) and perinatal (at 1 year) dog exposure and Can f 1 in dust samples (at 1 year)	Cat: no association with AR at 13 years old (OR prenatal 1.2; 95% CI 0.44–3.82); (OR perinatal 1.33; 95% CI 0.53–3.42); (OR Fel d 1 1.10; 95% CI 1.2–4.96) Dog: no association with AR at 13 years old (OR prenatal 0.95; 95% CI 0.21–4.3); (OR perinatal 0.86; 95% CI 0.19–3.89); (OR Can f 1 1.0: 95% CI 0.87–1.16)
Illi et al.[842]	2014	3	Prospective birth cohort	513 children (5 years old) from PAULA study	Cat allergen exposure at 3 months (measured as allergen levels in the living room floor and in the mother's or child's mattress) and cat ownership 0–1 years old	No association with current AR and cat allergen exposure or cat ownership 0–1 years of age (OR not reported as value, only in figure)
Kellberger et al.[885]	2012	3	Prospective population-based cohort	2810 adolescents (15–18 years old)	Pet (cat, dog, hamster, guinea pig, rabbit) ownership at 0–1 years old	No association with incidence/persistence of physician-diagnosed AR
Lodrup Carlsen et al.[886]	2012	3	Prospective birth cohort (pooled analysis of 11 cohorts)	22,840 children (6–10 years old)	Pet (cat, dog, bird, rodent) ownership at 0–2 years old	No association with AR (OR cat only 1.02; 95% CI 0.8–1.3); (OR dog only 0.8; 95% CI 0.6–1.1); (OR cat and dog 0.8; 95% CI 0.4–1.4); (OR bird only 1.3; 95% CI 0.9–1.8); (OR rodent only 0.8; 95% CI 0.5–1.5)
Lampi et al.[866]	2011	3	Prospective birth cohort	5509 adults (31 years old)	Maternal work with farm animals (cows, pigs, sheep, poultry, minks) during pregnancy	No association with AR (OR 0.9; 95% CI 0.7–1.2)
Sandini et al.[859]	2011	3	Prospective birth cohort	1223 children (5 years old) born to allergic families	Dog/cat at home at 0–2 years old or 0–5 years old	No association with AR (OR 0–2 years 0.98; 95% CI 0.54–1.79); (OR 0–5 years 0.93; 95% CI 0.54–1.61)

(Continues)

TABLE VIII.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Chen et al.[887b]	2008	3	Prospective birth cohorts	2355 children (6 years old) from GINI (intervention and nonintervention) and LISA studies	Dog ownership or regular contact outside home in first year of life	No association with AR (LISA: OR dog ownership 0.5, 95% CI 0.2–1.2; OR regular contact 1.4, 95% CI 0.9–2.3); (GINI intervention: OR dog ownership 0.8, 95% CI 0.4–1.6; OR regular contact 1.3, 95% CI 0.8–1.9); (GINI nonintervention: OR dog ownership 0.9, 95% CI 0.4-2.0; OR regular contact 0.5, 95% CI 0.3–0.9)
Chen et al.[888]	2007	3	Prospective birth cohort	2166 children (4–6 years old, hay fever: 66/1599) from LISA study	Cat allergen exposure at 3 months (measured as Fel d 1 levels from children's or parents' mattress)	No association with doctor-diagnosed hay fever (OR parents' mattress 0.9; 95% CI 0.5–1.5); (OR children's mattress 0.7; 95% CI 0.4–1.1)
Marinho et al.[46b]	2007	3	Whole-population birth cohort	815 children (5 years old) from MAAS study	Cat and dog ownership and major allergen exposure at 0–5 years old (measured as allergen levels recovered from child's bed, child's bedroom floor, parental bed, and lounge floor)	No association with current rhinoconjunctivitis (unadjusted OR cat ownership 1.14; 95% CI 0.71–1.83); (unadjusted OR Fed d 1 exposure 1.02; 95% CI 0.91–1.13); (unadjusted OR dog ownership 1.0; 95% CI 0.58–1.70); (unadjusted OR Can f 1 exposure 1.03; 95% CI 0.91–1.17)
Kulig et al.[754]	2000	3	Prospective birth cohort	587 children (7 years old) from MAAS study	Cat (Fel d 1) exposure at 0–18 months (measured as allergen levels obtained from carpet dust samples) Pets in household (at 18 months)	Fel d 1 exposure: no association with SAR (OR not reported) Pets in household: no association with SAR (OR not reported)

Abbreviations: aOR, adjusted odds ratio; AR, allergic rhinitis; CI, confidence interval; COPSAC, Copenhagen Prospective Study on Asthma in Childhood; GINI, German Infant Nutritional Intervention; LISA, Lifestyle-Immune-System-Allergy; LOE, level of evidence; MAAS, Manchester Asthma and Allergy Study; OR, odds ratio; PAULA, Perinatal Asthma and Environment Long-term Allergy; RR, relative risk; SAR, seasonal allergic rhinitis.

[a]All ORs are adjusted unless differently specified and are reported with 95% CI.

[b]Part of Gao meta-analysis.

TABLE VIII.B.1.d Evidence table – risk factors for development of allergic rhinitis: in utero and early childhood exposure to fungal allergens

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Early exposure to fungal allergens as a risk factor for AR						
Behbod et al.[890]	2015	3	Birth cohort	406 children (12–13 years old) asthmatic/ allergic parents from metropolitan Boston, Massachusetts	Exposure to high levels of culturable *Aspergillus* in bedroom airborne dust at 0–3 months	Risk factor for doctor-diagnosed AR (HR 1.39; 95% CI 1.11–1.74)
				265 children (12–13 years old) asthmatic/allergic parents from metropolitan Boston, Massachusetts	Exposure to high levels of culturable *Cladosporium* from outdoor air at 0–3 months	Risk factor for doctor-diagnosed AR (HR 2.12; 95% CI 1.14–3.92)
Tischer et al.[889]	2011	3	Meta-analysis of six prospective birth cohorts	30,746 children (3–10 years old)	Exposure to visible mold and/or dampness at 0–2 years	Risk factor for AR symptoms at age 6–8 years (OR 1.12; 95% CI 1.02–1.23) or at any point age 3–10 years (OR 1.18; 95% CI 1.09–1.28)
Ellie et al.[891]	2021	4	Cross-sectional	7366 children attending daycare/elementary school from CCHH (3–8 years old)	Perinatal home indoor exposure to visible mold/flooding damage/suspected moisture problem	Risk factor for doctor-diagnosed rhinitis based on visible mold (OR 1.55; 95% CI 1.13–2.14); flooding damage (OR 2.2; 95% CI 1.38–3.25); moisture problem (OR 1.49; 95% CI 1.10–2.03)
Deng et al.[894]	2016	4	Cross-sectional	2598 children (3–6 years old) attending kindergarten	Prenatal (whole pregnancy) or postnatal (from birth to current) exposure to indoor mold/dampness	Risk factors for rhinitis-like current symptoms: prenatal (OR 1.5; 95% CI 1.2–1.9); postnatal (OR 2.1; 95% CI 1.6–2.8)
Lin et al.[895]	2016	4	Cross-sectional	4246 children (3–8 years old) from 18 daycare centers	Visible indoor mold (weekly/sometimes vs. never) at 0–2 years	Risk factor for new onset of rhinitis symptoms (OR 1.3; 95% CI 1.01–1.6) Exposure was a significant risk factor for the remission of rhinitis (OR 0.6; 95% CI 0.3–0.9)
Lam et al.[883]	2014	4	Cross-sectional	508 preschool children (4–6 years old)	Exposure to moisture/mold <1 year	Risk factor for rhinoconjunctivitis (OR 2.1; 95% CI 1.2–3.8)

(Continues)

TABLE VIII.B.1.d (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions[a]
Kim et al.[882]	2012	4	Cross-sectional	4554 school children (mean age 9.50 years old, SD 1.73)	Mold exposure in house during infancy	Risk factor for current AR (OR 1.8; 95% CI 1.4–2.4)
Lombardi et al.[871]	2010	4	Cross-sectional	20,016 children (median age 7 years old) from SIDRIA-2 Study	Mold exposure at 0–1 year	Risk factor for current rhinoconjunctivitis (unadjusted OR 1.4; 95% CI 1.2–1.6)
Ibargoyen-Roteta et al.[872]	2007	4	Cross-sectional	3360 school children (5–8 years old)	Having mold on walls at 0–1 year	Risk factor for allergic rhinoconjunctivitis (OR 2.5; 95% CI 1.5–4.0)
Kuyucu et al.[896]	2006	4	Cross-sectional	2774 children (9–11 years old)	Dampness/mold at 1 year	Risk factor for AR (OR 1.7; 95% CI 1.3–2.3)
Bornehag et al.[897]	2005	4	Cross-sectional	10,851 children (1–6 years old)	Visible mold or damp spots in the child's or parent's bedroom at 1–6 years	Risk factor for rhinitis (OR 2.7; 95% CI 1.4–5.4)
Early exposure to fungal allergens is not associated with AR						
Thacher et al.[898]	2017	3	Birth cohort	3798 adolescents (16 years old) from BAMSE study; 785 with AR	Exposure to mold or dampness at 2 months	Risk factor for AR (OR 0.88; 95% CI 0.74–1.05, $p = 0.14$); and for NAR (OR 1.41; 95% CI 1.03–1.93, $p = 0.03$)
Deng et al.[894]	2016	4	Cross-sectional	2598 children (3–6 years old) attending kindergarten	Prenatal (during the whole pregnancy) or postnatal (from birth to the current) exposure to indoor mold or dampness	No association with AR: prenatal (OR 0.7; 95% CI 0.4–1.1); postnasal (OR 1.0; 95% CI 0.6–1.7)
Yang et al.[876]	2014	4	Cross-sectional	7389 school children (mean age 13.9 years, SD 0.9)	Mold exposure during infancy	No association with AR (OR 0.99; 95% CI 0.8–1.3)
Biagini et al.[899]	2006	4	Cross-sectional	585 infants (1-year old) born to families with at least 1 parent with positive SPT	High mold exposure (mold in 1 room ≥ 0.2 m^2 or a combined area of visible mold and water damage on the same surface ≥ 0.2 m^2) during early infancy (average 7.5 months) Low mold exposure (mold in one room <0.2 m^2 or a combined area of visible mold and water damage on the same surface <0.2 m^2) during early infancy (average 7.5 months)	No association with AR at low (OR 1.2; 95% CI 0.6–2.5) or high levels (OR 3.2; 95% CI 0.7–14.8)

Abbreviations: AR, allergic rhinitis; BAMSE, Barn/Child Allergy Milieu Stockholm Epidemiology; CCHH, China Child Health and Home study; CI, confidence interval; HR, hazard ratio; LOE, level of evidence; NAR, non-allergic rhinitis; OR, odds ratio; SD, standard deviation; SIDRIA-2, Studi Italiani sui Disturbi Respiratori del l'Infanzia el Ambiente; SPT, skin prick test.

[a]ORs are adjusted unless otherwise specified.

TABLE VIII.B.2 Evidence table – risk factors for development of allergic rhinitis: in utero and early childhood exposure to food allergens

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
du Toit et al.[903]	2018	2	Randomized, open-label, controlled trial	640 children (60 months of age)	Diet containing or avoiding peanut/ peanut products from 4–11 months until 60 months of age in high-risk infants	Risk of developing AR at age 60 months not significantly different between those who consumed or those who avoided peanut/peanut products
Alduraywish et al.[919]	2016	2	Meta-analysis of high-risk birth cohorts	2621 children (4–8 years old), 4 birth cohorts	Food sensitization in first 2 years of life	Risk factor for AR (OR 3.1; 95% CI 1.9–4.9)
Ierodiakonou et al.[902]	2016	2	SRMA of observational studies, subgroup analysis (GRADE)	10,313 children (4 years or younger); 3112 children (5–14 years old)	Introduction of dietary fish before 6–12 months old	Reduced risk for AR at age ≤4 years (OR 0.59; 95% CI 0.40–0.87; high heterogeneity [$I^2 = 59\%$]) Reduced risk for AR at age 5–14 years (OR 0.68; 95% CI 0.47–0.98) In sensitivity analysis excluding studies with high/unclear risk bias, the reduced risk for AR at age ≤4 was not significant
Zeiger and Heller[915]	1995	2	RCT	165 children (7 years old): 59 food avoidance 106 standard diet	Maternal avoidance of cow's milk, egg, and peanut during last trimester of pregnancy and lactation; infant avoidance of cow's milk until age 1 year, egg until age 2 years, and fish until age 3 years	No association with development of AR by age 7 years Children with food allergy by age 4 years had a higher prevalence of AR and asthma at 7 years
Lilja et al.[916]	1989	2	RCT	163 infants (18 months old) of high-risk mothers: 79 mothers with egg and milk restricted diet 83 had daily ingestion of one egg and 11 oz milk	Maternal diet very low in egg and milk during last 3 months of pregnancy	No association with the development of AR at 18 months
Falth-Magnusson and Kjellman[917]	1987	2	RCT	212 infants (18 months old) of high-risk mothers: 104 mothers on milk and egg avoidance diet 108 mothers on normal diet including milk and egg	Maternal diet avoiding egg and milk from 28 weeks of pregnancy to delivery and low levels egg and cow's milk during 6 months of lactation	No association with the development of rhinoconjunctivitis at 18 months

(Continues)

TABLE VIII.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ekelund et al.[926]	2021	3	Prospective birth cohort	6796 children (6 years old)	Effect of timing of introducing complementary foods into infant's diet	No association of timing of introducing complementary foods into the diet and AR at age 6
Fong et al.[904]	2021	3	Prospective birth cohort	1456 adults (age 18–26 years old)	Food allergy or food allergen sensitization at age 4–10 years	No association with food allergy at age 4 and 10 and rhinitis at age 18 or 26 Food allergen sensitization at age 4 increased risk for rhinitis at age 18 (OR 3.93; 95% CI 1.58–9.78, $p = 0.003$) Food allergen sensitization at age 10 increased risk for rhinitis at age 18 (OR 13.26; 95% CI 4.60–38.25, $p < 0.001$) and at age 26 (OR 2.59; 95% CI 1.26–5.30, $p = 0.009$)
Oien et al.[906]	2019	3	Prospective birth cohort	2245 children (6 years old)	Effect of early introduction of fish into infant's diet	Earlier versus later introduction of fish into the diet (e.g., <9 months vs. 12 months) is associated with reduced risk of allergic rhinoconjunctivitis (OR 0.86; 95% CI 0.75–0.98)
Markevych et al.[907]	2017	3	Prospective birth cohort	2518 children (age 3–15 years old)	Diet diversity within the first 12 months of life	In children with early skin symptoms, the introduction of 8 food groups before 12 months reduced the risk of AR (OR 0.73; 95% CI 0.46–1.14) In children without early skin symptoms, high food diversity increased the risk of AR (3rd vs. lowest quartile for foods introduced: OR 2.12; 95% CI 1.04–4.29)
Nwaru et al.[911]	2014	3	Prospective birth cohort	442 high-risk children (6 years old)	Effect of dietary diversity throughout the first 12 months of life	Less diet diversity increased risk of AR at age 6 If <7 (vs. >8) food items in diet at 6 months ($p = 0.02$) If <10 (vs. >11) food items in diet at 12 months ($p < 0.001$)

(Continues)

TABLE VIII.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Roduit et al.[912]	2014	3	Prospective birth cohort	848 children (6 years old)	Effect of dietary diversity throughout the first 12 months of life	No association with AR at age 6 if ≥6 (vs. 0–5) food items in diet at 12 months ($p = 0.31$)
Maslova et al.[909]	2013	3	Population-based birth cohort	11,269 children (7 years old)	Maternal diet with avoidance or very low to very high fish intake from pregnancy weeks 12–30	Maternal diet low in fish intake (weekly and monthly) reduced the risk of AR at age 7 (OR 0.80; 95% CI 0.5–1.3) Maternal diet high in fish intake or total avoidance of fish was not associated with AR
Nwaru et al.[913]	2013	3	Prospective birth cohort	3112 children (5 years old)	Effect of early introduction of cereals, fish, and egg into the infant's diet	Introduction of rye, oat, barley <5–5.5 months associated with reduced risk of AR (OR 0.66; 95% CI 0.50–0.87) Introduction of fish <9 months associated with reduced risk of AR (OR 0.63; 95% CI, 0.48–0.84) Introduction of egg <11 months associated with reduced risk of AR (OR 0.72; 95% CI 0.55–0.94) Note: study also included in Ierodiakonou et al.[902] systematic review
Maslova et al.[908]	2012	3	Population-based birth cohort	38,389 children (7 years old)	Maternal diet to include ≥1 serving tree nuts/week or to have ≥1 serving of peanuts/pistachios/w from mid-pregnancy to delivery	Maternal tree nut ingestion associated with reduced risk for self-reported AR at age 7 (OR 0.80; 95% CI 0.64–1.01) Maternal ingestion of peanuts/pistachios had no association with self-reported AR at age 7
Virtanen et al.[914]	2010	3	Prospective birth cohort	1288 children (5 years old)	Introduction of foods into infants' diet and association with AR at age 5	Introduction of fish ≤6 months or between 6 and 8.5 months associated with a dose dependent reduced risk of AR at age 5 (6 months: HR 0.34; 95% CI 0.22–0.54) (6–8.5 months: HR 0.28; 95% CI 0.57–0.70)

(Continues)

TABLE VIII.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zutavern et al.[925]	2008	3	Population-based, prospective birth cohort	2073 children (6 years old)	Delayed introduction of solid food beyond 4–6 months	No association with the development of AR at age 6
Willers et al.[918]	2007	3	Longitudinal birth cohort	1253 children (5 years old)	Maternal intake of oily fish ≥1×/week versus avoidance of fish from weeks 20–32 of pregnancy	Maternal diet high in oily fish reduced the risk of AR at age 5 (OR 0.37; 95% CI 0.14–0.98)

Abbreviations: AR, allergic rhinitis; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HR, hazard ratio; LOE, level of evidence; OR, odds ratio; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis.

In a subgroup meta-analysis of observational studies, the introduction of fish into the infant's diet before 6–12 months was associated with a reduced risk for AR at 4 and 14 years.[902] Three additional prospective birth cohort studies support this conclusion.[906,913,914] One prospective birth cohort found that introduction of rye, oat, and barley before 5–5.5 months and egg before 11 months reduced the risk of AR at 5 years old.[913] However, there are conflicting conclusions regarding the timing of introduction of complementary foods and risk for AR.[925,926]

While guidelines have recommended that all infants have a diverse diet, the evidence is both limited and conflicting on whether this reduces the risk of AR.[927] Food diversity has been reported to increase,[907] decrease,[911] decrease if there are concurrent skin symptoms,[907] or have no effect[912] on the risk of developing AR in childhood.

Current guidelines as well as a Cochrane systematic review recommend an unrestricted maternal diet during pregnancy as avoidance of highly allergenic foods is unlikely to substantially reduce the risk of atopic disease, including AR, in the offspring.[928–931] Furthermore, it is recommended that complementary foods are introduced into the diet of all infants, regardless of atopic risk, at 4–6 months of age as avoidance or delayed introduction has not been shown to reduce atopic disease.[928] Guidelines have not made recommendation on the early introduction into the infant's diet of any specific foods to prevent the development of AR.

Risk factors – in utero and early childhood exposure to food allergens

Aggregate grade of evidence: A (Level 2: 6 studies, level 3: 12 studies; Table VIII.B.2)

VIII.B.3 | Pollution

According to the World Health Organization (WHO), air pollution is defined as "contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere."[932] Pollutants, produced through traffic-related combustion and industrial activity, generally include NO and nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide and dioxide (CO and CO_2), as well as PM <10 μm (PM_{10}) and PM <2.5 μm ($PM_{2.5}$). The effect of air pollution on human morbidity is well-known, though the relationship with AR is complex.[1,933,934] It is thought that through oxidative stress pathways, pollutants may stimulate the expression of antioxidant genes and recruitment of inflammatory cells to the nasal mucosa, though the mechanisms remain unclear.[935,936]

At the time of ICAR-Allergic Rhinitis 2018,[1] the strongest evidence in the literature suggested minimal or no significant associations between air pollutants and AR development.[782,937–941] Kim et al.[942] found that the incidence of AR was not significantly associated with exposure to air pollutants, while Codispoti et al.[943] reported that diesel exhaust particle exposure at age 1 was associated with allergen sensitization at ages 2 and 3, though not to a significant degree. In a pooled prospective cohort, air pollution was reported to not be associated with adverse effects on rhinoconjunctivitis.[944]

In more recent years, the interest in understanding a potential relationship between air pollution and AR has further increased. Li et al.[945] reported a positive association between air pollution and AR while Burte et al.[946] found that individuals with AR living in highly polluted areas were more likely to experience more severe nasal symptoms. Evaluating environmental air pollutants from 2013 to 2015, Teng et al.[947] reported that levels of PM are strongly associated with the prevalence of AR. In another study, ozone and NO_2, oxidant air pollutants, were associated with an 8% increased risk of AR.[948] A meta-analysis by

Zou et al.[949] reported increased AR prevalence in children with exposure to high levels of NO_2, SO_2, PM_{10}, and $PM_{2.5}$. This was further supported by an SRMA by Lin et al.[950] who reported that $PM_{2.5}$ exposure may be correlated with childhood AR. Hao et al.[951] studied children aged 2–4 years and found that those with family stress and boys compared to girls were particularly vulnerable to increased risk of AR with early exposure to traffic-related air pollution (Table VIII.B.3).

Co-exposure of diesel exhaust and indoor or outdoor inhalant allergens were found to induce changes in lung protein concentrations, alter DNA methylation patterns of bronchial epithelial cells, and result in lung function impairment.[952–954] In a controlled allergen challenge facility study by Ellis et al.,[955] participants with ragweed-induced AR aggravated by exposure to diesel exhaust particle were effectively treated with fexofenadine hydrochloride, resulting in reduced AR symptoms, compared to placebo.

The evidence demonstrating the role of air pollution on AR severity has certainly advanced. In 2018, the European Institute of Innovation and Technology launched the "Impact of air POLLution on sleep, Asthma and Rhinitis" (POLLAR) project, in efforts to use machine learning to better evaluate the relationship between sleep disorders, air pollution, and AR across six European countries.[956] The recognition of the impact of pollution on AR is highlighted by the 2020 consensus paper published in the *World Allergy Organization Journal* which summarizes strategies to manage pollution-induced AR symptoms.[957]

Much of the current literature demonstrating the detrimental effects of air pollution on AR prevalence and severity has been from Europe and Asia. As air pollution affects all countries, future studies from all continents are needed to explore this global problem.

Risk factors – pollution

Aggregate grade of evidence: C (Level 3: 8 studies, level 4: 7 studies; Table VIII.B.3)

VIII.B.4 | Tobacco smoke

Most prospective cohort studies and systematic reviews presented in ICAR-Allergic Rhinitis 2018[1] have found no correlation between active or passive tobacco smoke and AR.[962–965] One study suggested that tobacco smoke may have a protective effect against the development of AR.[966] Similarly, pathophysiology studies examining this relationship have contradictory findings. It has been shown that tobacco smoke negatively impacts the barrier function of the bronchial epithelium leading to increased allergen penetration.[967] A recent study in an AR mouse model showed that intranasal exposure to a tobacco smoke solution exacerbated the allergic response and increased eosinophil levels and IL-5 expression in the respiratory epithelium.[968] Conversely, nicotine has been shown to suppress type 2 responses to allergens, effectively acting as an immunosuppressant.[969]

Since the last ICAR-Allergic Rhinitis 2018,[1] two large meta-analyses have investigated the impact of tobacco smoke on AR.[970,971] Skaaby et al.[970] performed a Mendelian randomization meta-analysis of data from 22 studies in the Causal Analysis Research in Tobacco and Alcohol (CARTA) consortium and the UK Biobank. The smoking-increasing allele of rs1051730/rs16969968 was associated with a lower odds ratio of AR in current smokers. They saw similar results in their observational analysis; current smokers had a lower risk of hay fever than never smokers, and, accordingly, they saw an inverse dose–response relationship between smoking heaviness and hay fever. These results suggest that smoking may decrease the risk of AR. Zhou et al.[971] also systematically reviewed 16 studies in a meta-analysis of maternal tobacco smoke exposure during pregnancy and AR. This study found that maternal passive smoking during pregnancy but not maternal active smoking during pregnancy increases the risk of their offspring developing AR (Table VIII.B.4).

Recent birth cohort and prospective cohort studies have contributed to our understanding of tobacco's effect on AR development. A meta-analysis was performed on the Mechanisms of the Development of ALLergy consortium,[972] including five European birth cohort studies and 10,080 participants followed from pregnancy to 14–16 years of age. In this cohort, maternal smoking was not associated with a significant increase in rhinoconjunctivitis during childhood and adolescence. However, in children who developed AR, maternal smoking of 10 or more cigarettes per day during pregnancy was associated with persistent, rather than transient, rhinoconjunctivitis. Abramson et al.[172] performed an analysis of questionnaire and sIgE data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) to assess secondhand smoking's impact on AR risk. They found that while those with AR were significantly less likely to be current or former smokers, there were no significant associations between secondhand smoking and AR.

It is known that AR represents a risk factor for asthma onset or worsening. A cross-sectional study by Ciprandi et al.[973] reported a clustering analysis to identify the subset of patients with AR at a higher risk of asthma development. This subset of patients had characteristics that

TABLE VIII.B.3 Evidence table – risk factors for development of allergic rhinitis: pollution

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Li et al.[945 a]	2022	3	SRMA, cross-sectional, and cohort studies	Exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO) on the prevalence of AR across ages	Diagnosis of AR	Air pollution positively associated with AR prevalence
Lin et al.[950b]	2021	3	SRMA, cross-sectional, and cohort studies	Exposure to $PM_{2.5}$ and PM_{10}: High exposure Low exposure	Diagnosis of AR among children	Particulate matter exposure may increase prevalence of childhood AR, with $PM_{2.5}$ having greater effect
To et al.[948]	2020	3	Prospective cohort	Exposure to oxidant air pollutants: High exposure Low exposure	Diagnosis of AR, birth through adolescence	Oxidant air pollutants, specifically O_3 and NO_2, associated with an 8% increased risk of AR
Zou et al.[949c]	2018	3	Meta-analysis, cross-sectional, and cohort studies	Exposure to NO_2, SO_2, PM_{10}, or $PM_{2.5}$: High exposure Low exposure	Self-reported diagnosis of AR	Air pollution (specifically NO_2, SO_2, PM_{10}, and $PM_{2.5}$) increase the risk of AR in children
Teng et al.[947]	2017	3	Time-series study	Exposure to $PM_{2.5}$ and PM_{10}, SO_2, NO_2, and O_3: High exposure Low exposure	Diagnosis of AR from 2013 to 2015	Significant association between levels of particulate pollutants and prevalence of AR
Codispoti et al.[943]	2015	3	Prospective cohort	High DEP exposure (≥66th percentile) Low DEP exposure (<66th percentile)	Development of AR from age 1 to 4	DEP exposure at age 1 associated with allergen sensitization at ages 2 and 3, though not significantly
Gehring et al.[944]	2015	3	Prospective birth cohort	Exposure to NO_2, $PM_{2.5}$, and PM_{10}: High exposure Low exposure	Effect of air pollution on rhinoconjunctivitis in ages 4 to 14-16	Air pollution not associated with adverse effects on rhinoconjunctivitis
Kim et al.[942]	2011	3	Prospective pediatric cohort	Exposure to NO_2, O_3, SO_2, CO, PM_{10}: Metropolitan cities Industrial areas	AR sensitization during 2-year timespan	Exposure to ozone in industrial areas associated with AR
Hao et al.[951]	2021	4	Case–control	Exposure to PM_{10} and NO_2 in males with or without family stress: High exposure Low exposure	Diagnosis or parent-reported symptoms of AR at age 2–4 years	Early exposure to PM_{10} and NO_2 among young boys with family stress may increase risk of AR
Singh et al.[939]	2018	4	Cross-sectional	Frequent passage of trucks near home (almost all day)	Prevalence and severity of AR and rhinoconjunctivitis in children ages 6–7 and 13–14	Frequent passage of trucks near home associated with AR in both age groups

(Continues)

TABLE VIII.B.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chiang et al.[938]	2016	4	Case–control	Exposure to SO_2: High exposure Low exposure	AR diagnosis in children 11–14 years old	Children exposed to higher levels of SO_2 had significantly higher incidence of AR
Kim et al.[782]	2016	4	Cross-sectional	Daily concentrations of SO_2, NO_2, O_3, CO, and PM_{10}: High exposure Low exposure	Development of AR by age 6–7	Exposure to CO within the first year of life associated with increased risk of AR
Jung et al.[940]	2015	4	Cross-sectional	Traffic-related air pollution exposure within 200 m home area: Distance from main road (<75, 75–150, 150–225, or >225 m) Length of main road (0, 1–165, 165–254, and >254 m) Proportion of the main road area (0,.1–1.94, 1.94–3.58, and >3.58%)	Measurements of pulmonary functions and allergic sensitization in children 6–14 years old	Positive association between distance to and the length of main road with the prevalence of AR
Shirinde et al.[941]	2015	4	Cross-sectional	Frequency of trucks passing near homes on weekdays (traffic-related air pollution): Never Seldom Frequently through the day Almost all day	Self-reported AR in children 13–14 years old	Frequency of trucks passing near residences almost all day on weekdays significantly associated with rhinitis
Anderson et al.[937]	2010	4	Cross-sectional	Exposure to PM_{10}: High exposure Low exposure	Prevalence of rhinoconjunctivitis in age groups 6–7 and 13–14 years	Positive association between PM_{10} and hay fever in the 6–7-year age group and rhinoconjunctivitis/atopy in the 13–14-year age group

Abbreviations: AR, allergic rhinitis; DEP, diesel exhaust particles; LOE, level of evidence; PM, particulate matter; SRMA, systematic review and meta-analysis.
[a]The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Kim et al.,[942] Chung et al.,[958] Deng et al.,[894] Liu et al.,[959] Wang et al.[960]
[b]The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Chung et al.,[958] Deng et al.,[894] Liu et al.,[959] Kim et al.[961]
[c]The following individual studies from ICAR 2018 are included in this meta-analysis: Chung et al.,[958] Deng et al.,[894] Liu et al.,[959] Wang et al.,[960] Kim et al.[961]

included longer AR history and smoking, among others that also represent risk factors for evolving asthma. These results suggest that smoking may be a possible risk factor for asthma development in people with AR.

Another area of interest is electronic cigarettes and heated tobacco products and their impact on AR. In 2020, a survey study of Korean youth reported that current smokers of conventional tobacco cigarettes had a higher risk of AR than those using heated tobacco products and electronic cigarettes. However, the use of heated tobacco products and electronic cigarettes among conventional tobacco smokers increases the apparent risk of AR and asthma.[974] Future research should focus on understanding the effects of these new products on a mechanistic level.

TABLE VIII.B.4 Evidence table – risk factors for development of allergic rhinitis: tobacco smoke

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zhou et al.[971]	2021	2	SR, case–control, and cross-sectional studies	Active maternal smoking during pregnancy Passive maternal smoking during pregnancy	AR diagnosis in offspring	Passive maternal smoking during pregnancy significantly associated with AR in offspring Cross-sectional studies: active maternal smoking during pregnancy significantly associated with AR in offspring
Thacher et al.[972]	2018	2	Meta-analysis, birth cohort studies	Maternal smoking during pregnancy Exposure to passive smoke during infancy	Self-reported rhinoconjunctivitis in first 14–16 years of life	Maternal smoking during pregnancy not associated with rhinoconjunctivitis Maternal smoking of ≥10 cigarettes/day during pregnancy associated with children developing persistent rhinoconjunctivitis
Skaaby et al.[970]	2017	2	Meta-analysis, population-based studies	Never smokers Former smokers Current smokers Ever smokers	Association between smoking-associated SNPs and disease outcomes (hay fever, asthma, and allergic sensitization)	Current smokers had lower risk of hay fever and allergic sensitization than never smokers Current smokers had lower risks of hay fever and allergic sensitization per smoking-increasing allele
Abramson et al.[172]	2016	3	Cross-sectional birth cohort	Active smoking Non-smoker Ex-smoker Current smoker	Self-reported AR and detectable sIgE	No independent association between passive smoking and AR Non-smoker and ex-smoker status associated with a greater risk of AR than current smoker
Chung et al.[974]	2020	4	Cross-sectional	Korean students aged 13–18 years classified on tobacco product user status: Conventional cigarette Electronic cigarette Heated tobacco products	AR and asthma risk	Heated tobacco product and electronic cigarette use in combination with tobacco smoking using conventional cigarette associated with an increased risk of AR and asthma compared to each individual type of tobacco smoking
Ciprandi et al.[973]	2019	4	Cross-sectional	Patients with AR	Asthma risk	Cluster including smoking, among other factors, is associated with asthma risk

Abbreviations: AR, allergic rhinitis; LOE, level of evidence; sIgE, allergen-specific IgE; SNP, single nucleotide polymorphism; SR, systematic review.
[a]Studies included in systematic reviews and meta-analyses are not listed separately in the evidence table.

In summary, there have been few large prospective cohort studies or systematic reviews examining the effect of tobacco smoke exposure on the development of AR since ICAR-Allergic Rhinitis 2018. The studies presented herein predominantly found no correlation between active or passive tobacco smoke and AR. However, some studies suggest that tobacco may decrease AR risk, a finding that warrants further investigation.

Risk factors – tobacco smoke

Aggregate grade of evidence: C (Level 2: 3 studies, level 3: 1 study, level 4: 2 studies; Table VIII.B.4)

VIII.B.5 | Socioeconomic factors

SES describes the social standing of a group or individual and is determined by a combination of income, occupation, and education. The association of SES with AR was described as early as the 1800s.[975] The concept of SES and its correlation with AR is similar to the hygiene hypothesis, which theorizes that a potential reduction in an individual's microbial colonization can result in an increase in allergic disease (discussed below).[976] (See Section VIII.C.3. Hygiene Hypothesis for additional information on this topic.) As an example, Wee et al.[977] conducted a large cross-sectional study in over 60,000 school-aged children and found that higher SES was associated with both improved hand hygiene and increased odds of developing AR. The role of SES in the development of AR has additional, complex underpinnings, and likely accounts for variations in a multitude of factors, including housing conditions, air quality, water supply, education, and access to care, to name a few (Table VIII.B.5).

The ISAAC studies are among the largest multi-institutional studies evaluating prevalence of AR in children across the globe. Phase 1 and 3 ISAAC studies examined prevalence patterns of AR in ~1.2 million children in 98 countries.[756–759] Like most studies of AR prevalence, these studies were open, survey-based cross-sectional studies. A post-hoc analysis of the ISAAC Phase 1 and 3 study data found a positive correlation between a country's gross national income per capita and national prevalence of AR. However, while statistically significant, the correlation was weak ($r = 0.328$ for 6–7 years, 0.206 for 13–14 years).[758]

Chen et al.[978] performed a large survey-based cross-sectional study in 173,859 adults participating in a Kaiser Permanente multiphasic health check-up from 1964 and 1972. Their study used educational level as a marker for SES and found that post-graduate education was associated with increased odds of hay fever. A subsequent study by Li et al.[979] conducted in 23,971 children aged 6–13 years old in eight metropolitan cities in China found that both parental education and household income per capita predicted a higher prevalence of allergic disease. Hammer-Helmich et al.[980] performed a cross-sectional, survey-based study of SES and its association with hay fever in 9720 participants aged 3, 6, 11, and 15 years in Denmark. They found parental education level was a socioeconomic factor associated with increased risk of hay fever (OR 1.68). Income showed no association.

Studies of SES and its impact on risk of AR highlight the role that study participant education may play on the reporting of AR symptoms, or its diagnosis. This is illustrated by a study performed by Mercer et al.,[981] who evaluated 4947 children aged 13–14 in South Africa and found that residents living in low SES, but attending high SES schools, showed significantly higher prevalence of rhinitis symptoms than children in low SES schools. This suggests that education and access to medical care may affect differences in reporting in survey-based, cross-sectional studies.

Not all studies have demonstrated a positive relationship of AR with higher SES. A cross-sectional study performed in Bolu, Turkey including 1403 subjects observed that poor living conditions and income was associated with a greater risk of self-reported AR.[982] Similarly, Lewis et al.[983] examined allergen sensitization patterns in 458 adult women and found that lower SES was associated with increases in tIgE, number of allergen sensitizations, and sIgE levels. In a separate prospective cohort study performed in 4089 families in Sweden, Almqivst et al.[984] found increased SES (using parent occupation as a measure of SES) to be associated with lower risk of AR at age 4. Similarly, a prospective cohort performed by Grabenhenrich et al.[848] among 941 children up to age 20 in Germany showed no association between SES and AR development. And finally, using IgE-based sensitivity testing (in addition to symptom-based testing), Ahn et al.[784] found that only high income (and not education or occupation) was associated with symptom-based AR, but not IgE-based AR.

Thus, while most of the available evidence indicates that higher SES is associated with increased risk of AR, the data is not uniform. SES is related to a myriad of factors, many of which play an important role in the development of AR.

Risk factors – socioeconomic factors

Aggregate grade of evidence: C (Level 2: 7 studies, level 3: 9 studies, level 4: 1 study; Table VIII.B.5)

VIII.C | Protective factors

VIII.C.1 | Breastfeeding

Breastfeeding is considered to have several benefits for mothers and infants. WHO guidelines recommend breastfeeding for 6 months and European Academy of Allergy and Clinical Immunology (EAACI) guidelines

TABLE VIII.B.5 Evidence table – risk factors for development of allergic rhinitis: socioeconomic factors

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wee et al.[977]	2020	2	Cross-sectional	Children ($n = 60,392$), South Korea	Prevalence of AR	Wealth and education associated with greater hand hygiene and greater odds of AR
Ahn et al.[784]	2016	2	Cross-sectional	Children and adults ($n = 35,511$), South Korea	Symptom- and IgE-based AR	Higher income associated with symptom-based AR but not IgE-based AR
Lee et al.[985]	2016	2	Cross-sectional	Children ($n = 75,643$), South Korea	Prevalence of AR	Greater affluence and education increased risk of AR
Li et al.[979]	2011	2	Cross-sectional	Children ($n = 23,791$), China	Prevalence of AR	Parental education, income predicts increased AR prevalence
Braback et al.[986]	2005	2	Cross-sectional	Young adults ($n = 1,239,705$)	Prevalence of AR	Decreased association between low SES and AR with time
Mercer et al.[981]	2004	2	Cross-sectional	Children ($n = 4947$)	Prevalence of AR symptoms	Education associated with AR
Chen et al.[978]	2002	2	Cross-sectional	Adults ($n = 173,859$), Northern California, US	Age-adjusted prevalence of AR	Post-graduate education positively associated with hay fever in adult men and women
Penaranda et al.[987]	2016	3	Cross-sectional	Children ($n = 1576$) and adults ($n = 3153$)	Prevalence of AR	Children, adolescents, and adults from higher SES had increased odds of reporting AR symptoms
Grabenhenrich et al.[848]	2015	3	Prospective cohort	Children ($n = 941$), Germany	Prevalence of AR	Parental income and education had no association with AR development
Hammer-Helmich et al.[980]	2014	3	Cross-sectional	Children ($n = 9720$), Denmark	Prevalence of hay fever symptoms at 3, 6, 11, 15 years	Children born to parents of low education had greater odds of developing hay fever; no association with income
Mallol et al.[758]	2013	3	Cross-sectional	Children (approximately 1.2 million), global	Prevalence of AR symptoms	Country affluence showed positive correlation with AR symptoms
Almqvist et al.[984]	2005	3	Prospective cohort	Children ($n = 4089$ families), Sweden	Prevalence of AR at 4 years	Higher SES decreases risk of AR
Lewis et al.[983]	2001	3	Cross-sectional	Adults ($n = 458$), North America	Prevalence of allergen sensitivities	Sensitivity is associated with lower income and education level

(Continues)

TABLE VIII.B.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bergmann et al.[988]	2000	3	Prospective cohort	Children and adults ($n = 1314$ families)	Prevalence of AR symptoms and sensitivity testing	Higher SES (as measured by family education, occupation, and income level) is associated with AR in adults, but not their children
Lewis and Britton[989]	1998	3	Prospective cohort	Children ($n = 6000$), British Isles	Prevalence of AR symptoms	Social advantage independently predicts risk of AR
Goh et al.[990]	1996	3	Cross-sectional	Children ($n = 6238$), Singapore	Prevalence of AR	Higher SES associated with better housing and higher household income
Talay et al.[982]	2014	4	Cross-sectional	Adults ($n = 1403$), Turkey	Prevalence of AR symptoms	Poor living conditions and low income were associated with increased odds of current AR

Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E; LOE, level of evidence; SES, socioeconomic status; US, United States.

advise exclusive breastfeeding for 4–6 months.[991,992] ICAR-Allergic Rhinitis 2018 also documented that breastfeeding has been strongly recommended due to its multiple benefits in general; the policy level was "option" for the specific purpose of AR prevention.[1] Several mechanisms have been suggested to explain how breastfeeding might prevent allergic disease. Breast milk contains immunomodulatory factors that stimulate host defense mechanisms and immune response.[993,994] Although the association of breastfeeding with the development of allergic disease has been investigated in many studies, there is no consensus on whether breastfeeding is effective in preventing AR.

A recent SRMA revealed that exclusive or non-exclusive breastfeeding for 6 or more months may have protective effects on the development of AR up to 18 years of age.[995] A 2019 systematic review that included one cluster RCT and five prospective cohort studies examined the relationship between shorter versus longer durations of any human milk feeding (whether or not it was fed at the breast) and AR in childhood.[996] The only statistically significant association was found by Codispoti et al.,[997] noting that longer duration of breastfeeding was associated with a lower risk of AR in 3-year-old African Americans (odds ratio [OR] 0.8; 95% CI 0.6–0.9). The authors stated that published data are insufficient to determine whether the duration of any human milk feeding was associated with AR[996] (Table VIII.C.1).

The results from a questionnaire-based cross-sectional study of 4–6-year-old Shanghai children suggested that exclusive breastfeeding for greater than 6 months reduced the risk of hay fever (OR 0.93; 95% CI 0.89–0.97) and rhinitis (OR 0.97; 95% CI 0.94–0.99) compared to those who were never breastfed.[998] Food Allergy and Intolerance Research (FAIR) birth cohort in the Isle of Wight, UK, also showed exclusive breastfeeding for greater than 4 months reduced the risk of rhinitis (OR 0.36; 95% CI 0.18–0.71) from birth up to 10 years of age.[991] A recent cohort study of children with AR compared to non-allergic rhinitis in Korea showed that breastfeeding for 12 or more months had a significantly lower prevalence of AR compared with breastfeeding for less than 6 months, and the association was still valid, accounting for age, sex, mode of delivery, number of siblings, parental atopy history, and living area (OR 0.54; 95% CI 0.34–0.88).[999] However, in one study using a large population-based cohort (336,364 participants) from the UK, researchers found that breastfeeding increased the risk of hay fever when adjusted for body mass index, birth weight, SES, home area, and year of birth (OR 1.11; 95% CI 1.06–1.16).[1000]

These inconsistencies in studies, which are mainly observational surveys, can possibly be influenced by demographic, socioeconomic, educational, ethnic, cultural, psychological status, and study design.[999,1001,1002] In addition, since it is difficult to distinguish between AR and viral respiratory infection at a young age, the protective effect of breastfeeding against viral infection has possibly been confused as a protective effect on AR.[1003] Furthermore, differences in methodological factors such

TABLE VIII.C.1 Evidence table – protective factors against development of allergic rhinitis: breastfeeding

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hoang et al.[995]	2022	2	SRMA	23 observational studies: 161,611 children aged 2–18 years	Association between prolonged breastfeeding and AR symptoms later in life	Prolonged breastfeeding (at least 6 months) provides protection against AR
Gungor et al.[996]	2019	2	Systematic review	One cluster RCT and 5 prospective cohort studies: children aged 3–9 years, varied by study	Association of AR with duration of any human milk in childhood	Limited evidence does not suggest associations between the duration of any human milk feeding and AR in childhood
Ekelund et al.[926]	2021	3	Prospective cohort	PACT study: 6802 children at 2 and 6 years of age	Association between breastfeeding duration and AR	Longer breastfeeding (≥6 months) associated with a reduced risk of AR up to 6 years
Han et al.[999]	2019	3	Prospective cohort	ARCO-kids study: 1374 children aged 4–12 years	Association between breastfeeding duration and development of AR in childhood	Long-term breastfeeding (≥12 months) associated with lower risk of developing childhood AR
Ek et al.[1000]	2018	3	Population-based cohort	336,364 Caucasian participants aged 37–73 years	Association between breastfeeding and risk of hay fever	Breastfeeding associated with increased risk for hay fever
Bion et al.[991]	2016	3	Prospective birth cohort	IoW cohort: 1456 subjects at the ages of 1 or 2, 4, 10, and 18 FAIR cohort: 988 subjects at the ages of 1, 2, 3, and 10	Effects of breastfeeding on long-term outcome for rhinitis	Protective effect of breastfeeding on long-term allergic outcomes is inconsistent, but exclusive breastfeeding for >4 months protects against repeated rhinitis in the FAIR cohort
Huang et al.[998]	2017	4	Cross-sectional	CCHH study: 13,335 children aged 4–6 years in China	Association between breastfeeding durations and prevalence of hay fever and rhinitis among preschool children	Children exclusively breastfed >6 months had reduced risk of hay fever and rhinitis

Abbreviations: AR, allergic rhinitis; ARCO, Allergic Rhinitis Cohort; CCHH, China, Children, Homes, Health; FAIR, Food Allergy and Intolerance Research; IoW, Isle of Wight; LOE, level of evidence; PACT, Prevention of Allergy among Children in Trondheim; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis.

[a]The systematic reviews in this table are appropriately inclusive of previously published studies on this topic.

as duration of breastfeeding, any or exclusive breastfeeding, diagnostic criteria of AR, comorbid allergic disease, and the follow-up period may account for discrepancies in assessing the association between breastfeeding and AR.

Overall, considering the literature review on the association between breastfeeding and AR, breastfeeding should be recommended due to various positive effects on general health and possible protective effects on AR.

Protective factors – breastfeeding

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study; Table VIII.C.1)
Benefit: Benefits on general health of infant and possible protection against AR, especially in young children.
Harm: None.

Cost: Low.
Benefits-harm assessment: Slight preponderance of benefit over harm for protection against AR. Large preponderance of benefit over harm for breastfeeding for all infants, unless there is a contraindication. The benefit of breastfeeding for all infants inextricably influences this recommendation.
Value judgments: Evidence suggests that breastfeeding may reduce the risk of AR without harm.
Policy level: Recommendation for breastfeeding due to various positive effects on general health and possible protective effects on AR.
Intervention: Breastfeeding for at least 4–6 months should be encouraged unless contraindicated.

VIII.C.2 | Childhood exposure to pets

Pet-keeping families are concerned about the effects of pets on their children with regard to allergic diseases; however, the recommendations of guidelines for AR in relation to childhood pet exposure remain conflicting.[1,1004,1005] ICAR-Allergic Rhinitis 2018 stated that early pet exposure may reduce the development of AR and its protective effect is stronger in non-allergic families with dog exposure.[1]

A recent SRMA investigating the association between pet exposure and the risk of AR revealed the protective effect of early cat exposure (RR 0.60; 95% CI 0.33–0.86) or dog exposure (RR 0.68; 95% CI 0.44–0.90) on the development of AR.[852] Furthermore, early cat ownership in the first 2 years of life has been associated with a significantly lower risk of AR compared to non-ownership (OR 0.51; 95% CI 0.28–0.92)[860] (Table VIII.C.2).

A prospective birth cohort study in Finland revealed that having a dog in the house in the first year of life seemed to protect against AR (OR 0.72; 95% CI 0.53–0.97) by the age of 5 years compared to those without.[853] Additional studies support the finding that exposure to pets during childhood reduces the risk of AR.[1006,1007] Nevertheless, these studies did not make a firm conclusion about the protective effect of pet exposure on the development of AR. Heterogeneous factors such as the timing of exposure, duration of exposure, animal species, dose of exposure (number of household pets, environmental exposure vs. ownership), and avoidance behavior may be the reason.[852,1008]

Furthermore, some studies have shown conflicting results. A cross-sectional survey conducted in first graders (6–8 years old) in Taiwan demonstrated that having a cat in the first year of life was associated with an increased risk of AR.[856] In addition, one study in Chinese children aged 0–8 years old showed a negative effect of pet keeping (aOR 3.60; 95% CI 2.07–6.27) for AR after adjustment for avoidance behavior.[1009] However, these results should be interpreted with caution because of ethnic differences, family inheritance, and other environmental risk factors that may confound of the association between pet keeping and AR. Although the exact mechanism of the effects of pet exposure on allergic disease remains unclear, it has been suggested that environmental exposure may increase or decrease the risk of AR according to the stage of immune system development.[852,1010–1012]

Overall, the causal relationship between pet exposure in childhood and the protective effect of AR is inconsistent; thus, no strong advice can be provided regarding childhood exposure to pets. Nevertheless, pet exposure at birth or in the first year of life may reduce the risk of AR.

Protective factors – childhood exposure to pets

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 2 studies, level 4: 2 studies; Table VIII.C.2)
Benefit: Exposure to pets at birth and in the first year of life has potential benefits of decreasing risk of AR.
Harm: Pet keeping in childhood could have a negative effect, especially in Asians.
Cost: Various.
Benefits-harm assessment: Difficulty distinguishing between benefits and harm.
Value judgment: There is conflicting evidence that childhood pet exposure prevents the development of AR.
Policy level: Option.
Intervention: Recommendation to expose or avoid pets for the prevention of AR in children cannot be provided based on current evidence.

VIII.C.3 | Hygiene hypothesis

The *hygiene hypothesis* originated from the observation that frequent and recurrent infections in early childhood appear to protect against the development of AR later in life.[1013] Over time, the *hygiene hypothesis* evolved to the *biodiversity hypothesis*, which expands the scope from the protective effect of infection from single microbes to the protective effect of microbial variety during development.[1014] The *microbiota hypothesis* was later proposed to confine the causative microbes specifically to those living in or on the human body and their impact on our immune system.[691,699]

TABLE VIII.C.2 Evidence table – protective factors against development of allergic rhinitis: childhood exposure to pets

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dharmage et al.[1012]	2012	2	Systematic review	19 studies: 9 longitudinal, 8 cross-sectional, 8 case–control studies	Association between cat exposure and AR	Inconsistent association Cat exposure during the first year may be protective against AR or sensitization
Gao et al.[852]	2020	3	SRMA	6 studies reported rhinitis: 1 case–control, 5 cohort studies	Association between exposure to cats or dogs and AR	Potential protective effect of exposure to cats and dogs, especially early cat ownership, on the development of AR
Ojwang et al.[853]	2020	3	Prospective population-based birth cohort	Finnish DIPP study	Association between exposure to indoor pets and farm animals during infancy and the risk of allergy by age 5	Having a dog in the house in the first year of life associated with reduced risk of developing AR by age 5 years
Ho and Wu[856]	2021	4	Cross-sectional	23,630 Taiwanese children aged 6–8 years	Association of AR with cat or dog keeping during the first year of life or in the past 12 months	Having a cat in the first year of life may increase the risk of rhinitis
Luo et al.[1009]	2018	4	Cross-sectional	7366 Chinese children aged 0–8 years	Relationship between pet keeping in childhood and allergy	Negative effect of pet keeping on diagnosed rhinitis after adjustment for avoidance behavior

Abbreviations: AR, allergic rhinitis; DIPP, Type I Diabetes Prediction and Prevention; LOE, level of evidence; SRMA, systematic review and meta-analysis.
[a]The systematic reviews in this table are appropriately inclusive of previously published studies on this topic.

An SRMA was conducted to determine the effect of the number of siblings on AR development; this analysis assessed 53 studies with 300,062 participants.[1015] They saw a strong inverse association between many siblings (three or more) and the development of AR. Similarly, a large international cohort study based on questionnaire data for children aged 6–7 and 13–14 years also saw an inverse association between the number of siblings and AR but only in affluent countries[1016] (Table VIII.C.3).

It has also been observed in several studies that exposure to early-life farming may protect against childhood allergic diseases particularly, exposure to farm animals and stables.[1017–1027] In a recent meta-analysis by Campbell et al.,[1017] the risk of sensitization measured by sIgE or SPT in childhood or adulthood was 40% lower among children who had lived on a farm during the first year of life. Further, a 2017 US case–control study showed farm exposure in utero provides even greater protection against sensitization in adulthood.[1018] While an isolated exposure to bacterial endotoxin was claimed to have a similar protective effect, the results thus far have been inconclusive.[1028,1029]

Increased diversity in the gut and skin microbiome has been associated with a protective effect on atopy.[686,689,691,694,1030–1032] Recently, three large cohort studies have reported that reduced bacterial diversity in the infant's intestinal flora within the first 6 years of life predisposes them to a higher risk of developing AR.[687,691,1033] Notwithstanding this, a meta-analysis of 29 trials did not find supplementation of probiotics to pregnant mothers or infants beneficial in preventing atopy.[1034] A publicly available American Gut Project questionnaire and database was used in a study to determine the fecal microbiota richness and composition in adults with AR.[694] They found an imbalance (dysbiosis) of gut flora with higher *Bacteriodes* and reduced *Clostridia* taxa in this population. In addition, the role of *Helicobacter pylori* has been investigated, with inconsistent findings.[1035–1037] Interestingly, in a meta-analysis of 21 studies assessing the association between *H. pylori* infection and allergic dis-

TABLE VIII.C.3 Evidence table – protective factors against the development of allergic rhinitis: hygiene hypothesis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Campbell et al.[1017]	2015	1	SRMA	29 studies: 26 cross-sectional, 3 longitudinal Meta-analysis of 8 studies	Association of farm exposure with sensitization in childhood or adulthood	Protective effect of farm exposure in infancy on allergic disease outcomes in childhood and adulthood in majority of the studies Exposure during adulthood had no consistent relationship with sensitization
Cuello-Garcia et al.[1034]	2015	1	SRMA	29 RCTs in infants	Association of AR with probiotic supplementation to pregnant mothers, breastfeeding women, or infants	No effect on allergies
Lionetti et al.[1037]	2014	1	SRMA	21 studies: 11 case–control, 10 cross-sectional	Relationship between *H. pylori* and atopy/allergic diseases	Some evidence of inverse association between atopy/allergic diseases and *H. pylori* infection Inconsistent pooled results from case–control and cross-sectional studies require further investigation
Karmaus and Botezan[1015]	2002	1	SRMA	53 studies: Hay fever, 17 studies, $n = 253{,}304$ Sensitization, 16 studies, $n = 46{,}758$	Association of sensitization and AR with three or more siblings versus no siblings	Higher number of siblings was associated with less atopy Effect was not explained by hygiene factors
House et al.[1018]	2017	3	Nested case–control	Farmers and spouses: Cases: asthma, $n = 1198$ Controls: no asthma, $n = 2031$	Association of sensitization, rhinitis, eczema, and asthma with living on a farm when born and with being exposed to farm environment when mother was performing farm activities during pregnancy	Early-life farm exposure associated with less atopy No association with asthma
Ruokolainen et al.[1038]	2017	3	Cross-sectional	Follow-up of earlier cross-sectional study, 98 children in Finnish and 82 children in Russian Karelia Additional samples from 88 children in Russia	Difference of nasal and skin microbiota composition and diversity between Finnish and Russian young people Association of sensitization with microbiota	Lower prevalence of allergic diseases and sensitization remained throughout 10 years follow-up Higher abundance and microbial diversity in Russia may explain the difference *Acinetobacter lwoffii* oligotype profile differed in Finnish sensitized subjects Causal relationship not proven

(Continues)

TABLE VIII.C.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Fujimura et al.[689]	2016	3	Prospective cohort	298 children followed until age 4 years	Association of sensitization and asthma at age 2 years with fecal microbiota in neonates targeted at age 1 month ($n = 130$) or 6 months ($n = 168$)	Suggests that reduced colonization of *Bifidobacteria*, *Lactobacillus*, *Faecalibacterium*, *Akkermansia*, and *Malazzesia* during the neonatal period may influence the risk of multi-sensitization predictive for asthma
Hua et al.[694]	2016	3	Cross-sectional	1879 adult subjects	Association of seasonal allergy with fecal microbial biodiversity	Reduced fecal biodiversity and altered composition associated with increased allergy No association with asthma and eczema
Arrieta et al.[1030]	2015	3	Nested case–control	319 children followed from birth until 5 years of age	Association of sensitization and wheezing at 1 year with fecal microbiota at age 3 months and 1 year	Suggests that reduced colonization of *Faecalibacterium*, *Lachnospira*, *Veillonella*, and *Rothia* during the first 3 months of life may increase the risk of atopic asthma
Strachan et al.[1016]	2015	3	Cross-sectional	Children aged 6–7 years in 31 countries ($n = 210,200$), and 13–14 years in 52 countries ($n = 337,226$)	Association of hay fever with three or more siblings versus no siblings	Protective effect of older and total number of siblings on self-reported allergic rhinitis Effect significantly stronger in affluent countries
Valkonen et al.[1039]	2015	3	Stratified cross-sectional	GABRIELA-study, 224 children aged 6–12 years	Association of sensitization with mattress bacterial diversity	Exposure to more diverse bacterial flora associated with less sensitization
Holster et al.[1035]	2012	3	Prospective cohort	545 Dutch children	Association between *H. pylori* and AR	No association between *H. pylori* and AR
Bisgaard et al.[691]	2011	3	Prospective cohort	253 high asthma risk children followed from birth to age 7 years	Association of sensitization and AR with high fecal microbial biodiversity	Reduced bacterial diversity associated with higher risk of sensitization and AR in childhood
Ege et al.[1040]	2011	3	Cross-sectional	PARSIFAL study: 489 rural and suburban children GABRIELA study: 444 rural children	Association of sensitization with microbes in mattress (PARSIFAL) and in airborne dust (GABRIELA)	Farm children had less asthma and atopy Indoor microbial exposure much higher and diverse in farm homes Microbial diversity related to asthma but not to atopy
Tischer et al.[1029]	2011	3	Nested case–control	678 children at the age 6 years from German ($n = 346$) and Dutch ($n = 332$) birth cohorts	Association of rhinitis and asthma with mattress dust biological components of mold and endotoxin	Inconsistent results Microbial exposures at home had different effects on allergy in German and Dutch birth cohorts

(Continues)

TABLE VIII.C.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
von Hertzen et al.[1041]	2007	3	Cross-sectional	563 children aged 7–16 years in Finnish and Russian Karelia	Association of sensitization with microbial content in drinking water samples from school kitchens	Microbial count much higher and sensitization much lower in Russia High count of microbes associated with less atopy
Akiner et al.[1036]	2020	4	Cross-sectional	274 children and adults	Association between *H. pylori* infection and allergy	Positive correlation between *H. pylori* infection and AR
Abrahamsson et al.[686]	2014	4	Case–control	47 infants (20 with IgE-associated eczema and 27 healthy controls) followed until 7 years of age	Association of sensitization, asthma, and AR with fecal diversity in infancy	Low microbial diversity associated with asthma later in childhood No association with sensitization or rhinitis
Sjogren et al.[687]	2009	4	Prospective cohort	47 Swedish infants followed up to 5 years of age	Protective effect of early infancy gut microbiota against development of AR	Diverse gut microbiota early in life might prevent allergy development
Simpson and Martinez[1028]	2010	5	Narrative review	6 rural studies, 10 urban studies	Association of sensitization with exposure to endotoxin	Exposure to endotoxin protective in over 50% of the studies Other farming-associated factors related to reduced risk to sensitization independently Endotoxin may be marker of other protective factors
Stsepetova et al.[1033]	2007	5	Cross-sectional	40 Estonian children	Composition of intestinal microbiota in allergic and non-allergic children	Less diverse gut microbiota associated with allergic children

Abbreviations: AR, allergic rhinitis; GABRIELA, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community Advanced Study; IgE, immunoglobulin E; LOE, level of evidence; PARSIFAL, Prevention of Allergy-Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis.

eases, a significant inverse association was found between *H. pylori* infection with atopy from the case–control studies while an association was seen between allergic disease and *H. pylori* infection from the cross-sectional studies.[1037]

Lower biodiversity on the skin and in the home living environment is associated with an increased risk of atopy.[1031] Ruokolainen et al.[1038] performed a comparative study of the microbiota of skin and nose in randomly selected school children from urban and rural areas. They saw that rural school children had increased microbial diversity on their skin and in their noses and this was associated with lower allergy prevalence compared urban school children.

In summary, there is some evidence of the protective effect of the hygiene hypothesis on AR from epidemiological studies but more studies that evaluate causality are needed. (See Section VI.J. Microbiome and Section XI.B.9. Probiotics for additional information on this topic.)

Protective factors – hygiene hypothesis

Aggregate grade of evidence: B (Level 1: 4 studies, level 3: 12 studies, level 4: 3 studies, level 5: 2 studies; Table VIII.C.3)

IX | ALLERGIC RHINITIS DISEASE BURDEN

IX.A | Individual burden

IX.A.1 | Quality of life

High quality evidence evaluating the impact of AR on QOL continues to show AR patients suffer from decreased general and disease-specific QOL due to impacts on physical and mental health.[1042–1047] These studies also show that treatment of AR with INCS, oral antihistamines, and AIT leads to improved QOL. Validation of QOL metrics in AR continues. There has been a trend toward use of disease specific QOL metrics, especially the RQLQ.[1048] As this has become more accepted, the use of general health related QOL metrics such as Short Form 12 and 36 (SF-12/36) has decreased.[1049,1050] A measure of QOL used in CRS, the SNOT-22, has now been studied in AR.[1051] This study showed SNOT-22 was able to assess QOL and response to treatment in AR. Olfaction, an objective measure of QOL also typically used in CRS, has also been studied in AR recently. Olfactory dysfunction was identified in 44% of patients with AR.[1052] The use of SNOT-22 and objective measures of olfaction could simplify implementation of QOL monitoring for both diseases from a clinical standpoint (Table IX.A.1).

Despite the availability of disease specific QOL instruments, many studies continue to rely on unvalidated methods to assess QOL. This leads to difficulty comparing outcomes between some studies. A recent SRMA evaluated the outcomes of medical therapy with INCS, oral antihistamines, or AIT for AR. Treatment with oral antihistamines and AIT had a statistically significant impact on QOL. Despite near universal acceptance of INCS for the treatment of AR, meta-analysis of the impact of INCS on QOL could not be performed due to a lack of available data.[1043] There are numerous individual RCTs evaluating the effect of INCS,[1053] oral antihistamines,[1054–1057] and AIT.[1058–1061] The overarching findings in these individual RCTs is that these treatments improve QOL.

While numerous studies exist comparing changes in symptoms with treatment for AR,[1062] direct, head-to-head comparisons of changes in QOL with different treatments for AR are lacking. There is only one study comparing the impact of monotherapy with INCS (mometasone) to combination therapy with INCS and oral antihistamine (mometasone + levocetirizine) or INCS and leukotriene D4 receptor antagonist (mometasone + montelukast) on QOL as measured with the 14-question mini-RQLQ. This study found that polytherapy with mometasone and levocetirizine or montelukast improved QOL more than mometasone alone; no difference was seen between montelukast or levocetirizine when added to mometasone.[1063]

New evidence evaluating the impact of AR on QOL in children and in the parents of children with AR is emerging. As expected, these studies show impacts on QOL in this population. More surprisingly, they show impacts on parental QOL as well.[1064–1067] In one study, parents overestimate their children's QOL.[1068] This focus on assessing QOL in children and adolescents with AR was built on prior work measuring general QOL in children with instruments such as KINDL.[1069] Disease-specific instruments (Pediatric Rhinoconjunctivitis Quality of Life Questionnaire [PRQLQ] and RhinAsthma Patient Perspective [RAPP]-children) have now been developed to measure the impact of AR on QOL in pediatric and adolescent populations.[1064,1070] In children and adolescents with persistent AR, those with nasal obstruction secondary to septal deviation or turbinate hypertrophy have the worst QOL.[1067] Nasal endoscopy should be considered in patients in this population not responding to therapy to ensure nasal obstruction is not contributing.

Variations in QOL in AR patients have not been prospectively studied over time. Most studies are either cross-sectional or have short follow-up periods with few time points at which QOL is assessed. Control groups from RCTs and meta-analyses of RCTs can provide insight into long-term variation in QOL in AR, however. Two RCTs have studied the effect of oral antihistamines with a follow-up period of at least 6 months.[1056,1057] These RCTs show that both the placebo and treatment groups experience clinically and statistically significantly improvements in generic and disease specific QOL, but the improvement is greater in the treatment arm. A more recent meta-analysis of a combination INCS and intranasal antihistamine showed short-term but not long-term QOL improvement with this treatment.[1042] This latter finding, however, was based on a single study.[1071] AIT RCTs have longer follow-up periods (12 months to 3 years) and show similar results, with placebo patients either remaining at baseline or improving to a lesser degree than the treatment arms.[1058,1059,1061] As expected, patients with seasonal AR have worse QOL during seasons in which they are exposed to allergens and improved QOL outside of these seasons.[1072]

TABLE IX.A.1 Evidence table – individual burden of allergic rhinitis: quality of life

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chen et al.[1042]	2022	1	SRMA	51 full text manuscripts screened, 5 studies with data extracted ($n = 2055$), 1947–2021	TNSS, TOSS, RQLQ, RCAT	Intranasal antihistamine-INCS provides short-term but not long-term QOL improvement
Zhang et al.[1043]	2022	1	SRMA	2671 full text manuscripts screened, 22 studies with data extracted ($n = 4673$), 1947–2020	TNSS, VAS, RQLQ, PNIF	Improvement in symptom scores and PNIF are seen with INCS treatment Oral antihistamines improve symptom scores and QOL Studies on the impact of INCS on QOL are lacking
Li et al.[1044]	2021	1	SR	1341 full text manuscripts screened, 171 studies with data extracted ($n = 33,843$), 1947–2020	RQLQ, TNSS, VAS, PNIF, nasal airflow	AR has a greater impact on PROMs than non-allergic rhinitis Subdomain impacts are variable PROMs do not correlate with demographics, comorbidities, or nasal airflow
Calderon et al.[1045]	2019	1	SR	102 full text manuscripts screened, 55 studies reviewed, 1997–2018	Symptom, medication, disease control, QOL scores	Symptom and medication scores have not been validated in AR Disease control and QOL scores have been extensively validated Use of disease control or QOL scores as a primary end point in clinical trials will require a paradigm shift in clinical and regulatory communities
Linneberg et al.[1046]	2016	1	SR	544 full text manuscripts screened, 50 studies with data extracted, 1886–2014	RQLQ, mini-RQLQ, SF-36, SF-12, cost data	Patients with AR suffer from decreased QOL in terms of both physical and mental health Those with perennial HDM allergy had decreased QOL compared to those with seasonal pollen allergy
Hahn-Pedersen et al.[1047]	2014	1	SR	544 full text manuscripts screened, 50 studies with data extracted, 2000–2014	RQLQ, SF-36, cost data	AR patients have significantly worse general and disease-specific QOL with physical, practical and activity domains most affected SCIT improves QOL and symptoms
Aruthra and Kumar[1073]	2021	2	Cross-sectional	AR, $n = 40$	RQLQ	AR negatively impacts QOL

(Continues)

TABLE IX.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Passali et al.[1052]	2021	2	Cross-sectional	AR, $n = 1063$	Sniffin' Sticks olfactory test	Olfactory dysfunction in 44% of AR patients
Bosnic-Anticevich et al.[1065]	2020	2	Cross-sectional	Children with AR, $n = 1541$	ISAAC, Healthy Days questionnaire, CARATKids, ARIA, ARIA VAS	Parent-perceived burden of AR in their children is high Driven by inadequate symptom control and misconceptions about AR treatment
Pedregal-Mallo et al.[1058]	2020	2	Open-label CT	HDM AR ($n = 103$): AIT, $n = 52$ Control, $n = 51$	Mini-RQLQ, ESPRINT-15	AIT provides larger improvements in HRQOL than symptomatic treatment
Sikorska-Szaflik et al.[1068]	2020	2	Cross-sectional	Children with AR, $n = 208$	T4SS, VAS, KINDL	AR negatively impacts QOL Parents overestimate their children's QOL
Hwang et al.[1066]	2019	2	Cross-sectional	Parents with children in daycare or primary school, $n = 22{,}904$	EQ-5D-5L, EQ VAS	Parents of children with AR have lower HRQOL
Segall et al.[1071]	2019	2	DBRCT	Perennial AR ($n = 601$): Olopatadine-mometasone, $n = 400$ Placebo, pH 3.7, $n = 100$ Placebo, pH 7.0, $n = 101$	TNSS, PNSS, RQLQ	Treatment led to improved symptom and QOL scores at 6-weeks but QOL improvements not significant at 52-weeks
Zhu et al.[1074]	2019	2	Open-label RCT	AR ($n = 255$): ARCT group, $n = 126$ Control, $n = 129$	ARCT, RQLQ, medication adherence, BIP-Q	Stepping down medical therapy in patients with controlled AR results in similar clinical outcomes at reduced cost
Bousquet et al.[1075]	2018	2	Cross-sectional	Users of *Allergy Diary* smartphone app, $n = 1287$	EQ-5D VAS, WPAIAS	Mobile technology measuring ARIA score can be used to detect severe AR that impacts QOL
Hoehle et al.[1076]	2017	2	Cross-sectional	AR, $n = 150$	EQ-5D VAS, SNOT-22, NOSE, RCAT	Sleep and otologic symptoms have the greatest negative impact on QOL
Filanowicz et al.[1077]	2016	2	Cross-sectional	SCIT ($n = 200$): Allergic asthma, $n = 101$ AR, $n = 99$	RQLQ	QOL significantly affected by AR SCIT significantly improved QOL in asthma and AR
Jaruvongvanich et al.[1078]	2016	2	Cross-sectional	AR, $n = 200$	SF-12, TSS	Extra-nasal symptoms in AR correlate with physical and mental health QOL domains

(Continues)

TABLE IX.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Song et al.[1079]	2015	2	Cross-sectional	Adolescents (n = 6407): Likely AR from stratified sample, n = 515 Cluster sample, n = 814	VAS	AR in 15.8%–19.4% AR impacts QOL, sleep, emotions, and memory
Bousquet et al.[1054]	2013	2	RCT	AR (n = 716): Desloratadine, n = 360 Placebo, n = 356	Symptoms scores, sleep questionnaire, RQLQ, WPAI-AS	Desloratadine improves symptoms, QOL, and functional impairment
Bousquet et al.[1080]	2013	2	Cross-sectional	AR, n = 900	VAS, RQLQ, TSS	20% mild intermittent, 17% mild persistent, 15% moderate–severe intermittent, 48% moderate-severe persistent Severity and duration of AR impact on QOL Ocular symptoms impact RQLQ more than nasal obstruction Sneezing/rhinorrhea do not impact RQLQ
Katelaris et al.[1081]	2013	2	Cross-sectional	AR, n = 303	Telephone or in-person interviews	AR impacts work/school performance, general QOL, and sleep quality
Tatar et al.[1063]	2013	2	RCT	AR (n = 56): Mometasone, n = 14 Mometasone-levocetirizine, n = 21 Mometasone-montelukast, n = 21	Mini-RQLQ TSS	QOL significantly affected by AR Combination of mometasone with levocetirizine or montelukast improves QOL more than mometasone alone
de la Hoz Caballer et al.[1082]	2012	2	Cross-sectional	Primary care patients, n = 616	SF-36, generic HRQOL, WPAI	AR impacts productivity to a greater magnitude than hypertension and DM type II, but less than the impact of depression
Meltzer et al.[1083]	2012	2	Cross-sectional	Nasal allergy, n = 522 Control, n = 400	Non-validated phone interview questions	Patients with AR rate overall health lower, have worse sleep function, and decreased productivity than those without AR
Yamada et al.[1053]	2012	2	DBRCT, crossover	Perennial AR (n = 57): mometasone	TSS, Japanese RQLQ, ESS, QOL score, nasal nitric oxide	Nasal mometasone improves nasal symptoms, QOL, and sleep quality; and decreases nitric oxide
Hoiby et al.[1059]	2010	2	DBRCT	AR (n = 53): SCIT, n = 27 Placebo, n = 26	Symptom score, RQLQ, medication score, immunologic markers	SCIT reduces symptom and medication scores and improves QOL compared to placebo

(Continues)

TABLE IX.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Holmberg et al.[1055]	2009	2	DBRCT	AR ($n = 584$): Desloratadine, $n = 293$ Placebo, $n = 291$	RQLQ, symptom score	Desloratadine improves RQLQ and symptom score significantly compared to placebo
Stull et al.[1084]	2009	2	Cross-sectional	AR, $n = 404$	Symptom scale, nocturnal RQLQ, WPAI, MOS-12 Sleep, PANAS-X	Nasal congestion more strongly correlated to outcomes Ocular symptoms can have significant impact on QOL
Witt et al.[1085]	2009	2	RCT	AR ($n = 981$): Acupuncture, $n = 487$ Control, $n = 494$	SF-36	Acupuncture improves QOL more than control at 3 months
Brinkhaus et al.[1086]	2008	2	RCT, crossover	AR ($n = 5237$): Randomized ($n = 1068$); acupuncture ($n = 487$); control ($n = 494$) Not randomized, received acupuncture ($n = 4256$)	RQLQ, SF-36	QOL significantly affected by AR Acupuncture group improved more than conventional medical care
Petersen et al.[1087]	2008	2	Cross-sectional	AR, $n = 248$ AR and asthma, $n = 121$	RQLQ, 15D	AR patients have worse QOL during allergen exposure 15D generates more comprehensive view of impact on QOL than RQLQ
Ciprandi et al.[1088]	2007	2	Cross-sectional	AR, $n = 123$	RQLQ	QOL significantly affected by AR Greater than two sensitivities, eosinophil count, and nasal flow related to QOL Eye symptoms correlate most strongly to QOL
Canonica et al.[1056]	2006	2	DBRCT	AR ($n = 551$): Levocetirizine, $n = 278$ Placebo, $n = 273$	RQLQ, SF-36	QOL significantly affected by AR Levocetirizine improves QOL compared to placebo
Colas et al.[1061]	2006	2	DBRCT	AR ($n = 60$): SCIT, $n = 41$ Control, $n = 19$	RQLQ, symptoms score, medication score, VAS, SPTs	QOL significantly affected by AR SCIT improves RQLQ, symptom and medication scores
Di Rienzo et al.[1060]	2006	2	DBRCT	AR ($n = 34$): SLIT, $n = 19$ Placebo, $n = 15$	RQLQ	QOL significantly affected by AR SLIT improved QOL compared to placebo
Bachert et al.[1057]	2004	2	DBRCT	Persistent AR ($n = 551$): Levocetirizine, $n = 278$ Placebo, $n = 273$	SF-36, RQLQ, TSS	Levocetirizine improves QOL and decreases symptom scores and disease-related costs

(Continues)

TABLE IX.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Radcliffe et al.[1089]	2003	2	DBRCT	Seasonal AR (n = 183): Enzyme potentiated desensitization, n = 90 Placebo, n = 93	RQLQ, problem-free days	Enzyme potentiated desensitization does not improve QOL or symptom scores compared to placebo
Gerth van Wijk et al.[1090]	2000	2	DBRCT	Perennial AR (n = 26): Capsaicin, n = 13 Control, n = 13	Nasal challenge, VAS, RQL, immunologic markers	Capsaicin does not sufficiently control rhinitis symptoms
Leynaert et al.[1091]	2000	2	Cross-sectional	Young adults (n = 850): AR but not asthma, n = 240 AR and asthma, n = 76 Neither AR nor asthma, n = 349	SF-36	Both asthma and AR impact QOL AR impacts emotional and mental health, social activities, and activities of daily living Comorbid asthma caused more physical limitations than AR alone
Juniper et al.[1048]	1991	2	DBRCT	AR (n = 145): RQLQ questionnaire development (n = 85) Validation (n = 60): beclomethasone 200 μg qDay (n = 30); beclomethasone 400 μg PRN (n = 30)	RQLQ	Patients experience impaired QOL through systemic, sleep, emotional symptoms, and practical/activity limitations Beclomethasone use correlated to RQLQ
Fasola et al.[1064]	2020	3	Cohort	Children with AR and asthma, n = 50	RhinAsthma-children, PAQLQ, PRQLQ, KiddyKINDL, KidKINDL, VAS, GRC	RAPP-children is a valid, five-item questionnaire for assessing HRQOL in children aged 6–11 years with concomitant asthma and rhinitis
Husain et al.[1051]	2020	3	Cohort	Persistent AR, n = 353	SNOT-22, EQ-5D, EQ-5D VAS, RCAT	SNOT-22 has utility to assess QOL and symptom control in AR
Cuesta-Herranz et al.[1092]	2019	3	Cohort	AR undergoing SCIT, n = 120	RQLQ, ARIA	SCIT treatment increases QOL Reduction in asthma symptoms with SCIT
Gillman et al.[1093]	2019	3	Non-randomized cohort	Nasal obstruction (n = 67): Allergic, n = 34 Nonallergic, n = 33	NOSE, EOB, mini-RQLQ	AR patients have worse allergy related QOL compared to non-allergic patients After septoplasty and IT reduction allergy related QOL improves
Baiardini et al.[1094]	2017	3	Cohort	Children with AR, n = 100	Novel, unvalidated HRQOL survey	RhinAsthma-Children has good validity and internal consistency, can capture impacts of respiratory allergy on HRQOL

(Continues)

TABLE IX.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Novakova et al.[1095]	2017	3	Cohort	AR treated with SLIT, $n = 191$	RQLQ	SLIT significantly improved QOL
Schwanke et al.[1096]	2017	3	Non-randomized cohort	AR ($n = 40$): SCIT, $n = 29$ SLIT, $n = 11$	RQLQ	Only SCIT had a statistically significant improvement in QOL Study limited by small sample size
Valls-Mateus et al.[1067]	2017	3	Cohort	Children and adolescents with persistent AR undergoing medical treatment ($n = 142$): Responders, $n = 49$ Non-responders, $n = 93$	VAS, PRQLQ, AdolRQLQ	Lack of response to medical treatment has a large impact on QOL Septal deviation and IT hypertrophy is associated with worst QOL
Bukstein et al.[1097]	2016	3	Non-randomized cohort	Perennial AR treated with beclomethasone nasal spray, $n = 527$	RCAT, treatment satisfaction, WPAI, PSQI, mini-RQLQ	Beclomethasone improves QOL, school-related activities, satisfaction, productivity, sleep quality
Cingi et al.[1098]	2013	3	Non-randomized cohort	Perennial AR treated with desloratadine-montelukast, $n = 40$	Acoustic rhinometry, RQLQ	Desloratadine-montelukast improves nasal obstruction and QOL
Demoly et al.[1099]	2013	3	Cohort	AR, $n = 990$	VAS, RQLQ, TSS	VAS can detect QOL variations with high sensitivity
Ciprandi et al.[1100]	2010	3	Cohort	AR undergoing SLIT, $n = 167$	RQLQ	QOL significantly affected by AR SLIT improves QOL and symptoms
Cadario et al.[1101]	2008	3	Cohort	AR undergoing SLIT, $n = 40$	Non-validated patient satisfaction survey, VAS, RQOL	QOL significantly affected by AR SLIT improves QOL and symptoms
Laforest et al.[1102]	2005	3	Cohort	Seasonal AR, $n = 83$ Asthma, $n = 52$	Mini-RQLQ, SF-12	QOL significantly affected by seasonal AR and asthma Female gender, rural residence, lower education levels associated with worse QOL in seasonal AR
Majani et al.[1072]	2001	3	Cohort	Seasonal AR, $n = 33$	SF-36, SAT-P	QOL significantly affected by AR during peak season

Abbreviations: AdolRQLQ, Adolescent Rhinoconjunctivitis Quality of Life Questionnaire; AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; ARCT, Allergic Rhinitis Control Test; BIP-Q, Brief Illness Perception Questionnaire; CARATKids, Control of Allergic Rhinitis and Asthma Test for Children; CT, controlled trial; 15D, Generic 15 Dimension Instrument for measuring health related quality of life; DBRCT, double blind randomized controlled trial; DM, diabetes mellitus; EOB, Ease-of-Breathing scale; EQ-5D, Euro-QOL 5-dimension questionnaire; ESPRINT-15, Cuestionario ESPañol de Calidad de Vida en RINiTis; ESS, Epworth Sleepiness Scale; GRC, Global Rating of Change scale; HDM, house dust mite; HRQOL, health-related quality of life; INCS, intranasal corticosteroid; ISAAC, International Study of Asthma and Allergies in Childhood questionnaire; IT, inferior turbinate; LOE, level of evidence; MOS-12 Sleep, Medical Outcomes Study 12-Item Sleep Scale; NOSE, Nasal Obstruction Severity Evaluation; PANAS-X, Positive and Negative Affect Schedule-Expanded Form; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PNIF, peak nasal inspiratory flow; PNSS, Physician-assessed Nasal Symptom Score; PRN, as needed; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; PROMs, patient reported outcome measures; PSQI, Pittsburgh Sleep Quality Index; qDay, daily; QOL, quality of life; RCAT, Rhinitis Control Assessment Test; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RQOL, Rhinitis Quality of Life; SAT-P, Satisfaction Profile; SCIT, subcutaneous immunotherapy; SF-12/36, Short Form (12 or 36 questions); SLIT, sublingual immunotherapy; SNOT-22, Sinonasal Outcome Test 22-item; SPT, skin prick test; SR, systematic review; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score; TSS, Total Symptom Score; T4SS, Total 4 Symptom Score; VAS, visual analog scale; WPAI, Work Productivity and Activity questionnaire; WPAIAS, Work Productivity and Activity Allergy Specific questionnaire.

Disease burden – quality of life

Aggregate grade of evidence: B (Level 1: 6 studies, level 2: 35 studies, level 3: 15 studies; Table IX.A.1)
Benefit: Successful treatment of AR leads to improved overall and disease specific QOL.
Harm: Depending on the specific treatments for AR, there are variable levels of harm (Table II.C).
Cost: Treatments for AR have variable costs.
Benefits-harm assessment: The benefits of treating patients with AR to improve QOL likely outweigh risks of treatment.
Value judgments: Validated measures of QOL should be utilized in future studies of treatments for AR.
Policy level: Recommendation.
Intervention: Validated measures of QOL should be utilized in future studies of treatments for AR.

IX.A.2 | Sleep disturbance

AR affects 20%–30% of adults and children with OSA and sleep disordered breathing (SDB).[1103,1104] Multiple studies have investigated the relationship between AR and sleep in adults and children. The general conclusion from the aggregate data is that similar to overall and rhinitis specific QOL, AR negatively impacts sleep quality, and the successful treatment of AR reduces sleep disturbance. Overall, the data is of low to moderate strength, with the overall quality of the data being higher for adults than for the pediatric population. For the adult population, there is strong evidence supporting the conclusion that AR negatively impacts sleep.[1105–1109] This data deals with subjective reporting of daytime sleepiness, sleep quality, and symptoms usually through validated tools, in the setting of testing the effect of INCS and montelukast (Tables IX.A.2.-1 and IX.A.2.-2).

In children, lower quality data suggest that AR is associated with sleep disturbance in the form of increased risk of snoring, SDB, and OSA. However, the findings here are not uniform, with some studies suggesting that while the prevalence of AR is high in the OSA population, AR might not impact disease severity.[1104,1110] Furthermore, AR has been suggested to be a risk factor for deterioration of OSA QOL after adenotonsillectomy.[1111] Additionally, AR may increase the risk of nocturnal enuresis in children.[1112]

Two studies looked at variations in sleep symptoms with changes in nasal inflammation over time. Nasal cytokine level alterations are associated with changes in the polysomnogram (PSG)[1113] and AR patients have worse PSG parameters and sleep disturbance when their symptoms are present or during their peak allergen season.[1114] The data on PSG parameters in adults is mixed. Most studies that perform PSG found that AR worsens PSG parameters[1103,1113–1122]; however, two studies found either no difference or a modest change.[1123,1124]

AR patients have improvements of sleep quality, daytime sleepiness, sinonasal symptoms, and QOL after treatment with INCS[1105–1107,1125] or a combination of INCS and montelukast.[1105] Additionally, AR has been associated with worse sleep fragmentation[1118,1126] and snoring.[1116,1127] In addition to reducing sleep disturbance, treatment of AR has been suggested to also improve CPAP compliance.[1128] (See Section XIII.K. Associated Conditions – Sleep Disturbance for additional information on this topic.)

Disease burden - sleep disturbance

Aggregate grade of evidence: B (Level 2: 5 studies, level 3: 8 studies, level 4: 50 studies Tables IX.A.2.-1 and IX.A.2.-2).
Benefit: AR negatively impacts sleep quality. Successful management of AR leads to decreased sleep disturbance in adults and children.
Harm: Medical management of AR is generally low risk and medications have low side-effect profiles. AIT is associated with rare serious adverse events (Table II.C).
Cost: Associated costs consist of the direct costs of allergy testing and medical management, and indirect cost of increased time and effort for AIT.
Benefits-harm assessment: The benefits of treating patients with AR may outweigh any associated risks.
Value judgments: In patients with AR, the successful control of symptoms with medical management or AIT can lead to important improvements in sleep disturbance. The level of available evidence is stronger for the adult population compared with the pediatric population.
Policy level: Treatment of AR to improve sleep disturbance – Recommended in adults. Option in children.
Intervention: INCS, oral antihistamines, montelukast, and AIT are appropriate options, when medically indicated, to improve sleep disturbance in patients with AR.

IX.B | Societal burden

AR has a high prevalence globally and imposes negative effects on QOL and therefore a burden to individuals and

TABLE IX.A.2.-1 Evidence table – individual burden of allergic rhinitis: sleep (adults)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Fried et al.[1129]	2022	2	SRMA	28 articles, $n = 8515$ AR patients	RQLQ, ESS, PSQI	Treatment of AR improves subjective sleep quality
Liu et al.[1120]	2020	2	SRMA	27 articles, $n =$ 19,444,043	Sleep duration, sleep quality, PSQI, PSG, daytime functioning	AR associated with more sleep disturbances and lower sleep efficiency, worse daytime function Overall study quality low to very low
Shanqun et al.[1105]	2009	2	Placebo-controlled RCT	AR and OSA ($n = 89$): Montelukast-budesonide, $n = 44$ Placebo, $n = 45$	ESS, RQLQ, RSS, CSAQLI, symptoms diary	Montelukast-budesonide improves AR and OSA QOL, sleep quality and daytime somnolence
Mansfield and Posey[1109]	2007	2	Placebo-controlled RCT	Fluticasone, $n = 16$ Placebo, $n = 16$	TOVA, ESS, TSS	Fluticasone improves daytime sleepiness, cognitive performance, and nasal symptoms
Munoz-Cano et al.[1130]	2018	3	Prospective cohort	AR, $n = 670$	Sleep quality, MOSSS	AR symptoms negatively impact sleep quality
Parikh et al.[1128]	2014	3	Prospective cohort	OSA and rhinitis, $n =$ 43	ESS, symptoms scores, CPAP compliance	Control of rhinitis (with varying regimens of INCS, antihistamines, leukotrienes inhibitors, anticholinergics, etc.) important for OSA control Rhinitis control assessed via symptoms scores, OSA control assessed via ESS No difference between AR and non-allergic rhinitis
Acar et al.[1115]	2013	3	Prospective cohort	OSA and AR treated with INCS, $n = 80$	ESS, PSG	INCS improve sleep quality and AR symptoms Addition of antihistamine did not have effect
Colas et al.[1131]	2012	3	Prospective cohort	AR, $n = 2275$	TSS, RQLQ, PSQI	AR disease severity has strong relationship with sleep disturbance
Gurevich et al.[1106]	2005	3	Crossover trial	Perennial AR, crossover trial of nasal budesonide, $n = 26$	ESS, sleep diary, questionnaire	Budesonide reduces nasal congestion, daytime somnolence/fatigue, and improves sleep quality
Hughes et al.[1107]	2003	3	Crossover trial	Perennial AR, crossover trial of nasal budesonide and placebo, $n = 22$	ESS, FOSQ, RQLQ, symptom diary	Budesonide improves daytime fatigue and sleep quality
Craig et al.[1108]	1998	3	Crossover trial	AR, crossover trial of nasal flunisolide and placebo, $n = 20$	Symptom and sleep diary	INCS improve symptoms and subjective sleep compared to controls
Berson et al.[1121]	2020	4	Case–control	AR with HDM allergy, $n = 47$ Control, $n = 53$	PSG	AR leads to increased risk of moderate/severe respiratory disturbances during sleep

(Continues)

TABLE IX.A.2.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Pace et al.[1122]	2020	4	Case–control	AR, $n = 20$ NARES, $n = 20$ Control, $n = 20$	PSG	60% of NARES, 25% of AR, and 10% of control patients had OSA
Romano et al.[1132]	2019	4	Survey study	AR, $n = 511$	Sleep questionnaire	AR negatively impacts sleep metrics and daily functioning
Berson et al.[1119]	2018	4	Case–control	AR, $n = 67$ Non-allergic rhinitis, $n = 33$	ESS, PSG	AR worsens sleep quality
Roxbury et al.[1133]	2018	4	Survey study	Subjects from NHANES database, $n = 5563$, 36.5% with self-reported AR	Sleep questionnaire (latency, duration, habits, etc.)	AR associated with poor sleep parameters (prolonged latency, insomnia, OSA, sleep disturbances, medication use, daytime function)
Bozkurt et al.[1124]	2017	4	Case–control	Persistent AR and OSA symptoms, $n = 150$ Control, $n = 95$	SPT, PSG	Persistent AR did not affect PSG parameters compared to controls
Gadi et al.[1135]	2017	4	Cross-sectional	Sleep clinic patients, $n = 157$	History, laboratory testing	62% OSA 53% AR in OSA No difference in AR/atopy between OSA and non-OSA
Leger et al.[1134]	2017	4	Prospective, cross-sectional	Adults with AR, $n = 907$	ESS, insomnia severity, sleep questionnaire	AR induced by HDM (especially severe and persistent) negatively impacts sleep
Zheng et al.[1103]	2017	4	Cross-sectional	OSA, $n = 240$, 27% with AR	PSG	AR does not influence severity of OSA
Lavigne et al.[1117]	2013	4	Case–control	OSA and AR, $n = 34$ OSA without rhinitis, $n = 21$	PSG, nasal biopsies	In AR, INCS reduce nasal inflammation and improve PSG parameters
Park et al.[1136]	2012	4	Case–control	OSA and AR, $n = 37$ OSA without rhinitis, $n = 75$	ESS, stress, score, fatigue score, coping score, RQLQ	AR in OSA increases stress and fatigue, worsens sleepiness, and QOL
Meng et al.[1123]	2011	4	Case–control	Persistent AR, $n = 98$ Control, $n = 30$	PSG	PSG parameters showed modest changes in persistent AR patients
Rimmer et al.[1126]	2009	4	Case–control	Persistent AR, $n = 10$ Control, $n = 10$	Actigraphy	AR has increased sleep fragmentation and reduced sleep quality
Udaka et al.[1137]	2007	4	Survey study	Daytime workers, $n = 3442$	Questionnaire, ESS, SF-36	Severity of nasal obstruction (non-validated questionnaire) correlates with worse ESS and lower QOL
Leger et al.[1138]	2006	4	Controlled, cross-sectional	AR, $n = 591$	SDQ, ESS, symptom score	All dimensions of sleep impaired by AR Disease severity correlated with degree of sleep impairment

(Continues)

TABLE IX.A.2.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Canova et al.[1139]	2004	4	Case–control	OSA, $n = 72$ COPD controls, $n = 44$	Symptom score, spirometry, SPT	OSA more likely to be sensitized to perennial allergens (11% in OSA vs. 2.3% COPD)
Mintz et al.[1140]	2004	4	Uncontrolled open-label study	AR, $n = 651$	NRQLQ, PSQI	Treatment with triamcinolone improves nocturnal rhinitis QOL and sleep quality
Stuck et al.[1141]	2004	4	Case–control	Seasonal AR, $n = 25$ Control, $n = 25$	ESS, SF-36, PSG	Seasonal AR leads to increased daytime sleepiness compared to controls
Krouse et al.[1113]	2002	4	Case–control	AR, $n = 4$ Control, $n = 4$	PSG, serum, and nasal cytokines	Differing cytokine levels associated with variations in PSG
Camhi et al.[1127]	2000	4	Survey study	Subjects from TESOAD with sleep problems/snoring, $n = 437$	Questionnaire	AR risk factor for snoring
Young et al.[1116]	1997	4	Survey and case series	Survey subjects, $n = 4297$ Objective testing subjects, $n = 911$	Questionnaire, PSG	AR and nasal obstruction associated with snoring, daytime sleepiness, and SDB
Janson et al.[1142]	1996	4	Cross-sectional study	Random sample of the ECRHS, $n = 2661$	SPT, methacholine challenge, questionnaire	AR independently associated with difficulty initiating sleep and daytime sleepiness (OR 2.0)
McNicholas et al.[1114]	1982	4	Case series	AR, $n = 7$	Nasal resistance, PSG	When symptoms present, AR patients have worse OSA symptoms AR patients have high nasal resistance
Lavie et al.[1118]	1981	4	Case–control	AR, $n = 14$ Control, $n = 7$	PSG	AR patients had 10-fold increase in micro-arousals versus controls

Abbreviations: AR, allergic rhinitis; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CSAQLI, Calgary Sleep Apnea Quality of Life Index; ECRHS, European Community Respiratory Health Survey; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HDM, house dust mite; INCS, intranasal corticosteroid; LOE, level of evidence; MOSSS, Medical Outcomes Study Sleep Scale; NARES, non-allergic rhinitis with eosinophilia; NHANES, National Health and Nutrition Examination Survey; NRQLQ, Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire; OR, odds ratio; OSA, obstructive sleep apnea; PSG, polysomnogram; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RSS, Rhinitis Symptom Score; SDB, sleep disordered breathing; SDQ, Sleep Disorders Questionnaire; SF-36, 36-item Short Form Survey; SPT, skin prick test; SRMA, systematic review and meta-analysis; TESOAD, Tucson Epidemiology Study of Obstructive Airway Disease; TOVA, Test of Variables Attention; TSS: total symptom score.

society. Due to its chronicity and prevalence, AR poses a significant socioeconomic burden.[1167,1168] The true burden of AR involves direct, indirect, and societal costs. Direct costs relate to financial expenditures on healthcare related to AR, including the diagnosis, prevention, and management of disease. Indirect costs are due to loss of productivity related to disease including job loss, absenteeism, and presenteeism. Additional costs include costs due to reduced QOL and societal costs related to an individual's symptoms and subsequent reduced QOL.[1169–1172]

In the US, AR is the fifth most burdensome chronic condition when considering total cost.[1173] Direct costs of AR in the US exceed $4.5 billion per year.[1174–1178] Likewise, AR represents a large direct economic burden in several other countries.[1171,1179,1180] Medication expense makes up most of the direct cost, but additional costs include office visits, testing, and procedures.[1005] These costs are even higher when considering patients with related illnesses such as asthma, allergic conjunctivitis, and CRS.[1169,1181,1182] Despite many treatments being available over-the-counter,

TABLE IX.A.2.-2 Evidence table – individual burden of allergic rhinitis: sleep (children)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lin et al.[1143]	2013	2	SRMA	18 articles	Association between AR and SDB	Most studies show association between AR and SDB in children, but all studies were low level of evidence
Lai et al.[1112]	2018	3	Controlled cohort study	AR, $n = 327,928$ Non-allergic rhinitis, $n = 327,061$	Questionnaire on nocturnal enuresis	AR increases risk of nocturnal enuresis
Lee et al.[1144]	2021	4	Survey study	Adolescents, $n = 1936$, 23.7% with AR	Sleep questionnaire	AR associated with inappropriate sleep duration
Giraldo-Cadavid et al.[1145]	2020	4	Cross-sectional	AR children at high altitude, $n = 99$	PSG	AR in children at high altitude associated with more severe OSA
Liu et al.[1104]	2020	4	Case–control	SDB, $n = 660$, 25.8% with AR and SBD, 19.4% with AR and OSA	PSG, sleep questionnaire	AR has high prevalence in SDB group but does not impact severity of sleep disorders
Bilgilisoy Filiz et al.[1110]	2018	4	Case–control	AR, $n = 143$ Control, $n = 144$	PSQI, IRLSSG	AR did not impact restless leg syndrome or sleep quality
Perikleous et al.[1146]	2018	4	Cross-sectional	Asthma, $n = 65$ AR, $n = 18$ Asthma + AR, $n = 57$	ACT, PSQ, sleep-related breathing disorder scale	AR in children with asthma increased SDB
Leger et al.[1134]	2017	4	Cross-sectional	Children with AR, $n = 843$	ESS, insomnia severity, sleep questionnaire	AR induced by HDM (particularly severe and persistent) negatively impacts sleep
Di Francesco and Alvarez[1147]	2016	4	Case series	SDB undergoing T&A, $n = 135$	PSG	AR affected REM sleep in children with SDB without OSA AR is not an aggravating factor in AHI severity
Chimenz et al.[1148]	2015	4	Case series	AR and adenoid grade I-II, $n = 32$ AR and adenoid grade III-IV, $n = 27$	History	AR may influence development of nocturnal enuresis
Kim and Han[1111]	2015	4	Prospective cohort	SDB undergoing T&A, $n = 70$	OSA-18, SPT, questionnaire	AR may be risk factor for deterioration of OSA QOL after T&A
Koinis-Mitchell et al.[1149]	2015	4	Cross-sectional	Non-white Latino and African American urban children, $n = 195$	Clinical evaluation and follow-up	Poor AR and asthma control related to high frequency of sleep problems and poor sleep hygiene
Poachanukoon et al.[1150]	2015	4	Case–control	AR, $n = 65$ Control, $n = 104$	Questionnaire	Higher incidence of sleep disturbance in AR

(Continues)

TABLE IX.A.2.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kwon et al.[1151]	2013	4	Survey study	Children with AR, $n = 85{,}002$	National survey data	Association between late sleep time and short sleep duration with AR
Bhattacharjee et al.[1152]	2010	4	Cross-sectional	Children undergoing T&A for OSA, $n = 578$	PSG	39% of OSA children have AR pre-operatively
Li et al.[1153]	2010	4	Survey study	Children, $n = 6349$	Questionnaire	HS associated with AR (OR 2.9; 95% CI 2.0–4.2)
Vichyanond et al.[1154]	2010	4	Case series	Children with rhinitis, $n = 302$	History	Upper airway obstruction associated with non-allergic rhinitis
Barone et al.[1155]	2009	4	Case–control	Children from sleep disorders clinic, $n = 149$ Controls, $n = 139$	PSG	AR associated with OSA, OR 2.24
Sogut et al.[1156]	2009	4	Cross-sectional	Turkish children, $n = 1030$	Questionnaire	AR associated with HS (OR 3.7; 95% CI 1–13)
Liukkonen et al.[1157]	2008	4	Cross-sectional	Children in Helsinki, $n = 2100$	Questionnaire	AR more common in snorers
Kalra et al.[1158]	2006	4	Cross-sectional	Children in CCAAPS, $n = 681$	Questionnaire	29% of patients with HS have positive SPT, significant association
Goldbart et al.[1159]	2005	4	Case series	SDB, $n = 24$	PSG, lateral neck x-ray	Montelukast treatment for 16 weeks decreased adenoid size and respiratory sleep disturbances
Ng et al.[1160]	2005	4	Cross-sectional	School children, $n = 3047$	Questionnaire	AR associated with witnessed apnea
Sogut et al.[1161]	2005	4	Cross-sectional	Turkish children, $n = 1198$	Questionnaire	AR associated with HS (OR 4.23; 95% CI 2.14–8.35)
Chng et al.[1162]	2004	4	Cross-sectional	School children, $n = 11{,}114$	Questionnaire	Snoring in 34%, AR associated with snoring (OR 2.9; 95% CI 2.06–4.08)
Kidon et al.[1163]	2004	4	Cross-sectional	Children with AR undergoing SPT, $n = 202$	History	17% of AR patients reported HS
Mansfield et al.[1164]	2004	4	Case series	Children with AR, $n = 14$	PSG, RQLQ	Treating AR decreases AHI
Anuntaseree et al.[1165]	2001	4	Cross-sectional	Randomly selected children, $n = 1142$	PSG, questionnaire	Prevalence of HS 8.5%, OSA 0.69%. OR 5.27 in children with AR
McColley et al.[1166]	1997	4	Case series	Children with HS, $n = 39$	PSG	Positive skin test associated with OSA

Abbreviations: ACT, Asthma Control Test; AHI, apnea-hypopnea index; AR, allergic rhinitis; CCAAPS, Cincinnati Allery and Air Pollution Study; CI, confidence interval; ESS, Epworth Sleepiness Scale; HDM, house dust mite; HS, habitual snoring; IRLSSG, international restless leg syndrome study group criteria; LOE, level of evidence; OR, odds ratio; OSA, obstructive sleep apnea; OSA-18, 18-item quality of life survey for obstructive sleep apnea; PSG, polysomnogram; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; REM, rapid eye movement sleep; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SDB, sleep disordered breathing; SPT, skin prick test; SRMA, systematic review and meta-analysis; T&A, tonsillectomy and adenoidectomy.

US medication costs for only AR are estimated to exceed $1 billion (US),[1175] and patients with AR are also more likely to utilize clinic visits, further driving direct costs.[1174,1183]

AR leads to increased direct costs in countries around the world.[1169] A 2021 US study demonstrated that AR patients had annual mean costs of $218 (US) for clinic visits and procedures, and additional $111 (US) for medications.[1175] In a 2020 Dutch study comparing 350 AR patients to controls, those with AR spent an additional €208 per year in direct costs.[1179] In a 2016 study of 8001 Swedish residents, direct costs attributable to AR were €210 per individual per year.[747] A 2017 French study demonstrated median direct costs of €159 for AR without asthma and €375 for AR with asthma.[1184] Studies from Turkey showed increased costs of $79 to $139 (US) for AR patients.[1185] Studies from South Korea and India also demonstrate significant direct costs.[1186–1188]

Despite its perception as a nuisance disorder, AR has significant effect on QOL and accounts for substantial indirect costs related to missed work or school and poorer productivity. AR results in 3.5 million missed workdays and 2 million missed school days.[1189] However, indirect costs account for a larger proportion of the burden of AR than the direct costs.[1178] In the US, AR has been shown to contribute to greater than $5 billion (US) in lost productivity yearly.[1190] These costs include absenteeism, but health impairments of AR are often not severe enough to cause absenteeism. AR symptoms can interfere with cognitive functioning, resulting in fatigue and impaired learning, concentration, and critical thinking leading to presenteeism or reduced productivity while at work.[1191] As such, presenteeism accounts for the majority of reduced productivity related to AR.[1192–1194]

In the US, AR is the most prevalent condition among the workforce, and accounted for 52 symptomatic days per year with a mean productivity loss of $518 (US) per employee per year.[1195] In the UK, impaired productivity and/or missed work occurred as a result of AR in 52% of patients.[1183] In India, 37% percent of surveyed patients with AR endorsed presenteeism and AR was responsible for $460 (US) loss per patient annually.[1188] In Sweden, indirect costs were calculated to be €751 per patient annually.[747] In The Netherlands, indirect costs were estimated to be €3681 per patient annually, and presenteeism accounted for the majority of lost productivity.[1179] In a Spanish study, presenteeism made up 95% of the loss in productivity and was estimated €1772 per year.[1192]

Additionally, there are indirect economic losses that come from caregivers missing work while a child is absent from school. In a Swedish study, the cost of caregiver absenteeism comprised 19% of the mean total costs per year. The cost related to caregiver absenteeism was highest for women aged 30–44 years.[1196]

AR is also the most prevalent chronic disorder among children, as such it has a significant impact on education.[1197,1198] On any given day in the US, approximately 10,000 children are absent from school because of AR.[1199] AR can alter sleep quality resulting in daytime sleepiness, impaired cognition, and poorer memory in children that significantly affects the learning process and impacts school performance.[1120,1198,1200] Even when present during school hours, children with AR exhibit decreased productivity. Conditions associated with AR such as rhinosinusitis, ETD and associated conductive hearing loss may enhance the learning dysfunction.[1198]

Additionally, AR has been associated with negative impact on mental health with functional decline as well as major depression, further reducing overall QOL.[1076,1201,1202] This relationship has been shown in studies from Europe, the US, and Asia.[1202]

AR represents a significant personal and socioeconomic burden that will likely worsen as the prevalence continues to increase.[1203,1204] It can reduce productivity and QOL in affected patients and contribute to comorbid conditions. This results in a significant impact to the overall health system.[1199]

X | EVALUATION AND DIAGNOSIS

X.A | History and physical examination

X.A.1 | History

A crucial component in the diagnosis of suspected AR rests on clinical history.[5,31,1005,1205,1206] This includes symptoms experienced, timing of symptoms, duration, frequency, patient occupation/school/home environmental exposures that elicit symptoms, and any measures or medications that improve or worsen symptoms.[5,31,1005,1205–1207] Other comorbid conditions in the past medical history, such as asthma, OSA, family history of atopic disorders, and medications currently taken should be gathered.[5,31,1005,1205–1207] Patient response to self-treatment with over-the-counter medications is helpful information, and with advancing technology mobile applications may allow for the potential collection of patient symptomatology to identify symptom patterns that may be very useful for treating providers.[1208]

Classic symptoms of AR include nasal congestion or obstruction, nasal pruritis, rhinorrhea, and sneezing. In addition, patients may complain of other symptoms associated with comorbidities including ocular pruritis, erythema, and/or tearing (allergic conjunctivitis), oral cavity or pharyngeal pruritis (allergic pharyngitis), throat clearing, and wheezing or cough (reactive airway

disease and/or asthma).[5,31,1005,1205–1207] Snoring or sleep-disordered breathing, aural congestion or pruritis, and wheezing are other frequent symptoms.[5,31,1206,1207] In the coronavirus disease 2019 (COVID-19) era, symptoms of hyposmia or anosmia, cough, and/or sore throat, which potentially may also be associated with AR, may cause confusion, and should prompt consideration for other diagnoses, such as active COVID-19 infection.[1207,1209,1210]

Patients with suspected AR will commonly present with multiple complaints, frequently with two or more symptoms.[1207,1208,1210] Perennial AR patients have a tendency to report more congestive symptoms (sinus pressure, nasal blockage/congestion, and snoring) than seasonal AR patients.[1209] Also, perennial AR patients more frequently complain of sore throat, cough, sneezing, rhinorrhea, and postnasal drip.[1207] Prior to the COVID-19 pandemic, symptoms of rhinorrhea, sneezing, sniffing, hyposmia/anosmia, nasal obstruction, and itchy nose ranked highest in diagnostic utility among symptoms of AR; however, the diagnostic utility of hyposmia/anosmia, nasal obstruction, and congestion may be less given the overlap in COVID-19 symptomology.[1207,1209,1211]

Despite the dearth of high-level evidence, many guidelines suggest that history of two or more symptoms consistent with AR is sufficient for making the diagnose of AR[5,31,1005,1205,1210,1211] (Table X.A.1). Since AR lacks pathognomonic physical examination findings, physical examination alone to diagnose AR has been shown to have poor predictive value.[1212] The reliability and predictive value of the patient history for AR exceeds that of the physical exam alone.[1212] In clinical practice, the presumptive diagnosis of AR is often made by only history, even more so during the pandemic with increased utilization of telemedicine where a physical examination is limited.[1210,1211,1213]

Patient history

Aggregate grade of evidence: D (Level 4: 5 studies, level 5: 7 guidelines or expert recommendations; Table X.A.1)
Benefit: Improves accuracy of diagnosis, avoids unnecessary referrals, testing, or treatment.
Harm: Potential misdiagnosis or inappropriate treatment.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Using history to make a presumptive diagnosis of AR is reasonable and would not delay treatment initiation. History should be combined with physical examination, which may not be possible in some scenarios such as telemedicine. Confirmation with diagnostic testing is required for progression to AIT or targeted avoidance therapy, or desirable with inadequate response to treatment.
Policy level: Recommendation.
Intervention: Despite low level evidence specifically addressing this area, history is essential in the diagnosis of AR.

X.A.2 | Physical examination

Whenever possible, it is important to include physical examination as part of the evaluation of suspected AR patients.[5,31,1005,1205,1210,1213] Telemedicine may complicate this part of the evaluation, but a limited visual examination may be obtained.[1213] An assessment of head and neck organ systems should be completed with the use of any necessary personal protective equipment.[31,1005,1205,1213] If there are patient complaints of wheezing or coughing with allergic triggers or comorbid conditions of asthma, the physical examination may include auscultation of the lungs.[5]

An unremarkable physical examination is common for AR patients, particularly those with intermittent exposure.[1209] Observation alone may reveal possible signs suggestive of AR, which can be useful during telemedicine visits. These signs include mouth-breathing, nasal itching or a transverse supratip nasal crease, throat clearing, periorbital edema, or "allergic shiners" (dark discoloration of the lower lids and periorbital area).[31,1205] Ear examination may reveal retraction of the tympanic membrane or transudative fluid, although evidence for association of effusion with AR is low level. Anterior rhinoscopy may reveal IT hypertrophy, congested/edematous nasal mucosa, purplish or bluish nasal mucosa, and clear rhinorrhea.[31,1005,1205] Eye examination may reveal conjunctival erythema and/or chemosis.[31,1205]

Physical examination by itself is more variable and poorly predictive of the diagnosis of AR when compared to history-taking, with the average sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) of the patient history higher than those of the physical examination.[1212] Most guidelines recommend a physical examination as part of the diagnosis of AR, despite a lack of high level evidence; however, pandemic conditions and the utilization of telemedicine may limit the completeness or possibility of physical examination[1213] (Table X.A.2). Without a physical examination, other potential causes of symptoms such as CRS may not be fully evaluated or eliminated, so if there are limits placed by

TABLE X.A.1 Evidence table – use of history taking in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bousquet et al.[1208]	2018	4	Observational	Adults with AR and asthma symptoms	VAS of five categories	Strong correlations between severity of categories of global assessment, eye, nose, and work
Costa et al.[1211]	2011	4	Cohort	Adults with AR	Physician interview and structured questionnaire	Many patients diagnosed on history alone without confirmatory testing
Raza et al.[1212]	2011	4	Cross-sectional	Adults with AR	History Physical examination SPT	Physical examination alone yields unreliable and inconsistent results in diagnosing AR
Shatz[1207]	2007	4	Survey	Adults and children >12 years old with AR Physicians of group 1	Self-completed patient questionnaire Physician record	Persistent AR patients reported more symptoms than intermittent AR patients
Ng et al.[1209]	2000	4	Case-control	Adults with AR	History Physical examination SPT sIgE	Rhinorrhea, sneezing, sniffing, impaired sense of smell, blocked nose, edematous nasal mucosa, and itchy nose ranked highest diagnostic utility
Scadding et al.[1210]	2020	5	Expert recommendations		Recommendations for allergic disease and AIT during the COVID-19 pandemic	Overlap between COVID and allergic symptoms can be confusing Evaluation and treatment of allergic disease can be managed during a pandemic
Shaker et al.[1213]	2020	5	Expert recommendations		Recommendations for atopic disorder evaluation/care during the COVID-19 pandemic	Evaluation and treatment require triage and adjust, when necessary, from face-to-face visits to telemedicine
Scadding et al.[1206]	2017	5	Guideline		Recommendations for management of AR and non-allergic rhinitis	AR diagnosis is made by history and physical examination, supported by diagnostic tests
Seidman et al.[1005]	2015	5[a]	Guideline		Recommendations on diagnosis and treatment of AR	Clinical diagnosis of AR made with a history and physical examination

(Continues)

TABLE X.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wallace et al.[31]	2008	5	Guideline		Recommendations on the diagnosis and treatment of rhinitis	Thorough allergic history remains the best diagnostic tool available
Small et al.[1205]	2007	5	Guideline		Recommendations on diagnosis and treatment of rhinitis	History of allergic symptoms is essential in the diagnosis of AR
Bousquet et al.[5]	2001	5	Guideline		Recommendations on the diagnosis and treatment of AR in asthmatic patients	Symptom type and timing (obtained through history) is essential to correct diagnosis

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; COVID-19, coronavirus disease 2019; LOE, level of evidence; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test; VAS, visual analog scale.

[a]Seidman et al. Clinical Practice Guideline LOE upgraded to 4 in other ICAR sections; although recommended, direct evidence for history and physical exam in AR remains poor and substantiates LOE 5 designation in this section.

telemedicine, additional diagnostic measures may need to be considered, such as a CT scan of the sinuses. A patient history combined with a physical examination improves diagnostic accuracy.[1212]

Physical examination

Aggregate grade of evidence: D (Level 4: 2 studies, level 5: 6 guidelines; Table X.A.2)
Benefit: Possible improved diagnosis of AR with physical examination findings, along with evaluation and/or exclusion of alternative diagnoses.
Harm: Possible patient discomfort from routine examination, not inclusive of endoscopy.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm, potential misdiagnosis, and inappropriate treatment if used in isolation.
Value judgments: Telemedicine is a safe and useful tool in pandemic conditions but does limit what can be gleaned from physical examination. Without the use of nasal endoscopy, it is possible some physical examination findings may be missed.
Policy level: Recommendation.
Intervention: When possible, physical examination should be performed with appropriate personal protective equipment to aid in the diagnosis of AR and exclusion of other conditions. When combined with patient history, it increases diagnostic accuracy and may exclude alternative causes of symptoms.

X.A.3 | Nasal endoscopy

Diagnostic nasal endoscopy may complement the evaluation of patients with suspected AR. Several case series and cross-sectional studies have evaluated the association of endoscopic findings with the diagnosis and severity of AR (Table X.A.3).

Ziade et al.[1214] studied a prospective cohort of adult patients with AR symptoms and skin testing confirmation, showing that mucosal edema and bluish discoloration of the ITs were highly predictive of the severity of AR disease ($p < 0.05$) when comparing patients with mild versus moderate/severe AR. Conversely, early studies by Jareoncharsri et al.[1215] and Eren et al.[1216] evaluated a population of adults and children with AR confirmed by allergy testing, concluding that findings of nasal endoscopy do not provide a reliable diagnosis or correlate with specific nasal symptoms of AR.

Additionally, Ameli et al.[1217] evaluated a large cohort of children with suspected AR and confirmed with skin testing, reporting that endoscopic findings of IT or MT septal contact as well as pale mucosa and large adenoid volume were highly predictive for AR. Notably, there were conflicting results in a previous study by the same group that reported no predictive role of pale mucosa as an endoscopic sign for AR.[1218] The possible explanation could be related to the smaller sample analyzed in the previous study.

Polypoid change of the MT has also been correlated with the diagnosis of AR as shown by White et al.,[1219] who described 16 patients with polypoid changes/polyps of the MT, all of which had positive allergy testing. Hamizan et al.[1220] reported that multifocal, diffuse, and polypoid edema – the highest grades of MT edema – had

TABLE X.A.2 Evidence table – use of physical examination in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Raza et al.[1212]	2011	4	Cross-sectional	Adults with AR	History Physical examination SPT	Physical examination alone yields unreliable and inconsistent results in diagnosing AR
Ng et al.[1209]	2000	4	Case–control	Adults with AR	History Physical examination SPT sIgE	Physical examination is performed to eliminate other potential causes of symptoms
Shaker et al.[1213]	2020	5	Expert recommendations		Recommendations for atopic disorder evaluation and care during the COVID-19 pandemic	Evaluation and treatment require triage and adjust, when necessary, from face-to-face visits to telemedicine
Scadding et al.[1206]	2017	5	Guidelines		Recommendations for management of AR and non-allergic rhinitis	AR diagnosis is made by history and physical examination, supported by diagnostic tests
Seidman et al.[1005]	2015	5[a]	Guidelines		Recommendations on diagnosis and treatment of AR	Clinical diagnosis of AR made with history and physical examination
Wallace et al.[31]	2008	5	Guidelines		Recommendations on the diagnosis and treatment of rhinitis	All organ systems potentially affected by AR should be examined Typical allergic findings are supportive of but not specific for AR
Small et al.[1205]	2007	5	Guidelines		Recommendations on diagnosis and treatment of rhinitis	Physical examination findings aid in supporting the diagnosis of AR
Bousquet et al.[5]	2001	5	Guidelines		Recommendations on the diagnosis and treatment of AR in asthmatic patients	Lung examination is recommended in asthmatic patients with symptoms of AR

Abbreviations: AR, allergic rhinitis; COVID-19, coronavirus disease 2019; LOE, level of evidence; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test.
[a]Seidman et al. Clinical Practice Guideline LOE upgraded to 4 in other ICAR sections; although recommended, direct evidence for history and physical exam in AR remains poor and substantiates LOE 5 designation in this section.

the strongest association with allergy, with positive predictive values of 85.15%, 91.7%, and 88.9%, respectively. Brunner et al.[1221] compared the clinical characteristics of patients with isolated polypoid change of the MT versus paranasal sinonasal polyposis, finding a higher prevalence of AR in patients with polypoid MT changes compared to patients with conventional sinonasal polyposis (83% vs. 34%, $p < 0.001$).

Central compartment atopic disease (CCAD), first described in the multi-institutional case series by DelGaudio et al.[1222] in 2017, is a phenotype of nasal inflammatory disease which presents with isolated polypoid changes

TABLE X.A.3 Evidence table – use of nasal endoscopy in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ameli et al.[1217]	2019	2	Prospective cross-sectional	Children with suspected AR	Nasal endoscopy Allergy testing	Middle turbinate contact, pale nasal mucosa, and large adenoid volume were predictive for AR
Ziade et al.[1214]	2016	2	Prospective cross-sectional	Adults with rhinitis and nasal obstruction	Nasal endoscopy Allergy testing	Inferior turbinate mucosal edema and bluish discoloration were predictive of AR severity
Hamizan et al.[1220]	2017	3	Cross-sectional	Adults with rhinitis and nasal obstruction	Nasal endoscopy Allergy testing	Middle turbinate edema is useful as a nasal endoscopic feature to predict presence of inhalant allergy
DelGaudio et al.[1223]	2019	4	Case series	Adults with AERD with suspected CCAD and AR	Nasal endoscopy Allergy testing	CCAD endoscopic findings in AERD were significantly associated with clinical allergy
Brunner et al.[1221]	2017	4	Case series	Adults with PCMT or paranasal sinus polyposis	Nasal endoscopy Allergy testing Total eosinophils	PCMT has a greater association with AR compared to sinonasal polyposis
DelGaudio et al.[1222]	2017	4	Case series	Adults with central compartment polypoid edema	Nasal endoscopy Allergy testing CT scan	Edema and polypoid changes of the central compartment are strongly associated with inhalant allergy
White et al.[1219]	2014	4	Case series	Adults with isolated middle turbinate polypoid edema	Nasal endoscopy Allergy testing	Isolated middle turbinate polypoid edema is associated with positive allergy testing
Eren et al.[1216]	2013	4	Case series	Adults with rhinitis	Nasal endoscopy AR diagnosis	Nasal endoscopic findings do not provide reliable diagnosis of AR
Ameli et al.[1218]	2011	4	Case series	Children with suspected AR	Nasal endoscopy AR diagnosis	Inferior or middle turbinate septal contact was predictive for AR, whereas pale turbinates were not
Jareoncharsri et al.[1215]	1999	4	Case series	Adults and children with perennial AR	Nasal endoscopy Nasal symptoms	No significant correlation between individual symptoms and endoscopic findings

Abbreviations: AERD, aspirin exacerbated respiratory disease; AR, allergic rhinitis; CCAD, central compartment atopic disease; CT, computed tomography; LOE, level of evidence; PCMT, polypoid changes of the middle turbinate.

involving the superior nasal septum with or without the MT and/or superior turbinate, and is strongly associated with inhalant allergy. All patients in the series had positive allergy testing. In a subsequent case series, the same authors found that 81.9% of patients with AERD had central involvement of disease, with 100% of patients with endoscopic central compartment disease having clinical AR.[1223] (See Section XIII.B.3. Central Compartment Atopic Disease for additional information on this topic.)

Despite early inconsistent reports, the current body of evidence has shown that certain nasal endoscopy findings, particularly central compartment polypoid changes, are predictive factors for the presence and severity of AR and nasal endoscopy may aid in the identification or exclusion of other possible causes of symptoms, such as nasal polyposis or CRS.

Nasal endoscopy

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 1 study, level 4: 7 studies; Table X.A.3)
Benefit: Possible improved diagnosis with visualization of middle or inferior turbinate edema, pale/bluish discoloration, or isolated central compartment polypoid changes and/or edema, which have been associated with AR.
Harm: Possible patient discomfort.
Cost: Moderate equipment and processing costs, as well as procedural charges.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Nasal endoscopy may increase diagnostic sensitivity among children and adults with allergic rhinitis.
Policy level: Option.
Intervention: Nasal endoscopy may be considered as a diagnostic adjunct in the evaluation of patients with suspected AR.

X.A.4 | Radiologic studies

Radiographic workup is not recommended for the routine diagnosis of AR. Although some radiographic findings have been associated with AR, there are no high-quality studies demonstrating a role for imaging in the diagnosis of AR.

For patients that undergo imaging, certain radiologic patterns described in the literature may indicate an allergic role in their disease process. Several studies have demonstrated association between inflammatory changes to the central compartment mucosa and aeroallergen reactivity, resulting in the CRS phenotype of CCAD.[1224–1228] Other studies have described evidence of radiographic changes among patients with known AR, including the association for smaller maxillary sinuses and enlargement of the septal swell region.[1229,1230]

Radiology studies incur additional cost and demonstrate little diagnostic value for AR. There is also concern for ionizing radiation with CT scanning, along with risk for future malignancy.[1231–1233] These factors preclude the routine utilization of radiographic studies for the diagnosis of AR.

Radiologic studies

Aggregate grade of evidence: D (Level 3: 1 study, level 4: 7 studies; Table X.A.4)
Benefit: Some radiologic findings, particularly those associated with central compartment edema/polyposis, may alert the clinician to the possibility of an associated allergic etiology.
Harm: Unnecessary radiation exposure, unnecessary cost.
Cost: High equipment and processing costs. Additional costs for interpretation of studies by radiologist.
Benefits-harm assessment: Preponderance of harm over benefit.
Value judgments: Long-term risks of ionizing radiation outweigh potential benefit.
Policy level: Recommendation against.
Intervention: Routine use of imaging is not recommended for the diagnosis of AR.

X.B | Skin testing

X.B.1 | Skin prick testing

SPT, in conjunction with clinical history and physical examination, can confirm the diagnosis of AR and help to differentiate AR from non-allergic types of rhinitis. The confirmation of an IgE-mediated process can guide avoidance measures and direct appropriate pharmacologic therapy. Allergy testing is crucial for the initiation of AIT, and therefore, skin testing should be utilized in eligible patients when AIT is being considered.

SPT is performed with lancets, which come in a variety of forms. Generally, lancets are designed to limit skin penetration depth to 1 mm. However, varying amounts of pressure applied to the delivery device can alter the depth of skin penetration, which ultimately influences the skin reaction to an antigen.[1235] Prick testing devices

TABLE X.A.4 Evidence table – use of radiologic studies in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lee et al.[1227]	2021	3	Cross-sectional	Children with CRS	Radiologic evidence of CCAD Allergy testing	Radiologic CCAD phenotype in children is associated with allergen sensitivity and asthma
Abdullah et al.[1228]	2020	4	Cross-sectional	Patients with CRSwNP	Nasal endoscopy CT scan Allergy testing	Allergic phenotype of CRSwNP has worse symptomatic and radiologic disease burden
Hizli et al.[1230]	2020	4	Cross-sectional	Patients with IT hypertrophy with and without AR	CT scan Allergy testing	Septal body areas were greatest in patients with AR
Roland et al.[1226]	2020	4	Cross-sectional	Patients with CRSwNP	CT scan	CT scans can identify patients with CCAD phenotype due to low Lund–MacKay scores, septal disease, and oblique middle turbinates
Hamizan et al.[1224]	2018	4	Cross-sectional	CRS patients without sinus surgery	CT scan Allergy testing	Central radiologic disease patterns associated with inhalant allergy
Sharhan et al.[1234]	2018	4	Cross-sectional	Patients with septal deviation	CT scan Allergy testing	IT size is not associated with AR
DelGaudio et al.[1222]	2017	4	Case Series	Patients with sinonasal symptoms and CT imaging of central disease	CT scan Allergy testing	Radiographic central compartment disease is associated with inhalant allergy
Kaymakci et al.[1229]	2015	4	Cross-sectional	Patients with nasal symptoms and suspected AR	Allergy testing CT scan	Patients with AR showed smaller overall maxillary sinus volumes

Abbreviations: AR, allergic rhinitis; CCAD, central compartment atopic disease; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CT, computed tomography; IT, inferior turbinate; LOE, level of evidence.

can come as single or multiple lancet devices. Multiple lancet devices have the advantage of being able to rapidly apply multiple antigens to the skin at one time with a more consistent amount of pressure.[1236,1237] Wheal size, sensitivity, and reproducibility all differ from one device to another; therefore, any clinician performing SPT must thoroughly familiarize themselves with the testing device they choose to utilize in their practice.[1236–1238] The lancet can be dipped into a well containing an antigen and then applied to the skin, or droplets of antigen can be placed on the skin and then using the lancet, a prick made through the droplet. When an antigen is applied to the skin of a sensitized patient, the antigen cross-links IgE antibodies on the surface of cutaneous mast cells resulting in degranulation and release of mediators (including histamine) which leads to the formation of a wheal and flare reaction within 15–20 min.[1239,1240]

The volar surfaces of the forearms and the back are the most common testing sites for SPT. Choice of site is directed by the age and size of the patient, the presence of active skin conditions in a testing location, or significant tattooing in the testing area, which could impact interpretation. Reactivity of different body sites can vary, as the back is overall more reactive than the forearm. Within each site, there may be variability as well, as middle and upper parts of the back are more reactive than the lower back. Tests should be applied 2 cm or greater apart as placing them closer to one another can allow spreading of allergen

solution between test sites.[1241] After approximately 20 min, the results are read by measuring the size of the wheal by its greatest diameter. Wheals that are greater than or equal to 3 mm in diameter, when compared to the negative control, are considered positive.

The number and choice of antigens used in testing vary considerably between clinical practices. A panel of antigens representing an appropriate geographical profile of allergens that a patient would routinely be exposed to is recommended. Positive (histamine) and negative (saline, 50% glycerin or 50% glycerinated human serum albumin with saline) controls should always be included. Regarding allergen extracts, variability in quality and potency between commercially available extracts has been demonstrated.[1242,1243] Therefore, whenever possible, standardized allergens should be used.[1244] With advancements in molecular biology, new techniques for extraction, characterization, and production of allergens have been developed allowing for production of recombinant or purified allergens which may increase the sensitivity, specificity, and diagnostic accuracy of tests.[1245]

Given the limited depth of penetration, SPT is safe with very rare reports of anaphylaxis and no reported fatalities.[1246] SPT can be performed in any age group and is of value in pediatric populations given the speed at which multiple antigens can be applied and the limited discomfort experienced during testing. Aside from an excellent safety profile, SPT has reported sensitivity and specificity of around 80%.[1244,1246,1247] It is felt to be more sensitive than serum sIgE testing with the added benefits of lower cost and immediate results.[1246,1248,1249] Despite numerous studies aimed at comparing SPT, single intradermal tests, and serum sIgE testing, evidence marking one form of testing as superior to the others is lacking.[1005]

Skin testing is not appropriate in all patients. Absolute contraindications to SPT in the evaluation of AR include uncontrolled or severe asthma, severe or unstable cardiovascular disease, and pregnancy. Skin conditions including dermatographia and AD are relative contraindications to SPT given the possibility of false positives. Concurrent β-blocker therapy is also a relative contraindication.[1250] Certain medications and skin conditions can interfere with skin testing and are covered in detail in other sections. (See Section X.B.4. Issues that may Affect the Performance or Interpretation of Skin Tests for additional information on this topic.)

Several errors may occur during SPT and impact the results and reliability. Since heterogeneity can be introduced when using multiple different test devices, it is recommended that the same device type can be used routinely in one's clinical practice to improve the reliability, comparability, and interpretation of testing.[1251] Personnel who apply tests should be appropriately trained and periodically monitored for quality control. Common errors with SPT include placing the test sites too close together (less than 2 cm), pressing too hard or creating deep punctures that cause bleeding, insufficient penetration of the skin by the puncture instrument, and spreading of allergen solutions across the field during the test by wiping away the solution.[1251]

There is a large body of evidence detailing the use of SPT in clinical practice. Based upon several prospective studies and systematic reviews, SPT has been demonstrated to be a safe method of allergy testing with sensitivity and specificity of greater than 80% (Table X.B.1). It has not been shown to be inferior to serum sIgE testing or single intradermal testing and is less expensive than serum sIgE testing. SPT does carry a risk of anaphylaxis, but no deaths from SPT have been reported. It is also associated with some discomfort during testing; however, the discomfort is generally less than that experienced during an intradermal test. Reviewing the available literature, a preponderance of benefit over harm exists for SPT. Therefore, the use of SPT is recommended in situations where the diagnosis of AR needs to be confirmed or a patient with presumed AR has failed appropriate empiric medical therapy and AIT is being considered.

Skin prick testing

Aggregate grade of evidence: B (Level 1: 1 study, level 3: 2 studies, level 4: 7 studies, level 5: 2 studies; Table X.B.1)
Benefit: Confirm AR diagnosis and direct appropriate pharmacologic therapy, initiation of AIT, as well as avoidance measures.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. See Table II.C.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Patients can benefit from identification of their specific sensitivities. SPT is a quick and relatively comfortable way to test several antigens with accuracy similar to other available methods of testing.
Policy level: Recommendation.
Intervention: Regular use of the same SPT device type will allow clinicians to familiarize themselves with it and interpretation of results may therefore be more consistent. The use of standardized allergen extracts can further improve consistency of interpretation.

TABLE X.B.1 Evidence table – use of skin prick testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Nevis et al.[1252]	2016	1	SRMA	Studies evaluating the diagnostic accuracy of SPT	Accuracy of SPT	Pooled estimate for SPT sensitivity and specificity was 85% and 77%, respectively SPT is accurate in discriminating subjects with or without AR
Wood et al.[143]	1999	3	Prospective cohort	Patients with cat allergy determined by history and a cat-exposure model	Compared predictive values of SPT, intradermal test and RAST in the diagnosis of cat allergy	SPT and RAST values exhibited excellent efficiency in diagnosis of cat allergy Single intradermal added little to the diagnostic evaluation Overall sensitivity and specificity of SPT was 79% and 91%, respectively
Tschopp et al.[1249]	1998	3	Prospective cohort	Randomly selected sample of 8329 Swiss adults	Compared the sensitivity, specificity, PPV and NPV of SPT, IgE levels and fluoroenzyme immunoassay in diagnosing AR	Sensitivity of fluoroenzyme immunoassay was significantly higher than SPT and IgE However, SPT was significantly more specific and had a better PPV SPT was the most efficient test to diagnose AR
Seidman et al.[1005]	2015	4[a]	Guideline	N/A	N/A	Clinicians should perform and interpret or refer for sIgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or the diagnosis is uncertain Aggregate evidence grade B
Bernstein et al.[1246]	2008	4[a]	Practice parameter	N/A	N/A	Sensitivity of SPT ranges from 85%–87%, specificity ranges between 79% and 86% Many studies have verified the sensitivity and specificity of SPT Aggregate evidence grade B
Gungor et al.[1253]	2004	4	Prospective case–control	NPT positive NPT negative	Sensitivity and specificity of SPT versus SET for diagnosing AR	SPT was more sensitive (85.3% vs. 79.4%) and specific (78.6% vs. 67.9%) than SET as a screening procedure for multiple antigens SPT had a greater PPV (82.9% vs. 75%) and NPV (81.5% vs. 73%) than SET None of these differences were statistically significant

(Continues)

TABLE X.B.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Krouse et al.[1254]	2004	4	Prospective case–control	*Alternaria* SPT positive *Alternaria* single intradermal #2 positive *Alternaria* negative	Acoustic rhinometry of minimal cross-sectional area of nasal cavity	Analysis of NPT showed sensitivity of 42% and specificity of 44% for SPT using *Alternaria* antigen
Krouse et al.[1255]	2004	4	Prospective case–control	Timothy grass SPT positive Timothy grass single intradermal #2 positive Timothy grass negative	Acoustic rhinometry of minimal cross-sectional area of nasal cavity	Analysis of NPT showed sensitivity of 87% and specificity of 86% with multi-test application of Timothy grass antigen
Zarei et al.[1256]	2004	4	Prospective case–control	NPT positive NPT negative	Wheal size that best identifies clinical allergy to cat based on NPT	On SPT with cat antigen, a wheal size of ≥3 mm had a sensitivity of 100% and specificity of 74.1%; improved with increasing size of wheal
Pumhirun et al.[1257]	2000	4	Prospective case–control	Perennial rhinitis patients	Compared sensitivity and specificity of intradermal test to SPT and sIgE assay for *D. pteronyssinus* and *D. farinae*	SPT for *D. pteronyssinus and D. farinae* were 90.4% and 86.4% sensitive and 99.5% and 93.1% specific, respectively This compared to sensitivity of 96.3% and 88.9% and specificity of 96.2% and 88.9% of sIgE assay
Ansotegui et al.[1251]	2020	5	Position paper	N/A	N/A	For type I IgE-mediated allergic disease, skin tests are first-line approach for indicating the presence of allergen specific IgE antibodies In vitro serum IgE detection with the use of highly purified allergen or recombinants is an alternative diagnostic procedure
Heinzerling et al.[1258]	2013	5	Review	N/A	N/A	SPT is a reliable method to diagnose AR with specificity of 70%–95% and sensitivity of 80%–90% for inhalant allergies Further standardization of SPT is needed

Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E; LOE, level of evidence; N/A, not applicable; NPT, nasal provocation test; NPV, negative predictive value; PPV, positive predictive value; RAST, radio allegro-sorbent test; s, allergen-specific; SET, skin endpoint titration; SPT, skin prick test; SRMA, systematic review and meta-analysis.

[a]LOE upgraded from typical assignment of 5 due to systematic review of the literature, extensive history of guideline development, and peer review process.

X.B.2 | Intradermal skin testing

Intradermal skin testing is one of the oldest forms of allergy testing, originally described in 1911. In this technique, 0.02–0.05 ml of diluted allergen extract is introduced into the dermis with a needle. The dilutions used are 100- to 1000-fold less concentrated than those used for SPT. The response is measured at 10–15 min after injection. A significant wheal and flare reaction suggests the presence of preformed IgE bound to the surface of cutaneous mast cells, and thus a type 1 hypersensitivity to the tested allergen. Intradermal testing is considered to be more sensitive than SPT, but not necessarily more capable of identifying clinically relevant allergy.[1246] Intradermal testing may be used as a primary diagnostic modality and its performance for some allergens, such as *Alternaria*, may be similar to SPT or in vitro testing.[1259] A more common approach is to perform intradermal testing after a negative SPT to identify lower level allergic sensitivity. Some allergists also use intradermal testing in a titrated fashion (using multiple allergen dilutions) with the goal of more accurately quantifying allergic sensitization or as a means to select a starting dose for AIT.[1260] Intradermal dilutional testing (IDT) is roughly equivalent to SPT in the diagnosis of inhalant allergy,[1253] and IDT endpoint correlates with SPT wheal size.[1261] However, the role of intradermal testing for aeroallergen sensitivity is controversial due to concerns about the performance characteristics (sensitivity and specificity) of single intradermal tests relative to SPT.[1262]

As with any skin test, intradermal skin testing should be performed in conjunction with appropriate positive and negative controls. A negative control should include appropriately diluted test solutions (e.g., glycerin for aqueous glycerinated extracts). A positive control should contain diluted histamine base (e.g., 10 mg/ml).[1246] Measurement of the wheal and flare response is used to determine a positive result; however, thresholds for a positive test may vary because studies have not been performed to standardize test grading. A wheal size 2–4 mm larger than the negative control is often used as the threshold for a positive test.[1246,1262]

Assessment of the sensitivity and specificity of intradermal testing is hampered by multiple variables in the published studies. These include the concentration and volume of allergen injected, the definitions of a positive test, variation in allergens tested, and the "gold standard" comparator used for analysis.[1263] As a stand-alone diagnostic test for AR, using studies with nasal provocation as the reference standard, estimates for sensitivity for intradermal testing range between 60% and 79%, while specificity is in the range of 68%–69%.[143,1253] In comparison, a meta-analysis of SPT trials had pooled estimates of 88.4% sensitivity and 77.1% specificity for SPT,[1264] suggesting superiority of SPT as a stand-alone allergy diagnostic test. Nevertheless, intradermal tests are still used when a highly sensitive skin test is desired. This may be particularly important when testing with non-standardized allergen extracts (e.g., molds, trees) (Table X.B.2).

Intradermal tests are also employed when SPT is negative but history strongly suggests an allergic sensitivity, and may be particularly useful in patients with lower skin sensitivity.[1246] Negative intradermal testing may be helpful in ruling out IgE-mediated disease.[1262] On the other hand, the addition of intradermal testing in the setting of SPT negativity may result in 20% more positive allergy skin testing results, and the clinical significance of these results is an important question that needs to be resolved.[1265] Positive intradermal tests may merely be due to non-specific irritant phenomena.

Because intradermal testing has traditionally been considered more sensitive than SPT, it is often used as an add-on test in the setting of a negative SPT result when allergy is suspected. Theoretically, an intradermal test will be able to identify a clinically significant sensitivity that is otherwise not detected on SPT. However, many studies have failed to show an added benefit of intradermal testing in this setting. For example, Krouse et al.[1255] showed that adding intradermal testing to SPT only increased the sensitivity from 87% to 93% for Timothy grass allergy when nasal provocation was used as the comparator. In a similar study with *Alternaria*, Krouse et al.[1254] determined that adding intradermal testing to SPT increased the sensitivity from 42% to 58%. These studies suggest marginal increase in sensitivity that may vary based upon the allergen being tested.

Nelson et al.[1266] studied individuals with a history of seasonal AR and clinical history of grass allergy. One group had negative SPT but positive intradermal tests, while another group had negative SPT and negative intradermal tests. In both groups, 11% of individuals had a positive nasal challenge with timothy grass, demonstrating that the addition of an intradermal test did not improve the diagnostic accuracy of skin testing as judged by the "gold standard" of nasal provocation plus clinical history. Additionally, in a study of patients with clinical cat allergy and negative SPT, a positive intradermal test did not increase the likelihood of a positive cat allergen challenge.[143] There was no difference between those who had positive or negative intradermal testing (24% vs. 31%). Thus, while about 30% of patients with a clear clinical history of cat allergy had a positive cat allergen challenge despite a negative SPT, the addition of an intradermal test did not improve the diagnostic accuracy of skin testing.

Schwindt et al.[1267] studied 97 subjects with allergic rhinoconjunctivitis symptoms. SPT was followed by intradermal testing if SPT was negative. If patients were SPT negative and intradermal test positive, a nasal challenge was performed against five different allergens. If SPT with the multi-test II device was negative, only 17% of

TABLE X.B.2 Evidence table – use of intradermal skin testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Larrabee and Reisacher[1265]	2015	3	Retrospective cohort	87 patients with AR who underwent IDST after (−) SPT	IDST positivity	21% more were IDST(+) compared to SPT
Sharma et al.[1269]	2008	3	Cohort	69 mouse lab workers	Nasal challenge compared to SPT, IDST, sIgE	SPT better than IDST or sIgE in predicting (+) nasal challenge
Schwindt et al.[1267]	2005	3	Cohort	97 subjects: SPT followed by IDST if SPT(−) If SPT(−) and IDST(+) nasal challenge performed for five allergens	Using history as gold standard, SPT, IDST and nasal challenge results compared	If SPT(−), only 17% had (+) IDST that corresponded with history None corresponded with (+) nasal challenge If SPT(−), then (+) IDST unlikely to identify clinically relevant sensitivity
Simons et al.[1270]	2004	3	Retrospective cohort	34 patients tested for aeroallergen sensitivity with IDT and SPT	Comparison of SPT and IDT	100% had at least one positive IDT; 50% negative on SPT More patients tested positive on IDT versus SPT SPT wheal size and IDT endpoint correlated for several allergens IDT may be more sensitive than SPT
Wood et al.[143]	1999	3	Prospective cohort	120 patients with symptoms from cat exposure	Cat exposure challenge, symptom scores, FEV_1	IDST added little value beyond SPT and RAST
Niemeijer et al.[1263]	1993	3	Cohort	497 patients with suspected allergy Standardized grass pollen, tree pollen, cat, HDM tested	IDST, RAST, clinical history	Ideal cutoff for positive IDST is wheal diameter 0.7 times the size of histamine control IDST has 83% predictive value versus RAST and 77% predictive value versus history
Niemeijer et al.[1271]	1993	3	Cohort	41 patients tested with varying concentrations of Phleum and *D. pteronyssinus*	SPT, IDST, sIgE Adjusted wheal sizes compared to RAST class score	Optimum concentration of tested allergens was 1:10 for SPT, 1:1000 for IDST
Hurst and McDaniel[1272]	2021	4	Case series	371 patients with AR, asthma, chronic otitis media with effusion	SPT, IDT results compared to AIT outcomes	52% more sensitizations detected with IDT Patients who had (−) SPT with (+) IDT responded to AIT

(Continues)

TABLE X.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Erel et al.[1273]	2017	4	Case series	4223 patients with AR or asthma	Rate of (+) IDST if (−) SPT	44% of (−) SPT had a (+) IDST, mostly seen in HDM and fungal allergy
Peltier and Ryan[1261]	2007	4	Cohort	134 volunteers Simultaneous SPT and IDT for five common allergens	SPT wheal size versus IDT endpoint	IDT endpoint correlates with SPT wheal size
Peltier and Ryan[1274]	2006	4	Cohort	86 volunteers tested simultaneously for mold allergens with SPT and IDT	SPT wheal size versus IDT endpoint	If clinical symptoms, SPT wheal size and IDT endpoint correlated IDT identified 10% more positive results compared to SPT alone
Seshul et al.[1275]	2006	4	Case series	134 patients with suspected allergy screened with SPT then IDT	IDT performed if SPT (+)	93% of SPT(+) were also IDT(+) SPT wheal size had low-moderate correlation with IDT endpoint
Purohit et al.[1276]	2005	4	Cohort	18 patients with birch allergy sIgE against rBet v 1, IDT, basophil histamine release assay	Correlations among IDT endpoint, serum sIgE, provocation thresholds for basophil histamine release	IDT endpoint correlated with basophil histamine release IDT endpoint did not correlate with rBet v 1 serum sIgE
Gungor et al.[1253]	2004	4	Case series	62 patients with ragweed allergy	Nasal provocation, rhinomanometry	Sensitivity and specificity of IDT comparable to SPT
Krouse et al.[1255]	2004	4	Prospective case–control	37 patients with Timothy grass allergy: Group I: SPT(+) Group II: SPT(−), IDST(+) Group III: SPT(−), IDST(−)	SPT and IDST compared with nasal provocation	IDST after SPT increased the sensitivity from 87% to 93%
Krouse et al.[1254]	2004	4	Prospective case–control	44 patients with AR: Group I: SPT(+) Group II: SPT(−), IDST(+) Group III: SPT(−), IDST(−)	Nasal allergen provocation for *Alternaria* compared to skin tests	IDST after SPT increased the sensitivity from 42% to 58%
Nelson et al.[1266]	1996	4	Prospective case–control	70 subjects: Group I: SAR, SPT(−), IDST(+) Group II: SAR, SPT(+) Group III: SAR, SPT(−), IDST(+) Group IV: no rhinitis	Nasal challenge with Timothy grass compared to skin tests	(+) IDST after (−) SPT did not indicate the presence of clinically significant sensitivity

(Continues)

TABLE X.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Escudero et al.[1259]	1993	4	Prospective case–control	66 patients, 31 with *Alternaria* allergy SPT, IDST, challenge tests, sIgE	Comparison of test methods versus clinical history and nasal/bronchial challenge	SPT, IDST, and challenge more sensitive than serum sIgE All testing methods had similar specificity
Brown et al.[1277]	1979	4	Case series	311 subjects with and without allergy complaints	SPT versus IDST (if prick negative), paper radioimmunosorbent test, or RAST	No relationship between sIgE and SPT(−)/IDST(+) results
Reddy et al.[1278]	1978	4	Case series	34 patients with perennial rhinitis, (−) SPT for 60 allergens but with at least one positive IDST evaluated with RAST, nasal provocation, leukocyte histamine release	RAST, nasal provocation, and leukocyte histamine release compared to IDST positivity, SPT negativity	SPT(−)/IDST(+) did not have a positive RAST nor a positive leukocyte histamine release In contrast, (+) SPT was associated with (+) RAST and leukocyte histamine release assay When SPT(−), (+) IDST not likely to indicate the presence of allergy

(−), negative; (+), positive. Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; FEV_1, forced expiratory volume in one second; HDM, house dust mite; IDST, intradermal skin test; IDT, intradermal dilutional testing; LOE, level of evidence; RAST, radioallergosorbent test; SAR, seasonal allergic rhinitis; sIgE, allergen-specific immunoglobulin E.

subjects had a positive intradermal test that corresponded with clinical history. None of these positive intradermal results corresponded with a positive nasal challenge. Taken together, these studies suggest that intradermal testing may not improve the diagnosis of allergy in subjects with a negative SPT.

Intradermal testing for inhalant allergens is considered safe. However, systemic reactions, such as anaphylaxis, and even death, have been reported after intradermal testing. The risks of intradermal testing may be reduced by testing with more dilute solutions in individuals with suspected high-level sensitivity or by performing SPT as an initial screening test. The risk of intradermal testing is significantly higher in medication allergy and IgE-mediated food allergy and therefore not recommended.[1268]

In summary, intradermal testing is an option for the diagnosis of AR due to aeroallergens, especially when using non-standardized allergen extracts. This form of testing demonstrates no clear superiority over SPT when comparing sensitivity and specificity, though results may vary by allergen tested. Single dilution intradermal testing has not been adequately studied in comparison to IDT, though IDT results may approximate SPT results, especially in patients with high level sensitivity. For some allergens such as *Alternaria*, there appears to be a gain in sensitivity when intradermal testing is used as a confirmatory test following negative SPT.

Intradermal skin testing

Aggregate grade of evidence: C (Level 3: 7 studies, level 4: 13 studies; Table X.B.2)
Benefit: May improve identification of allergic sensitization in patients with low-level skin sensitivity or with non-standardized allergens.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. See Table II.C.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Benefit over harm when used as a stand-alone diagnostic test, when used to confirm the results of SPT, and as a quantitative diagnostic test.

Value judgments: Intradermal skin tests may not perform as well as SPT in most clinical situations.
Policy level: Option for using intradermal testing as a stand-alone diagnostic test for individuals with suspected AR. Option for using intradermal testing as a confirmatory test following negative SPT for non-standardized allergens.
Intervention: Intradermal testing may be used to determine aeroallergen sensitization in individuals suspected of having AR.

X.B.3 | Blended skin testing techniques

The combined use of SPT and intradermal testing for a specific allergen is referred to as "blended" allergy testing.[1261,1274,1279] One example, originally described by Krouse and Krouse[1280] as a method to establish an "end-point" for a specified allergen, was described as "modified quantitative testing" (MQT) and serves as an example of a blended technique. MQT involves an algorithm where SPT is used initially to apply an antigen. Depending upon the SPT result, an intradermal test may or may not be applied.[1261,1274,1279,1280] With these results, the algorithm is used to determine an endpoint for each antigen tested.[1261,1274,1279,1280] The endpoint is considered to be a safe starting point for AIT.[1280] Other protocols may combine the use of SPT and intradermal testing but not for the purposes of establishing an endpoint.[1273,1281] Instead, an intradermal test may be used following a negative SPT to determine allergen sensitization.[1273,1281]

AIT based on the results of MQT has shown to be successful and to induce immune system changes in line with other skin testing techniques.[1280] However, literature is

TABLE X.B.3 Evidence table – use of blended skin testing techniques in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Erel et al.[1273]	2017	4	Case series	4233 adult patients with AR ± asthma	ID test placed following negative SPT for individual antigens	44% of patients with negative SPT had positive result with follow up ID test
Tantilipikorn et al.[1281]	2015	4	Case series	82 adult patients with AR and negative SPT to HDM	ID to HDM sIgE to HDM	Fair to moderate correlation to HDM sIgE ID test after negative SPT can be considered an alternative to sIgE
Fornadley[1279]	2014	4	Review	Skin testing techniques	Review of various skin testing techniques	MQT has been shown to be a valid form of skin testing
Lewis et al.[1282]	2008	4	Cost-effectiveness analysis	Skin testing techniques	Comparison of sIgE, IDT, MQT from a payer perspective	MQT most cost-effective when AR prevalence is 20% or higher
Peltier and Ryan[1261]	2007	4	Cohort	134 adults with AR	IDT with five antigens MQT protocol with five antigens	MQT is a safe alternative to IDT for determining starting doses for AIT
Krouse, et al.[1280]	2006	4	Case series	Nine adults with AR	MQT sIgE and sIgG4 for three antigens SNOT-20, AOS, RSDI	MQT-based AIT results in immune system changes and QOL improvements
Peltier and Ryan[1274]	2006	4	Cohort	86 adults with AR	IDT with six mold antigens MQT with six mold antigens	MQT is a safe alternative to IDT for determining starting doses for AIT for fungal allergens

Abbrevitions: AIT, allergen immunotherapy; AOS, Allergy Outcome Scale; AR, allergic rhinitis; HDM, house dust mite; ID, intradermal; IDT, intradermal dilutional testing; LOE, level of evidence; MQT, modified quantitative testing; QOL, quality of life; RSDI, Rhinosinusitis Disability Index; sIgE, allergen-specific immunoglobulin E; sIgG4, allergen-specific IgG4; SNOT-20, Sinonasal Outcome Test (20 item); SPT, skin prick test.

lacking in protocols involving blended skin testing (Table X.B.3).

Specifically for MQT, advantages attributed to it include the provision of both qualitative data (sensitization to a specific allergen) and quantitative data (testing endpoint upon which AIT starting dose can be based) in less time than IDT.[1261,1274,1279] Disadvantages include the additional risk and time involved in placing intradermal tests. MQT has been shown to be more cost-effective when the prevalence of AR in a population is 20% or higher when compared to IDT and in vitro testing methods.[1206,1282]

Blended skin testing techniques

Aggregate grade of evidence: D (Level 4: 7 studies; Table X.B.3)
Benefit: Ability to establish an endpoint in less time than intradermal dilutional testing, potential to determine allergen sensitization after negative SPT.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. Additional time and discomfort versus SPT alone. See Table II.C.
Cost: Moderate cost of testing procedure.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: While AIT can be based off SPT results alone, endpoint-based AIT may have possible benefits of decreased time to therapeutic dosage.
Policy level: Option.
Intervention: Blended skin testing techniques, such as MQT, are methods that can be used to determine a starting point for AIT or confirm allergic sensitization.

X.B.4 | Issues that may affect the performance or interpretation of skin tests

X.B.4.a | *Medications*

Medications that inhibit mast cell degranulation or block histamine H_1 receptors antagonists may suppress appropriate skin test responses. For this reason, it is important to assess the medications patients are taking prior to allergy skin testing.

There is substantial variation in the suppressive effects that H_1 antihistamines have on the allergen and histamine induced wheal and flare responses,[1283,1284] with the duration of suppression dependent on the tissue concentration and half-life of the medication.[1285] Orally ingested antihistamines typically suppress skin test responses for 2–7 days after stopping the medication.[1286,1287] Topical antihistamines may also suppress skin wheal and flare responses.[1288] Furthermore, H_2 receptor antagonists like ranitidine can reduce skin whealing responses,[1289,1290] and a combined suppressive effect of H_1 and H_2 antihistamines on skin whealing has been demonstrated.[1291] Antidepressants with antihistaminic properties (such as doxepin) impair the wheal and flare,[1292] but newer antidepressant classes such as selective serotonin reuptake inhibitors do not alter allergy skin test reactivity[1293] (Tables X.B.4.a.-1 and X.B.4.a.-2).

Omalizumab, a monoclonal anti-IgE antibody, suppresses the allergy the skin test response by interfering with IgE-mediated mast cell degranulation. A placebo-controlled RCT noted significant reduction in the allergen-induced skin wheal response after 4 months of omalizumab[1294]; whereas skin test response returned to normal within 8 weeks of discontinuation of omalizumab in another study.[1250]

Hill and Krouse[1295] and Simons et al.[1296] found no effect of montelukast on intradermal skin tests, and Cuhadaroglu et al.[1297] noted that allergic patients treated with zafirlukast had no change in SPT results. Therefore, leukotriene modifying agents do not appear to affect skin test results.

Most studies indicate that systemic steroid treatment does not alter skin test results,[1298,1299] but some less rigorous retrospective studies contradict these findings.[1300,1301] Topical steroid treatment does suppress the wheal and flare reaction in treated skin areas, according to several studies.[1302–1305] Allergy skin tests should not be performed in areas that are being treated with topical steroid medications in order to avoid false negative results.

Several classes of medications have not been adequately studied with respect to their effect on allergy skin test responses. Benzodiazepines have been implicated as possibly suppressing skin test responses.[1306,1307] Calcineurin inhibitors demonstrate conflicting findings. Tacrolimus has been shown to inhibit SPT whealing,[1305] whereas pimecrolimus does not appear to affect skin whealing responses.[1308] Herbal preparations are understudied in this area, so it is unclear which of these agents could interfere with allergy skin test responses. More et al.[1309] performed a double-blind placebo-controlled, single dose crossover study in 15 healthy volunteers, examining the histamine induced skin test response. None of the 23 herbal supplements evaluated suppressed the histamine induced wheal response.

All allergy skin testing should be performed after application of appropriate positive controls (e.g., histamine)

TABLE X.B.4.a.-1 Timing of medication discontinuation prior to allergy skin testing

H_1 antihistamines	Should be discontinued 2–7 days prior to testing. *Aggregate grade of evidence*: A (Level 2: 3 studies, level 3: 3 studies, level 4: 1 study)
H_2 antihistamines	Ranitidine may suppress skin whealing response, leading to false negative results. Should be discontinued 2 days prior to testing. *Aggregate grade of evidence*: A (Level 2: 2 studies, level 3: 1 study, level 4: 1 study)
Topical antihistamines (nasal, ocular)	Should be discontinued 2 days prior to testing. *Aggregate grade of evidence*: Unable to determine from one level 2 study.
Anti-IgE (omalizumab)	Results in negative allergy skin test results. May suppress skin whealing response for 4–6 months. *Aggregate grade of evidence*: A (Level 2: 1 study, level 3: 1 study)
Leukotriene modifying agents	May be continued during testing. *Aggregate grade of evidence*: A (Level 2: 2 studies, level 3: 1 study)
Tricyclic antidepressants	Antidepressants with antihistaminic properties suppress allergy skin test responses. Should be discontinued 7–14 days prior to testing. *Aggregate grade of evidence*: B (Level 2: 1 study, level 4: 1 study)
Topical (cutaneous) corticosteroids	Skin tests should not be placed at sites of chronic topical steroid treatment. *Aggregate grade of evidence*: A (Level 2: 3 studies, level 3: 1 study)
Systemic corticosteroids	Systemic corticosteroid treatment does not significantly impair skin test responses. *Aggregate grade of evidence*: C (Level 2: 1 study, level 3: 1 study, level 4: 2 studies; conflicting results)
Selective serotonin reuptake inhibitors (SSRIs)	Do not suppress allergy skin test responses. *Aggregate grade of evidence*: C (Level 3: 1 study, level 4: 1 study)
Benzodiazepines	May suppress skin test responses. Should be discontinued 7 days prior to testing. *Aggregate grade of evidence*: C (Level 4: 2 studies)
Topical calcineurin Inhibitors (tacrolimus, picrolimus)	Conflicting results regarding skin test suppression. *Aggregate grade of evidence*: C (Level 2: 2 studies; conflicting results)

to verify that the histamine induced skin test reaction is intact at the time of testing. This practice helps to mitigate against unknown factors – potentially medications – causing inappropriate interpretation of skin test results.

X.B.4.b | *Skin conditions*

Allergy skin tests rely upon the wheal and flare reaction induced by allergen-specific mast cell degranulation. However, mast cell degranulation can occur via a variety of non-immunologic mechanisms including minor skin trauma. Individuals with an exaggerated "triple response of Lewis" are considered to have "dermatographia" or "urticaria factitia," and may comprise 2%–5% of the population.[1246] Dermatographism may interfere with interpretation of allergy skin tests. Therefore, a negative control test should also be performed at the time of skin testing. In general, the negative control test consists of a prick with an applicator device (including the diluent), or placement of an intradermal wheal with inert diluent, in the case of intradermal testing. While an allergen induced skin wheal and flare may be compared to that induced by a test with mere diluent, results must always be interpreted with caution in the setting of dermatographia.

The skin of patients with other urticarias, AD, allergic contact dermatitis, etc. also may not respond appropriately to the trauma, histamine, glycerin, or allergen that are inherent in skin testing. Skin reactions could be exaggerated, or the effect of allergen-induced mast cell degranulation could be obscured. Common sense dictates that allergy skin tests should not be performed at sites of active dermatitis, but clinical studies to investigate this phenomenon are lacking.[1311] In some cases, it may be preferable to perform in vitro sIgE testing in patient with skin disease or dermatographism, but this is not based on data or outcomes from controlled studies.

Issues that may affect the performance or interpretation of skin tests – skin conditions

Aggregate grade of evidence: N/A (no identified studies)
Benefit: Correct identification of aeroallergen sensitivity.
Harm: Discomfort of skin test.
Cost: Low-moderate.
Benefits-harm assessment: Accurate skin test results justify discomfort and negligible cost of control tests.

Value judgments: In vitro allergy tests may be more appropriate than skin tests, in patients with dermatographia, urticaria, or other generalized dermatitis.
Policy level: Recommendation.
Intervention: Allergy skin tests should be performed in areas without active dermatitis or other lesions. Positive and negative control tests should be used in conjunction with allergy skin testing for AR.

X.C | In vitro testing

X.C.1 | Serum total IgE

IgE is the hallmark immunoglobulin in atopic disease. Atopy, or reactivity to otherwise innocent allergens can be determined by dermal reactivity (e.g., SPT), or by determining sIgE to a certain allergen in serum. The total IgE (tIgE) level in serum can also be determined. As atopy is not disease-specific, the question arises whether serum tIgE has any place in the evaluation and diagnosis of AR.

From the literature, roughly two study approaches to determine the role of tIgE are identified: population-based studies (e.g., birth cohorts, school health surveys, or general population approaches) and hospital-based studies including patients visiting otorhinolaryngology or allergy clinics. Data from the first approach show conflicting evidence. In some studies, tIgE is related to AR diagnosis;[1312–1315] in others it is less clear.[1316,1317] Moreover, it seems from these studies that other comorbidities, especially asthma, give rise to elevated tIgE.[1314,1315] However, the presence of asthma is not accounted for in most studies, possibly confounding the outcomes. Another weakness of population-based studies is that the diagnosis of AR depends on questionnaires, symptom scores, or self-reported diagnosis. This might lead to overdiagnosis of AR in these studies as the distinction with non-allergic rhinitis, common colds, or other nasal diseases can be challenging (Table X.C.1).

Hospital-based studies have the advantage of improved diagnostics but have the risk of selection bias. At any rate, these studies also show a mixed picture about the role of tIgE in the diagnosis of AR. Overall, the levels of tIgE are higher in AR versus non-allergic rhinitis[1318–1320] or versus controls.[1321,1322] Some studies investigated the correlation between serum sIgE and tIgE[1323,1324] showing a good overall fit. In hospital-based studies, the influence of asthma is seen as well[1325] but again not accounted for in most reports.

Taken together, an elevated tIgE is indicative of an atopic condition,[1326] though not necessarily AR specifically. As such, tIgE is not required in the diagnostic pathway for AR. Many authors conclude that obtaining a serum tIgE can be helpful but is only a preliminary or supportive criterion for AR. Especially if an SPT is performed, there seems to be little added value of obtaining a serum tIgE, as it requires venipuncture which can be bothersome for children. In population-based studies, tIgE can be supportive of AR, given that the study methodology allows for differentiation between atopic conditions such as asthma or AD in the study population.

Although in general obtaining a serum tIgE is not advised as a routine diagnostic approach, it can be needed or helpful in specific situations. For example, it has been suggested that monitoring of the efficiency of AIT may be done by evaluating the ratio between sIgE and tIgE; this is discussed in detail in a position paper from EAACI.[1327] Allergic broncho-pulmonary aspergillosis is the only clinical condition described to date, where the presence of high levels of tIgE is strictly related to disease severity.[1251] However, these specific cases are exceptions to the rule that serum tIgE is not needed for the diagnosis and evaluation of AR.

Serum total IgE

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 11 studies; Table X.C.1)
Benefit: Possibility to suspect allergy or atopy in a wide screening.
Harm: Cost of test, undergoing of venipuncture, low level does not exclude AR.
Cost: Low, dependent on country and local healthcare environment.
Benefits-harm assessment: Slight preponderance of benefit over harm. In addition, the ratio tIgE/sIgE may be useful to interpret the real value of sIgE production and predict treatment outcomes with AIT.
Value judgments: The evidence does not support routine use.
Policy level: Option.
Intervention: Assessment of tIgE may be useful to assess overall atopic status; furthermore, in selected cases it might help guide therapy (i.e., monitor efficacy of AIT).

X.C.2 | Serum allergen-specific IgE

Determining the presence of sIgE that verifies allergen sensitization is the cornerstone of diagnostic testing in

TABLE X.B.4.a.-2 Evidence table – medication effect on skin testing response

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Gradman and Wolthers[1305]	2008	2	Randomized crossover, cohort	12 children with atopic eczema treated with topical mometasone or tacrolimus ×2 weeks	SPT for 10 allergens	Topical mometasone and tacrolimus reduced wheal diameter Topical mometasone reduced histamine-induced wheal
Kupczyk et al.[1290]	2007	2	DBRCT, crossover	21 atopic subjects treated with ranitidine, loratadine, or placebo ×5 days	Wheal, flare, pruritis following SPT with histamine and allergen	Ranitidine: reduced wheal (41%), flare (16%), allergen-induced wheal (23%), and flare (22%) Loratadine: reduced wheal (51%), flare (33%), allergen-induced wheal (40%), and flare (44%) Ranitidine and loratadine both reduced pruritis score
Spergel et al.[1308]	2004	2	DBRCT, within subject comparison	12 adults with AD and AR or asthma	Allergen SPT wheal and flare, before/after topical 1% pimecrolimus cream	1% pimecrolimus cream does not significantly impact SPT results
Hill and Krouse[1295]	2003	2	DBRCT	23 atopic subjects treated with loratadine, montelukast, or placebo	Intradermal whealing response	Loratadine, but not montelukast, reduced the intradermal wheal diameter after allergen injection
More et al.[1309]	2003	2	RCT	15 subjects received single-blind dose of placebo, fexofenadine, 23 other herbals	Histamine 1 mg/ml wheal at baseline and 4 h after dose of herbal preparation	Fexofenadine significantly reduced SPT wheal size versus placebo None of the 23 herbal preparations showed significant effect on wheal size versus placebo
Noga et al.[1294]	2003	2	DBRCT	35 moderate–severe asthmatics treated with placebo or omalizumab	SPT for allergen before and 16 weeks after treatment	Omalizumab caused significant reduction in SPT wheal size versus placebo
Pearlman et al.[1288]	2003	2	RCT	78 patients with seasonal AR: single dose versus 2 weeks of azelastine nasal spray	Inhibition of histamine induced wheal	2 weeks of azelastine inhibited wheal/flare from histamine, returned to baseline at 48 h after cessation

(Continues)

TABLE X.B.4.a.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Simons et al.[1296]	2001	2	DBRCT, crossover	12 allergic participants treated with fexofenadine, montelukast, or placebo	Intradermal histamine, LTD4, allergen, placebo injection	Montelukast did not significantly decrease early or late phase cutaneous allergic responses Fexofenadine significantly decreased early and late responses
Simons and Simons[1310]	1997	2	DBRCT, crossover	20 adult males received single dose oral fexofenadine or loratadine	SPT response	Fexofenadine and loratadine both inhibited SPT wheal and flare response for 24 h
Miller and Nelson[1289]	1989	2	DBRCT	23 healthy subjects treated with ranitidine or placebo ×7 doses	Histamine and compound 48/80 induced SPT wheal and flare	Ranitidine reduced histamine wheal and flare by 22% No significant reduction in compound 48/80 wheal and flare
Pipkorn et al.[1304]	1989	2	DBRCT, placebo-controlled	10 patients with AR treated with clobetasol cream or placebo BID ×2–4 weeks	Allergen SPT wheal and flare	Clobetasol treated skin had reduced wheal and flare response Histamine induced wheal reduced at 4 weeks by topical steroid
Rao et al.[1292]	1988	2	Randomized trial	33 healthy subjects received single dose desipramine or doxepin	Daily histamine SPT	Desipramine inhibits wheal response for 2 days Doxepin inhibits wheal response for 4 days
Andersson and Pipkorn[1303]	1987	2	DBRCT	17 patients with AR treated with topical clobetasol ×1 week	Histamine SPT Allergen SPT	Topical clobetosol significantly suppresses allergen induced wheal and flare response
Slott and Zweiman[1299]	1974	2	DBRCT, crossover	15 atopic patients treated with methylpred-nisolone	Intradermal wheal size for histamine, allergen, and compound 48/80	No effect of 7 days methylprednisolone on intradermal wheal size
Cook et al.[1286]	1973	2	DBRCT	18 adults with skin test positive AR treated with chlorpheniramine, tripelennamine, promethazine, hydroxyzine, or diphenhydramine ×3 days	Intradermal wheal size suppression	All antihistamines suppressed wheal size to varying degrees Hydroxyzine suppressed responses for 4 days after cessation versus 2 days for diphenhydramine

(Continues)

TABLE X.B.4.a.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Isik et al.[1293]	2011	3	Cohort	24 subjects started on SSRIs for depression	Histamine and allergen induced SPT wheal responses	SSRIs fluoxetine, sertraline, and escitalopram did not significantly affect SPT whealing responses
Corren et al.[1250]	2008	3	Cohort	40 patients with perennial AR undergoing omalizumab treatment	Dust mite allergen skin test reactivity	Omalizumab significantly reduces allergy skin test reactivity
Narasimha et al.[1302]	2005	3	Cohort	26 subjects treated with topical clobetasol application	Histamine induced wheal response	Topical clobetasol inhibited SPT whealing response to histamine at the site of topical application; dose- and duration-dependent
Cuhadaroglu et al.[1297]	2001	3	Cohort	Zafirlukast 20 mg BID for at least 5 days: Nine patients with AR/asthma Eight controls	SPT to histamine and allergens	Zafirlukast did not suppress histamine or allergen induced wheal and flare response
Des Roches et al.[1298]	1996	3	Case–control	Long-term systemic steroids: 33 patients with steroid dependent asthma 66 in matched cohort	Codeine and dust mite induced SPT response	Systemic steroid therapy does not alter SPT reactivity to codeine or allergen
Harvey and Schocket[1291]	1990	3	Cohort	10 healthy subjects treated with hydroxyzine, cimedtidine, or both	Titrated intradermal histamine wheal	Hydroxyzine inhibited cutaneous wheal response to histamine, cimetidine did not Two drugs together significantly reduced whealing versus either alone
Almind et al.[1287]	1988	3	Cohort	23 healthy individuals treated with dex-chlorpheniramine, astemizole, cyproheptadine, loratidine, or terfenadine ×2 days	Effect on histamine SPT wheal Duration of SPT wheal suppression	All antihistamines suppressed SPT wheal response to histamine Duration of suppression exceeded 72 h for all agents tested
Long et al.[1283]	1985	3	Cohort	18 subjects, 10 had positive SPT to grass or ragweed allergens Six different antihistamines Pretreatment with hydroxyzine or chlorpheniramine	Effect on SPT wheal and flare reaction to histamine, morphine, or allergen	Antihistamines varied in their ability to suppress SPT wheal response Administration of hydroxyzine for 3 weeks reduced skin test suppression, suggesting induction of tolerance

(Continues)

TABLE X.B.4.a.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Phillips et al.[1284]	1983	3	Cohort	10 atopic subjects received injection of ketotifen, clemastine, chlorpheniramine, or sodium cromoglycate	Inhibition of allergen and histamine induced wheals	Ketotifen, clemastine, and chlorpheniramine but not sodium cromoglycate significantly inhibit skin whealing responses
Geng et al.[1301]	2015	4	Case–control	52 cases with negative histamine control tests 125 controls	Predictors of negative histamine control test	ICU stay, systemic steroid use, H_2 blockers, and older age associated with negative histamine control test
Shah et al.[1306]	2010	4	Retrospective cohort	Histamine SPT responses in patients with exposure to a variety of medications	SPT wheal area and SPT positivity	H_1 antagonists impaired whealing responses within 3 days of discontinuation Tricyclic antidepressants, benzodiazepines, mirtazapine, quetiapine had wheal suppression Other SSRIs and SNRIs as well as H_2 antagonists not independently associated with wheal suppression
Duenas-Laita et al.[1307]	2009	4	Uncontrolled cohort	42 drug abusers taking alprazolam TID	Histamine (10 mg/ml) SPT and allergen skin tests	All subjects taking alprazolam had negative histamine SPTs Incomplete data reported
Olson et al.[1300]	1990	4	Retrospective cohort	Skin test with codeine and histamine: 25 atopic patients on chronic systemic steroids 25 controls	Intradermal skin test reactivity	Chronic systemic steroid use reduces codeine induced wheal response but not histamine induced wheal response

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BID, twice daily; DBRCT, double-blind randomized controlled trial; ICU, intensive care unit; LOE, level of evidence; SPT, skin prick test; RCT, randomized controlled trial; LTD4, leukotriene D4; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TID, three times daily.

suspected allergic conditions. The assessment of sIgE can be done by skin tests, serological immunoassays, and/or cellular immunoassays.[1251]

Serological immunoassays detect and measure the level of serum sIgE. Innovations in molecular biology have revolutionized the procurement, characterization, and production of allergens through recombinant and phage methods.[1328] The ability to perform serum sIgE immunoassays with recombinant or highly purified allergens has increased the sensitivity, specificity, and diagnostic accuracy of these tests.[1245] Additionally, development of miniature computer-driven autoanalyzers and nanotechnology-based devices, enhanced signal detection instrumentation, and new solid phase chip and particle materials have

TABLE X.C.1 Evidence table – use of serum total immunoglobulin E in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jacobs et al.[1315]	2014	2	Cross-sectional	547 children (6–14 years old) from randomly selected households: 265 with AR (per ARIA), (+)SPT 192 with asthma	Correlation between tIgE and AR ± asthma	tIgE significantly associated with AR in children with asthma (OR 2.3; 95% CI 1.5–3.5) AR can be diagnosed if tIgE ≥ 100 kU/L both in asthmatics (PPV 85.1%, NPV 68%) and non-asthmatics (PPV 77.8%, NPV 90.9%)
Tu et al.[1316]	2013	2	Population-based cohort	1321 children (5–18 years old) from PATCH study; rhinitis based on self-reported diagnosis and/or medication use for AR	Correlation between tIgE and AR	tIgE for diagnosing AR: AUC: 0.70 (0.67–0.73), optimal cut-off 89.0 U/ml Overall insufficient accuracy of tIgE to detect allergic diseases regardless of cutoff value
Salo et al.[1314]	2011	2	Cross-sectional	7398 subjects (>6 years old) from NHANES 2005–2006; hay fever and allergies defined as self-reported doctor-diagnosed	Association of tIgE level with current hay fever	Association of current hay fever and 10-fold increase of tIgE (OR 1.86; 95% CI 1.44–2.41) ORs for different age, race, and gender groups not relevantly different Highest tIgE and sIgE found in asthmatics
Marinho et al.[1313]	2007	2	Whole-population birth cohort	478 children (5 years) from MAAS	tIgE levels and correlation with current rhinitis or rhincoconjunctivitis	Borderline association between tIgE and current rhinitis (OR 1.2; 95% CI 1.02–1.3) or current rhinoconjunctivitis (OR 1.3; 95% CI 1.1–1.5), not significant in multivariate analysis
Qamar et al.[1322]	2020	3	Prospective case–control	221 consecutive patients from otolaryngology department: 121 with AR (per ARIA), (+)SPT; mean age 25.3 (5–45) years; 41.3% with asthma 100 controls; mean age 24.9 (8–41) years	tIgE levels in AR versus controls	Mean tIgE in AR 493.30 ± 258.55 versus 228.12 ± 81.85 IU/ml in controls ($p < 0.001$) tIgE >150 IU/ml: 82.4% sensitivity, 71.7% specificity, 73.6% PPV, 81.0% NPV
Sharma et al.[1321]	2019	3	Retrospective case–control	155 patients, mean age 33.2 years: 113 AR cases (per ARIA) 42 controls	tIgE levels in AR versus controls	Mean log tIgE in cases: 5.65 (tIgE 814.36 IU/ml), and in controls: 4.43 (tIgE 96.62 IU/ml), $p < 0.001$ No difference between age groups

(Continues)

TABLE X.C.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Li et al.[1320]	2016	3	Retrospective cohort	610 adults, 349 with AR, median age 27.0 (23.0–42.0) years, from otolaryngology department	tIgE levels in AR versus NAR	tIgE: AR 166.0 (58.4–422.5) IU/ml, NAR 68.8 (24.5–141.0) IU/ml, $p < 0.001$
Park et al.[1317]	2016	3	Follow-up of cross-sectional study	567 schoolchildren from 3rd/4th grade of elementary schools at first study, now from 5th/6th grade	Correlation of tIgE at baseline and development of allergic symptoms at follow-up	In 191 children without allergic sensitization initially, tIgE >17.7 IU/ml associated with risk for allergic sensitization (46.3% sensitivity; 85.3% specificity; OR 4.8) tIgE may be helpful to predict sensitization but not complaints
Chung et al.[1324]	2014	3	Retrospective cohort	1073 patients, mean age 36.9 (1–91) years from an otolaryngology clinic (2006–2010), symptoms and findings consistent with AR	Correlation between sIgE and tIgE	tIgE >150 IU/ml: AUC 0.88, 89.6% PPV, ~52% NPV (estimated from figure) tIgE <10 IU/ml: 89.6% NPV
Karli et al.[1323]	2013	3	Retrospective cohort	295 patients, mean age 33.9 (6–80) years, with at least two nasal complaints (itching, obstruction, runny discharge, sneezing) and/or positive findings on anterior rhinoscopy	Correlation between sIgE (for inhalant and food allergens) and tIgE, categorized as <20, 20–100, and >100 U/ml	23.7% had tIgE <20 U/ml 38.3% had tIgE between 20 and 100 U/ml 33.8% had tIgE >100 U/ml 108 had positive sIgE for inhalant allergens, 85.2% of these had tIgE above 20 U/ml
Demirjian et al.[1326]	2012	3	Prospective cohort	125 consecutive patients, mean age 57 years, referred to allergy/immunology clinic, 89 with AR by SPT	tIgE as predictor of atopy	tIgE levels >140 IU/ml is suggestive of an atopic etiology for patients with rhinitis signs/symptoms
Jung et al.[1319]	2011	3	Prospective cohort	442 consecutive patients with AR symptoms, median age 33 (8–76) years, from otolaryngology department	Discrimination of AR (defined as symptoms with positive sIgE)	tIgE of 98.7 IU/ml strong predictor of AR: AUC 0.79 (0.74–0.83), 75.2% sensitivity, 69.7% specificity, OR 6.93 (95% CI 4.29–9.62), 71.3% PPV, 73.7% NPV tIgE (IU/ml): AR 468.6 ± 733.4, NAR 118.4 ± 180.8, $p < 0.001$

(Continues)

TABLE X.C.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kalpaklioglu and Kavut[1318]	2009	3	Retrospective case–control	323 consecutive and unselected patients from tertiary clinic, mean age 31.8 years, 205 with AR, asthma equally present in both groups	tIgE levels between AR and NAR	tIgE: AR 261 (359), NAR 126 (172), $p < 0.01$ Differences in complaints and seasonality between AR and NAR
Satwani et al.[1325]	2009	3	Cross-sectional	258 patients from pediatric medicine unit, 0.5–12 years old, 172 with AR based on complaints, 92.2% with asthma	Correlation between elevated (higher than non-specified reference values) tIgE and AR	No association between tIgE and AR Strong association of tIgE with asthma
Ando and Shima[1312]	2007	3	Cross-sectional	370 school children, 9–10 years old, 98 with AR No information on overlap with asthma or atopic eczema	tIgE levels between AR and healthy controls	tIgE: AR 230.4 (157.6–337.0), patients without rhinitis 96.5 (76.9–121.1), $p < 0.001$

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; AUC, area under the curve; CI, confidence interval; LOE, level of evidence; MAAS, Manchester Asthma and Allergy Study; NAR, non-allergic rhinitis; NHANES, National Health and Nutrition Examination Survey; NPV, negative predictive value; OR, odds ratio; PATCH, Prediction of Allergies in Taiwanese Children; PPV, positive predictive value; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test; tIgE, total immunoglobulin E.

improved the diagnostic accuracy and consistency of in vitro tests.[1329,1330] Furthermore, increased knowledge of molecular allergen components allow clinicians to predict the risk of severe allergic reactions and to identify the most appropriate AIT extract selections for each patient.[1330]

Derived from the original radio allegro-sorbent test (RAST), new methods of sIgE immunoassay, like enzyme-linked immunosorbent assay (ELISA), fluorescent enzyme immunoassays, and/or chemiluminescent assays are available. These measurements of serum sIgE can be done using single allergen (singleplex: one assay per sample) or through a predefined panel that includes several allergens (multiplex: multiple assays per sample). Singleplex tests allow the clinician to choose select allergens as dictated by the clinical history.[1251] Multiplex tests provide results of a broad array of preselected allergens.

The multiplex test is important in diagnosis of polysensitized patients. Multiplex platforms are slowly being implemented in many allergy care centers outside of research and tertiary care centers, although currently the most widely used systems are singleplex. Some, like Thermo Fisher ImmunoCAP, have an extensive amount of scientific literature demonstrating their efficacy.[1331] Each test has certain characteristics based on the detection method used, the dynamic range of reading of the instrument, time and conditions for the incubation, amount of allergen in the tube, and characteristics of the anti-IgE.[1251,1330] There are three different kinds of serum sIgE assays available: qualitative, semi-quantitative, and quantitative. Qualitative assays are useful to determine if the patient is sensitized to common allergens, providing positive, negative, or borderline sIgE results to a mix of allergens without measuring the IgE concentration. Semi-quantitative assays grade response by reporting a series of classes (e.g., class I–VI). Quantitative assays report sIgE antibody concentration. Most singleplex platforms are quantitative assays; multiplex is semi-quantitative.

Multiplex platforms or panels of 10–12 selected allergens (i.e., pollens, cat, and mite) will detect up to 95% of patients who would have been identified on a larger battery.[1332,1333] If the test is negative, absence of allergy is probable.[1329]

Serum sIgE testing may also be beneficial for selecting allergens for AIT. In polysensitized patients, it can be difficult to determine the most relevant allergen(s) on SPT. In these situations, molecular allergy using components will help to discriminate the most relevant allergens and thus better guide AIT.[1334] In addition, serum sIgE seems to correlate with the severity of AR symptoms.[1335–1339] Since patients with more severe symptoms appear to respond better to AIT than those with milder symptoms, serum sIgE may help in the selection of candidates for AIT and possibly predicting the response.[1335,1340]

SPT has advantages and disadvantages when compared to sIgE tests. As a general concept, SPT is more sensitive, whereas serum sIgE detection is more quantitative than SPT.[1251]

There are several advantages of serum sIgE over skin testing. The safety profile is excellent as the risk for anaphylaxis is non-existent. It is the preferred testing method in individuals at high risk for anaphylaxis.[1341] Undergoing SPT is also limited by the presence of certain medical conditions.[1341] When SPT is contraindicated, serum sIgE testing offers a safe and effective option for determining the presence of IgE-mediated hypersensitivities. Additionally, where certain medications can alter SPT results, serum sIgE testing is not similarly impacted. Finally, in very young patients in which SPT may prove too stressful, serum sIgE can be considered.

There are some important limitations to serum sIgE testing. While patients are accepting of both in vitro and in vivo allergy testing, many prefer SPT because it allows for immediate feedback and visible results.[1340] Unless molecular allergy diagnostic approach with allergenic components is used (precision allergy medicine diagnosis or PAMD@),[1330] serum sIgE to regular allergens cannot accurately predict the risk of severe allergic reaction. If PAMD@ is not used, cross-reacting allergens and polysensitizations can confound in vitro testing, leading to false positive results.[1342]

While SPT results may vary based on the quality of the extracts, as well as clinicians administering and interpreting the test, serum sIgE testing results can vary from one laboratory to another. One study sent blinded samples of the same sera, diluted and undiluted, to 6 major commercial laboratories and compared the results to the expected curve from an ideal assay. Out of the six laboratories, only two demonstrated precision and accuracy in their results.[1343] Further studies have demonstrated poor agreement on results from testing the same sera by different commercially available assay systems.[1343–1345] These factors introduce notable heterogeneity in serum sIgE testing. Clinicians should be familiar with the platform used for serum sIgE testing at their institution and to understand any limitations inherent to that platform.

Studies have shown that serum sIgE testing has a sensitivity range of 67%–96% and specificity range of 80%–100%.[143,1249,1257,1345,1346] Further, serum sIgE correlates well with NPT and SPT for AR diagnosis.[1249,1257,1278,1345,1347] While there is good evidence to show that serum sIgE is often equivalent to SPT, it is generally accepted that SPT is more sensitive.[143,1005,1348] A recent position paper from the World Allergy Organization (WAO) stated that skin tests are still considered first line and that serum sIgE testing should be considered as a complimentary or alternative diagnostic tool.[1251] Based on the literature, serum sIgE testing is a reasonable alternative to SPT and is safe to use in patients who are not candidates for SPT. All sIgE tests should be evaluated within the framework of a patient's clinical history (Table X.C.2).

Serum allergen-specific IgE

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 2 studies, level 3: 6 studies, level 4: 6 studies, level 5: 1 study; Table X.C.2)
Benefit: Confirms diagnosis and directs appropriate pharmacological therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance, directs AIT.
Harm: Adverse events from testing including discomfort from blood draw, inaccurate test results, false positive test results, misinterpreted test results.
Cost: Moderate cost of testing.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Patients can benefit from identification of their specific sensitivities. Further, in some patients who cannot undergo SPT, serum sIgE testing is a safe and effective alternative.
Policy level: Recommendation.
Intervention: Serum sIgE testing may be used in patients who cannot undergo allergy skin testing. Use of highly purified allergen or recombinants can increase the sensitivity, specificity, and diagnostic accuracy of sIgE tests. Rigorous proficiency testing on the part of laboratories may also improve accuracy.

X.C.3 | Nasal allergen-specific IgE

AR is frequently diagnosed by history alone in clinical practice.[182] When objective testing for confirmation of the diagnosis is needed, SPT or in vitro testing for serum sIgE is performed. However, the nasal mucosa of patients with AR has been shown to produce sIgE locally, providing a potential alternative method for objective testing for AR.[450–453,529,1354]

Collection of nasal secretions is typically done by nasal lavage, through absorption of the secretions with absorbent materials, or directly with solid sIgE testing substrates.[458,1355–1357] Collection of mucosal tissue can be achieved with either tissue biopsy or with a cytology brush.[450,1358] There is no consensus on which technique is superior, and most appear to yield similar results in identifying nasal sIgE.[1359,1360] Cut-off values for nasal sIgE levels

TABLE X.C.2 Evidence table – use of serum allergen-specific immunoglobulin E in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tian et al.[1349]	2017	1	SRMA	Studies assessing performance characteristics of sIgE for Der p	Diagnostic accuracy of Der p 1 sIgE and Der p 2 sIgE measurement in to diagnose *D. pteryonyssinus* allergy	Der p 1: sensitivity 84%, specificity 97%, diagnostic OR 166.57, AUSROC 0.94 Der p 2: sensitivity 87%, specificity 100%, diagnostic OR 17342.35, AUSROC 0.98
Knight et al.[1350]	2018	2	Prospective cohort, single-blind	232 allergic patients with prior SPT	sIgE measured by HYTEC, 288 compared to SPT	SPT and sIgE showed >70% concordance (range 74%–88% per allergen) sIgE: sensitivity 57%–95%, specificity 82%–97%, PPV 21%–92%, NPV ≥90%
van Hage et al.[1351]	2017	2	Prospective cohort, single-blind	Batches of positive and negative serum	Consistency of performance and results for ImmunoCAP ISAC 112 across multiple testing sites	Good consistency in analytical performance across sites Low frequency of false positives (0.014%)
Chinoy et al.[1352]	2005	3	Prospective cohort	118 patients with AR and/or bronchial asthma	Compare skin test reactivity with serum sIgE	For four indoor allergens, skin test more sensitive than RAST Skin test and RAST scores had weak to moderate correlation
Wood et al.[143]	1999	3	Prospective cohort	Patients with cat allergy determined by history Cat exposure model	Compared the predictive values of SPT, ID, and RAST in diagnosis of cat allergy	SPT and RAST values had excellent efficiency in cat allergy diagnosis ID added little to the diagnostic evaluation Sensitivity and specificity of RAST were 69% and 100%, respectively
Tschopp et al.[1249]	1998	3	Prospective cohort	Randomly selected sample of 8329 Swiss adults	Compared the sensitivity, specificity, PPV, and NPV of SPT, total IgE levels, and fluoroenzyme immunoassay in diagnosing AR	Sensitivity of fluoroenzyme immunoassay significantly higher than SPT and total IgE SPT was more specific and had better PPV SPT was the most efficient test to diagnose AR
Ferguson and Murray[1347]	1986	3	Prospective cohort	168 children with clinical suspicion of allergy to cats and/or dogs	Compared the predictive values of skin tests and RASTs in children with history of allergy to cats and/or dogs	RAST sensitivity 71%–74%, specificity 88%–90% SPT sensitivity 68%–76%, specificity 83%–86%

(Continues)

TABLE X.C.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ownby and Bailey[1346]	1986	3	Prospective cohort	Children aged 4–19 years	Diagnostic levels by MAST and RAST were compared to skin test reactions for ragweed, grass, house dust mite	MAST: sensitivity 59%, specificity 97%, efficiency 72% RAST: sensitivity 67%, specificity 97%, efficiency 78% Neither MAST nor RAST was as sensitive as skin test
Wide et al.[1348]	1967	3	Prospective cohort	31 allergic patients	Acoustic rhinometry of minimal nasal cavity cross-sectional area	Good correlation between provocation tests and in vitro tests for allergy
Bignardi et al.[1353]	2019	4	Retrospective cohort	793 patients referred for respiratory allergy	SPT and sIgE by IFMA procedure for five allergens	Using SPT result as the target condition, statistically significant values of AUC were found for sIgE, ranging from 0.84 to 0.94
Nam and Lee[144]	2017	4	Retrospective cohort	2635 patients who underwent SPT and sIgE	sIgE measured by Phadia CAP compared to SPT	Moderate agreement between SPT and sIgE (75.8%) Sensitivity of CAP higher than SPT wheal size (72.8%) Specificity of CAP higher than SPT wheal size (78.2%) SPT mean wheal size and sIgE levels correlated for all allergens except *T. putrescentiae*
Seidman et al.[1005]	2015	4[a]	Clinical practice guideline	N/A	N/A	Clinicians should perform and interpret or refer for sIgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or the diagnosis is uncertain Aggregate level of evidence grade B
Bernstein et al.[1246]	2008	4[a]	Review-practice parameter	N/A	N/A	Sensitivity of serum sIgE ranges 50%–90% with an average of 70%–75% sIgE may be used with history and physical for diagnosis of allergy and may be preferable in certain clinical conditions Aggregate level of evidence grade B–C

(Continues)

TABLE X.C.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Pumhirun et al.[1257]	2000	4	Prospective case–control	Perennial rhinitis patients	Compared sensitivity and specificity of ID to SPT and sIgE assay for *D. pteronyssinus* and *D. farinae*	Serum sIgE for *D. pteronyssinus* and *D. farinae* had sensitivity of 96.3% and 88.9%, specificity of 96.2%, and 88.9% SPT sensitivity 90.4% and 86.4%, specificity of 99.5% and 93.1%
Reddy et al.[1278]	1978	4	Prospective case series	34 patients with perennial rhinitis but negative SPT 19 patients with perennial rhinitis and positive SPT Healthy controls	Determine the clinical relevance of positive intracutaneous test when epicutaneous test is negative	Good agreement between SPT, RAST, and NPT Poor agreement between positive ID at 1:1000 concentration and SPT, RAST, and NPT
Ansotegui et al.[1251]	2020	5	World Allergy Organization position paper	N/A	N/A	For type I IgE-mediated allergic disease, skin tests are considered first-line approach for presence of sIgE antibodies In vitro serum IgE detection with the use of highly purified allergen or recombinants is an alternative

Abbreviations: AR, allergic rhinitis; AUSROC, areas under the summary receiver operating curve; ID, intradermal; IgE, immunoglobulin E; LOE, level of evidence; MAST, multiple allegro-sorbent test; NPT, nasal provocation test; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RAST, radio allergo-sorbent test; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test; SRMA, systematic review and meta-analysis.

[a]LOE upgraded due to established methodology, several rounds of review, long history of EBM guideline development.

that indicate a diagnosis of AR are debated and consensus has yet to be established. It is generally accepted that levels of nasal sIgE will be lower than levels of serum sIgE in patients with AR[1357,1361,1362] (Table X.C.3).

Outside of a few circumstances, the clinical utility of nasal sIgE testing in patients with AR is limited. However, in patients with negative SPT and negative serum sIgE with a history suggestive of AR, nasal sIgE testing may detect sIgE in their nasal secretions and/or mucosa.[446,455,456,458,461,463,473,1356,1363] This phenomenon is referred to as LAR. LAR is a type of rhinitis characterized by typical allergic symptoms with local sIgE production and positive response to NPT, without positive SPT or serum sIgE testing.[445] (See Section VI.A.3. Local IgE Production and Section X.D.2. Local Allergen Challenge Testing for additional information on these topics.) The strictest diagnostic criteria for LAR require a positive NPT and evidence of sIgE in nasal secretions or nasal mucosa, as some studies have shown sIgE in control patients with negative results on NPT.[248,1365–1367]

Currently, patients with negative SPT and/or negative serum sIgE testing are given the diagnosis of non-allergic rhinitis. Several studies have investigated the results of nasal sIgE testing in patients with non-allergic rhinitis to achieve a greater understanding of what portion of patients diagnosed with non-allergic rhinitis have evidence of LAR. A recent systematic review of studies that measured nasal sIgE in mucus collected from the nasal cavity in patients diagnosed with non-allergic rhinitis showed sIgE to be present in 7.4%–13.4% of subjects.[1368] The results of this study contrast with a 2017 systematic review that analyzed the results of NPT in patients with AR and non-allergic rhinitis. The 2017 study found 24.7% of patients with non-allergic rhinitis had positive NPT.[267] This analysis did not include measurements of nasal sIgE limiting direct comparison to the more recent study. The origin of this disagreement between these two reviews is unclear but may be related to low quantities of nasal sIgE in nasal secretions or flaws in the methodology for testing for nasal sIgE.

TABLE X.C.3 Evidence table – nasal allergen-specific IgE the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hamizan et al.[1368]	2019	1	SRMA	21 studies included Data extracted from 14 studies 484 subjects with NAR 1946–2017	Nasal sIgE	Nasal sIgE present in 7.4%–13.4% of NAR subjects Patients with a personal or family history of atopy or allergy should be considered for nasal sIgE
Eckrich et al.[248]	2020	2	Cross-sectional	Collection via cotton swab: NAR, $n = 21$ AR, $n = 24$ Control, $n = 25$	NPT, nasal tIgE, nasal sIgE, serum tIgE, serum sIgE	Nasal sIgE present in subjects with AR but not those with NAR, challenging LAR concept
Santamaria et al.[1366]	2020	2	Cross-sectional	Collection via nasal lavage: AR, $n = 25$ NAR, $n = 25$ Control, $n = 18$	NPT, nasal sIgE, serum sIgE, SPT	Nasal sIgE does not predict response to NPT in patients with NAR
Schiavi et al.[1370]	2020	2	RCT	Collection technique not reported: SLIT Control	NPT, nasal sIgE, rhinomanometry, spirometry	Nasal sIgE is reduced after a course of SLIT
Hamizan et al.[1361]	2019	2	Cross-sectional	Collection via inferior turbinate biopsy: AR, $n = 154$ Asymptomatic, $n = 6$	Nasal sIgE, serum sIgE and/or SPT	sIgE testing of inferior turbinate biopsy with a threshold of 0.1 kUA/L is a sensitive test for detection of AR
Campo et al.[1357]	2018	2	Cross-sectional	Collection via direct application of sIgE solid phase testing substrate: LAR, $n = 14$ AR, $n = 20$ Control, $n = 16$	Nasal sIgE	Nasal sIgE ≥0.1450 kUA/L is an optimum cut point for differentiating subjects with LAR and AR from controls
Gelardi et al.[1365]	2016	2	Cross-sectional	Collection via nasal mucosa curette: AR, $n = 15$ NAR, $n = 12$ Control, $n = 14$	Symptom VAS, SPT, serum sIgE, nasal sIgE, nasal cytology	Nasal sIgE was detected in control subjects Nasal sIgE may be spontaneous in NAR and not indicate the presence of LAR
Kim et al.[1367]	2016	2	Cross-sectional	Collection via cotton ball: NPT positive, $n = 39$ NPT negative, $n = 21$	NPT, nasal sIgE	Nasal sIgE detected in all patients, no difference between NPT groups No comparison pre- and post-NPT performed
Krajewska-Wojtys et al.[1364]	2016	2	Cross-sectional	Collection via nasal lavage: NAR adolescents, $n = 101$ AR, $n = 115$	NPT, nasal sIgE	Nasal sIgE detected in 53% of subjects diagnosed with NAR Levels of nasal sIgE increased after NPT
Lee et al.[1371]	2016	2	Cross-sectional	Collection via nasal lavage: NAR children, $n = 12$ AR children, $n = 15$ NAR adults, $n = 9$ AR adults, $n = 15$	Nasal sIgE	AR with higher nasal sIgE to HDM than NAR, no difference between adults and children Correlation between nasal and serum IgE only in children

(Continues)

TABLE X.C.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bozek et al.[459]	2015	2	Cross-sectional	Collection via nasal lavage: Elderly patients with rhinitis, $n = 219$	NPT, nasal sIgE	LAR and AR common in elderly patients (21% with LAR, 40.2% with AR, and 38.8% with NAR)
Sakaida et al.[1372]	2014	2	Cross-sectional	Collection via suction of nasal secretions: Symptomatic, $n = 24$ Asymptomatic but sensitized, $n = 9$ Not sensitized, $n = 13$	Nasal sIgE	93% had nasal sIgE, higher levels in sensitized subjects, correlation between nasal and serum sIgE
Fuiano et al.[1363]	2012	2	Cross-sectional	Collection via cellulose membrane: Perennial AR, children, $n = 20$ Perennial NAR, children, $n = 36$	NPT, nasal sIgE	Nasal sIgE to *Alternaria* detected in 69% of positive NPT
Lopez et al.[461]	2010	2	Cross-sectional	Collection via nasal lavage: LAR, $n = 40$ Control, $n = 50$	NPT, nasal sIgE, total nasal IgE, tryptase, ECP, symptoms	Nasal sIgE present in patients with LAR Levels of sIgE increase after NPT in some patients with LAR
Powe et al.[1373]	2010	2	Cross-sectional	Collection via cotton ball: AR, $n = 90$ NARES, $n = 90$ Control, $n = 90$	Nasal immunoglobulin free light chains	Free light chains increased in AR and NAR nasal mucosa, suggesting role in hypersensitivity
Ahn et al.[1374]	2009	2	Cross-sectional	Collection via mucosal biopsy: AFRS, $n = 11$ CRSsNP, $n = 8$ Control, $n = 9$	Nasal sIgE, tIgE, histologic immunolocalization	Nasal sIgE to fungi and other antigens found in mucosa of subjects with AFRS
Rondon et al.[463]	2009	2	Cross-sectional	Collection via nasal lavage: LAR, $n = 30$ Control, $n = 30$	Nasal sIgE, tIgE, tryptase, ECP	30% with nasal sIgE LAR have local production of sIgE, mast cell/eosinophil activation
Rondon et al.[455]	2008	2	Cross-sectional	Collection via nasal lavage: Seasonal NAR, $n = 32$ AR to pollen, $n = 35$ AR to HDM, $n = 30$ Control, $n = 50$	NPT, nasal sIgE	Nasal sIgE to grass pollen detected in 35% NAR patients with positive NPT, and with similar sIgE profile as AR
Rondon et al.[456]	2007	2	Cross-sectional	Collection via nasal lavage: NAR, $n = 50$ AR to HDM, $n = 30$ Control, $n = 30$	NPT, nasal sIgE	Nasal sIgE to HDM detected in 22% of patients with NAR with positive NPT
Powe et al.[446]	2003	2	Cross-sectional	Collection via mucosal biopsy: NAR, $n = 10$ AR, $n = 11$ Control, $n = 12$	Nasal sIgE	Nasal sIgE to grass detected in 30% of patients with NAR No nasal sIgE to HDM detected

(Continues)

TABLE X.C.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
KleinJan et al.[529]	2000	2	Cross-sectional	Collection via mucosal biopsy: Seasonal AR, $n = 12$ Perennial AR, $n = 16$ Control, $n = 12$	Nasal B and plasma cells with IgE	sIgE produced in nasal tissue of AR patients but not healthy controls
KleinJan et al.[1354]	1997	2	Cross-sectional	Collection via mucosal biopsy: Seasonal AR, $n = 11$ Perennial AR, $n = 10$ Control, $n = 10$	Nasal sIgE to grass and HDM	sIgE to grass and HDM found in seasonal and perennial AR subjects, respectively
Takhar et al.[453]	2005	3	Cross-sectional, nonconsecutive	Collection via mucosal biopsy: AR, $n = 12$ Control, $n = 4$	Nasal mRNA and gene transcripts	Allergen stimulates local class switching to IgE in the nasal mucosa
Durham et al.[451]	1997	3	Cross-sectional, nonconsecutive	Collection via mucosal biopsy: AR, $n = 21$ Control, $n = 10$	NPT, nasal IgE heavy chain	Local IgE synthesis and cytokine regulation occur is the nasal mucosa of AR patients
Huggins and Brostoff[458]	1975	3	Cross-sectional, nonconsecutive	Collection via filter paper: NAR, $n = 14$ AR, $n = 6$ Control, $n = 5$	SPT, NPT, serum and nasal sIgE to HDM	Nasal sIgE in AR and NAR patients with positive NPT, but not in controls
Castelli et al.[1375]	2020	4	Case series	Collection via nasal sponge: Children and adults with seasonal AR, $n = 161$	Nasal sIgE, serum sIgE, nasal secretion total protein	Microarray testing of nasal secretion is feasible for detection of sIgE, high specificity but low sensitivity versus serum sIgE
Hamizan et al.[1359]	2019	4	Case series	Adults undergoing turbinate surgery ($n = 157$), collection techniques: Cytology brush Nasal biopsy	Nasal sIgE, serum sIgE, SPT	Cytology brush collection had similar results to tissue biopsy on sIgE testing
Saricilar et al.[1362]	2018	4	Case series	Adults with nasal obstruction ($n = 47$), collection techniques: Cytology brush Curette Dental brush	Nasal sIgE, SPT, serum sIgE, total protein	Cytology brush collects more protein from nasal mucosa than curette or dental brush Cut point 0.14 kUA/L gave a sensitivity of 75% and specificity of 86% for AR
Ahn et al.[1356]	2017	4	Case series	Children with rhinitis: Spray, $n = 30$ Cotton swab, $n = 52$	Nasal sIgE, serum sIgE, SPT	Nasal sIgE correlates with serum sIgE with either collection method LAR identified in a subset of patients with NAR
Becker et al.[247]	2016	4	Case series	Collection via cotton ball: NARES, $n = 19$	Nasal sIgE	No detectable nasal sIgE in any of the patients
Ota et al.[1358]	2016	4	Case series	Collection via mucosal biopsy: AR, $n = 11$	Nasal and serum sIgE	Detection of sIgE in inferior turbinate mucosa and serum

(Continues)

TABLE X.C.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zicari et al.[473]	2016	4	Case series	Collection via nasal lavage: NAR children, $n = 20$	NPT, nasal sIgE	66.7% had positive NPT; of these, 75% had nasal sIgE to HDM and/or grass pollen
Reisacher[1360]	2012	4	Case series	Collection via mucosal brush: AR, $n = 18$	Nasal sIgE, SPT	Nasal sIgE in 75% of subjects Local sIgE is found in subjects with negative SPT
Coker et al.[450]	2003	4	Case–control	Collection via mucosal biopsy: AR, $n = 6$ Control, $n = 1$	Nasal IgE heavy chain	Somatic hypermutation, clonal expansion, and class switching occurs within the nasal mucosa of AR patients
Sensi et al.[1376]	1994	4	Case series	Collection via nasal lavage: Children with asthma and rhinitis, $n = 18$	Nasal and serum sIgE measured after allergen avoidance	Nasal sIgE may be more sensitive marker of antigen exposure than serum sIgE
Platts-Mills[452]	1979	4	Case series	Collection via nasal lavage: AR, $n = 50$	Nasal IgG, IgA, and IgE	Antibody response in AR patients is local in the nasal mucosa

Abbreviations: AFRS, allergic fungal rhinosinusitis; AR, allergic rhinitis; CRSsNP, chronic rhinosinusitis without nasal polyps; ECP, eosinophil cationic protein; HDM, house dust mite; Ig, immunoglobulin; IgE, immunoglobulin E; LAR, local allergic rhinitis; LOE, level of evidence; NAR, non-allergic rhinitis; NARES, non-allergic rhinitis with eosinophilia syndrome; NPT, nasal provocation test; RCT, randomized controlled trial; sIgE, allergen-specific immunoglobulin E; SLIT, sublingual immunotherapy; SPT, skin prick test; SRMA, systematic review and meta-analysis; tIgE, total immunoglobulin E; VAS, visual analog scale.

Differentiating LAR from non-allergic rhinitis is important in patients with symptoms of rhinitis that are not adequately managed with pharmacologic therapy. While both would typically respond to treatment, identification of offending allergens in LAR may permit allergen avoidance and/or allow for treatment with AIT. Patients who are classified as non-allergic rhinitis would not typically be candidates for AIT; however, for patients with LAR, treatment with AIT is an option.[445] In this population, early studies suggest that AIT can decrease symptoms and medication usage and improve QOL.[1369] Therefore, in patients with symptoms of AR but negative SPT and/or negative in vitro testing for serum sIgE whose symptoms are not fully controlled on appropriate pharmacologic therapy, assessment of nasal sIgE to investigate for possible LAR could be considered.

Nasal allergen-specific IgE

Aggregate grade of evidence: C (Level 1: 1 study, level 2: 21 studies, level 3: 3 studies, level 4: 11 studies; Table X.C.3)

Benefit: Patients with non-allergic rhinitis found to have nasal sIgE may have LAR and could benefit from avoidance or AIT.

Harm: Measurement of nasal sIgE is minimally invasive. No significant adverse effects have been reported. Possible discomfort from sample collection.

Cost: Associated costs include the direct costs of testing and indirect cost of increased time and effort for performing nasal sIgE diagnostic test.

Benefits-harm assessment: The benefits of identifying patients with an allergic component to their rhinitis may outweigh associated risks.

Value judgments: In patients with non-allergic rhinitis who also have risk factors for atopic disease and have inadequate response to pharmacotherapy, testing for nasal sIgE may be helpful in confirming a diagnosis of LAR and allowing for treatment with AIT. There is no consensus for levels of nasal sIgE that indicate sensitivity.

Policy level: Option.

Intervention: Measurement of nasal sIgE is an option in patients with non-allergic rhinitis suspected of having LAR to support this diagnosis and guide AIT if pharmacologic therapies are inadequate. Consensus for levels of nasal sIgE indicating AR need to be established.

X.C.4 | Correlation between skin testing and in vitro sIgE testing

Factors that influence sensitivity and specificity of SPT include patient demographics, technician expertise, specific methodologies employed, quality of reagents, and what allergen is being tested.[147,1377–1382] SPT wheal size and sensitivity depend on the choice of control reagents used for testing, specific device selection, angle of penetration, amount of allergen, and skill of the technician.[147,1251,1378] A 2016 SRMA indicates that SPT is an accurate test that when utilized along with a detailed clinical history, helps confirm the diagnosis AR.[1252]

The performance and reliability of serum sIgE testing depends on choice of reagents, age of equipment, and patient demographics.[1269] Sensitivity and specificity are affected by the cutoff value of a positive test.[1383] In a Korean population, SPT was found to be superior to ImmunoCAP for measuring HDM sensitivity if the patient was less than 30 years of age; for the group older than age 50, ImmunoCAP was more sensitive.[1384]

Several studies have compared serum sIgE to SPT.[143,144,1350,1353,1383,1385,1386] Both techniques yield good sensitivity and are generally well correlated; however, interpretation of the results depends to some extent upon the gold standard reference used to define allergic status, namely environmental chambers, nasal challenge, and validated questionnaires.

Microarray allergy testing systems have been introduced more recently to offer a comprehensive in vitro allergen test panel. There are several commercially available multiplex platforms: Thermo Fisher ImmunoCAP ISAC (Immuno-solid phase Allergen Chip) which contains 112 allergen molecules; MADx Allergen Explorer 2 (ALEX2) containing 117 purified allergens plus 178 allergenic components and Euroline microstrips.[1330] The implementation of molecular allergy diagnostic approach (PAMD@) is increasingly entering into routine care.

Selection and interpretation of allergen testing is not based on sensitivity and specificity alone. The intended physiological mechanism to be evaluated also needs to be considered. SPT measures end-organ pathological mechanisms associated with sIgE bound to the surface of mast cells. Serum sIgE and microarray approaches measure circulating IgE that may or may not represent downstream allergic inflammatory responses.

The average pooled sensitivity of SPT is 85% which tends to be slightly higher than that of serum sIgE.[1252] This can vary depending on the allergen being tested and the characteristics of the patient. SPT is often chosen as the first line diagnostic instrument to detect sensitivity to aeroallergens based on accuracy, convenience, cost, and speed. In cases where dermatographism is present and/or patients are unable to wean off medications that affect skin testing, serum sIgE testing may be a better choice.

The role of small volume blood testing through emerging microarray multiplex (multiple assays per sample) technology is evolving. Multiplex assays are especially suited for use in patients with complex sensitization patterns or symptoms. In polysensitized patients, PAMD@ makes it possible to distinguish between primary and cross-sensitization. This is very important for appropriate prescription of AIT. Specific molecular sensitization patterns obtained in multiplex platforms may predict the risk for AR and asthma. PAMD@ is beginning to be used worldwide.

Correlation between skin testing and in vitro sIgE testing

Aggregate grade of evidence: B (Level 1: 3 studies, level 2: 5 studies, level 3: 4 studies, level 4: 5 studies, level 5: 2 studies, Table X.C.4)

X.C.5 | Basophil activation testing

The BAT is an in vitro test for reactivity to specific allergens. It uses the propensity of activated basophils to express CD63 or CD203c. A BAT may have various ways of reporting results: the number of activated basophils as a full number or dichotomized (negative/positive, often at a cut-off of 10% or 15%) and dose–response curves to indicate basophil sensitivity to increasing allergen extract concentrations. As such, BAT is a functional measurement. Per allergen, different concentrations and cut-offs might be needed, making the comparison of studies challenging at times.

BAT is often performed in food, medication, and insect venom allergies, as it avoids bothersome or high-risk provocations. To diagnose AR, the clinical history, along with measurement of sIgE or skin testing is usually sufficient. As these tests are inexpensive, fast, and safe, one may wonder whether there is a place for BAT in diagnosis of AR.[1389]

In HDM sensitive children, BAT has excellent sensitivity (82%–100%) and specificity (96%–100%).[1390] Similar findings were reached in 31 grass pollen sensitive adults: sensitivity 87%–100% and specificity 100%.[1391] In a combined study in 47 children with HDM and/or grass pollen

TABLE X.C.4 Evidence table – correlation between skin testing and in vitro sIgE testing

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Nevis et al.[1252]	2016	1	Systematic review	AR	SPT accuracy	Various factors determine SPT accuracy
Westwood et al.[1331]	2016	1	Systematic review	AR	Microarray results	Utility and cost of microarray testing needs further validation
Gendo et al.[1387]	2004	1	Systematic review	AR	Utility of allergy testing	History and pre-test probability determine allergy testing utility
Knight et al.[1350]	2018	2	Cross-sectional	AR	Concordance between SPT and sIgE	Overall concordance between SPT and sIgE was >70%
Tversky et al.[147]	2015	2	RCT	All subjects	Wheal and flare of various devices	Results of SPT depend on device, technique and control reagents chosen
de Vos et al.[1388]	2013	2	Cross-sectional	AR and asthma	Concordance of SPT and serology	SPT and serology are discordant
Jung et al.[1384]	2010	2	Cross-sectional	HDM allergies	ImmunoCAP versus SPT	Sensitivity and specificity depend on demographics of patients
Pastorello et al.[1385]	1995	2	Cross-sectional	AR	ImmunoCAP versus SPT	Specific IgE accuracy depend on cutoff values
Haxel et al.[1386]	2016	3	Retrospective cohort	AR	Nasal challenge versus SPT versus RAST	Nasal challenge should be performed to confirm eligibility to HDM AIT
Sharma et al.[1269]	2008	3	Cohort	Mouse allergies	RAST versus SPT versus ID	Sensitivity and specificity differ among various tests
McCann et al.[1382]	2002	3	Cohort	AR	SPT measurements	SPT results are not reproducible across centers
Wood et al.[143]	1999	3	Cohort	Cat allergies	RAST versus SPT versus ID	Sensitivity and specificity differ among various tests
Bignardi et al.[1353]	2019	4	Case series	AR	SPT and sIgE	SPT and sIgE are fairly concordant; different sensitivity and specificity depending on the allergen
Nam and Lee[144]	2017	4	Case series	AR	SPT and sIgE	Higher sensitivity and specificity of sIgE than SPT
Tantilipikorn et al.[1281]	2015	4	Case series	AR	ID versus in vitro	ID testing has higher sensitivity and lower specificity than sIgE for HDM
Choi et al.[1383]	2005	4	Case series	HDM allergies	RAST versus SPT	sIgE cutoff level determines sensitivity and specificity
Nelson et al.[1266]	1996	4	Case series	AR to grass	ID versus challenge	ID positive may not be relevant if SPT negative

(Continues)

TABLE X.C.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ansotegui et al.[1251]	2020	5	World Allergy Organization position paper	N/A	N/A	SPT is considered the first-line approach
Steering Committee[1330]	2020	5	World Allergy Organization consensus paper	N/A	N/A	PAMD@ can be important in polysensitized patients

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; HDM, house dust mite; ID, intradermal; LOE, level of evidence; PAMD@, precision allergy molecular diagnostic applications; RCT, randomized controlled trial; RAST, radio allegro-sorbent test; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test.

allergy, sensitivity of BAT for HDM allergy was 90%, with 73% specificity at a cut-off of 12.5% activated basophils, whereas sensitivity for grass pollen was 96%, with 93% specificity at 11% cut-off.[1392] BAT is also able to distinguish between AR based on HDM allergy and irrelevant HDM-sensitization.[1393] For birch allergy, BAT sensitivity was shown to increase after the pollen season compared to placebo.[1394] Results of BAT are valid in both in-season and pre-season measurements.[1395] A more general approach with a mixed group of 30 allergic children with aeroallergen AR or asthma showed increased levels of activated basophils compared to controls[1396] (Table X.C.5).

These studies show that BAT can be used as a diagnostic tool in AR. The usefulness of BAT as evaluation for the effect of treatment (especially AIT) is less clear.

In a very small study with Japanese cedar AR patients, clinical effects were not correlated to BAT outcomes.[1397] In a double-blind RCT with 98 grass pollen sensitive patients receiving sublingual immunotherapy (SLIT) or placebo, there were no differences in BAT outcomes after 2 and 4 months of therapy.[1398] In another study, long-term differences were found between HDM and grass pollen sensitive patients treated with dual SLIT or placebo; basophil activation in the treatment group was significantly decreased after 24 months compared with baseline.[1399] SLIT for Parietaria showed reduced basophil activation in 16 patients after 12 months of treatment.[1400]

For grass pollen subcutaneous immunotherapy (SCIT), some changes were found in BAT outcomes in 16 patients after 9 months of follow-up compared to placebo, but these changes were not correlated to clinical outcomes.[1401] In another study with 50 grass pollen sensitized patients, SCIT gave a clear reduction in BAT outcomes 3–5 years after treatment.[1402] These results were confirmed in a smaller study with 18 patients treated with grass pollen SCIT; here, early changes in BAT outcomes were related to late clinical improvement.[1403]

In HDM-sensitized patients, no apparent changes in BAT outcomes 24 months after SCIT were found, whereas in mugwort-sensitized patients, basophil reactivity was reduced at this timepoint.[1404] Feng et al.[1405] were able to find changes in basophil activation after 2 years of SCIT for HDM in 35 patients. Two months of SCIT in HDM sensitive patients with ($n = 24$) or without ($n = 19$) other sensitizations showed improved clinical scores but increased BAT outcomes, especially in polysensitized patients.[1406] When comparing SCIT and SLIT in grass pollen sensitive patients, both lowered basophil sensitivity compared to controls at 15 months. However, the effect was larger in SCIT.[1407]

The evidence summarized above suggests that BAT is possibly of value in long-term outcomes of AIT and possibly more sensitive in SCIT treated patients. However, the lack of correlation of BAT outcomes to clinical parameters in many studies shows that the application in BAT to evaluate AIT in clinical practice is not obvious.

The studies mentioned above used either CD63 or CD203c positivity as marker for basophil activation. In a small study with 16 SLIT-treated patients, both markers were compared, showing that both were sensitive to treatment, but only CD203c data were correlated to clinical improvement.[1400] Ma and Qiao[1408] used a mixed cohort of 18 children treated for AR showing that both CD63 and CD203c-based BAT correlated to clinical remission of symptoms. This suggests that technical choices in the execution of BAT influence outcomes and usability in practice.

In summary, the role of BAT in the diagnosis and evaluation of AR in clinical practice is limited. In most cases a detailed history with sIgE measurements or skin testing will suffice. In specific cases (e.g., contraindication for skin testing or conflicting results), though, BAT could be considered. The use of BAT to monitor reactivity to treatment is not advised in daily clinical practice.

TABLE X.C.5 Evidence table – use of basophil activation testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mahmood et al.[1394]	2019	2	DBRCT	Blood donors with birch pollen allergy, pre-seasonal supplementation with *Agaricus blazei* murill extract ($n = 27$) or placebo ($n = 27$)	BAT sensitivity to birch allergen	BAT based on CD63 positivity, positive cut-off 10% increase versus baseline Sensitivity to birch allergen in placebo group enhanced after season BAT assay can be used as a sensitivity marker in pollen allergy
Aasbjerg et al.[1407]	2014	2	RCT	40 patients with grass pollen AR treated with SCIT ($n = 15$), SLIT ($n = 15$), or control ($n = 10$)	Changes in serum measurements including BAT	BAT based on CD63 or CD203c positivity SCIT and SLIT lowered basophil sensitivity versus controls; effect larger in SCIT BAT outcomes not correlated to other markers
Kepil Ozdemir et al.[1401]	2014	2	DBRCT	31 patients with grass pollen AR (28 polysensitized) treated with preseasonal SCIT ($n = 16$) or placebo ($n = 15$)	Change in BAT and symptom scores	BAT based on CD203c positivity Activated basophil levels not correlated to clinical outcomes
Swamy et al.[1399]	2012	2	RCT, phase 1	30 AR subjects with HDM and Timothy grass allergy treated with dual SLIT ($n = 20$) or placebo ($n = 10$)	Clinical outcomes and laboratory markers, including BAT	BAT based on CD203c positivity HDM SLIT decreased basophil activation in treatment group at 24 months versus baseline BAT can be useful to monitor changes from SLIT
Van Overtvelt et al.[1398]	2011	2	DBRCT	98 patients with grass pollen AR treated with SLIT or placebo for 4 months	Basophil activation after 2 and 4 months of therapy	BAT based on CD203c positivity No significant changes in basophil activation between groups at any of the time points
Ma and Qiao[1408]	2021	3	Prospective cohort	18 children (aged 3–13 years) with SPT positive AR treated with regular treatment, which could include AIT, until clinical remission obtained	Change of BAT outcomes with clinical remission of complaints	BAT based on CD63 or CD203c positivity CD63: positive basophils before treatment 74.35% (52.0–81.8), after treatment 41.5% (24.5–80.4), $p < 0.05$ CD203c: positive basophils before treatment 69.2% (43.7–81.3), after treatment 42.1% (15.2–81.0), $p < 0.05$ BAT may be used as biological indicator for therapeutic effects

(Continues)

TABLE X.C.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Qiao and Chen[1396]	2021	3	Prospective cohort	Children with AR or asthma ($n = 30$) and healthy controls ($n = 15$), no information on treatment status	Difference in baseline basophil activation	BAT based on CD203c positivity Activated basophils in allergic children 91.1% versus 6.10% in controls, $p < 0.05$
Schmid et al.[1403]	2021	3	Randomized, open prospective	Adults with grass pollen AR treated with SCIT ($n = 18$) or controls ($n = 6$)	Effect of SCIT on BAT outcomes	BAT based on CD63 positivity BAT in SCIT group: 447-fold decrease in basophil sensitivity in first year of treatment, remained 100-fold lower than baseline and 10-fold lower during the follow-up year, $p = 0.03$ Decrease in basophil sensitivity after 3 weeks of SCIT predicted long-term improvement BAT can predict clinical response to SCIT
Feng et al.[1405]	2020	3	Prospective cohort	55 subjects HDM asthma and/or AR; 21 patients under 15 years and 34 adults, SCIT ($n = 35$) and regular treatment ($n = 20$)	Changes in basophil reactivity up to 2 years of SCIT compared to regular treatment	BAT based on CD63 positivity 0.15 μg/ml allergen concentration: basophil activation decreased in the SCIT group from week 16 to 104 15 μg/ml allergen concentration: no changes in SCIT or control group Basophil sensitivity can be used as marker for SCIT efficacy
Zidarn et al.[1393]	2019	3	Prospective cohort	Subjects with positive SPT to HDM with ($n = 17$) or without ($n = 19$) symptoms, and controls ($n = 13$)	Usefulness of BAT to distinguish between AR and irrelevant HDM sensitization	BAT based on CD63 positivity BAT threshold >15%, 3.33 ng/ml in symptomatic patients, 33.3 ng/ml in asymptomatic group BAT can help clinicians to distinguish between HDM-AR patients and asymptomatic subjects
Caruso et al.[1400]	2018	3	Prospective cohort	Patients with AR sensitized to Parietaria by SPT ($n = 26$), receiving SLIT ($n = 16$) or regular treatment ($n = 10$)	Changes in basophil reactivity after 12 months of SLIT compared to regular treatment, relation with symptoms	BAT based on CD63 or CD203c positivity Both CD63 and CD203c BAT showed reduced activation after 12 months of SLIT versus control Symptom reduction only related to reduced basophil activation based on CD203c

(Continues)

TABLE X.C.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim et al.[1404]	2018	3	Prospective cohort	17 patients with sensitivity for HDM ($n = 10$), mugwort ($n = 3$), or both ($n = 4$), receiving SCIT	Changes in basophil reactivity after 12 and 24 months of SCIT	BAT based on CD63 positivity For HDM, no change observed For mugwort, SCIT basophil reactivity was reduced after 24 months of SCIT Basophil response not useful for reflecting clinical response of AIT for HDM and mugwort
Ogulur et al.[1392]	2017	3	Prospective cohort	47 children with AR (± asthma and AD) sensitized to HDM and/or grass pollen, 15 children without atopy (negative SPT)	Performance of BAT to diagnose AR	BAT based on CD63 positivity Cut-off for HDM: 12.5% activated basophils, AUC 0.94, sensitivity 90%, specificity 73%, PPV 0.70, NPV 0.91 Cut-off for grass pollen: 11% activated basophils, AUC: 0.94, sensitivity 96%, specificity 93%, PPV 0.98, NPV 0.88
Soyyigit et al.[1406]	2016	3	Prospective cohort	Adult patients with AR ± asthma, SPT positive for HDM only ($n = 19$) or for HDM and other inhalant allergens ($n = 24$), HDM SCIT versus placebo	Changes in BAT per group (mono/polysensitized) by placebo or SCIT treatment	BAT based on CD203c positivity Polysensitized pts had significantly higher baseline BAT reactivity to 1.6 and 0.16 mg/ml allergen After SCIT, BAT at 1.6 mg/ml of allergen significantly increased in the polysensitized
Zidarn et al.[1402]	2015	3	Non-randomized cohort	50 adult patients with grass pollen AR treated with SCIT ($n = 30$) or regular treatment ($n = 20$), followed 1–2 years after SCIT completion	Changes in BAT	BAT based on CD63 positivity At 0.1 μg/ml grass pollen, baseline versus end of study nonsignificant At 1.0 μg/ml grass pollen: baseline 56.2% (2.6–92.6), end of study 12.1% (0.9–88.6), $p = 0.004$ At 10 μg/ml grass pollen: baseline 89.7% (14.2–100), end of study 67.3% (5.6–96.6), $p = 0.008$ BAT is a possible biomarker for long-term clinical tolerance in AR

(Continues)

TABLE X.C.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Özdemir et al.[1391]	2011	3	Prospective cohort	31 adult patients with seasonal AR for grass pollen without asthma and nine healthy controls	Feasibility of BAT to diagnose grass pollen allergy	BAT based on CD203c positivity At various concentrations of grass pollen extract, BAT distinguishes AR from control, with 100% specificity, sensitivity 87%–100%
González-Muñoz et al.[1390]	2008	3	Prospective cohort	24 children with HDM-based AR and/or asthma, atopic control group of 23 children with HDM negative SPT but positive to other allergens, non-allergic controls	Quality of BAT to diagnose HDM allergy	BAT based on CD63 positivity Best testing parameters for HDM versus atopic controls: at 8% activated basophils as cut-off with 16 μg/ml allergen concentration, AUC: 1.0, sensitivity 100%, specificity 100% Analysis of allergen-induced CD63 upregulation by flow cytometry is reliable for diagnosis of HDM allergy in pediatric patients
Saporta et al.[1395]	2001	3	Prospective cohort	13 adult patients with seasonal AR	Variance of BAT results pre- and in-season	BAT based on CD63 positivity BAT test at the peak of activation higher pre-season than in-season (85.4% [77.2–92.5] vs. 62.2% [58.0–72.8], $p = 0.01$) BAT can be used both pre-season and in-season to diagnose seasonal AR
Nagao et al.[1397]	2008	4[a]	Prospective cohort	9 patients with allergy to Japanese cedar pollen receiving rush SCIT with 12 months follow-up	Effect of rush SCIT on BAT results	BAT based on CD203c positivity Reduction of CD203c expression was found after SCIT in four patients Does not confirm BAT is useful for monitoring all patients

Abbreviations: AD, atopic dermatitis; AIT, allergen immunotherapy; AR, allergic rhinitis; AUC, area under the curve; BAT, basophil activation test; CD, cluster of differentiation; DBRCT, double-blind randomized controlled trial; HDM, house dust mite; LOE, level of evidence; NPV, negative predictive value; PPV, positive predictive value; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test.

[a]LOE downgraded due to very small number of patients.

Basophil activation testing

Aggregate grade of evidence: C (Level 2: 5 studies, level 3: 13 studies, level 4: 1 study; Table X.C.5)
Benefit: May help diagnose AR in specific cases where common approaches are not possible or show conflicting results.
Harm: Discomfort of venipuncture.
Cost: Moderate cost of performing the test, plus venipuncture. Cost depends on the local situation and availability.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: The evidence does not support routine use for the diagnosis of AR or for following AIT response.
Policy level: Option.
Intervention: Application of BAT in specific situations where other diagnostic procedures for AR are not possible or conflicting. Potentially useful for monitoring AIT if other methods fail or show conflicting results.

X.C.6 | Component resolved diagnostic testing

The implementation of molecular allergy diagnostic approach, or PAMD@, is increasingly entering into routine clinical care.[1330] Although PAMD@ may initially appear complex to interpret, with increasing experience, the information gained is relevant and allows improved management of allergic diseases. By measuring sIgE to purified natural or recombinant allergens, PAMD@ allows clinicians to evaluate allergen sensitization at the individual protein level, thus allowing potential identification of disease-eliciting molecules.

In addition to potentially improving diagnostic accuracy, molecular diagnostics (MD) can also aid in distinguishing cross-reactivity phenomena from true co-sensitization and resolving low-risk markers from high-risk markers of disease activity. When compared to diagnosis based on sIgE determination and/or SPT with raw commercial extracts, MD may improve the identification of disease-causing allergen sources and the prescription of AIT.[1330,1409–1412] Changes in AIT prescriptions as a result of MD have demonstrated cost-effectiveness.[1413] A real-life study showed that although SPT was less expensive, MD allowed a more precise prescription of AIT, which substantially reduced treatment costs and the combined costs for diagnosis and treatment.[1414] MD may also aid with risk stratification by identifying certain patterns of sensitization to pollen allergens that are at higher risk of adverse reaction during AIT.[1415,1416] Clinicians should keep in mind that all in vitro test results should be evaluated in context of the clinical history since allergen sensitization does not necessarily imply clinical symptoms.

Patients with a broader polymolecular IgE sensitization pattern to mites, epithelia, and pollen allergens have a trend toward more severe disease and more comorbidities.[51,1417] The presence of IgE antibodies against allergenic molecules may be determined using a singleplex or multiplex measurement platform (ISAC, ThermoFisher-Scientific, Uppsala, Sweden; Alex[2] MacroArray Diagnostics, Vienna, Austria). It should be noted that the results of singleplex and multiplex platforms are not interchangeable, and, in general, sensitivity is higher for singleplex platforms.[1330,1409] Singleplex platforms are quantitative assays and multiplex are semi-quantitative.

In the case of mite sensitivity, Der p 1 and Der p 2 for *D. pteronyssinus* sensitize the majority of mite-allergic patients, with double sensitization to groups 1 and 2 being common.[1418] Recently, Der p 23 has been described also as a frequent allergen and associated with increased asthma risk.[1330,1419] Other good markers of sensitization are Lep d 2 for *Lepidoglyphus destructor* (storage mite, with limited cross-reactivity with other HDMs)[1420] and Blo t 5 for *Blomia tropicalis* (non-Pyroglyphidae mite).[1421] Der p 10 is a tropomyosin, which can cause cross-reaction with tropomyosin from crustaceans (shrimp, crab, lobster) and mollusks (oyster, mussel, scallop), but it is not a marker of sensitization to mites.[1422,1423] A better clinical response to AIT was observed in patients sensitized only to Der p 1 and/or Der p 2, when compared to patients with a broader IgE response.[1424]

In dog allergy, patients display a more complex pattern, with several allergens being recognized by around 50% of patients and 25% of patients being monosensitized to Can f 5.[1425–1428] The pattern of sensitization should be kept in mind since the content of dog allergens in AIT extracts is very heterogeneous.[1429] In the case of cat allergic patients, Fel d 1 is clearly the major allergen, but other allergens also seem important such as Fel d 4 and Fel d 7.[1430–1432] A list of dog, cat, and horse aeroallergens is shown in Table X.C.6.-1.

Allergens related to sensitization to cockroaches are Bla g 1, Bla g 2, Bla g 4, and Bla g 5, although in certain populations, tropomyosins (Bla g 7 and/or Per a 7) can be important.[1433]

Alt a 1 is a major allergen that is recognized in approximately 80%–100% of *Alternaria*-allergic patients.[1434] There

TABLE X.C.6.-1 Mammalian allergens (www.allergen.org)

	Specific component	Percent sensitization	Cross-reactivity
Dog	Can f 1 (lipocalin)[a]	50%–90%	Fel d 7
	Can f 2 (lipocalin)[a]	20%–33%	
	Can f 3 (serum albumin)[a]	25%–59%	70%–80% with other serum albumins
	Can f 4 (lipocalin)	35%–46%	
	Can f 5 (arginine esterase, prostatic kallikrein)	30%–70%; monosensitization 25%	
	Can f 6 (lipocalin)[a]	23%–61%	Fel d 4 and Equ c 1
	Can f 7 (epididymal secretory protein E1)	17%	
Cat	Fel d 1 (secretoglobin)[a]	90%; monosensitization 30%	
	Fel d 2 (serum albumin)[a]	14%–54%	70%–80% with other serum albumins
	Fel d 3 (cystatin)	10%–38%	
	Fel d 4 (lipocalin)[a]	63%; monosensitization 6%	Can f 6 and Equ c 1
	Fel d 5W (IgA)	38%	
	Fel d 6W (IgM)	?	
	Fel d 7 (lipocalin)[a]	38%	Can f 1
	Fel d 8 (latherin-like protein)	19%	
Domestic horse	Equ c 1 (lipocalin)[a]	76%–100%	Can f 6 and Fel d 4
	Equ c 2 (lipocalin)	50%	
	Equ c 3 (serum albumin)[a]	36%	70-80% with other serum albumins
	Equ c 4 (latherin)	77%	
	Equ c 6 (lysozime)	?	

[a]Allergens currently available for molecular diagnosis.

are 23 *Aspergillus fumigatus* allergens, but the main ones are Asp f 1, Asp f 2, Asp f 3, Asp f 4, and Asp f 6, with Asp f 1 being the most important.[1409,1435]

Markers of sensitization to several pollens are summarized in Table X.C.6.-2. Sensitization to profilin has been associated with more severe respiratory symptoms in grass-allergic patients, as well as sensitization to the minor olive allergens Ole e 7 and Ole e 9.[1416,1436] Specific markers of sensitization to grass pollen include IgE antibodies to Phl p 1 and/or Phl p 5. Phl p 6 is contained only in Pooideae grasses and Phl p 4 can be used as a marker of sensitization to non-Pooideae grasses. As allergens from groups 1, 2, 5, and 6 are only expressed in grasses and not in other plants, they detect a genuine sensitization to grasses.[1437]

In summary, PAMD@ in AR can help to better define the sensitization, better predict disease severity, better select patients and allergens for AIT and may predict the efficacy of AIT. However, it is not recommended for routine use in daily clinical practice at this time.

Component resolved diagnostic testing

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 2 studies, level 4: 11 studies, level 5: 1 study; Table X.C.6.-3)
Benefit: Reliable. May help in identification and selection of suitable allergens for AIT, as well as possibly improving safety of AIT.
Harm: Discomfort of venipuncture.
Cost: Moderate cost of testing, minimal cost of venipuncture; depends on local availability.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Molecular diagnosis may be a useful tool for assessment of AR in some scenarios, especially in polysensitized patients.
Policy level: Option.
Intervention: Component resolved diagnostic testing is an option for diagnosis of AR by specialists.

TABLE X.C.6.-2 Pollen allergens

Pollen	Specific components	Percent sensitization[1330]	Cross-reactivity components
Ragweed	Amb a 1 (peptate lyase)[a]	100%	Amb 1 and Art v 6
	Amb a 4 (defensin-like)	20%–40%	Amb v 8 (profilins)
	Amb a 6 (LTP)	20%	Amb v 9 (polcalcins)
	Amb a 8 (profilin)	35%–50%	
	Amb a 9 (polcalcin)	10%–15%	
	Amb a 10 (polcacin)	10%–15%	
	Amb a 11 (cysteine protease)	66%	
Mugwort	Art v 1 (defensin)[a]	95%	Art v 3 (ltps)
	Art v 3 (LTP)[a]	22%–70%	Art v 4 (profilins)
	Art v 4 (profilin)	35%	Art v 5 (polcalcins)
	Art v 5 (polcalcin)	10%–28%	Art v 6 and Amb 1
	Art v 6 (peptate lyase)	26%	
Parietaria, wall pellitory	Par j 1 (LTP)	95%	Par j 2 (ltp)
	Par j 2 (LTP)[a]	80%	Par j 3 (profilins)
	Par j 3 (profilin)	?	Par j 4 (polcalcins)
	Par j 4 (polcalcin)	6%	
Russian thistle or saltwort	Sal k 1 (Pectinesterase)[a]	70%	Sal k 4 (profillins)
	Sal k 4 (profilin)	46%	
	Sal k 5 (Ole-1 like)	30%–60%	
Goosefoot	Che a 1 (trypsin inhibitor)	70%	Chea a 2 (profilins)
	Che a 2 (profilin)	55%	
	Che a 3 (polcalcin)	46%	
Timothy	Phl p 1 (expansin)[a]	95%	Phl p 4 (berberines)
	Ph l p 2 (?)	55%	Phl p 7 (polcalcins)
	Phl p 3 (?)	60%	Phl p 11 (trypsin inhibibitors)
	Phl p 4 (berberine bridge enzymes)[a]	70%	Phl p 12 (profilin)
	Phl p 5 (ribonuclease)[a]	50%–95%	Phl p 5 & Phl p 2 & Phl p 6
	Phl p 6 (?)[a]	44%–75%	
	Ph l p 7 (polcalcin)[a]	10%	
	Ph l p 11 (Ole-1 like)	32%–43%	
	Ph l p 12 (profilin)[a]	15%	
	Ph l p 13 (polygalacturonase)	50%	
Bermuda grass	Cyn d 1 (expansin)[a]	100%	Cyn d 1 and Phl p 1
	Cyn d 4 (berberine bridge enzyme)	100%	
Alder	Aln g 1 (PR-10)	100%	Aln g 1 (PR 10)
	Aln g 4 (polcalcin)	18%	
Birch	Bet v 1 (PR-10)[a]	95%	Bet v 1 (PR10)
	Bet v 2 (profillin)[a]	22%	Bet v 2 (profilins)
	Bet v 3 (polcalcin)[a]	10%	Bet v 4 (polcalcins)
	Bet v 4 (polcalcin)	5%	
	Bet v 6 (isoflavone reductase)	32%	
	Bet v 7 (cyclophilin)	21%	
Olive	Ole e 1 (trypsin inhibitors)[a]	90%	Ole e 2 (profilins)
	Ole e 2 (profilin)	50%	Ole e 3 (polcalcins)
	Ole e 3 (polcalcin)	?	
	Ole e 4 (?)	80%	
	Ole e 5 (superoxide dismutase)	35%	
	Ole e 6 (?)	15%	
	Ole e 7 (LTP)[a]	47%	
	Ole e 8 (polcalcin)	?	
	Ole e 9 (glucanase)[a]	68%	
	Ole e 10 (X8 domain protein)	90%	
	Ole 11 (pectin methylesterase)	?	
	Ole e 12 (isoflavone reductase)	4-33%	

(Continues)

TABLE X.C.6.-2 (Continued)

Pollen	Specific components	Percent sensitization[1330]	Cross-reactivity components
Japanese cedar	Cry j 1 (pectate lyases) Cry j 2 (polygalacturonase)	98% 82%	Japanese cedar, mountain cedar and cypress pollen
Cypress	Cup a 1 (pectate lysases)[a] Cup a 3 (thaumatin-like) Cup a 4 (polcalcin)	100% 50% 10%	Cup a 4 and polcalcins
Ash	Fra e 1 (Ole 1-like)	87%	Fra e 1 and ole e 1
Plane tree	Pla a 1 (invertase inhibitor)[a] Pla a 2 (polygalacturonases)[a] Pla a 3 (LTP)[a]	87% 83% 45%	Pla a 3 (ltp)

Abbreviation: LTP, lipid transfer protein.

[a]Allergens currently available for molecular diagnosis.

X.D | Allergen challenge testing

X.D.1 | Environmental exposure chambers (allergen challenge chambers)

Environmental exposure chambers (EEC) have been used for decades to study the impact of exposures to well-defined atmospheres of a variety of substances such as allergens, particulate and gaseous air pollutants, chemicals, or climate conditions. Valid exposure conditions with high temporal and spatial stability are technically demanding, limiting the number of EECs worldwide. In addition to the opportunity to use EEC for mechanistic studies on the effect of environmental pollutants on human health, it is also an interesting way to do efficacy testing of new drugs by allergen challenge in the chamber setting with induction of symptoms in patients with allergic disease. Presently, there are 15 allergen challenge chamber (ACC) facilities around the globe focusing on allergen exposure.[1451]

Our understanding of the pathophysiology of allergic diseases has been enhanced by ACC studies. A prime example of this is knowledge gained that controlled allergen exposure exacerbates AD.[1452] Also, the impact of exposure with pollen allergen fragments[1453] and the aggravating effect of diesel exhaust particles on AR symptoms have been shown.[955] Furthermore, the importance of the integrity of the epithelial barrier for induction of local and systemic inflammatory responses has been investigated in patients with allergic rhinoconjunctivitis using the ACC setting,[1454] as well as severity phenotypes of allergic asthma and rhinoconjunctivitis.[1455,1456]

The use of ACC in clinical trials for efficacy testing of investigational new drugs and their acceptance by regulatory authorities is peremptorily dependent on the technical and clinical validation of ACCs. ACC have been intensively validated regarding specificity and dose-dependency of symptom induction, as well as technical aspects such as temporal stability and spatial homogeneity of the allergen exposure.[1457–1465] Also, repeatability of outcome measures in the ACC has been systematically investigated and verified for TNSS,[1466] peak nasal inspiratory flow (PNIF),[1467] conjunctivitis symptoms,[1468,1469] and inflammatory nasal biomarkers.[1470] Remarkably, epigenetic changes in peripheral blood mononuclear cells and nasal epithelia after allergen challenge have recently been demonstrated, with baseline epigenetic status predicting symptom severity.[1471] Given the level of technical and clinical validation, ACCs have been used in clinical drug development to study pharmacological properties of new drugs during phase 2 trials, such as optimal dose,[1472–1474] onset of action,[1475–1481] and duration of action.[1482–1484] In this respect, numerous clinical trials have been conducted using parallel-group or cross-over designs in order to test the efficacy of drugs with prophylactic therapeutic potential, such as INCS,[1485–1489] or with immediate therapeutic activity, such as antihistamines.[1490–1496] Novel anti-inflammatory compounds,[1497–1501] drug-free nasal fluids,[1502,1503] and probiotics[1504,1505] have also been tested by this method. Additionally, the efficacy of AIT[1506–1517] and air cleaners[1518,1519] has been tested, as well as the influence of allergic nasal symptoms on the absorption of nasally applied drugs.[1520] Major advantages in the ACC setting compared to field studies are better signal-to-noise ratios, a safeguarded minimum level of symptomatology in the ACC, and reproducibility of symptoms through allergen dose consistency allowing intra-individual comparisons.

A variety of validation studies of allergen atmospheres in ACCs have been published, including grass,[1457,1462] birch,[1458] HDM,[1463,1521,1522] Japanese cypress,[1523] and ragweed.[1524] While regulatory authorities accept the use of ACC in phase 2 of drug development, they have been reluctant to approve them in pivotal phase 3 studies because their clinical validation is still imperfect.[1525–1527] Differences between natural exposure and ACC studies exist, for example, with regards to exposure time (continuous versus intermittent), exposure atmosphere complexity (natural mix versus artificial purity), selection of study

TABLE X.C.6.-3 Evidence table – component resolved diagnostic testing for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Martinez-Cañavate et al.[1438]	2018	2	Observational study	281 children with seasonal AR, positive SPT to olive and grass pollen	sIgE to Phl p 1 + 5, Ole e 1, and Phl p 7 + 12 Composition of AIT	When the molecular diagnosis results were known, specialists altered prescribed AIT in 52.87% of cases
Moreno et al.[1439]	2014	2	Observational study	1263 patients with seasonal AR, positive SPT to grass and olive pollens	sIgE levels to Ole e 1 and Phl p 1 + 5 Comparison before and after obtaining the sIgE results	71.2% of patients positive to Ole e 1 and Phl p 1 + 5 14% positive only to Phl p 1 + 5 12% positive only to Ole e 1 In 56.8% of patients, AIT would be changed based on in vitro data
Stringari et al.[1440]	2014	2	Observational study	651 children with moderate-to-severe pollen-related AR, positive SPT to grass, cypress, olive, mugwort, pellitory, and/or Betulaceae pollen	IgE sensitization to Phl p 1, Phl p 5, Bet v 1, Cup a 1, Art v 1, Ole e 1, Par j 2, and Phl p 12 (profilin) AIT prescription was modeled on SPT responses first and then remodeled considering CRD	After CRD, AIT prescription or composition was changed in 42%
Letran et al.[1441]	2013	2	Observational study	175 patients with a diagnosis of spring pollinosis	SPT In vitro study of the application of a specific recombinant IgE protocol (nOle e 1, rPhl p 1-5b, rPhl p 12, rPhl p 7, and rPru p 3)	Choice of immunotherapy was changed in more than 50% of patients
Nolte et al.[1442]	2015	3	Cohort	1905 subjects screened for a Timothy grass SLIT trial	Serum sIgE measured post hoc by ImmunoCAP ISAC Symptom and medication score during pollen season Adverse events	Trend toward higher efficacy and increased treatment related adverse events in subjects with higher pretreatment Phl p IgE levels
Sastre et al.[1416]	2015	3	Cohort	192 patients with rhinitis and/or asthma sensitized to grass pollen receiving 4-week updosing with five injections	Adverse drug reactions evaluated following EAACI guidelines	Sensitization to Phl p 1 + Phl p 5 or Phl p 1 + Phl p 5 + Phl p 12 significantly associated with a higher frequency of local or systemic reactions ($p = 0.001$)
Rodinkova et al.[1443]	2022	4	Case series	10,651 Ukrainian adults and children with HDM allergy	Pattern of sensitization to individual molecules and geographical location	Simultaneous sensitization to Der f 2 and Der p 2 allergens most common The established pattern of population sensitization to HDM in Ukraine is a good prognostic marker of AIT efficacy

(Continues)

TABLE X.C.6.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Rodriguez-Dominguez et al.[1424]	2020	4	Case series	Patients with HDM allergy undergoing AIT	Serum and nasal secretion samples at baseline, 7, 15, 33, and 52 weeks while undergoing AIT tested for IgE and IgG reactivity to 15 microarrayed HDM allergen molecules	Patients sensitized exclusively to Der p 1 and/or Der p 2 but not to any of the other important HDM allergens (e.g., Der p 5, Der p 7, Der p 21, and Der p 23) showed greater reduction in symptoms after 1 year of treatment (median VAS score reduction of 59.33%) than did patients with additional sensitizations to Der p 5, Der p 7, Der p 21, and/or Der p 23
Arroabarren et al.[1444]	2019	4	Retrospective case series	Patients with HDM-induced respiratory allergy who received AIT extract for at least 3 years	Serum levels of *D. pteronyssinus* components (Der p 1, Der p 2, Der p 10, and Der p 23 and Lep d 2) VAS and/or the Global Score of Combined Rhinitis and Asthma Symptoms and Rescue Medication	No association between the clinical efficacy of AIT based on HDM and sensitization to mite allergens
Chen et al.[1445]	2019	4	Retrospective case series	Patients with HDM allergy treated with AIT in a double-blind placebo-controlled clinical study	Post hoc analysis of serum IgE and IgG reactivity against a comprehensive panel of HDM allergens Respiratory symptoms during controlled HDM exposure in the Vienna Challenge Chamber	Der p 1, Der p 2, and Der p 23 were the most frequently recognized *D. pteronyssinus* allergens AIT performed with HDM extracts inducing IgG antibodies mainly to Der p 1 and Der p 2 was beneficial for patients sensitized exclusively to Der p 1 and/or Der p 2 but not those sensitized to other HDM allergens
diCoste et al.[1446]	2017	4	Case series	36 patients with allergic rhinoconjunctivitis treated with SLIT	sIgE to Phl p 1, 2, 4, 5, 6, 7, 11, and 12 Symptom and medication scores evaluated before and after one year of SLIT	SLIT with a grass pollen is efficacious irrespective of patient's baseline sensitization to either single or multiple grass pollen molecular allergens Patients with few sensitizations have greater improvement in combined symptom and medication score

(Continues)

TABLE X.C.6.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Saltabayeva et al.[1414]	2017	4	Case series	95 patients with pollen-induced allergy	SPT with a local panel of tree pollen, grass pollen, and weed pollen allergen extracts sIgE for marker allergen molecules (nArt v 1, nArt v 3, rAmb a 1, rPhl p 1, rPhl p 5, rBet v 1) Direct and indirect costs	Costs for SPT-based diagnosis lower than the costs for allergen molecule-based sIgE Allergen molecule-based serology was more precise in detecting disease-causing allergen sources
Uriarte and Sastre[1427]	2016	4	Case series	159 patients with rhinitis/asthma sensitized to dog, cat, and horse	sIgE to whole extracts and to pet recombinant allergens	Can f 1 associated with persistent rhinitis Can f 2 associated with asthma diagnosis Can f 3 associated with moderate/severe rhinitis and asthma diagnosis Can f 5 associated with persistent and moderate/severe rhinitis Fel d 2 associated with moderate/severe rhinitis and asthma diagnosis Equ c 1 associated with moderate/severe rhinitis Equ c 3 associated with persistent rhinitis, asthma diagnosis and severe asthma
Darsow et al.[1447]	2014	4	Cases series	Sera of 101 adults with grass pollen allergy	sIgE against Timothy grass pollen: rPhl p 1, rPhl p 2, nPhl p 4, rPhl p 5b, rPhl p 6, rPhl p 7, rPhl p 11, and rPhl p 12 Nasal and conjunctival provocation tests	Increased number of sensitizations to Timothy grass allergens correlated to a positive reaction in the conjunctival (4.9 vs. 3.6, $p = 0.003$) and nasal provocation tests (4.5 vs. 2.2, $p = 0.0175$)
Sastre et al.[1448]	2012	4	Case series	141 patients with allergic rhinoconjunctivitis and/or asthma sensitized to pollen with or without concomitant food allergy	SPT Micro-array-based panel of allergens (ISAC) Indication of AIT and use of allergens following EAACI recommendations, based on clinical history and SPT results before and after obtaining the ISAC results	Agreement in AIT indication before and after ISAC results found in only 46% of patients Very low agreement regarding indication and use of allergens for AIT before and after performing molecular diagnosis

(Continues)

TABLE X.C.6.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tripodi et al.[1449]	2012	4	Case series	200 children with grass pollen AR, asthma, or both ascertained through validated questionnaires	SPT sIgE assays with nine pollen extracts Sera reacting against P pratense were tested for the individual molecules (rPhl p 1, rPhl p 2, rPhl p 4, nPhl p 4, rPhl p 5b, rPhl p 6, rPhl p 7, rPhl p 11, and Phl p 12) sIgE individual sensitization profiles matched against an experimental AIT preparation containing Phl p 1, Phl p 2, Phl p 5, and Phl p 6	Molecular profile of the experimental AIT preparation matched only 4% of patients
Duffort et al.[1450]	2006	4	Case series	Olive pollen extract batches from several suppliers were analyzed	Not applicable	Batches analyzed for Ole e 1 and Ole e 9 content as well as biological activity 10-fold variation between the extreme values was found for the biological activity of the batches analyzed Ole e 1 concentration showed a 25-fold variation Variability of Ole e 9 concentration extremely high, up to 161 times
Schoos et al.[1428]	2021	5	Review	Studies on CRD for pet components published between 1997 and mid-2020	Not applicable	CRD has a role in developing patient-tailored treatment that could reduce health care costs, save time for patients, reduce adverse effects, and improve patient quality of life

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; CRD, component resolved diagnostics; EAACI, European Academy of Allergy and Clinical Immunology; HDM, house dust mite; Ig, immunoglobulin; LOE, level of evidence; sIgE, allergen-specific immunoglobulin E; SLIT, sublingual immunotherapy; SPT, skin prick test; VAS, visual analog scale.

population (all-comers vs. allergen challenge responders), and sample size (higher in field studies than in ACC to achieve comparable statistical power). To promote the implementation of ACC in phase 3 clinical trials, an EAACI initiated task force gathers and evaluates data on their clinical validation. Minimal technical requirements have already been identified.[1528] Hybrid approaches combining ACC and field study might provide proper robustness to determine drug efficacy.[1451,1529]

In summary, numerous well-designed RCTs using technically validated ACCs for efficacy testing of investigational new drugs with detailed analysis of dose–response, onset of action, and duration of action underline the value of ACCs in clinical drug development of AR medicines.

X.D.2 | Local allergen challenge testing

Challenging target organs with allergens could demonstrate reactivity when SPT and/or serum sIgE tests are unconvincing or inconsistent with patient symptoms and exam. NPT and conjunctival provocation test (CPT) may

be used for AR and rhinoconjunctivitis diagnosis, respectively, in these circumstances.[50,1530,1531]

NPT aims to reproduce the upper airway response to nasal allergen exposure.[1532,1533] The only test fulfilling such requirements directly is the EEC; allergens administered during NPT usually exceed the levels of natural exposure. (See Section X.D.1. Environmental Exposure Chambers for additional information on this topic.) NPT can be administered by several devices: syringes, droppers, sprays, or disks, each with limitations.[1532] Positive NPT can be assessed by symptom scales, rhinometry, PNIF, nasal lavage inflammatory markers, and nasal nitric oxide (nNO).[1533] NPT contraindications include acute rhinosinusitis, recent AR exacerbation, history of anaphylactic reactions, severe general diseases (cardiopulmonary diseases with reduced lung capacity), and pregnancy.[1534] Reported sensitivities and specificities of NPT range between 83.7%–93.3.% and 72.7%–100%, respectively (Table X.D.2). A standardized NPT, suggested by Gosepath et al.,[1534] has been defined by the EAACI position paper, although NPT utilization for AR diagnosis may decrease due to emerging tools like molecular allergy diagnostics and BAT.[1389,1535–1537]

The characteristics and safety of NPT were investigated in 518 children and 5830 adults by Eguiluz-Gracia et al.,[49] with 11,499 challenges and only four local adverse reactions noted. Reproducibility, positive and negative predictive values of three consecutive NPT in 710 subjects were 97.32%, 100%, and 92.91%, respectively, with no false-positive results. Comparison between NPT and EEC in patients with cat allergy resulted in similar clinical and immunological responses. The authors suggested that selecting a specific allergen challenge method should depend on the study objectives and costs when investigating cat allergy.[1538] Regarding HDM, Wanjun et al.[1539] studied the relationship between the severity of AR and various diagnostic tests noting that NPT, SPT wheal size, and serum sIgE correlated with each other; only NPT was associated with the nasal symptom severity. Joo et al.[1540] evaluated the EAACI NPT protocol, concluding that standardized NPT could help diagnose AR caused by HDM. Finally, Xiao et al.[1541] found that, in assessing HDM allergic patients' candidacy for AIT, NPT is valuable and safe for confirming the diagnosis before treatment, especially in Der p 1-positive or low sIgE patients.

NPT is crucial in diagnosing occupational rhinitis and LAR. Occupational rhinitis diagnosis requires "objective demonstration of the causal relationship between rhinitis and the work environment through NPT with the suspected agent(s)."[1542] Occupational rhinitis diagnosis is challenging and should be suspected in patients with adult-onset rhinitis; NPT is the gold standard for diagnosis when immunological tests are unavailable or unreliable.[128]

For LAR, the SPT and serum sIgE are negative and diagnosis requires the measurement of local IgE in nasal secretions or a positive NPT.[469] Measuring local sIgE in the clinic is not readily available or practical, making NPT critical. Of note, NPT with HDM, pollens, and *Alternaria* was positive in 100% of 22 adults with previously diagnosed LAR[1543]; however, in 28 children with non-allergic rhinitis, NPT was positive in only 25% of subjects.[474] In another study involving 62 symptomatic patients with negative SPT, the prevalence of LAR to HDM was 24.2%, with sneezing noted as a more dominant symptom in LAR versus non-allergic rhinitis.[1544]

CPT is generally performed by instilling 20–30 μl of an allergen solution into the inferolateral quadrant of the conjunctiva, using a control diluent in the contralateral eye.[1530] A positive CPT response results in a reaction 5–20 min after testing with ocular itching/pruritis, tearing, redness/conjunctival erythema, and possibly edema. A study of 20 children with seasonal rhinoconjunctivitis tested three times with CPT reported good reproducibility.[1545] CPT sensitivity and specificity in HDM-allergic patients were reported as 90% and 100%, respectively.[1546] A systematic review contributed to the EAACI guidelines for the practice of CPT with grade B evidence for identifying the allergen trigger.[1547] It was concluded that allergists should be more familiar with CPT due to its simplicity. However, symptom scales need to be validated, allergen extract standardization should be improved, and CPT indications in patients with non-allergic conjunctivitis remain uncertain. Only one recent trial has been published which assessed a group of children monosensitized to Can f 5 from dogs. Interestingly, reference SPT and CPT demonstrated different reactions to male and female dog extracts, suggesting tolerance to female dogs.[1548]

Local allergen challenge testing (provocation testing)

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 7 studies; Table X.D.2)
Benefit: May assist in confirming diagnosis of AR in specific cases when immunological tests are unavailable or unreliable. NPT is crucial in diagnosing occupational rhinitis and LAR.
Harm: Not necessary if first- and second- line tests are indicative for AR diagnosis.
Cost: Depending on the local situation and availability of equipment and staff, costs may be high.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: The evidence does not support routine use for diagnosis of AR, but provoca-

tion testing is useful for diagnosis of occupational rhinitis and LAR.
Policy level: Option for diagnosis of AR when skin or in vitro tests are equivocal or unreliable. Recommendation for diagnosis of LAR and occupational rhinitis.
Intervention: Application of NPT is useful in LAR and to confirm occupational rhinitis.

X.E | Nasal cytology and histology

Nasal cytology (NC) is a diagnostic procedure that evaluates cell types present in the nasal mucosa.[1553] NC starts with sampling the surface cells of the nasal mucosa; typically with a Rhino-probe (Arlington Scientific, Springville, UT, USA).[1554] [1005] After sampling, staining using the May–Grunwald–Giemsa method allows identification of inflammatory (i.e., eosinophils, neutrophils, mast cells, and lymphocytes) and normal cells (ciliated and mucinous). At least 50 microscopic fields of the slides are then examined through a 1000× optical microscope.[1553] NC may directly detect bacteria, viruses, and fungi, as well as biofilms, demonstrating that biofilm is present not only in infectious rhinitis, but also in inflammatory and/or immune-mediated diseases.[1555] Specific cytological patterns can aid in classifying various forms of rhinitis, including AR, non-allergic rhinitis, and overlapping forms. The predominant cell type assessed by NC in AR is the eosinophil, followed by mast cells and basophils.[1556–1559] Elevated nasal eosinophil counts had an OR of 1.14 (95% CI 1.10–1.18) of identifying AR.[1557] NC in poly-allergic patients showed a more intense inflammatory infiltrate than in mono-allergic patients,[1558] and demonstrated seasonal changes of inflammatory cells, probably due to changes in allergen exposure.[1560]

Studies on NC performance in diagnosing AR or non-allergic rhinitis are limited (Table X.E.-1). In 2021, a study on 387 patients assessed the diagnostic performance of NC showing 100% sensitivity (95% CI 97–100), 49.6% specificity (95% CI 43%–56%); PPV of 56% (95% CI 50%–62%), and NPV of 100% (95% CI 96%–100%) with a non-allergic rhinitis prevalence of 39%.[1561] The accuracy of the test was 69.5% (95% CI 64.6%–74.0%). Such performance does not help to identify when it might be valuable to use, particularly with poor PPV. The ability of the NC to identify subjects affected by non-allergic rhinitis helps the clinician to inform the patient about the possibility or the reason for the low efficacy of the AR therapy in mixed rhinitis. NC has been evolving in the last years, and novel approaches have recently been proposed using nasal scraping to collect samples for measurement of inflammatory mediators and cytokines.[1562,1563]

Nasal histology (NH) was the only technique to study nasal tissues and cells for many decades. Biopsy-based investigations in the 1990s allowed researchers to define the role of the different inflammatory cells in AR.[531] After a tissue sample is taken from the MT, it is placed in buffered formalin and then stained with reagents (Giemsa, hematoxylin/eosin, periodic acid-Schiff, Masson trichrome, azure A, and chloroacetate esterase).[454,1564] The slides are then examined by an optical double-headed light microscope.

NC made it possible to obtain similar information as NH but without the potential risk for bleeding and allowing sequential sampling. Furthermore, following allergen challenge, NC revealed an increase in inflammatory cells not detected by histology; thus suggesting that the nasal secretions, which the NC collects together with the cells, and the nasal mucosa may represent two distinct cellular compartments with different expression of inflammatory cells.[1565] While NH is useful in pathophysiology research, it is hardly feasible for routine clinical use due to the expertise in tissue sampling and biopsy processing required.[1566] Table X.E.-2 shows studies on AR as evaluated by NH.

Nasal cytology

Aggregate grade of evidence: C (Level 1: 1 study, level 3: 3 studies, level 4: 3 studies; Table X.E.-1)
Benefit: Low costs and low invasiveness. Could help to detect eosinophils in non-allergic rhinitis and to diagnose a mixed rhinitis.
Harm: NC is minimally invasive and minimal adverse effects have been reported.
Cost: Associated costs include the direct cost of NC and indirect cost of increased time and effort for performing NC.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: The evidence does not support routine clinical use.
Policy level: Option.
Intervention: NC could help in cases of non-allergic rhinitis to suspect LAR or in cases of AR to diagnose a mixed rhinitis. It could be considered an option in cases of negative SPT and/or serum sIgE to evaluate the presence of mucosal eosinophils and consideration of LAR or type 2 inflammation. The cut-off values for determining NARES are not yet clear.

TABLE X.D.2 Evidence table – provocation testing for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Larson et al.[1538]	2020	2	RCT	Patients with cat allergy: 24 patients: NPT then EEC 12 patients: EEC then NPT 28-day delay between test modalities	TNSS PNIF Expression of cytokine and chemokine genes	EEC showed higher magnitude in TNSS and PNIF than NPT RT-PCR showed type 2 immune response after both types of allergen challenge
Gelis et al.[1549]	2022	3	Cohort	45 patients with shrimp allergy 10 controls	Sensitivity and specificity of NPT by VAS of symptoms Sensitivity and specificity of NPT by acoustic rhinometry	NPT had 90% sensitivity and 89% specificity according to EAACI criteria
Joo et al.[1540]	2021	3	Cohort	13 patients with HDM allergy 13 with non-allergic rhinitis Assessments at 15 and 30 minutes	Sensitivity and specificity of NPT by VAS of symptoms Sensitivity and specificity of NPT by PNIF, MCA, TNV by acoustic rhinometry	Sensitivity and specificity of NPT by VAS ranged 38.5%–100% and 86.4%–100%, respectively Sensitivity and specificity of NPT by PNIF, MCA, and TNV ranged 69.2%–100% and 72.7%–90.9%, respectively; TNV most effective
Eguiluz-Gracia et al.[49]	2019	3	Retrospective cohort	11,499 patients undergoing NPT: 10,963 allergic patients 536 healthy controls	NPT PPV and NPV Reproducibility of NPT Safety of NPT	PPV: 100%, NPV: 92.91% Reproducibility: three consecutive NPTs (710 patients): 97.35% concordance, no difference between spray or micropipette Safety: 4 with palatine pruritus, 2 with uvular edema, 1 with uvular and lingual edema, no lower airway AEs noted
Krzych-Fałta et al.[1550]	2016	3	Cohort	30 patients with aeroallergen allergy 30 controls	Sensitivity and specificity of NPT by optical rhinometry Sensitivity and specificity of NPT by TNSS	TNSS had 93.3% sensitivity and 77.4% specificity, optical rhinometry had 100% sensitivity and specificity for diagnosis of AR
de Blay et al.[1551]	2015	3	Cohort	49 patients with HDM allergy 39 controls	Sensitivity and specificity of NPT-R by clinical symptoms and rhinomanometry Safety	NPT-R had a sensitivity of 83.7% and a specificity of 100% No adverse reactions

(Continues)

TABLE X.D.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jang and Kim[150]	2015	3	Cohort	99 strongly positive SPT 53 weakly positive SPT 110 negative SPT to HDM	Sensitivity and specificity of NPT by acoustic rhinometry Sensitivity and specificity of NPT by TNSS	Diagnosis of AR: TNSS ≥6.5: 90.6% sensitivity, 77.4% specificity Acoustic rhinometry: 73.4% sensitivity, 58.1% specificity
Agarwal et al.[1552]	2013	3	Cohort	11 patients with mold allergy 11 controls	Results of NPT by optical rhinometry	No significant difference between allergic and control subjects

Abbreviations: AR, allergic rhinitis; EAACI, European Academy of Allergy and Clinical Immunology; EEC, environmental exposure chamber; HDM, house dust mite; LOE, level of evidence; MCA, minimal cross-sectional area; NPT, nasal provocation test; NPT-R, rapid nasal provocation test; PNIF, peak nasal inspiratory flow; RCT, randomized controlled trial; RT-PCR, reverse transcriptase polymerase chain reaction; SPT, skin prick test; TNSS, Total Nasal Symptom Score; TNV, total nasal volume; VAS, visual analog scale.

Nasal histology

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 7 studies, level 4: 2 studies; Table X.E.-2)
Benefit: May assist in evaluation of tissue eosinophilia and expression of mediators. May be useful in clinical research.
Harm: Small risk of complications (e.g., bleeding, infection).
Cost: Associated costs consist of the direct cost of NH and indirect cost of increased time and effort for performing NH.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: The evidence does not support routine clinical use.
Policy level: Recommendation against.
Intervention: NH may be helpful in clinical research or selected cases (e.g., evaluation of tissue eosinophils during surgery). Recommendation against in routine clinical practice for AR evaluation due to invasive nature of obtaining a specimen.

X.F | Rhinometry, acoustic rhinometry, and peak nasal inspiratory flow

Subjective measures of nasal obstruction have proven difficult to quantify as patient perceptions vary widely and often do not correlate with examination findings. Therefore, objective measures of nasal obstruction have been developed which measure physiologic parameters (e.g., peak nasal inspiratory/expiratory flow [PNIF/PNEF], airflow resistance or rhinomanometry) and non-physiologic parameters (e.g., nasal cavity cross-sectional area and volume, or acoustic rhinometry). These measures may be utilized pre- and post-decongestion to distinguish between nasal obstruction secondary to dynamic or fixed structural deformities. Objective tests can also be used to assess the effectiveness of interventions or treatments, to provide objective data when clinical examination findings are not consistent with patient symptoms, and to evaluate a response in NPT and as a medicolegal tool.

Rhinomanometry. This involves the objective measure of nasal airflow resistance or the ratio of nasal airway pressure to flow. A clinical classification for five classes of nasal obstruction based on rhinomanometry measures in the reference population has been published by a European group.[1580,1581] Rhinomanometry can be used in adults and children, and normative/reference values exist for both.[1582–1589] However, reference values vary widely as rhinomanometry results depend on factors such as ethnicity, height, sex, smoking status, adenoid tissue, and age.[1584,1590]

Rhinomanometry has certain disadvantages. It is expensive, time consuming and requires trained personnel.[142] Further, rhinomanometry is ineffective in the presence of complete obstruction of one or both nasal cavities or in the presence of a septal perforation.

Traditionally, nasal resistance has been calculated on one single volume value at one single pressure (i.e., 75 or 150 Pa). This is no longer recommended as this represents a portion of the curve where the pressure/volume flux

TABLE X.E.-1 Evidence table – nasal cytology for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
De Corso et al.[1567]	2022	1	Systematic review	26 experimental and clinical studies	Cut-off values of local eosinophil count to determine a diagnosis of NARES	Too much heterogeneity in sampling and cut-off values Eosinophil count should be reported as an absolute value for at least 10 fields
Ciofalo et al.[1561]	2022	3	Cohort	387 patients: 215 with nasal symptoms 172 controls	Diagnostic performance of NC to diagnose NAR	NC for the diagnosis of NAR: sensitivity 100%, specificity 49.6%, PPV 56%, NPV 100%, accuracy 69.5%
Phothijindakul et al.[1568]	2019	3	Prospective cohort	48 NAR patients with negative SPT	Diagnostic performance of NC (vs. NPT with three allergens) to diagnose LAR	Nasal eosinophilia for the diagnosis of LAR: sensitivity 80%, specificity 57.14%, PPV 57.14%, NPV 80%
Di Lorenzo et al.[1557]	2011	3	Cohort	AR, $n = 1107$ NAR, $n = 404$	NC eosinophil count	High eosinophil count had OR of 1.14 (95% CI 1.10–1.18) to identify AR
Gelardi et al.[1558]	2015	4	Case–control	AR patients, $n = 83$: Monosensitized, $n = 35$ Polysensitized, $n = 48$	Comparison of NC cell counts	Higher number of eosinophils ($p = 0.005$) and mast cells ($p = 0.001$) in polysensitized patients
Gelardi et al.[1569]	2014	4	Cohort	Patients with overlapping AR and NAR, $n = 671$	Sneezing in response to nasal endoscopy according to type of rhinitis found on cytology	Significantly higher rate of sneezing in patients with NARES, NARMA, and NARESMA ($p < 0.01$)
Gelardi et al.[1559]	2011	4	Case–control	AR patients, $n = 62$: Mild, $n = 30$ Moderate–severe, $n = 32$	Association of cell counts with ARIA stage of disease	Moderate-severe AR: significantly higher number of eosinophils ($p = 0.01$), mast cells ($p = 0.001$), neutrophils ($p = 0.046$), and lymphocytes ($p = 0.001$)

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CI, confidence interval; LAR, local allergic rhinitis; LOE, level of evidence; NAR, non-allergic rhinitis; NARES, non-allergic rhinitis with eosinophilia syndrome; NARESMA, non-allergic rhinitis with eosinophils and mast cells; NARMA, non-allergic rhinitis with mast cells; NC, nasal cytology; NPT, nasal provocation test; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SPT, skin prick test.

relationship is non-linear and a pressure of 150 Pa is often not achieved in normal relaxed breathing cycles.[1580,1591] To address these limitations, four-phase rhinomanometry (4PR) measures airflow resistance throughout the breathing cycle in four phases: the accelerating inspiratory phase, decelerating inspiratory phase, accelerating expiratory phase and decelerating expiratory phase.[1580,1581] Logarithmic measures taken during 4PR correlate significantly with subjective scores of nasal obstruction.[1592] 4PR overcomes many of the limitations of standard rhinomanometry; however, more studies using and validating 4PR and evaluating nasal cavities individually are required.

Acoustic rhinometry. This is a measure of nasal cavity volume, geometry, and cross-sectional area. Acoustic rhinometry can also localize the site of obstruction. Results of acoustic rhinometry are impacted by septal perforation and therefore, endoscopic examination is vital prior to acoustic rhinometry use. Acoustic rhinomanometry is limited in that it provides a static measure of a dynamic

TABLE X.E.-2 Evidence table – nasal histology in the pathophysiology of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
McHugh et al.[1570]	2020	1	Systematic review	18 studies	Identify and confirm clinical comorbid conditions associated with eosinophilic CRS	Odds of a patient having AR, aspirin sensitivity, asthma, and nasal polyposis significantly higher with increased tissue eosinophilia
Sivam et al.[1571]	2010	2	DBRCT	17 patients with SAR: Mometasone, $n = 10$ Placebo, $n = 7$	Olfactory function Histological analysis of olfactory region	Subjects receiving mometasone showed significantly lower numbers of eosinophils in the olfactory specimens
Uller et al.[1572]	2010	2	DBRCT	21 patients, grass or birch pollen AR: Budesonide, $n = 10$ Placebo, $n = 11$	Mucosal eosinophilia	Placebo: epithelial and subepithelial eosinophilia remained three days after allergen challenge Budesonide: eosinophilia reduced versus placebo
Asai et al.[1573]	2008	2	RCT	19 patients, ragweed pollen AR: AIT, $n = 12$ Placebo, $n = 7$	Allergen-induced CD4+–, CD4+ CD25+–, IL-10–, TGF-β-+ cells in nasal biopsies pre- and post-pollen season	No histologic differences at baseline After pollen season: AIT group had increase in CD4+CD25+ cells versus placebo group and versus baseline
Rak et al.[1574]	2005	2	RCT	41 patients with birch pollen AR: AIT versus budesonide in double-blind double-dummy fashion	CD1a+, IgE+ and FcεRI+ cells before and during birch pollen season	Budesonide showed significantly fewer CD1a+, IgE+, FcεRI+ cells during pollen season compared to preseason and compared to in-season AIT group
Plewako et al.[1575]	2002	2	RCT, single-blind	30 patients with grass pollen AR: Omalizumab, $n = 19$ Placebo, $n = 11$	Anti-CD4, CD8, anti-eosinophil peroxidase, anti-human neutrophil lipocalin, IgE and FcεRI in nasal biopsies	Eosinophil peroxidase-positive staining cells significantly increased in the placebo-treated group but not in the actively treated group
Pullerits et al.[1576]	2001	2	RCT	21 patients with grass pollen AR: Beclomethasone, $n = 16$ Placebo, $n = 5$	IL-16 expression during the pollen season	Prior to pollen season, IL-16 expression significantly higher in AR patients versus controls Pollen season increased IL-16 and CD4+ cells in placebo group, but not beclomethasone group

(Continues)

TABLE X.E.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wilson et al.[1577]	2001	2	RCT	37 patients with grass pollen AR: AIT, $n = 20$ Placebo, $n = 17$	Eosinophils, CD25+, CD3+ and IL-5 mRNA expression in nasal biopsies	400% increase in eosinophils during pollen season in placebo group, 20% increase in AIT group Seasonal increase also observed for CD25+ cells, CD3+ cells, and IL-5 mRNA-expressing cells in placebo group
Radulovic et al.[1578]	2008	4	Case–control	22 patients with grass pollen AR: AIT, $n = 13$ Control, $n = 9$	Foxp3+CD25+ and Foxp3+CD4+ cells in during and out of pollen season	During pollen season, Foxp3+CD25+ and Foxp3+CD4+ cells significantly increased in AIT group versus baseline Out of season, Foxp3+CD25+ and Foxp3+CD4+ cells greater in AIT group versus controls
Till et al.[1579]	2001	4	Case–control	46 patients with grass pollen AR: Fluticasone, $n = 23$ Control, $n = 23$	Nasal mucosal antigen-presenting cells, epithelial CD1a+ Langerhans cells, CD68+ macrophages, CD20+ B cells	Significant increase in CD1a+ Langerhans cells during the pollen season

Abbrevitions: AIT, allergen immunotherapy; AR, allergic rhinitis; CD, cluster of differentiation; CRS, chronic rhinosinusitis; DBRCT, double-blind randomized controlled trial; IgE, immunoglobulin E; IL, interleukin; LOE, level of evidence; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis; TGF, transforming growth factor.

process.[1593] Further, acoustic rhinometry may overestimate the cross-sectional area of the posterior nasal cavity due to leakage into patent sinuses.[1594]

Peak nasal inspiratory and expiratory flow. PNIF/PNEF is a test which carries the advantages of relatively low cost and ease of use. A minimally clinically important difference of 20 L/min has been defined and a lack of improvement of 20 L/min or 20% after decongestion may indicate a structural cause of obstruction.[1595–1597] An SRMA reported mean PNIF values in normal adults of 128.4 and 97.5 L/min for obstructed adults.[1598] However, standardized values have yielded inconsistent results due to multiple confounding factors including patient effort, pulmonary status, nasal valve collapse, smoking, height, and recent physical exercise.[1599,1600] It would appear that PNEF correlates best with symptoms of nasal obstruction.[1601] PNIF/PNEF measures should be supported by subjective measures to improve diagnostic accuracy.[1602]

In summary, many papers have reported a lack of correlation between objective measures of nasal patency and subjective perceptions of nasal obstruction.[1603] Possible reasons for this discrepancy include the failure to accommodate septal deviations and to evaluate individual nasal cavities separately and measuring values at one single pressure rather than the entire breathing cycle. In fact, correlations between objective and subjective measures have been found when nasal cavities were assessed individually.[1592,1603–1606] It has also been shown that patient symptoms do not necessarily correlate with the degree of measured obstruction.[1592,1604,1607] This discordance has been illustrated in studies that applied substances such as menthol or local anaesthetic to the nasal mucosa, resulting in a subjective change in nasal airflow with no corresponding change in resistance.[1608–1614] Therefore, nasal cavity volume, airflow, and resistance may only be a few of many factors contributing to the sensation of nasal obstruction.[1593] Finally, whilst symptoms are paramount, objective measures of the nasal airway are useful beyond correlating with patient symptoms. They are useful in identifying or excluding other causes of nasal obstruction (such as psychiatric or sensory pathology), in nasal aller-

gen challenges, in patient selection for surgery, and in the research setting.[1615]

Rhinomanometry

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 2 studies, level 3: 5 studies, level 4: 4 studies, level 5: 6 studies; Table X.F.-1)
Benefit: 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, use as a medicolegal tool and in nasal allergen challenges. Four-phase rhinomanometry correlates with subjective scores.
Harm: Low. Rhinomanometry has limited effectiveness in patients with complete nasal obstruction or septal perforation. The equipment is not portable and therefore requires a clinic visit and trained staff. The procedure may be considered time consuming.
Cost: High.
Benefits-harm assessment: Benefits outweigh harm.
Value judgments: For some patients, it may be important to avoid unnecessary costs in the diagnosis of AR; therefore, this procedure is less preferred.
Policy level: Option.
Intervention: Rhinomanometry is useful in distinguishing between structural and soft tissue causes of obstruction, when history and examination findings are not congruent, as well as a research tool. Better with individual nasal cavity assessment and 4PR.

Acoustic rhinometry

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 5 studies, level 4: 3 studies, level 5: 2 studies; Table X.F.-2)
Benefit: Improves patient selection for surgery, helps distinguish between structural and functional causes of nasal obstruction, evaluates a response in nasal allergen challenges, and functions as a medicolegal tool to demonstrate objective evidence of effectiveness of an intervention.
Harm: Low. Equipment is not portable therefore, requires a clinic visit and trained staff. Time-consuming. Leakage into sinuses may provide inaccurate results and lead to inappropriate treatment.
Cost: High.
Benefits-harm assessment: Benefits outweigh harm as harm is low.
Value judgments: For some patients, it may be important to avoid unnecessary cost in the diagnosis of AR, and thus acoustic rhinometry is less preferred.
Policy level: Option.
Intervention: Acoustic rhinometry is most useful in research setting as opposed to as a clinical diagnostic tool.

Peak nasal inspiratory flow

Aggregate grade of evidence: B (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study, level 5: 1 study; Table X.F.-3)
Benefit: Can improve patient selection for surgery, can evaluate a response in nasal allergen challenges, and can be used as a medicolegal tool to demonstrate objective evidence of effectiveness of an intervention.
Harm: Low. Risk of missing valve collapse and septal deviation as causes of obstruction.
Cost: Low.
Benefits-harm assessment: Benefits likely to outweigh harm as harm is low.
Value judgments: Relies on patient effort and does not assess individual nasal cavities. Unable to evaluate nasal valve collapse.
Policy level: Option.
Intervention: Use in conjunction with PROMs to improve utility.

X.G | Exhaled nitric oxide

NO is a volatile gas which functions as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator in the airway.[1634] NO is formed in the upper and lower respiratory tract with high concentrations found in the nasal cavity and paranasal sinuses,[1635–1637] and NO synthase is upregulated in ciliated respiratory epithelium and inflammatory cells in atopic patients. In adults, sex, menstrual cycle, pregnancy, recent consumption of high nitrate foods, recent exercise, and tobacco exposure may

TABLE X.F.-1 Evidence table – use of rhinomanometry for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mohan et al.[1593]	2018	1	Systematic review	Studies of nasal obstruction in patients >14 years old using subjective and objective measures, 2012–2017	N/A	No objective measures can be considered criterion standard and are insufficient to assess nasal obstruction
Van Spronsen et al.[1616]	2008[a]	1	Evidence-based review applying GRADE system	Studies evaluating the correlation between RM and subjective measures of nasal obstruction	RM, PNIF, ARM, VAS, questionnaires	RM and PNIF correlate better with subjective measures of nasal obstruction than ARM, AR not specifically assessed
Ta et al.[1617]	2021	2[b]	Systematic review	Patients with sinonasal disorders, including AR	PROMs (VAS, NOSE) and RM	Weak to moderate correlation between RM and PROMs One paper reported a strong correlation between VAS and AAR in AR patients Routine AAR not recommended
Vogt et al.[1618]	2002	2	Cross-sectional	Pooled data from RM tests (not specifically AR patients), $n = 5000$	RM (specifically Reff and VR)	LReff and LVR are normally distributed and correlated with VAS obstruction scores Flow measures at 75 and 150 Pa did not correlate with VAS
Iyer and Athavale[1619]	2020	3	Prospective prevalence cohort	AR, $n = 32$	AAR, spirometry, histamine challenge test	94% of moderate-severe AR had significantly elevated resistance versus 56% of mild AR patients
Pantin et al.[1620]	2019	3	Prospective validating cohort	AR and asthma, AR without asthma, $n = 24$	NAC, cytokines, ARM at 3 cm, RM, FEV_1, TNSS, NSS	No significant association between RM and symptom scores RM had poor-fair reproducibility, not a practical test
Garcia et al.[1605]	2016[a]	3	In vitro prospective cohort	CFD simulations based on 3D CT models, nasal obstruction patients pre- and post-surgery, $n = 15$	ARM and RM, NOSE, VAS (accounting for individual nostrils)	Post-op increase in mCSA accompanied by reduction in resistance, values correlated moderately on the most obstructed side Improvement in objective measures correlated with improvements in subjective patency measures

(Continues)

TABLE X.F.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wong and Eccles[1621]	2014	3[c]	In vitro, non-randomized comparative cross-sectional	Comparison of classic RM versus 4PR in measures of nasal resistance, $n = 4$ models	Nasal airway resistance using classic RM and 4PR	High level of conformity between values using both methods
Canakcioglu et al.[1603]	2009	3	Prospective cohort	7283 adult patients (mean age 31.72 years) with nasal obstruction, including AR ± NSD	AAR at 150 Pa	No difference in airway resistance between AR and non-AR groups if there were no NSDs Resistance higher in all groups with NSD
Brindisi et al.[1622]	2021	4	Case–control	AR or AR+asthma, 6–12 years old, gender matched controls, $n = 160$	nNO, FEV_1, AAR	Significant difference in nasal flow in AR versus controls (lower nasal flow in AR) Mild negative correlation between nNO and mean nasal flow
Hou et al.[625]	2018	4	Prospective case–control	Patients with AR and controls, $n = 106$	VAS, AAR at 75 Pa, nNO, ECP	Nasal resistance is a strong predictor of nasal obstruction and nNO; was also different between nostrils and was higher on the nostril with lower nNO
Wandalsen et al.[1623]	2016	4	Case–control validation	Children with AR undergoing NPT (7–18 years old) and controls, $n = 40$	ARM, RM	Comparing ARM to AAR, a cut-off to end the NPT represented by a reduction of 19%–21% in nasal volume in the first 5 cm had highest sensitivity and specificity
Passali et al.[1604]	2000	4[d]	Prospective cohort	Patients with nasal obstruction, $n = 60$	AAR at 150 Pa, ARM, MCCT, VAS	AAR significantly distinguished AR patients from patients with structural anomalies AAR more reliable than ARM in evaluating patency VAS did not correlate with AAR
Malizia et al.[1624]	2021	5[e]	Narrative review	Studies using RM to diagnose and manage AR in children	Utility of RM as a POCT for the diagnosis of AR in children Eosinophils	Eosinophil number correlated with nasal flow RM supported results of NPT Cost and training for RM require further exploration

(Continues)

TABLE X.F.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Rimmer et al.[1582]	2019	5	Position paper	Papers comparing AAR and 4PR Papers evaluating the correlation between symptoms and RM measures	N/A	VR correlates best with obstructive symptoms No difference in outcomes between 4PR and AAR (need for more studies comparing these methods) Nasal resistance reduces with age and is lower in girls
Valero et al.[1625]	2018	5	Position paper	Patients with nasal obstruction, including AR	Evaluation of nasal obstruction	No agreement on reference values Normal range of values presented Recommend 4PR for parameters that better correlate with subjective measures
Badorrek et al.[1470]	2017	5[f]	Prospective case–control	Patients with AR and controls in pollen challenge chamber, $n = 34$	TNSS and AAR at 150 Pa	TNSS increased and nasal flow reduced in AR patients and not in controls No correlation calculated
Takeno et al.[1626]	2017	5[g]	Retrospective case–control	Patients with AR ± asthma and healthy controls, $n = 119$	FeNO and nNO, symptom severity, AAR at 100 Pa and total resistance	No significant difference in nasal airway resistance across all groups
Demirbas et al.[1627]	2011	5	Expert opinion/literature review		N/A	RM is useful for diagnosis and assessment of treatments RM correlates poorly with subjective findings Single-point measures are not representative of the entire nasal breath 4PR correlates with nasal obstruction

Abbreviations: AAR, anterior active rhinomanometry; AR, allergic rhinitis; ARM, acoustic rhinometry; CFD, computational fluid dynamics; CT, computed tomography; ECP, eosinophil cationic protein; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; GRADE, Grading of Recommendations Assessment, Development and Evaluation; L, logarithmic value; LOE, level of evidence; MCCT, mucociliary clearance time; mCSA, mean cross-sectional area; N/A, not applicable; NAC, nasal allergen challenge; nNO, nasal nitric oxide; NOSE, Nasal Obstruction Symptom Evaluation; NPT, nasal provocation test; NSD, nasal septal deviation; NSS, nasal symptom score; PNIF; peak nasal inspiratory flow; POCT, point of care test; 4PR, four phase rhinomanometry; PROM, patient reported outcome measure; Reff, effective resistance; RM, rhinomanometry; TNSS, Total Nasal Symptom Score; VAS, visual analog scale; VR, vertex resistance.

[a]Paper not included in systematic review.[1617]

[b]LOE downgraded due to failure to include relevant studies and for misclassifying one included study.

[c]LOE downgraded as not blinded and study was in vitro using a nasal model which excludes the elasticity of the human nose which impacts nasal obstruction throughout all phases of nasal breathing.

[d]LOE downgraded as not all patients in the AR group were diagnosed with SPT or RAST.

[e]LOE downgraded as only included 3 studies.

[f]LOE downgraded due to the limited number of patients.

[g]LOE downgraded as retrospective and not blinded.

TABLE X.F.-2 Evidence table – use of acoustic rhinometry for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ta et al.[1617]	2021	2[a]	Systematic review	Patients with sinonasal disorders, including AR	Correlation between ARM and PROMs	Majority (9) studies showed no correlation with PROMs 4 studies showed variable strength of significant correlation In AR patients a weak-moderate correlation with PROMs was found
Eguiluz-Gracia et al.[1628]	2021	3	Validation cohort	AR, non-AR and controls, $n = 1895$	Discriminative power and pre- and post-test predictive power of NAC Optimal cut-off points for positivity NOSS, ARM	ARM differentiated AR from non-AR (sensitivity 99.7%, specificity 100%, PPV 100%, NPV 99.2%) and controls (sensitivity 99.7%, specificity 100%, PPV 100%, NPV 98.9%) ARM better diagnostic accuracy than NOSS
Pantin et al.[1620]	2019	3	Prospective validating cohort	AR with asthma AR without asthma, $n = 24$	NAC, cytokines, ARM at 3 cm, RM (posterior and passive anterior RM), FEV_1, TNSS, NSS	ARM closely associated with symptom scores ARM had excellent reproducibility
Aksoy et al.[1606]	2018	3	Prospective cohort	Children 8–18 years old with seasonal AR, $n = 37$	Hyposmia score, TNSS, nasal obstruction score, ARM and CCCRC tests during and out of pollen season	ARM scores reduced significantly during pollen season Only right sided volume scores correlated significantly with nasal obstruction score No correlations between ARM and TNSS or CCCRC
Garcia et al.[1605]	2016[#]	3	In vitro prospective cohort	CFD simulations based on 3D CT models, nasal obstruction patients pre- and post-surgery, $n = 15$	ARM and RM, NOSE, VAS (accounting for individual nostrils)	Modest correlation between mCSA and VAS on the most obstructed side Critical area beyond which constriction will increase resistance = 0.37 cm^2
Isaac et al.[1629]	2015	3[b]	Cohort	Children with nasal obstruction, 7–14 years old, $n = 65$	Correlation between ARM, symptoms, endoscopic findings VAS	Significant correlations between endoscopic scores and mCSA before decongestion No correlation between mCSA and VAS scores

(Continues)

TABLE X.F.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wandalsen et al.[1623]	2016	4	Case-control validation	Children with AR and controls undergoing NPT, 7–18 years old, n = 40	ARM, RM	Comparing ARM to AAR, cut-off to end NPT represented by reduction of 19%–21% in nasal volume in the first 5 cm had the highest sensitivity and specificity
Wandalsen et al.[1630]	2012	4	Prospective case–control	Children with AR and controls undergoing NPT, 6–18 years old, n = 40	Correlation between AAR (75 Pa) and ARM	Moderate-strong negative correlation in AR patients between nasal resistance and volume and mCSA between 2.2–5.4 cm
Passali et al.[1604]	2000	4[c]	Prospective cohort	Patients with nasal obstruction, n = 60	AAR at 150 Pa, ARM, MCCT, VAS	AR patients had statistically different volumes between left and right nostrils
Valero et al.[1625]	2018	5	Position paper	Patients with nasal obstruction (including AR)	Evaluation of nasal obstruction	ARM better than RM for NPT
Ozturk et al.[1631]	2004	5[d]	Prospective case–control intervention	Children aged 7–18 years with grass pollen AR and age-matched healthy controls, n = 52 Impact of triamcinalone acetonide nasal spray on nasal congestion during pollen season	ARM and PROMs	No association between symptom (congestion) scores and ARM found Paper not included in systematic review[1617]

Abbreviations: AAR, anterior active rhinomanometry; AR, allergic rhinitis; ARM, acoustic rhinometry; CCCRC, Connecticut Chemosensory Clinical Research Center; CFD, computational fluid dynamics; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; LOE, level of evidence; MCCT, mucociliary clearance time; mCSA, mean cross-sectional area; NAC, nasal allergen challenge; NOSE, Nasal Obstruction Symptom Evaluation; NOSS, Lebel nasal ocular symptom score; NSS, nasal symptom score; NPT, nasal provocation test; NPV, negative predictive value; PPV, positive predictive value; PROM, patient reported outcome measure; RM, rhinomanometry; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

[a]LOE downgraded due to failure to include relevant studies and for misclassifying one included study.

[b]Study used unvalidated subjective scoring systems, was not blinded and only 22% of population had AR.

[c]LOE downgraded as no data provided for correlation analysis.

[d]LOE downgraded due to uneven groups.

modify NO levels.[1638] Height and body surface area may also modify NO in pediatric population.[1638–1641]

Fractional exhaled nitric oxide (FeNO). FeNO is a measurement of NO in orally exhaled breath. The American Thoracic Society published recommendations for FeNO measurement.[1642] Briefly, the participant inhales through a NO filter to remove ambient NO. Then exhalation through a flow restrictor results in airflow limitation and creates a positive pressure exhalation, closing the velum and preventing contamination of the measurement with nasal NO. The orally exhaled breath is analyzed.

Although FeNO is highly variable in the healthy population, elevated levels are indicative of various types of inflammation in the respiratory tract. Elevated levels are found in AR, asthma, COPD, bronchiectasis, pulmonary sarcoidosis, and acute lung allograft rejection.[1643] FeNO is primarily utilized in the diagnosis and monitoring of therapeutic response and compliance in asthma,[1644–1647] but recent research has attempted to expand this testing for diagnosis of AR. Small studies have shown increased FeNO in AR patients, especially those with concomitant asthma.[1648–1651] This finding was also seen in a large population study from The Netherlands which showed

TABLE X.F.-3 Evidence table – use of peak nasal inspiratory flow for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mo et al.[1598]	2021	2[a]	SRMA	Studies reporting PNIF values for healthy and obstructed patients	Mean PNIF value in obstructed and unobstructed adult patients	Mean PNIF values for normal adult population 128.4 L/min, and for obstructed population 97.5 L/min
Ta et al.[1617]	2021	2[b]	Systematic review	Patients with sinonasal disorders (including AR)	Correlation between PROMs (VAS, NOSE) and PNIF	Weak correlation between PNIF and PROMs in AR More research required evaluating correlation between PNIF and PROMs
Wong et al.[1602]	2021	3[c]	Cross-sectional, blinded	Rhinitis and control, $n = 256$	PNIF, SNOT-22, VAS	PNIF cut-off of ≤95 L/min diagnostic for AR (72% sensitivity, 80% specificity, 64% PPV, 76% NPV) Diagnostic accuracy of PNIF increased to 97.6% when combined with SNOT-22 or VAS Weak correlation between PNIF and SNOT-22 and VAS
Sikorska-Szaflik and Sozanska[1632]	2020	3	Prospective cohort	Children with AR, $n = 208$	PNIF, QOL (KINDL-R questionnaire)	Strong correlation between PNIF and age, weight, and height Weak negative correlation between PNIF and QOL
Neighbour et al.[1633]	2018	3	Non controlled, non-randomized clinical trial	AR undergoing AIT, $n = 19$	TNSS, PNIF	Modest correlation between TNSS and PNIF
Boelke et al.[1467]	2017[d]	3[e]	DBRCT	Patients with AR, $n = 86$	PNIF in patients in allergy exposure chamber, PROMs	Provocation with allergens resulted in significant reduction in PNIF Changes in PNIF correlated with changes in PROMs
Kirtsreesakul et al.[1597]	2020	4[f]	Prospective cohort	Patients with AR, $n = 100$, 15–60 years old	Symptoms (Likert scale), PNEF, PNIF, NMCCTs before and after decongestion	PNEF improved more after decongestion and had better inverse correlation with NMCCTs than PNIF MCID of PNEF 27.93 L/min and of PNIF 19.74 L/min

(Continues)

TABLE X.F.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Valero et al.[1625]	2018	5	Position paper	Nasal obstruction	Objective measures of nasal obstruction	PNIF correlates with nasal resistance Not useful in the presence of valve collapse or severe obstruction Controversial correlation with VAS Better correlation with SNOT-22 and NOSE scores

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; KINDL-R, generic assessment of health related quality of life for children and adolescents; LOE, level of evidence; MCID, minimal clinically important difference; NMCCT, nasal mucociliary clearance time; NOSE, Nasal Obstruction Symptom Evaluation; NPV, negative predictive value; PNEF, peak nasal expiratory flow; PNIF, peak nasal inspiratory flow; PPV, positive predictive value; PROM, patient reported outcome measure; QOL, quality of life; SNOT-22, Sinonasal Outcome Test (22 item); SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

[a]LOE downgraded due to heterogeneity of included studies.

[b]LOE downgraded due to failure to include relevant studies and for misclassifying one included study.

[c]LOE downgrade due to vague inclusion criteria.

[d]Paper excluded from both systematic reviews.[1598,1617]

[e]LOE downgraded as study involved grass pollen exposure, yet participants were atopic to grass and/or birch pollen and/or HDM.

[f]LOE downgraded due to lack of blinding and significant gender asymmetry.

independent association of elevated FeNO in patients with positive skin testing, eczema, or AR[1643] (Table X.G.-1).

FeNO is positively correlated with symptoms of AR and allergic sensitization in pediatric patients, with one study showing a sensitivity and specificity of 81.1% and 78.6%, respectively, at a FeNO cut-off level of 18.4 ppb.[1641] Pediatric patients also show decreased FeNO after appropriate medical therapy.[1652–1654]

There are potential cofounders when using FeNO as a biomarker. First, a wide variety of normal results for FeNO are possible in a given population and are influenced by age, sex, smoking status, and lab sampling.[1655] Additionally, there is no agreed upon cut off to indicate an abnormal result for the diagnosis of AR versus asthma.[1642]

Nasal nitric oxide (nNO). Due to the non-invasive nature of NO measurement, there is interest in using this tool to differentiate allergic and non-allergic rhinitis. nNO is measured by chemiluminescence. A small catheter is placed into one nostril and ambient nasal gas is measured while the patient orally exhales through a flow resistor tube to ensure the velum is closed and only nasal cavity gas is measured.[1656] nNO is reduced in several rhinologic diseases, including primary ciliary dyskinesia and cystic fibrosis, but is elevated in AR.[1652,1656–1658]

Three small case–control studies have shown significant increase in nNO when comparing non-atopic healthy adults with atopic adults without asthma.[1657,1659,1660] Additionally, two systematic reviews (total $n = 953$ and $n = 4093$, respectively) showed significant increase in nNO in healthy controls versus patients with AR.[1661,1662] However, these results conflict with other small case-control studies showing no difference.[1663–1665] There is a reported nNO increase during pollen season in AR patients,[1660] and reduction after appropriate medical treatment of atopy[1638] (Table X.G.-2).

Various factors influence nNO values including medication use, recent allergen exposure, recent viral respiratory infection, and concomitant asthma. Additionally, there is no standardized application of nNO measurement, with groups performing testing on a variety of analyzers with variations in sampling flow rate and carbon dioxide monitoring.[1666] Even small differences in testing application dramatically changes captured NO, making comparisons across research groups and establishment of normative values challenging.[1656] There is currently no agreed upon cut off point for the diagnosis of AR.

Nitric oxide measurements

Aggregate grade of evidence:

- Fractional exhaled nitric oxide (FeNO): D (Level 4: 7 studies; Table X.G.-1)
- Nasal nitric oxide (nNO): C (Level 2: 2 studies, level 4: 6 studies; Table X.G.-2)

Benefit: Possible benefit in differentiation of allergic and non-allergic rhinitis through non-invasive testing. Possible benefit in monitoring treatment response.

Harm: No studies have shown harm with either exam.

Cost:
- FeNO: Relatively high. FeNO analyzers are approximately $7000–10,000 US, but testing is covered by some insurance plans.
- nNO: High. Chemiluminescence NO analyzers are approximately $30,000–50,000 US, and clinical testing is not covered by insurance in the US.

Benefits-harm assessment: Preponderance of benefit over harm.

Value judgments: There is inconsistent evidence in the ability of FeNO or nNO to differentiate adults and children with AR and non-allergic rhinitis. Most studies were of low evidence or small impact. There is no agreed upon cut-off value when performing FeNO or nNO for the diagnosis of AR.

Policy level:
- FeNO: Recommend against for routine diagnosis of AR.
- nNO: Recommend against for routine diagnosis of AR.

Intervention: History and physical, diagnostic skin testing, or sIgE testing should be the first line evaluation of AR. FeNO or nasal NO testing may provide additional diagnostic information if necessary but should not be routinely employed for AR diagnosis.

X.H | Use of validated subjective instruments and patient reported outcome measures

Validated clinical outcome surveys (VCOS) are simple, effective tools that may be used to evaluate and screen patients with suspected or known AR. They can be helpful in establishing a diagnosis of AR, assessing severity, or evaluating treatment response. Typical survey questions inquire about symptoms such as congestion, rhinorrhea, and sneezing; the questions may be referring to that instant, or to a time period of days or weeks. Although objective testing such as allergy skin testing and sIgE serology can help confirm or rule out the diagnosis, clinical history is indispensable in the evaluation of AR.[1668] In resource-poor settings, SPT, serologic testing, or other advanced technologies may not be available to confirm the diagnosis.[143,1331,1384,1669] Furthermore, VCOS offer a more structured and standardized means of obtaining the clinical history and assessing treatment response.

These PROMs focus on varying aspects of AR.[1670] They may primarily be symptom severity surveys such as the TNSS, or health-related QOL questionnaires such as the RQLQ. Surveys of medication usage (Daily Medication Score), disease prediction (Respiratory Allergy Prediction [RAP]), and disease control (Rhinitis Control Test) are also available. VCOS can be cross-validated with more objective tools such as NPT and SPT. These instruments are routinely utilized in clinical trials as objective, standardized measures to assess the efficacy of AR medications and are widely accepted in the academic allergy and rhinology community.[1671–1676] Recently, VCOS have been adapted for use in smartphone applications that track AR symptomatology and medication use.[1677–1682]

Table X.H.-1 lists several frequently used VCOS, outlining the targeted disease, number of questions, score range, symptoms, and/or medication questions included, and the context in which each is typically employed.[1064,1094,1099,1683–1698] The TNSS is typically administered as a daily survey comprised of only four questions focusing on runny nose, nasal itching, sneezing, and congestion. Some studies have used the TNSS as a reflective score calculated as the average of both the 12-h nighttime and 12-h daytime average (rTNSS). The TNSS can be combined with questions about rescue medication use to yield the Daily Combined Score and the Total Combined Rhinitis Score. Both have been used in many therapeutic intervention studies. The RQLQ is a more comprehensive survey that asks the patient to reflect upon the past week and includes global QOL questions.[1048] It can be administered either in the office or at home so that it may be easier to obtain daily scores. A limitation of this test may be potential recall bias attributable to the 7-day recall period (Table X.H.-2).

The Control of Allergic Rhinitis and Asthma Test (CARAT-10) evaluates rhinoconjunctivitis and asthma symptoms with a recall period of the preceding 4 weeks giving a broader evaluation of seasonal symptom control.[1691] The RAP test is a 9-question survey incorporating upper and lower respiratory queries as well as a question about medication use. It was validated in a study in which primary care physicians used it as a screening tool to determine whether patients needed referral for allergy testing.[1695]

If conjunctivitis is to be assessed simultaneously with rhinitis symptoms, then the Rhinoconjunctivitis Total Symptom Score (RTSS) can be combined with Rescue Medication Score (RMS) to yield the combined score (CS).[1696] The Rhinosinusitis Disability Index (RSDI) was initially developed for CRS, but was validated for AR, non-allergic rhinitis, and nasal obstruction. It has the unique prop-

TABLE X.G.-1 Evidence table – use of fractional exhaled nitric oxide in allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jang et al.[1650]	2020	4	Case–control	Pediatric patients with: Allergic asthma, n = 29 Asthma+AR, n = 38 AR, n = 43 Healthy controls, n = 28	Laboratory evaluation (eosinophil, IgE) SPT Spirometry FeNO	Elevated FeNO in allergic asthma and asthma + AR versus AR and healthy controls No difference in FeNO between AR and healthy controls
Choi et al.[1651]	2011	4	Case–control	Pediatric patients: Asthma, n = 118 AR, n = 79 Healthy control, n = 74	Laboratory evaluation (eosinophils, IgE) Spirometry FeNO	Elevated FeNO in asthma and AR versus healthy controls FeNO positively correlated to total IgE, number of positive SPTs, and peripheral eosinophils
Bencova et al.[1648]	2009	4	Case–control	Atopic individuals without asthma, n = 79 Non-atopic controls, n = 54	FeNO in pollen season FeNO out of season FeNO off and on medical therapy	Atopic individuals had elevated FeNO out of pollen season versus controls FeNO in atopic individuals increased in allergy season FeNO decreased with topical steroid and oral antihistamine treatment
Hervas et al.[1667]	2008	4	Case–control	Healthy children Asymptomatic atopy AR without recent exacerbation AR with one exacerbation in last month Allergic asthma without rhinitis Allergic asthma with rhinitis All groups, n = 15	Allergy sensitization FeNO Spirometry	All groups had statistically higher FeNO versus controls FeNO higher in patients with active AR, allergic asthma without rhinitis, and allergic asthma and rhinitis versus asymptomatic atopy and AR without recent exacerbation
Van Asch et al.[1643]	2008	4	Cohort	Netherlands birth cohort, 1982–1983 Participants examined at age 21, n = 361	Atopic status: history of asthma, allergy, eczema Medication use Spirometry FeNO	History of eczema, AR, smoking, atopic sensitization positively correlated with elevated FeNO Median FeNO higher in atopic asthma and eczema versus control
Franklin et al.[1641]	2003	4	Cohort	Australian birth cohort Participants examined at age 11, n = 155	Spirometry FeNO Eosinophils SPT	Elevated FeNO in children with asthma, atopy, recent wheeze versus controls FeNO >18.4 ppb had 81.1% sensitivity and 78.6% specificity for diagnosis of AR

(Continues)

TABLE X.G.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Martin et al.[1659]	1996	4	Case–control	Atopic individuals without asthma, *n* = 32 Non-atopic controls, *n* = 18	FeNO Nasal NO	Atopic individuals had higher FeNO in baseline oral breathing, breath-holding 10 s, breath-holding 60 s, and nasal breathing

Abbreviations: AR, allergic rhinitis; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; LOE, level of evidence; NO, nitric oxide; SPT, skin prick test.

erty of evaluating sexual function in AR patients.[1697,1698] The SNOT-22 has also been validated for use in AR patients.[1051]

In summary, VCOS are simple, effective tools that may be used to assist in making the diagnosis of AR, and in evaluating the efficacy of various therapies.

Use of validated subjective instruments and patient-reported outcome measures

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 2 studies, level 3: 5 studies, level 4: 13 studies; Table X.H.-2)
Benefit: Validated surveys offer a simple point-of-care option for screening and tracking symptoms, QOL, and control of allergic disease.
Harm: Minimal. Time to complete survey. Potential risk of misdiagnosis when based on survey data alone.
Cost: No financial burden to patients. Some fees associated with validated tests used for clinical research.
Benefits-harm assessment: Preponderance of benefit over harm. Risk of misdiagnosis leading to unnecessary additional testing. Likewise, there is a risk that false negative responses may lead to delay in testing and further management.
Value judgments: Validated surveys may be used as a screening tool and primary or secondary outcome measure.
Policy level: Recommendation.
Intervention: Validated surveys may be used to screen for AR, follow treatment outcomes and as a primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathological scenarios.

XI | MANAGEMENT

XI.A | Allergen avoidance and environmental controls

XI.A.1 | House dust mites

HDMs are a common trigger for AR.[1702] Therefore, reducing exposure to HDM through physical barriers and chemical treatments are potentially important options in the management of AR[1702–1706] (Table XI.A.1).

Physical techniques for HDM reduction, including heating, ventilation, barrier methods, air filtration, vacuuming, and ionizers, have shown inconsistent results for the treatment of AR.[1707–1713] While several interventions have reduced the concentration of environmental HDM antigens,[1707–1711] an associated improvement in clinical symptoms has not been reliably demonstrated. Ghazala et al.[1707] and Terreehorst et al.[1711] demonstrated a reduction in HDM antigen concentration with impermeable bedding as an isolated intervention but found no clinical benefits. Similar findings were reported by Antonicelli et al.[1714] following a trial of high-efficiency particulate air (HEPA) filtration.

Acaricides in household cleaners have been utilized as a chemical technique to reduce HDM concentration. Geller-Bernstein et al.[1715] evaluated an acaricide spray in the bedrooms of patients with HDM sensitization, demonstrating improved mean symptom scores versus control patients without acaricide. Similar findings were reported by Kneist et al.[1708] Using a crossover study design, Chen et al.[1716] investigated an acaricide containing bag placed beneath bed mattresses in children with AR and asthma, reporting improved AR symptom scores and disease specific QOL (measured using the RQLQ) for those in the intervention group compared to control.

Overall, no serious adverse effects were reported from the evaluated interventions. None of the studies evaluated cost-effectiveness.

Recent findings, as well as a 2010 Cochrane review[1717] suggest acaricides, either as a single measure or in combination with other measures, are the most effective

TABLE X.G.-2 Evidence table – use of nasal nitric oxide in allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wang et al.[1662]	2021	2	SRMA	Studies that measured nNO in AR and healthy control patients	nNO in AR, NAR, and controls Multiple subgroup comparisons including NO analyzer type, sampling technique, flow rates	9 studies showed significantly higher nNO in AR versus control and NAR 4 studies listed cut-off values to discriminate between AR and healthy controls
Ambrosino et al.[1661]	2020	2	SRMA	Studies that measured nNO in AR and healthy control patients	nNO via aspiration method in AR and controls nNO via exhalation method in AR and controls	30 studies showed significantly higher nNO using aspiration method 12 studies showed significantly higher nNO using exhalation method
Kalpaklioglu et al.[1660]	2021	4	Case–control	AR, $n = 337$ NAR, $n = 106$	TNSS nNO during pollen season and during off season	AR had significantly higher nNO levels versus NAR nNO significantly increased during pollen season in allergic patients
Lee et al.[1657]	2012	4	Case–control	AR, $n = 35$ Healthy controls, $n = 34$	nNO FeNO Laboratory evaluation (eosinophils, IgE)	nNO significantly higher in AR FeNO significantly higher in AR
Moody et al.[1664]	2006	4	Case–control	Perennial AR Non-atopic subjects	Validated symptom questionnaire FeNO nNO	nNO levels were not elevated in subjects with perennial AR versus non-atopics nNO was higher in HDM and cat allergic subjects
Maniscalco et al.[1663]	2001	4	Case–control	Topical administration of NO-synthase inhibitor to determine effect on nasal airway resistance: Non-atopic controls, $n = 9$ Seasonal AR, $n = 7$	nNO concentration measured pre/post NO-synthase inhibitor Nasal airway resistance	Baseline nNO concentration in AR was not significantly different from control group
Henriksen et al.[1665]	1999	4	Case–control	Pediatric patients with: Seasonal AR, $n = 19$ Perennial AR, $n = 27$ Healthy controls, $n = 12$	Spirometry nNO and FeNO	FeNO was significantly higher in AR children versus controls nNO was not different in AR versus controls
Baraldi et al.[1654]	1998	4	Case–control	Pediatric patients with: AR, $n = 21$ Healthy controls, $n = 21$	nNO at baseline nNO after 10 days of topical steroid or topical antihistamine	nNO significantly higher in AR versus controls Topical steroid significantly decreased nNO No difference in nNO with antihistamine

Abbreviations: AR, allergic rhinitis; FeNO, fractional exhaled nitric oxide; HDM, house dust mite; IgE, immunoglobulin E; LOE, level of evidence; NAR, non-allergic rhinitis; nNO, nasal nitric oxide; NO, nitric oxide; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score.

TABLE X.H.-1 Validated surveys used to diagnose AR or evaluate disease severity and treatment

Survey	Disease targeted	Number of questions	Symptom questions	Medication questions	Scoring range	Comments and indications
TNSS: Total Nasal Symptom Score	AR	4	Yes	No	0–12	Simple daily symptom score to evaluate AR severity and control; used in clinical trials
DMS: Daily Medication Score	AR, AC, asthma	Varies	No	Yes	0–36[a]	Varies depending on medication scoring
DCS: Daily Combined Score	AR, AC, asthma	Varies	Yes	Yes	0–48[a]	Combined symptom and medication score for clinical trials
TCRS: Total Combined Rhinitis Score	AR	Varies	Yes	Yes	0–24[a]	The sum of the combined symptoms medication scores
Mini-RQLQ: Mini-Rhinoconjunctivitis Quality of Life Questionnaire	Rhinoconjunctivitis	14	Yes	No	0–84	Shortened version of RQLQ often used in clinical trials
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire	Rhinoconjunctivitis	28	Yes	No	0–168	Reflective assessment of previous week's symptoms; often used in clinical trials
RhinAsthma (RhinAsthma children also available)	Rhinitis, asthma	30	Yes	No	120	Able to differentiate patients with rhinitis from those with both rhinitis and asthma
VAS: Visual Analog Scale	Rhinitis	1 or more	Yes	No	0–10 cm	Tool may be used to evaluate multiple symptomatology
RCAT: Rhinitis Control Assessment Test	AR, NAR	6	Yes	No	6–30[b]	Self-assessment of rhinitis symptom control
ARCT: Allergic Rhinitis Control Test	AR	5	Yes	Yes	5–25[b]	Self-assessment of ongoing AR symptoms control
CARAT-10: Control of Allergic Rhinitis and Asthma Test; CARATKids available for children	AR, NAR, asthma	10	Yes	Yes	0–30[b]	Used to compare groups in clinical trials
ACS: Allergy Control Score	Rhinitis, AC, asthma	10+ meds	Yes	Yes	0–60	Combined tool used for clinical trials and daily clinical practice
RC-ACS: Rhinoconjunctivitis Allergy Control Score	Rhinitis, AC	7+ meds	Yes	Yes	0–42	Similar to ACS but without asthma related questions
RAP: Respiratory Allergy Prediction	AR, asthma	9+ meds	Yes	Yes	0–9	Used to determine the need for referral and additional testing
SFAR: Symptom Score for Allergic Rhinitis	AR	8	Yes	No	0–16	Weighted score used to detect prevalence of AR
RMS: Rescue Medication Score	Rhinoconjunctivitis	Meds	No	Yes	0–3	Evaluates medication use only

(Continues)

TABLE X.H.-1 (Continued)

Survey	Disease targeted	Number of questions	Symptom questions	Medication questions	Scoring range	Comments and indications
RTSS: Rhinoconjunctivitis Total Symptom Score	Rhinoconjunctivitis	6	Yes	No	0–18	Evaluates symptoms only
CS: Combined Score	Rhinoconjunctivitis	6+ meds	Yes	Yes	0–3	Combined scores of RTSS/6 + RMS/2
RSDI: Rhinosinusitis Disability Index	AR, CRS, NAR	30	Yes	No	0–120	Physical, function, emotional subscales and total scores
SNOT-22: Sinonasal Outcome Test, 22-item	CRS, AR	22	Yes	No	0–110	Includes rhinologic and non-rhinologic domains
Global Assessment: Global Assessment of Severity of Allergy	Total nasal and non-nasal symptoms	1	Yes	No	1–7	Single question about rhinitis severity

Abbreviations: AC, allergic conjunctivitis; AR, allergic rhinitis; CRS, chronic rhinosinusitis; NAR, non-allergic rhinitis

[a]Maximum score may vary depending on specific number of symptom related questions and specific medication score included.

[b]Higher score equates to better control of disease. A score of 0 denotes zero control of symptoms.

intervention for reducing HDM levels and improving AR symptoms.

Allergen avoidance and environmental controls – house dust mite

Aggregate grade of evidence: B (Level 1: 2 studies, level 2: 12 studies; Table XI.A.1)

Benefit: Potential improvement in AR symptoms and QOL with reduced concentration of environmental HDM antigens.

Harm: None.

Cost: Low to moderate. However, cost-effectiveness was not evaluated.

Benefits-harm assessment: Benefit outweighs harm.

Value judgments: There is supporting evidence for the use of acaricides in reducing HDM concentration in children who have AR coexistent with asthma. In adults and children without concomitant asthma, the use of acaricides with/without bedroom-based control programs for reducing HDM concentration are promising, but further, high-quality studies are needed to evaluate clinical outcomes.

Policy level: Option.

Intervention: Acaricides used independently or alongside environmental control measures, such as air filtration devices, could be considered as options in the management AR.

XI.A.2 | Cockroach

Measures to control cockroach allergen concentrations within the home environment have been targeted at eliminating infestations and abating cockroach allergen. The three main intervention strategies used are: (1) education-based methods consisting of house cleaning measures and sealing cracks and crevices in highly infested areas; (2) physical methods using insecticides or bait traps; and (3) treatments combining education-based interventions with physical methods.[1720] The greatest challenges in controlling cockroach infestation and reducing allergen concentrations are in densely populated inner-city areas that contain multi-occupant housing.[1721,1722]

Most studies contain one or more interventions focused on German cockroach (Blattella germanica antigen 1 and 2 [Bla g 1, Bla g 2]) allergen levels,[1723–1731] however some studies included treatments targeted at reducing multiple allergens (e.g., HDM, cockroach, rodent, cat, and dog).[1732,1733] The majority of studies were RCTs designed to evaluate the efficacy of specific environmental control measures in reducing environmental allergens. These studies used a variety of interventions that included home-based education as well as physical methods such as pest control and insecticides.[1723–1728,1732,1733] Although Bla g 1 and Bla g 2 allergen levels were reduced below 8 U/g in some homes, clinical benefits in sensitized individuals were not achieved.[1724,1727–1730] One study found Bla g 1 concentrations could be decreased below targeted thresholds for most apartments using a building-wide cockroach control program[1731] (Table XI.A.2).

TABLE X.H.-2 Evidence table – use of validated clinical outcome surveys for the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Calderon et al.[1045]	2019	1	Systematic review	AR	Combined symptom-medication score for evaluating efficacy of AIT	Symptom scores have not been extensively validated No publications describing the validation of medication score Disease control scales extensively validated in AR but have disadvantages as primary efficacy criteria in clinical trials
Calderon et al.[1675]	2014	1	Systematic review	Seasonal AR	Comparison of scoring systems used in clinical trials investigating SLIT efficacy for seasonal AR	Multiple differences in trial scoring methods/design, making comparison difficult
Fonseca et al.[1691]	2010	2	Cross-sectional	Adults with AR and asthma	CARAT-10, medical evaluation ACT, VAS	CARAT-10 has high internal consistency and good concurrent validity, making it useful to compare groups in clinical studies
Annesi-Maesano et al.[1688]	2002	2	Cross-sectional	AR confirmed by physician & SPT Individuals by telephone interview	SFAR	SFAR value ≥7 allowed satisfactory discrimination between AR from those without (sensitivity 74%, specificity 83%, PPV 84%, NPV 74%)
Sousa-Pinto et al.[1680]	2021	3	Cohort	17,780 app users with AR	Daily VAS assessed in app and concurrent validity was assessed by correlation with EQ-5D, CARAT, and WPAI-AS	Concurrent validity was moderate-high Intra-rater reliability intraclass correlation coefficients ranged between 0.870 (VAS of global allergy symptoms) and 0.937 (VAS of allergy symptoms on sleep)
Bedard et al.[1677]	2019	3	Cohort	9121 AR patients in 22 countries	Mobile phone app daily VAS for: Overall allergic symptoms Nasal, ocular, asthma symptoms Work Medications	Confirms the usefulness of app in accessing and assessing behavior in patients with AR

(Continues)

TABLE X.H.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Galimberti et al.[1695]	2015	3	Cohort	AR, AC, asthma	Evaluation of RAP test used by PCPs to suggest allergy	RAP test is valid for screening allergic disease RAP test is useful for physicians other than allergists when evaluating rhinitis, suggesting need for allergy testing
Devillier et al.[1690]	2014	3	Cohort	806 children, adolescents and adults with grass-pollen-induced ARC	MCID of RTSS	RTSS versus RQLQ showed MCID of 1 MCID of RTSS determined with anchor-based methods (using the GRCS and the RQLQ) and a distribution-based method
Demoly et al.[1099]	2013	3	Cohort	902 AR pts	Self-assessment global score for AR control (five items scored from 1 to 5 assessing the rhinitis over the 2 previous weeks)	Self-assessment score for AR control was sensitive to change and correlated to the clinical expression of rhinitis Suggests self-completion questionnaire could be used to determine level of AR control
Fasola et al.[1064]	2020	4	Case series	Children with comorbid asthma and rhinitis	RAPP-children, RHINASTHMA, PAQLQ, CACT, KiddyKindl, VAS	RAPP-children is a valid, five-item questionnaire for assessing HRQOL in children 6–11 years with concomitant asthma and rhinitis
Glattacker et al.[1678]	2020	4	Case series	App users with pollen AR	Usability and changes in QOL, health literacy, and self-efficacy obtained through an app in Germany	Perceived subjective improvements due to the app: 55.9% reported being better informed about their allergy 27.3% noted improved QOL 33.6% reported better coping with their allergy 28.0% felt better prepared for physician consultation
Husain et al.[1051]	2020	4	Case series	Patients with AR	SNOT-22, EQ-5D, RCAT	SNOT-22 reliable and responsive in patients with AR

(Continues)

TABLE X.H.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kupczyk et al.[1699]	2020	4	Case series	Patients with asthma and rhinitis	Polish RAPP, SF-12, ACT, VAS, GRS	Confirmed reliability and validity of the Polish version of RAPP, useful tool in the assessment of HRQOL in patients with asthma + AR
Tosca et al.[1693]	2020	4	Case series	Children and adolescents from 3 allergy centers	CARAT, CARATkids, ACT, CACT, GINA disease control classification, VAS; and lung function	CARAT and CARATkids are disease-control measurements that give additional information to other tests
Werner et al.[1700]	2018	4	Case series	Asthma patients with and without AR	CARAT-10,ACQ, ACT, AQLQ(S)	German version of the CARAT-10 is an acceptable, reliable, and valid tool Recommended use in asthma patients with AR
Bousquet et al.[1679]	2017	4	Case series	1136 app users	VAS-global, VAS-nasal, VAS-ocular, VAS-asthma, VAS-work	Significant correlation between VAS-global and VAS-work Significant correlation between VAS-work and WPAI-AS
Emons et al.[1701]	2017	4	Case series	6–18 years old with asthma ± AR	CARATkids, ACT, VAS	CARATkids questionnaire is a reliable and valid tool to assess AR and asthma control among Dutch children; can also be used in adolescents
Devillier et al.[1676]	2016	4	Case series	AR: children, adolescents, and adults	RTSS, VAS, RQLQ	Although symptom perception differed in children versus older patients, assessments of treatment outcomes (RTSS, VAS, RQLQ) similar in all age groups VAS correlated well with the weekly mean RTSS and correlated moderately with the weekly mean RQLQ
Meltzer et al.[1686]	2013	4	Case series	AR, non-allergic rhinitis	RCAT, TNSS, Physician's Global Assessment	RCAT demonstrated adequate reliability, validity, and responsiveness; deemed acceptable and appropriate by patients

(Continues)

TABLE X.H.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hafner et al.[1683]	2011	4	Case–control	121 subjects: 81 with ARC 40 controls	ACS, pollen counts, global allergy severity, QOL, allergy-related medical consultations	Significant correlation between ACS and global allergy severity, QOL, and allergy-related medical consultations ($p < 0.0001$); scores were highly related to pollen counts ACS showed a good retest reliability and discriminated between patients with allergy and healthy controls (sensitivity 97%, specificity 87%)
Bousquet et al.[1689]	2007	4	Case series	AR categorized according to ARIA guidelines	VAS, RQLQ	A simple and quantitative method (VAS) can be used for the quantitative evaluation of severity of AR
Baiardini et al.[1692]	2003	4	Case series	148 consecutive patients: 46 asthma 53 ARC 49 asthma + ARC	RHINASTHMA	RHINASTHMA differentiates patients with rhinitis from those with rhinitis + asthma In stable condition, RHINASTHMA showed good reliability

Abbreviations: AC, allergic conjunctivitis; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AIT, allergen immunotherapy; AQLQ, Asthma Quality of Life Questionnaire; app, application; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; CACT, Childhood Asthma Control Test; CARAT, Control of Allergic Rhinitis and Asthma Test; EQ-5D, Euro-QOL 5-dimension questionnaire; GCRS, global rating of change scale; GINA, Global Initiative for Asthma; GRS, global rating scale; HRQOL, health related quality of life; LOE, level of evidence; MCID, minimal clinically important difference; NPV, negative predictive value; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PCP, primary care provider; PPV, positive predictive value; QOL, quality of life; RAP, Respiratory Allergy Prediction; RAPP, RhinAsthma Patient Perspective; RCAT, Rhinitis Control Assessment Test; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, Rhinoconjunctivitis Total Symptom Score; SF-12, 12-item Short Form Survey; SFAR, Score For Allergic Rhinitis; SLIT, sublingual immunotherapy; SNOT-22-Sinonasal Outcome Test (22 item); SPT, skin prick test; TNSS, Total Nasal Symptom Score; VAS, visual analog scale; WPAI-AS, Work Productivity and Activity Impairment Allergic Specific Questionnaire.

The most effective treatment for eliminating infestation and reducing allergen load was professional pest control.[1725] In one study that monitored cockroach populations and allergen concentrations over a 12-month period, findings revealed that insecticide bait traps placed by professional entomologists were more effective in reducing cockroach populations and cockroach allergen compared to dwellings that received numerous commercial applications of insecticide formulations to baseboards, cracks, and crevices.[1723] Bait traps, including labor and monitoring costs, were estimated to be less expensive than commercially applied insecticide sprays.[1723] The expense of integrated home management that consists of professional cleaning, education, and pest control was not found to be cost-effective. Thus, most investigators focused on assessing the efficacy of single interventions, such as extermination alone, in assessing potential cost benefits.[1725,1734] Arbes et al.[1725] and Sever et al.[1734] have noted that these measures were not found to be cost effective. Detailed information may be found in their publications, as this discussion was beyond the scope of this section. Families often had difficulty adhering to home-based intervention regimens over the course of the study, which reduced the efficacy of these treatments and subsequently resulted in increased cockroach allergen levels.[1728]

Although cockroach count could be significantly reduced in single-family homes using bait traps, reinfestation and high allergen levels remained an ongoing problem in multi-family buildings.[1730] Effectively controlling cockroach infestation and allergen levels within multi-family buildings and apartments requires implementation of a building-wide management program.[1731] Thus, it is difficult to dramatically reduce cockroach allergen levels in the home unless a significant reduction

TABLE XI.A.1 Evidence table – allergen avoidance: house dust mite

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Nurmatov et al.[1702]	2012	1	SR of RCTs	HDM impermeable bedding, 4 studies Acaricides, 2 studies HEPA filtration, 2 studies Acaricides and HDM impermeable bedding in isolation and combination, 1 study	HDM load Symptom scores Medication scores Disease-specific QOL	Environmental controls significantly reduced HDM load Acaricides most effective single method Combination therapies more effective than single interventions and may offer symptom relief
Sheikh et al.[1717]	2010	1	SR of RCTs	RCTs examining the effectiveness of environmental measures for HDM	Symptoms	Acaricides are the most effective method as a single measure or in combination with other measures to decrease HDM and improve symptoms
Chen et al.[1716]	2021	2	Randomized, double-blind, cross-placebo trial	Children with AR+asthma, acaricide containing bag under bed mattress, $n = 25$ Children with AR+asthma, placebo bag under bed mattress, $n = 25$	Symptom scores HDM concentration Disease specific QOL Adverse events	Acaricide group: improvement in rhinitis symptoms, QOL scores versus placebo group; decline in HDM antigen was reportedly "more obvious" No severe adverse events reported
Jeon et al.[1713]	2019	2	Single-blind parallel RCT	Children with AR, daily vacuuming of room and bed mattress, $n = 20$ Children with AR, daily vacuuming of room only, $n = 20$	Symptom scores Vacuum dust weight HDM (Der p 1 and f 1) concentration	Symptoms were lower in the intervention group after the 2-week trial Weight of dust collected was less for the intervention group Concentrations of Der p 1 and f 1 did not change in either group
Berings et al.[1712]	2017	2	Pilot, double-blind, crossover RCT	Adults with AR and probiotic impregnated bedding, $n = 20$ Adults with AR and placebo bedding, $n = 20$	HDM (Der p 1) concentration Symptom scores QOL scores Use of reliever medication	No difference in HDM levels between intervention and placebo bedding Differences in secondary outcome measures between intervention and placebo not significant
Stillerman et al.[1718]	2010	2	Double-blind crossover RCT	Adults with atopy and PAF Same adults with atopy, without PAF	Nasal symptoms Nocturnal RQLQ	PAF associated with improved nasal symptom and QOL scores

(Continues)

TABLE XI.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Brehler and Kniest[1719]	2006	2	Double-blind, parallel group RCT	Children with atopy and HDM impermeable bedding Children with atopy without HDM impermeable bedding	Allergy symptom scores Use of anti-allergic medication	HDM impermeable bedding associated with significant reduction in symptom scores No change in anti-allergic drug utilization
Ghazala et al.[1707]	2004	2	Randomized crossover study	Adults with atopy and use of impermeable encasings Adults with atopy without use of impermeable encasings	Allergen (Der p 1, Der f 1 and mite group 2) content Subjective clinical complaint	Impermeable encasings significantly reduce allergen concentration, without difference in subjective symptom scores
Terreehorst et al.[1711]	2003	2	Double-blind RCT	Children with atopy and HDM impermeable bedding Children with atopy without HDM impermeable bedding	Rhinitis-specific VAS Daily symptom score Nasal allergen provocation Der p 1 and Der f 1 concentration	Impermeable encasings significantly reduce allergen concentration, without difference in symptoms or nasal provocation testing
Moon and Choi[1709]	1999	2	Open RCT	Adults and children with atopy and multi-modality environmental control Adults and children with atopy and verbal advice on allergen avoidance	Change in HDM load Daily rhinitis symptom scores	Multi-modality environmental control associated with reductions in mean HDM concentration and nasal symptom scores
Geller-Bernstein et al.[1715]	1995	2	Double-blind RCT	Children with atopy and bedroom sprayed with Acardust acaricide Children with atopy without acaricide	Daily rhinitis and asthma symptom scores Medication use Twice weekly PEF	Acaricide associated with decreased mean symptom scores
Kniest et al.[1708]	1992	2	Double-blind matched-pair controlled trial	Adults and children with atopy and intensive home cleaning plus acaricide Adults and children with atopy and intensive home cleaning alone	Daily symptoms and medication scores Physician assessment Total and mite-specific IgE Blood and nasal eosinophils Guanine exposure	Acaricide associated with improvement in all outcome measures except for mite-specific IgE
Antonicelli et al.[1714]	1991	2	Randomized crossover study	Adults and children with atopy and HEPA filtration Adults and children with atopy without HEPA filtration	HDM concentration Rhinitis and asthma symptom score	HEPA filtration had no significant effect on rhinitis symptom scores

(Continues)

TABLE XI.A.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Reisman et al.[1710]	1990	2	Double-blind crossover RCT	Adults with atopy and Enviracare HEPA filtration Adults with atopy and placebo filtration	Particulate counts in bedroom air Symptom and medication scores Patients' subjective response to treatment	Enviracare HEPA filtration associated with improved particulate counts and symptom/medication scores

Abbreviations: AR, allergic rhinitis; HDM, house dust mite; HEPA, high-efficiency particulate air; IgE, immunoglobulin E; LOE, level of evidence; PAF, personal air filtration; PEF, peak expiratory flow; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SR, systematic review; VAS, visual analog scale.

in cockroach counts is maintained over time.[1723] Most studies did not include clinical endpoints. However, those that did evaluate clinical outcomes focused on asthma symptoms, hospitalizations or emergency room visits, and medication usage.[1732,1733] No studies included any assessment of symptoms or clinical endpoints associated with AR.

Allergen avoidance and environmental controls – cockroach

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 8 studies, level 3: 2 studies, level 4: 1 study; Table XI.A.2)
Benefit: Reduction in cockroach count but allergen concentrations (Bla g 1 and Bla g 2) often above acceptable levels for clinical benefits. No studies included clinical endpoints related to AR.
Harm: None noted.
Cost: Direct costs include multiple treatment applications or multi-interventional approaches. Indirect costs include potential time off work for interventions in home and labor intensity of cleaning measures to eradicate allergens.
Benefits-harm assessment: Balance of benefits and harms since lack of clear clinical benefits.
Value judgments: Control of cockroach populations especially in densely populated multi-family dwellings is important to control cockroach allergen levels.
Policy level: Option.
Intervention: Combination of physical measures (e.g., insecticide bait traps, house cleaning) and education-based methods seem to have the greatest efficacy. Additional research on single intervention approaches is needed with cost analysis, as well as investigation of clinical outcomes related to AR.

XI.A.3 | Pets

Pet avoidance and environmental control represent treatment options for AR due to animal allergy. Pet removal is a commonly cited strategy without high-quality outcomes evaluation and is associated with extremely poor compliance.[1706,1735–1737] One study evaluated compliance of 288 sensitized patients with pet removal recommendations; only 4% of those with direct exposure to home animals adhered to removal recommendations.[1735] However, pet avoidance has shown benefit in the secondary prevention of asthma among previously sensitized individuals and current asthma treatment guidelines recommend pet removal from a sensitized individual's home[1738,1739] (Table XI.A.3).

Environmental controls have been evaluated as strategies to decrease antigen exposure and symptoms of AR with mixed results. While most pet allergen environmental control studies focus on cats, less evidence is available for other allergenic pets, such as dogs, birds, and others. The utility of multi-modality environmental control (cat avoidance, weekly cleaning with removal of carpeting and upholstered furniture, etc.) was studied in 40 patients diagnosed with cat (Fel d 1) sensitization and resulted in significant improvements in nasal airflow and clinical symptoms.[1740] However, single-modality environmental control has not been associated with improved symptoms despite identified reductions in environmental antigens. Wood et al.[1741] evaluated HEPA filtration in a high-quality randomized controlled study of 35 patients with Fel d 1 sensitization, finding unchanged nasal symptom scores, sleep disturbance, rescue medication usage, and spirometry following a 3-month trial. Likewise, there is not good evidence to support the impact of dog allergen mitigation on improvement in clinical symptoms. Several studies of lower-quality evidence have evaluated the duration of antigen reduction following pet washing, finding that washing of cats and dogs must be completed at least twice weekly to maintain significant reductions in environmental antigens.[1742,1743]

TABLE XI.A.2 Evidence table – allergen avoidance: cockroach

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Le Cann et al.[1720]	2017	1	SR of RCTs	Home group interventions: Education-based methods Physical methods Combination of both Interventions, also included control measures for multiple allergens (HDM, CR, cat, dog)	Allergic and respiratory symptoms (cough, daytime symptoms, wheeze, nighttime symptoms) Lung function Medication use Urgent care use for respiratory symptoms	Supported effectiveness of home interventions in decreasing respiratory symptoms and urgent care use
Sever et al.[1723]	2007	2	RCT	Insecticide baits placed by entomologists and CR monitoring Pest control by randomly assigned commercial company Control group	No direct clinical endpoints	Significant reduction in CR counts in both treatment groups compared to control Insecticide bait traps more effective in reducing CR infestation than application of spray Elimination of CR populations results in greater reduction in CR allergen and exposure
Eggleston et al.[1732]	2005	2	RCT	Home-based education, CR and rodent extermination, mattress and pillow encasings, HEPA filters Control: no intervention until end of study	Primary outcome: Bla g 1 allergen level Secondary outcome: asthma symptoms	CR allergen reduced by 51% at 6 months in treatment group but not sustained at 1 year Modest effect on morbidity
McConnell et al.[1724]	2005	2	RCT	Education-based intervention for caregivers (sealing cracks and crevices, cleaning with bleach solutions, insecticide bait traps) Comparison group	No direct clinical endpoints	60% reduction in CR count in intervention group Greatest reduction in allergen level in homes with heavier CR infestation Levels still higher than median level associated with severe symptoms
Arbes et al.[1725]	2004	2	RCT, crossover	Combined intervention: occupant education, entomologist insecticide bait placement, professional cleaning Control: no intervention for months 0–6, insecticide bait application at months 6 and 9	No direct clinical endpoints	CR allergen levels reduced in 6 months with professional cleaning and insecticide bait traps Lower CR allergen levels maintained at 12 months with bait traps alone

(Continues)

TABLE XI.A.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Morgan et al.[1733]	2004	2	RCT, blocked randomization	Education-based intervention for caregivers (environmental remediation for multiple allergens), professional pest control provided for CR-sensitized children Control group: evaluation only	Asthma symptoms Use of health care services	Intervention group: reduced levels of CR allergen in bedroom were strongly correlated with decreased asthma-related morbidity
McConnell et al.[1726]	2003	2	RCT	Professional cleaning and professional pest control (insecticide bait traps) Professional cleaning and bait traps with no insecticide (placebo group) No cleaning or bait traps (control group)	No direct clinical endpoints	CR allergen concentration after professional cleaning and insecticides was low Decreased CR count in insecticide bait treatment group Homes with high initial CR counts had larger reductions in Bla g 2 CR allergen concentration Professional cleaning may help in homes with heavier CR infestation
Wood et al.[1727]	2001	2	RCT	Professional cleaning; insecticide bait traps, sodium hypochlorite Control homes: no cleaning, extermination, or bleach solution	No direct clinical endpoints	Professional extermination treatments reduced CR numbers and reduced median allergen levels by 80%–90% Cleaning solution did not add any improvements Unclear if this level of reduction is sufficient to have clinical benefits in CR-sensitized individuals
Gergen et al.[1728]	1999	2	RCT – Phase II of a multi-city study	Education based intervention for parents on asthma triggers, environmental controls, professional pest control, instruction on house cleaning protocol before and after extermination Control group	No direct clinical endpoints	CR allergen levels decreased within 6 months but returned or exceeded baseline levels by 12 months Compliance with cleaning protocol was poor
Wang et al.[1731]	2020	3	Single group, non-controlled time series	Building-wide CR control management program	No direct clinical endpoints	CR count reduced by 97.9% at 6 months and 99.9% at 12 months Bla g 1 and Bla g 2 concentrations significantly reduced from 0 to 6 months and 6 to 12 months

(Continues)

TABLE XI.A.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Williams et al.[1730]	1999	3	Single-blind, nonrandom stratified placebo control	Bait traps with insecticide Identical appearing placebo bait traps	No direct clinical endpoints	Treated homes had a significant decrease in number of CR compared to placebo, which continued for 6 months Minimal reduction in Bla g 1 and Bla g 2 allergen concentration No significant difference between active and placebo homes
Eggleston et al.[1729]	1999	4	Prospective case–control	Professional cleaning followed by professional pest control treatments	No direct clinical endpoints	CR numbers can be eliminated in most inner-city homes with insecticides applied by professional pest control technicians CR allergen levels decreased by 78%–93% over 8 months but mean allergen concentrations were still above threshold associated with asthma morbidity

Abbreviations: CR, cockroach; HDM, house dust mite; HEPA, high-efficiency particulate air; LOE, level of evidence; RCT, randomized controlled trial; SR, systematic review.

Allergen avoidance and environmental controls – pets

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 2 studies, level 4: 1 study; Table XI.A.3)
Benefit: Decreased environmental allergen exposure with possible reduction in symptoms and secondary prevention of asthma.
Harm: Emotional distress caused by removal of household pets. Financial and time costs of potentially ineffective intervention.
Cost: Low to moderate.
Benefits-harm assessment: Equivocal.
Value judgments: While several studies have demonstrated an association between environmental controls and reductions in environmental antigens, only a single, multi-modality RCT has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity. The secondary prevention and treatment of asthma in sensitized individuals must also be considered.
Policy level: Option.
Intervention: Pet avoidance and environmental control strategies, particularly multi-modality environmental controls among patients with diagnosed Fel d 1 sensitivity, may be presented as an option for the treatment of AR.

XI.A.4 | Rodents

Only a few high-quality studies have been published on rodent (i.e., mouse, rat, guinea pig, and hamster) avoidance and interventions to reduce exposure specifically related to AR. Most studies focus on changes in mouse allergen levels and asthma-related outcomes in inner-city children, which may not directly correlate with AR symptoms in other populations.[1732,1744–1748] While some RCTs have been conducted for mouse allergen, none have been performed for non-mouse rodent allergens. Demonstrating efficacy of rodent avoidance or interventions targeted to reduce exposure is difficult as most environmental interventions lead to non-specific removal of multiple allergens[140] (Table XI.A.4).

TABLE XI.A.3 Evidence table – allergen avoidance: pets

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bjornsdottir et al.[1740]	2003	2	RCT	Cat allergic patients with EC Cat allergic patients with unchanged environment	Environmental (settled dust) Fel d 1 levels Nasal inspiratory flow Nasal symptoms	Multi-modality EC associated with decreased allergen concentration, and improvement in nasal inspiratory flow and patient symptoms
Wood et al.[1741]	1998	2	RCT	Cat sensitive adults with HEPA filter Cat sensitive adults with placebo	Cat allergen levels (airborne and settled dust) Symptom scores Medication scores Spirometry	HEPA filters associated with reduced airborne, but not settled dust, cat allergen levels without effect on disease activity
Hodson et al.[1743]	1999	3	Non-randomized controlled cohort	Newly washed dogs undergoing daily collection of hair clippings and air assessment for seven days	Can f 1 levels from dog hair and circulating air	Dog washing must occur twice weekly to maintain reductions in allergen levels
Avner et al.[1742]	1997	3	Non-randomized controlled cohort	Cats undergoing weekly: Veterinary washing Immersion washing Immersion followed by 3 min rinse	Fel d 1 levels from cat hair and circulating air	Washing cats by immersion removes significant allergen reduces the quantity of airborne Fel d 1 Fel d 1 decrease is not maintained at 1 week
Sanchez et al.[1735]	2015	4	Cohort	Patients with diagnosed allergy	Sensitization to household animals Compliance with avoidance recommendations and EC	Avoidance recommendations may be impractical with high rates of sensitization, indirect exposure, and low rates of compliance

Abbreviations: EC, environmental controls; HEPA, high-efficiency particulate air; LOE, level of evidence; RCT, randomized controlled trial.

Observation studies of early exposure to rodents in childhood have yielded mixed results when evaluating future risk of rodent sensitization and the development of AR or allergic asthma.[879,885,886,1749] Larger controlled studies are needed.

Avoidance of workplace rodent exposure. Removal of rodent exposure is a management option for AR and asthma in those that are sensitized; however, as exposure can occur in various environments, comprehensively accomplishing this is challenging. When exposure primarily occurs at the workplace (e.g., laboratory worker handling rodents), reduction of allergen exposure can be accomplished by changing jobs or roles, use of personal protective devices, maintaining ventilation systems, and proper staff training.[140,1750]

Rodents as pets or pests. As various rodents can be kept as pets, many sensitized individuals or their caregivers are reluctant to remove the rodent from the living space, similar to other furry animals.[1735,1751] Conversely, individuals are generally willing to comply with recommendations to remove things they consider pests. Rodent predators such as cats can reduce rodent populations but are unlikely to eliminate an infestation. One observational inner-city study showed that the number of cats and cat allergen levels are inversely correlated with mouse allergen levels.[1752] No clinical outcomes were reported in this study. No recommendations can be made at this time, but the risks likely outweigh potential benefit due to the high reported co-sensitization rate for cat and mouse allergens, which could lead to worsening of allergic symptoms with cat introduction.[1752]

Integrated pest management for rodent infestation. Integrated pest management encompasses the initial removal of allergen reservoirs and habit modifications to reduce the risk of infestation recurrence.[140] These interventions include home-based education, rodent

TABLE XI.A.4 Evidence table – allergen avoidance: rodents

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Matsui et al.[1744]	2017	2	RCT	Professional integrated pest management + pest management education Pest management education alone	Primary outcome: maximal asthma symptom days Secondary outcomes: mouse antigen levels, spirometry measurements	No significant difference in any outcome measure between the interventions
DiMango et al.[1748]	2016	2	RCT	Multifaceted indoor allergen avoidance measures Sham intervention	Allergen levels (cat, dog, HDM, CR, mouse) Asthma-related outcomes (medication score, FEV_1 change, symptom scores, FeNO score and QOL)	Intervention group had a more significant decrease in allergen levels versus sham No change in medication requirements or other asthma clinical measures
Pongracic et al.[1746]	2008	2	RCT	Home rodent-specific environmental interventions No specific interventions	Mouse allergen levels (Mus m 1) Asthma-related outcomes	Significant decrease in Mus m 1 levels by 27.3% on the bedroom floor; no difference was found for allergen levels on the bed Reduction was associated with less missed school and sleep disruption but not medical utilization or asthma symptoms
Eggleston et al.[1732]	2005	2	RCT	Home-based education, CR and rodent extermination, mattress and pillow encasings, HEPA filters Control	Asthma symptoms	Mouse antigen not reduced despite application of effective rodenticide at 12 months Conclusions could not be drawn on asthma-related outcomes based on rodent extermination measures alone
Phipatanakul et al.[1747]	2004	2	RCT	Integrated pest management interventions No rodent-specific interventions	No clinical endpoints measured	Mouse allergen levels were significantly decreased by 78.8% with intervention versus control
Grant et al.[1745]	2020	3	RCT[a]	Professional integrated pest management + education Education alone	Lung function	Mouse allergen reduction was related to an increase in prebronchodilator FEV_1
Jacobs et al.[1749]	2014	3	Cross-sectional	511 children (6-14 years old)	Mouse allergen exposure and risk of AR	Higher mouse allergen levels were associated with 25% decreased odds of AR

(Continues)

TABLE XI.A.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kellberger et al.[885]	2012	3	Prospective population-based cohort	2810 adolescents (15–18 years old)	Incidence and persistence of physician-diagnosed AR at age 15–18	Furry animal (hamster, guinea pig, rabbit) ownership had no association with incidence/persistence of physician-diagnosed AR
Lodrup-Carlsen et al.[886]	2012	3	Prospective birth cohort (pooled analysis)	1989–1997: 11 European birth cohorts; 11,489 participants aged 6–10 years	Incidence of asthma, AR, and allergic sensitization during 6–10 years of age	Rodent exposure is protective against sensitization to inhalant allergens in general No association with clinical AR (OR rodent only exposure 0.8; 95% CI 0.5–1.5)
Bertelsen et al.[1751]	2010	3	Observational cohort	1019 children, pet ownership	No clinical endpoints measured	In children with AR, having an older sibling was associated with keeping or acquiring a furry pet
Sanchez et al.[1735]	2015	4	Observational ambispective cohort[b]	Patients with allergic sensitization to pets	Allergen sensitization to pets	Low sensitization rate to hamsters Most pet owners refused removal of their pet after provider recommendation due to emotional attachment
Phipatanakul et al.[140]	2012	4[c]	Evidence-based search	Exposure reduction of rodents	Not applicable	Reduction in rodent allergen exposure seems critical to mitigate symptoms but demonstrating efficacy remains challenging
Curtin-Brosnan et al.[1752]	2009	4	Case series	Inner-city children with asthma	No clinical endpoints measured	Inverse correlation between number of cats in household and cat allergen levels compared to mouse allergen levels
Anyo et al.[879]	2002	4	Observational cross-sectional	2729 primary school-aged children using parent-completed questionnaire on pet ownership	Allergen sensitization, symptoms, and atopic diagnoses	Furry pet (cat, dog, rodent) ownership associated with a lower risk of sensitization to pollen
Sakaguchi et al.[1750]	1989	5	Mechanism-based reasoning	Various dust respirators used for mouse housing room samples	No clinical endpoints measured	Respirators successfully removed between 65-100% of mouse allergens

Abbreviations: AR, allergic rhinitis; CI, confidence interval; CR, cockroach; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; HDM, house dust mite; HEPA, high-efficiency particulate air; LOE, level of evidence; OR, odds ratio; QOL, quality of life; RCT, randomized controlled trial.

[a]LOE downgraded due to selective outcome reporting.

[b]LOE downgraded due to selective sampling.

[c]LOE upgraded due to established methodology, several rounds of review, long history of EBM guideline development.

extermination via traps and rodenticide, HEPA filtration, sealing of holes and cracks with copper mesh, and thorough cleaning. Singular interventions, such as placing rodent traps alone, are unlikely to provide meaningful benefit, which is consistent with cockroach allergen mitigation literature.[140] (See Section XI.A.2. Allergen Avoidance – Cockroach for additional information on this topic.)

Several RCTs have been performed to evaluate the efficacy of integrated pest management in reducing indoor allergen levels; however, only six specifically address mouse allergen.[1732,1744–1748] Integrated pest management methods were highly variable between these studies, making direct comparisons difficult. In addition, the outcome measures evaluated were primarily mouse antigen levels and asthma-related outcomes (no rhinitis outcomes were reported) in low-income, inner-city populations, which limits the generalizability of the results. Three out of the six showed a reduction of mouse antigen levels with integrated pest management, one did not report this outcome, and two showed no significant difference. Asthma-related clinical endpoint results were mixed, but 1 study that utilized extensive integrated pest management interventions showed an increase in FEV_1 (forced expiratory volume in 1 second) in inner-city children when ≥75% reduction of mouse allergen levels was achieved.[1745]

In summary, avoidance measures for work-related exposures and pet rodent exposures may have significant benefit. For rodent infestations, integrated pest management reduces mouse allergen levels in the household, but meaningful clinical improvement remains unclear in mouse-sensitized patients.[1732,1744–1748] The generalizability of rodent-specific integrated pest management RCTs is very limited as they all mainly included low-income, inner-city populations in the northeastern US. No well-conducted studies have evaluated allergen reduction interventions for other rodents. Future research should concentrate on the effects of integrated pest management on rodent allergen levels in non-inner-city populations, rhinitis outcomes, and determining which interventions are highest yield to maximize cost-efficiency.

Allergen avoidance and environmental controls – rodents

Aggregate grade of evidence: C (Level 2: 5 studies, level 3: 5 studies, level 4: 4 studies, level 5: 1 study; Table XI.A.4)
Benefit: Reduces rodent allergen levels (specifically mouse allergen) but no information on AR outcomes.
Harm: Reduction in QOL of patient due to removal of pet rodent to whom patient is emotionally attached. Change in job position or role if primary rodent exposure is work-related.
Cost: Direct costs include the cost of interventions such as extermination and mitigating causal factors or loss of income if a job change occurs. Indirect costs include time off work for pest control appointments.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Careful patient selection based on exposure history. Heterogeneity of integrated pest management protocols makes quantification of benefit difficult.
Policy level: Option.
Intervention: Avoidance likely improves rodent-specific allergen exposure, especially when the interaction can be eliminated such as when it is work-related or with a pet rodent. Integrated pest management should be considered in select patients, such as pediatric inner-city patients that suffer from asthma and are mouse sensitized.

XI.A.5 | Pollen

For pollen sensitized patients, avoidance or environmental control measures are often the first recommended intervention to decrease exposure and symptoms.[31] This approach is derived from the experience in which nasal or inhalational allergen challenges induce inflammatory changes and clinical symptoms after exposure.[152] Education and avoidance measures often involve personal behavior changes, particularly when pollen counts are elevated. While complete avoidance of pollen triggers is rarely achievable, it also has undesirable consequences such as avoiding the outdoors.[1753] A more realistic goal is a reduction in exposure to pollens rather than complete elimination[1754] Further, evidence supporting such recommendations is often limited to expert opinion and clinical experience.

Dominant aeroallergens may vary significantly by geographical location, climate, and season. Understanding an individual's specific sensitization pattern is best characterized by the combination of history and physical examination along with skin testing or serum sIgE testing. This combined with local pollen data can guide when a patient may be most likely exposed to a particular allergen and, therefore, when avoidance measures may be most effective. Local pollen counts can be ascertained by

various sources including local media, phone applications, and trusted internet websites.

Practical interventions for pollen avoidance include keeping windows in homes and cars closed, drying clothes indoors, and staying inside when possible.[1755] Cabin air filters in cars, pollen screens, eyeglasses, and mouth-nose covering masks may reduce exposures.[1756] Pollen counts tend to be higher on sunny, windy days with lower humidity.[31] HEPA filters in air purifiers can decrease exposure and, when studied in *Artemisia* pollen sensitized patients, led to decreased allergy symptom scores compared to placebo filters.[1757] For individuals able to change immediate landscaping, choosing entomophilous or insect pollinated plants may be helpful in addition to selecting plants less likely to induce allergic symptoms.[1758] While allergen avoidance is endorsed by national and international guidelines,[182,1759] the clinical efficacy of these interventions has not been rigorously evaluated.

The previously mentioned pollen avoidance approaches apply more generally to one's surroundings. There have also been attempts with physical barriers in direct or close contact with mucosal membrane surfaces where pollens may adhere and cascade immune responses. One study enrolled 70 individuals with seasonal AR (primarily to grass) or polysensitized individuals without perennial sensitizations, where patients were randomized to receive wraparound eyeglasses in addition to medical treatment versus medical treatment alone for three successive pollen seasons.[1760] Patients provided wraparound glasses had improved ocular and nasal symptoms, in addition to improved RQLQ compared to medical therapy alone. Nasal filters have also been used as an avoidance tool to prevent symptoms of AR. In a randomized, double-blind placebo-controlled crossover trial, 65 grass sensitized adults were monitored in a natural exposure setting at a park while either wearing a nasal filter or placebo.[1761] Patients wearing nasal filters had significantly reduced TNSS scores compared to placebo. Other barrier protection measures have been assessed, including cellulose powder applied to the nose, pollen blocker cream, and microemulsion. In a systematic review, 15 RCTs involving data of these measures from 1154 patients were assessed with subgroup analysis according to the type of barrier protection studied.[1762] Compared to placebo, the barrier protection methods assessed each had improved symptom control by meta-analysis without increased adverse events (of note, nasal filter was not analyzed by meta-analysis due to insufficient data). Most of the included studies were small with heterogeneous study designs, but overall barrier methods may offer non-pharmacologic, symptomatic improvement to motivated patients (Table XI.A.5).

Allergen avoidance and environmental controls – pollen

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 3 studies; Table XI.A.5)
Benefit: Decreased symptoms and medication use with potential for improved QOL.
Harm: Interventions may vary in cost and efficacy of each may be inadequately defined.
Cost: Generally low monetary cost depending on strategy.
Benefits-harm assessment: Equivocal, most interventions with lower harm but not well-defined benefits.
Value judgments: Most pollen avoidance measures are based on clinical and expert opinion although trial-based evidence is available for some interventions.
Policy level: Option.
Intervention: Pollen avoidance strategies are generally well tolerated and lower cost, non-medication-based interventions that may have benefit with minimal harm to the patient, but further RCTs with larger populations would be needed to better characterize efficacy.

XI.A.6 | Occupational

Occupational rhinitis may be secondary to allergic or irritant responses and has been associated with a variety of agents, including animals, particulate matter from woods, grains, chemicals, and other substances.[152] Early diagnosis is crucial not only for managing rhinitis symptoms but also potentially preventing the development of coexisting occupational asthma.[124,1764] Regarding management, the most common strategy is avoidance or implementation of environmental controls. However, it is critical to prevent sensitization through appropriate occupational hygiene and safety practices with surveillance of symptoms and exposures in high risk environments.[1765]

Accurate diagnosis of occupational rhinitis may be suggested by periods of improvement during work avoidance such as planned time away from the workplace, when not exposed regularly to occupational allergens. NPT may be pursued but the validity of this testing is often poorly defined.[31] For patients with high clinical suspicion of occupational rhinitis, complete avoidance is recommended as the safest and most effective therapeutic option. If this is not possible due to socioeconomic consequences or otherwise, environmental control measures to reduce

TABLE XI.A.5 Evidence table – allergen avoidance: pollen

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chen et al.[1762]	2020	1	SRMA	15 RCTs evaluating barrier protection methods	Nasal symptom scores QOL Peak nasal inspiratory flow	Cellulose powder, microemulsion, pollen blocker cream provided symptomatic improvement versus control
Chen et al.[1763]	2018	2	RCT, double-blind	90 patients with *Artemisia* (mugwort) sensitization randomized to HEPA air purifier use versus placebo air filter	Symptom severity and QOL RQLQ	Allergy symptom scores significantly improved with HEPA air filter use
Comert et al.[1760]	2016	2	RCT	70 patients with seasonal AR randomized to medical therapy alone versus medical therapy + wraparound eyeglasses	Symptom scores Rescue medication use RQLQ	Wraparound eyeglasses improved symptoms, QOL, and rescue medication use versus medical therapy alone
Kenney et al.[1761]	2015	2	RCT, double-blind, crossover	65 grass allergic patients randomized to wearing nasal filters at a park on 2 successive days	TNSS	In a natural exposure setting, nasal filters reduced TNSS versus placebo

Abbreviations: AR, allergic rhinitis; HEPA, high-efficiency particulate air; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score.

exposure may be an acceptable alternative.[126] This may be accomplished with escalating interventions, starting with avoidance by the use of less problematic materials, improving ventilation of the areas involved, reducing time spent working with implicated materials, or utilizing protective gear for the patient.[1764]

Symptom improvement has been reported in clinical settings following effective avoidance. In a prospective study, 20 patients with specific inhalation challenge-confirmed occupational rhinitis (exposures including flour, animal proteins, tea, isocyanates, resins, and acrylates) were assessed at diagnosis and follow-up, with a mean time interval of 4.7 ± 1.3 years.[1766] At follow-up assessment, all patients had been removed from exposure and reported significant decreases in nasal symptoms and improvement in QOL. Similarly, a separate Finnish cohort of 119 patients was diagnosed with occupational rhinitis (exposures including flour, animal proteins, storage mites, latex, flowers or indoor plants, dried egg powder, organic acid anhydrides with human serum proteins, abache wood dust, human dandruff, and enzymes) with an average of 10 years since diagnosis. Health-related QOL for those no longer exposed to occupational allergens was similar to healthy controls, while it was impaired among those with continued exposures.[1767] Thus, complete avoidance appears to improve rhinitis symptoms and QOL, and when feasible, may be the best approach (Table XI.A.6).

However, if complete avoidance is not able to be achieved, there can be benefit to treatment approaches including decreased levels of exposure. In a group of 36 patients with latex-induced occupational asthma and a median follow up time of 56 months, 20 subjects with reduced exposure had improved asthma severity along with reduced rhinitis symptom severity scores.[1768] The other 16 patients without ongoing exposure (defined as latex gloves never used in the working environment) also had improvement in asthma and rhinitis symptom severity but had more loss of income and work disability. In a separate cross-sectional survey of patients with occupational asthma to platinum salts, transfer to low-exposure areas at work resulted in improved rhinitis symptoms

TABLE XI.A.6 Evidence table – allergen avoidance: occupational

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Castano et al.[1766]	2013	3	Prospective, observational cohort	20 patients with confirmed OR	Changes in nasal symptoms Disease specific QOL Nasal patency and inflammation	In OR, cessation of exposure led to improved QOL, rhinitis symptoms, and general well being
Airaksinen et al.[1767]	2009	3	Observational cohort	119 patients with OR in registry-based questionnaire	Changes in general and disease specific health related QOL survey	QOL was improved, similar to healthy controls in patients with OR who did not have ongoing occupational exposures
Vandenplas et al.[1768]	2002	3	Observational cohort	36 patients with latex induced occupational asthma with reduced or no exposure	Lung function assessment Questionnaire based asthma and rhinitis severity	Either reduced exposure or avoidance resulted in improvement in asthma and rhinitis symptoms
Merget et al.[1769]	1999	3	Cross-sectional	83 patients with platinum salt induced asthma with varying levels of reduced exposure	Lung function and bronchial hyperresponsiveness Skin and serum specific testing Reported symptoms of asthma, rhinitis	Rhinitis, conjunctivitis, dermatitis symptoms improved with decreased exposure while asthma did not
Taivainen et al.[1770]	1998	3	Prospective, open interventional	33 agricultural workers with asthma (24 with occupational asthma)	Asthma symptoms by peak expiratory flow rates Daily rhinitis symptoms	Powered dust respirator helmets diminished rhinitis symptoms and improved morning peak flow

Abbreviations: LOE, level of evidence; OR, occupational rhinitis; QOL, quality of life.

compared to high exposure areas.[1769] Where avoidance or decreased exposure by job location is not achievable, personal protective equipment may be sufficient to decrease symptoms of occupational rhinitis. In a group of agricultural workers, predominately with occupational asthma to cow dander or grains, use of a powered dust respirator helmet worn over a period of 10 months resulted in significantly reduced rhinitis symptoms and improved morning peak flow rate.[1770]

Overall, while most of the evidence is limited to small observational studies, complete avoidance of an inciting agent in occupational rhinitis likely provides the best improvement in symptoms and QOL and should be pursued when possible. Alternatively, occupation-specific interventions to decrease exposure may offer benefit to patients when complete avoidance cannot be accomplished. Further characterization of levels of exposure and most effective means of decreasing exposure is needed. (See Section V.B.3 Occupational Rhinitis for additional information on this topic.)

Allergen avoidance and environmental controls – occupational

Aggregate grade of evidence: C (Level 3: 5 studies; Table XI.A.6)

Benefit: Decreased allergen exposure may lead to reduction in symptoms, improvement in QOL, and possible reduced likelihood of developing occupational asthma.

Harm: Potential for socioeconomic harm with loss of wages or requiring changes in occupation.

Cost: Individually may vary if avoidance results in loss of income; for employers, potentially high cost depending on interventions or environmental controls required.

Benefits-harm assessment: Where possible from a patient-centered perspective, in occupational rhinitis complete avoidance is likely beneficial in improving health quality compared to ongoing exposures.

Value judgments: Based primarily on observational studies, allergen avoidance or decreasing exposure is recommended for all patients but can be nuanced depending on the resulting socioeconomic impact.
Policy level: Recommendation.
Intervention: Patients should be counseled to avoid or decrease exposure to inciting agents in occupational respiratory disease.

XI.B | Pharmacotherapy

XI.B.1 | Antihistamines

XI.B.1.a | *Oral H_1 antihistamines*

In AR, sIgE binds to mast cells and basophils which triggers the release of histamine. The effects of histamine include vasodilation, smooth muscle bronchoconstriction, increased endothelial permeability, and sensory nerve stimulation, contributing to the classic symptoms of AR.[1771] Antihistamines are inverse agonists of histamine and cause histamine receptors to convert to an inactive state.[1772] Antihistamines are classified as first, second, and third generation. However, herein we classify the second and third generation as newer-generation antihistamines (Table XI.B.1.a.-1). First-generation antihistamines (e.g., diphenhydramine and chlorpheniramine) have anticholinergic side effects and can cross the blood–brain barrier, resulting in central nervous system effects such as sedation and drowsiness.[1773,1774] These side effects can be more pronounced in the elderly, so first-generation antihistamines should be used with caution.[293] Newer-generation antihistamines (e.g., bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine) block peripheral H_1 receptors without crossing the blood–brain barrier which prevents central nervous system side effects. Several newer-generation antihistamines are metabolized in the liver by cytochrome p450 enzymes. As a result, prescribers should be conscious of concomitant administration of other drugs that are either processed by cytochrome p450 or drugs that are cytochrome p450 inducers because concurrent administration can either increase or decrease the plasma concentration of the antihistamine.[1774]

Given their use since the 1940s, there are numerous RCTs regarding the use of oral antihistamines for the management of AR. With this in mind, a summary of the highest grade of evidence published is provided (Table XI.B.1.a.-2).

There are several published guidelines regarding the use of oral antihistamines for the management of AR. In 2004 the ARIA group and EAACI released recommendations regarding the pharmacological criteria that commonly used AR medications should meet. Taking into consideration the efficacy, safety, and pharmacology, newer-generation antihistamines were shown to have a favorable risk-benefit profile and were recommended over first-generation oral antihistamines for the treatment of AR.[1775] The 2015 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Clinical Practice Guidelines and the 2019 Canadian Society of Allergy and Clinical Immunology position statement

TABLE XI.B.1.a.-1 List of commonly used newer-generation antihistamines[1005]

Antihistamine	Onset (h)	Duration (h)	Drug Interactions	Elimination (h)	Dosage	
					Adults	Children
Bilastine	2	24	Unlikely	14.5	20 mg QD	N/A
Cetirizine (Zyrtec)	0.7	>24	Unlikely	6.5–10	5–10 mg QD	2–5 years; 2.5 mg or 5 mg QD 6–12 y: 5–10 mg QD
Desloratadine (Clarinex)	2–2.6	>24	Unlikely	27	5 mg QD	2–5 years: 1.25 mg QD 6–11 years: 2.5 mg QD
Fexofenadine (Allegra)	1–3	>24	Unlikely	11–15	60 mg BID or 180 mg QD	2–11 years: 30 mg BID
Levocetirizine (Xyzal)	0.7	>24	Unlikely	7	5 mg QD	2–5 years: 1.25 mg QD 6–11 years: 2.5 mg QD ≥12 years: 2.5–5 mg QD
Loratadine (Claritin)	2	>24	Unlikely	7.8	10 mg QD or 5 mg BID	2–5 years; 5 mg QD ≥6 years; 10 mg QD

Abbreviations: BID, twice daily; QD, daily.

also recommended newer-generation antihistamines over first-generation antihistamines for the management of AR.[1005,1773]

The ARIA guidelines 2010 revision made a strong recommendation for newer-generation antihistamines that are non-sedating and do not interact with cytochrome p450.[1004] The ARIA guidelines 2016 revision made several recommendations regarding when to consider the use of oral antihistamines, taking into context other drugs available for the management of seasonal and perennial AR.[1167] In 2020, the ARIA group published the first GRADE-based guidelines that integrated real-world patient-reported experience and clinical studies to inform the management of AR.[1182] It provided a treatment algorithm that, in a nuanced manner, considered a patient's symptom severity with past and current medication use to clarify the role of newer-generation antihistamines for the management of AR.[1182] The standard dosing for newer-generation antihistamines is listed in Table XI.B.1.a.-1.

The decision on which newer-generation antihistamine to prescribe should be individualized to the patient and the dosing, drug interactions, side effects, the onset of action, and cost should be considered. A large study that examined all e-prescriptions of oral antihistamines ($n = 2280$) in Poland in 2018 found that approximately one in five prescriptions was not redeemed.[1776] This finding suggests the need for further studies regarding patient adherence to oral antihistamines, noting that various factors could influence patient adherence including lack of trust in the prescriber, cost and availability of the medication over the counter.

Excluding oral antihistamines only available by prescription, the cost of most newer-generation oral antihistamines is similar at ~$2 per day.[1777] As newer-generation oral antihistamines have fewer central nervous system side effects than first-generation oral antihistamines, their indirect costs to society are lower than first-generation oral antihistamines.[1771,1774,1777] The indirect costs amongst newer-generation oral antihistamines are similar given the similar side effect profiles.

Oral H_1 antihistamines

Aggregate grade of evidence: A (Level 1: 19 studies, level 4: 5 studies; Table XI.B.1.a.-2)
Benefit: Reduction in symptoms of AR.
Harm: Compared to first-generation oral antihistamines, newer-generation antihistamines have fewer central nervous system and anticholinergic side effects. The side effects of first-generation antihistamines can be more pronounced in the elderly. See Table II.C.
Cost: Inexpensive. Given their improved side effect profile, newer-generation oral antihistamines also have lower indirect costs than first-generation oral H_1 antihistamines.
Benefits-harm assessment: The benefits outweigh harm for use of newer-generation H_1 oral antihistamines for AR.
Value judgments: First-generation oral antihistamines are not recommended for the treatment of AR because of their central nervous system and anticholinergic side effects.
Policy level: Strong recommendation for the use of newer-generation oral antihistamines for AR.
Intervention: Newer-generation oral antihistamines can be considered in the treatment of AR.

XI.B.1.b | *Oral H_2 antihistamines*

Our understanding of the role of the H_2 receptor in mediating histamine-related nasal symptoms in AR is limited. There is no data comparing H_2-receptor antagonism efficacy to common first line therapy such as INCS, and only a few relatively small studies have investigated the impact of H_2-receptor antagonism. Most importantly, the clinical significance of the changes associated with H_2 antihistamines has not been clearly defined. Nonetheless, H_2 antihistamines possess relatively low risk (drug–drug interactions through decreased gastric acidity and inhibition of cytochrome p450)[1797] and low cost and have been supported by some studies for use in patients with recalcitrant nasal airway obstruction in combination with oral H_1 antihistamines.

There have been several RCTs that investigated the efficacy of H_2 antihistamines in improving objective measures such nasal airway resistance and nasal secretion. Wood-Baker et al.[1798] compared oral cetirizine to oral ranitidine. Objective measures of nasal airway resistance showed greater improvement with ranitidine; however, objective measures of nasal secretion decreased more with cetirizine. Despite very few studies showing efficacy of H_2 blockers alone, several studies have emphasized their potential utility in combination with H_1 antagonists. Taylor-Clark et al.[1799] found similar improvement in nasal airway resistance between cetirizine and ranitidine, but a significant improvement with the use of combination therapy. Wang et al.[1800] also showed improvement in nasal airflow with combination therapy of cimetidine and cetirizine. Havas et al.[1801] measured the nasal airflow resistive response to topical histamine and also found that combined histamine antagonism with diphenhydramine

TABLE XI.B.1.a.-2 Evidence table – oral H_1 antihistamines for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zhang et al.[1043]	2022	1	SR of 22 RCTs	Adult patients (n = 4673) treated with: INCS OAH AIT	TNSS VAS RQLQ PNIF	OAH treatment resulted in statistical but not clinically meaningful improvement in RQLQ PNIF was not statistically or clinically significant
Miligkos et al.[1778]	2021	1	SR of 45 RCTs	Children ≤12 years old on: OAH Montelukast Placebo	Adverse events Drug-related adverse events Treatment discontinuations	Newer-generation OAHs have a favorable safety and tolerability profile
Sastre[1779]	2020	1	SR of 15 RCTs	Adolescent and adult patients treated with ebastine	Relief of allergy symptoms Safety and tolerability	Ebastine is an effective and well-tolerated newer-generation antihistamine for the treatment of AR
Mullol et al.[1780]	2015	1	SR of 12 clinical trials	Patients with AR (≥6 years old) treated with rupatadine	Relief of allergy symptoms ARIA criteria Adverse events	Rupatadine is recommended for use in adults and children for persistent, intermittent, seasonal, and perennial AR
Ridolo et al.[1781]	2015	1	SR of 4 RCTs	Adult patients treated with: Bilastine Cetirizine Desloratadine	Subjective and objective measures TNSS RQLQ	Bilastine has similar efficacy to other second-generation oral antihistamines Improved TNSS & RQLQ, good safety profile
Compalati et al.[1782]	2013	1	SR of 10 RCTs	Patients (n = 2573; ≥6 years old) treated with rupatadine	Relief of allergy symptoms Adverse events	Favorable risk-benefit ratio for rupatadine in treating AR
Mosges et al.[1783]	2013	1	SR of 10 clinical trials	Patients (n = 140,853; ≥12 years old) treated with: Desloratadine Ebastine Fexofenadine Levocetirizine	TSS TNSS	Second-generation levocetirizine significantly improved symptom scores, especially in severe AR
Compalati et al.[1784]	2011	1	SR of 8 RCTs	Patients (n = 3532; ≥5 years old) treated with fexofenadine	TSS Individual symptoms (sneezing, rhinorrhea, itching congestion) Adverse events	Fexofenadine has good efficacy with improvement in outcome measures No significant adverse events versus placebo
Ferrer[1785]	2011	1	SR of 8 RCTs	Pediatric and adult patients treated with: Levocetirizine Desloratadine Fexofenadine	TSS PNIF Decongestion test QOL Pruritus ESS Wheal and flare Adverse events	Oral newer-generation antihistamines are well tolerated in adults and children Improvement in QOL and nasal obstruction Benefits outweigh harm Very low risk of sedation No QT prolongation

(Continues)

TABLE XI.B.1.a.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mosges et al.[1786]	2011	1	SR of 7 RCTs	AR patients ($n = 2238$; ≥6 years old treated with: Levocetirizine Loratadine	TSS DNS DES	Improvement in TSS, total five symptoms score, daytime nasal symptoms, and QOL
Bachert[1787]	2009	1	SR of 26 clinical trials	Patients (≥6 years old) treated with: Desloratadine Fexofenadine Levocetirizine Cetirizine Loratadine Terfenadine	TSS PNIF TSSC (with nasal obstruction) Nasal congestion and obstruction	OAH efficacious for improving subjective and objective measures, effective in relieving nasal congestion associated with AR
Katiyar and Prakash[1788]	2009	1	SR of 5 RCTs	Patients (≥12 years old) treated with: Rupatadine Ebastine Cetirizine Loratadine Desloratadine	ARIA criteria evaluated for: Intermittent, persistent, seasonal, perennial AR TSS DTSSm DSSm QT changes	Rupatadine is a non-sedative, efficacious, and safe OAH for AR
Bachert and van Cauwenberge[1789]	2007	1	SR of 8 RCT	Patients (≥12 years old) treated with desloratadine	Reviewed multiple outcomes in relation to the ARIA definitions of AR: TSS TNSS TNNSS PNIF Intermittent, persistent, seasonal, perennial AR	Desloratadine is well tolerated and efficacious for intermittent and persistent AR with reductions in congestion, TSS, TNSS, TNNSS, and improved QOL
Canonica et al.[1790]	2007	1	SR of 13 RCTs	Patients ($n = 3108$, ≥12 years old) treated with desloratadine	TSS TNSS Nasal airflow	Reduction in TSS, TNSS, and improved nasal airflow
Patou et al.[1791]	2006	1	SR of 4 RCTs	Adult patients ($n = 782$) treated with levocetirizine	Nasal obstruction	Improved nasal obstruction under artificial and natural allergen exposure
Hore et al.[1792]	2005	1	SR of 7 RCT	Adult patients treated with OAH or placebo	Nasal obstruction	OAH improve nasal obstruction by 22% over placebo
Passalacqua and Canonica[1793]	2005	1	SR of 8 RCTs	Patients (≥6 years old) treated with: Levocetirizine Desloratadine	Nasal symptoms Wheal flare response QOL TSS	Improved QOL and TSS for seasonal/perennial AR Levocetirizine has a faster onset

(Continues)

TABLE XI.B.1.a.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Greisner[1794]	2004	1	SR of 5 RCTs	Patients (≥13 years old) treated with: Cetirizine Desloratadine Fexofenadine Loratadine	Onset of action	Inconsistent results, onset of action is dependent upon how it is defined and measured
Limon et al.[1795]	2003	1	SR of 9 RCTs	Patients (≥12 years old) treated with desloratadine	TSS TNSS TNNSS Nasal congestion and airflow TASS	Desloratadine is a safe and efficacious for patients with seasonal/perennial AR Improved TSS, TNSS and TNNSS, TASS, nasal congestion Nasal congestion excluded in PAR group
Bedard et al.[1677]	2019	4	Cross-sectional	Patients using INCS and/or OAH who completed a mobile allergy diary ($n = 9122$)	VAS	Increased medication use associated with increased symptoms Patients treat themselves as needed for symptoms despite physicians recommending long-term treatment
Scadding[1796]	2015	4	Review of CS: ARIA, EAACI, Royal College of Paediatrics and Child Health	Oral antihistamines	–	Second-generation, non-sedating, antihistamines are recommended for mild-moderate AR and in combination for severe AR; sedating antihistamines should not be used
Seidman et al.[1005]	2015	4	SR with guideline (9 CPGs, 81 SR, and 177 RCTs)	Patients (≥2 years old) treated with OAH	Relieving allergy symptoms Adverse events	Strong recommendation to use non-sedating OAH, benefits outweigh harm
Brozek et al.[1004]	2010	4	Guideline	OAH	–	Strong recommendation to use second-generation OAH that do not cause sedation and do not interact with cytochrome p450 enzyme
Bousquet et al.[1775]	2004	4	ARIA/EAACI criteria for antihistamines	Desloratadine	ARIA/EAACI criteria efficacy, safety, pharmacology	Desloratadine recommended for treating patients with AR

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CPG, clinical practice guideline; CS, consensus statement; DES, daytime eye symptoms; DNS, daytime nasal symptoms; DSSm, Mean Daily Symptom Score; DTSSm, Mean Total Daily Symptom Score; EAACI, European Academy of Allergy and Clinical Immunology; ESS, Epworth Sleepiness Scale; INCS, intranasal corticosteroid; LOE, level of evidence; OAH, oral antihistamine; PNIF, peak nasal inspiratory flow; QOL, quality of life; QT, measure of time between the onset of ventricular depolarization and completion of ventricular repolarization on electrocardiogram; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SR, systematic review; TASS, Total Asthma Symptom Score; TNNSS, Total Non-Nasal Symptom Score; TNSS, Total Nasal Symptom Score; TSS, Total Symptom Score; TSSC, Total Symptom Severity Complex; VAS, visual analog scale.

hydrochloride and cimetidine was significantly more effective in reducing the nasal resistive response than H_1 antagonist alone. However, not all data regarding combination therapy has been conclusive with other studies finding no improvement in nasal airflow with the addition of an H_2 antihistamine.[1802,1803] Moreover, the clinical significance of these objective measures remain unclear (Table XI.B.1.b).

Alternatively, several studies have investigated the impact of H_2 antagonism on symptoms by employing PROMs. Subjects were asked to report some combination of congestion, blockage, itch, drainage, sneeze, eye symptoms, and asthma with a categorical severity measure. Three of the four studies examined symptoms after nasal allergen challenge, and none of these demonstrated efficacy of H_2 antihistamines in diminishing allergic symptoms, either alone, or conjunction with an H_1 antihistamine.[1800,1802–1804] The majority of RCTs investigating the efficacy of H_2 antihistamines are within the context of pre-treatment of a patient prior to a nasal histamine or allergen challenge. Only one study investigated the impact of an H_2 antagonist, cimetidine, in conjunction with chlorpheniramine in a real-world setting. Carpenter et al.[1804] randomized 23 subjects with known late-summer AR to receive alternating 2-week courses of either chlorpheniramine plus placebo during the season, or chlorpheniramine plus cimetidine. Symptom scores were recorded twice daily along with adjuvant medical therapies taken (specifically, oral corticosteroids). A significant reduction in medication use was reported by patients receiving both H_1 and H_2 antagonists (28 corticosteroid days vs. 44 corticosteroid days, $p < 0.02$) and decreased symptoms scores during one of the 8 weeks when weed pollen counts were high. A limitation of this study is its utilization of a first-generation antihistamine which is no longer utilized as first-line treatment of rhinitis symptoms. No current studies exist comparing INCS with second-generation antihistamines in combination with H_2 blockers.

The data existing on the use of H_2 antihistamines in AR is limited in scope and quality, with very little addition to the literature in the past decade. The objective findings of improved nasal airway resistance suggest that the H_2 histamine receptor does modulate nasal tissue response to histamine.[1798–1801] However, the clinical significance of this mechanism is not clear, particularly in the context of modern treatment algorithms.[1800–1804] Given the relatively manageable side effect profile and costs of H_2 antihistamines, they may offer patients with otherwise recalcitrant AR symptoms an additional treatment option. However, additional investigation on the efficacy of H_2 antihistamines in combination with other topical medications may be beneficial in the future.

Oral H_2 antihistamines

Aggregate grade of evidence: B (Level 2: 7 studies; Table XI.B.1.b)
Benefit: Decreased objective nasal resistance, and improved symptom control in 4 studies when used in combination with H_1 antagonists.
Harm: Drug–drug interaction (p450 inhibition, inhibited gastric secretion and absorption). See Table II.C.
Cost: Increased cost associated with H_2 antagonist over H_1 antagonist alone.
Benefits-harm assessment: Unclear benefit and possible harm.
Value judgments: No studies evaluating efficacy of H_2 antihistamines in context of INCS. There were two studies that showed no benefit for H_2 antagonist when used alone or as an additive to H_1 antagonist therapy.
Policy level: No recommendation. Available evidence does not adequately address the benefit of H_2 antihistamines in AR.
Intervention: Addition of an oral H_2 antagonist to an oral H_1 antagonist may improve symptom control in AR, but data is limited.

XI.B.1.c | *Intranasal antihistamines*

Two formulations of intranasal antihistamine are currently available in North America for use as a topical spray, azelastine hydrochloride, and olopatadine hydrochloride. The English-language literature was systematically reviewed for clinical trials of either of these formulations for the treatment of AR. A total of 44 papers were identified that reported results of RCTs of intranasal antihistamine monotherapy. This included 24 studies with an active treatment comparator arm[1479,1805–1827] and 29 studies with an inactive placebo arm.[1808,1809,1812–1814,1816,1818,1820,1822,1824,1825,1828–1845] Monotherapy with azelastine was reported in 37 studies[1479,1805,1806,1808,1810–1816,1818–1828,1831–1836,1840–1848] while monotherapy with olopatadine was reported in 10 studies.[1807,1809,1829,1830,1833,1835,1837–1839,1847] Some studies utilized multiple active treatment arms of antihistamine and/or corticosteroid (Table XI.B.1.c).

Patient-reported symptom scores or QOL assessments were the most frequently utilized outcome measures in the included studies. The most common outcome measure was the TNSS (23 studies), which summarizes the severity of the cardinal symptoms of sneezing, itching, congestion, and runny nose. Other outcome measures included the RQLQ (seven studies), the Total Ocular Symptom

TABLE XI.B.1.b Evidence table – oral H_2 antihistamines for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Taylor-Clark et al.[1799]	2005	2	RCT	Histamine challenge with premedication: PO cetirizine PO ranitidine PO cetirizine + PO ranitidine Placebo	Nasal airway resistance	Cetirizine and ranitidine improve nasal resistance alone Cetirizine-ranitidine combination improves nasal resistance beyond either alone
Juliusson and Bende[1802]	1996	2	RCT	Allergy challenge with premedication: PO terfenadine PO cimetidine PO terfenadine + PO cimetidine Placebo	Laser Doppler flowmetry Allergic symptoms	No difference in symptoms or flowmetry with cimetidine No additive effect of cimetidine with terfenadine
Wang et al.[1800]	1996	2	RCT	Allergy challenge with premedication: PO cetirizine PO cetirizine + PO cimetidine	Symptoms (itching, sneezing, rhinorrhea, congestion) Sneeze count Nasal airway resistance	Combination of cetirizine-cimetidine improved nasal airway resistance and nasal airflow over cetirizine alone
Wood-Baker et al.[1798]	1996	2	RCT	Allergy challenge with premedication: PO cetirizine PO ranitidine	Nasal lavage fluid protein concentration Nasal airway resistance	Ranitidine improved nasal resistance more than cetirizine Cetirizine decreased total protein and albumin more than ranitidine
Havas et al.[1801]	1986	2	RCT	Histamine challenge with premedication: PO diphenhydramine hydrochloride + PO cimetidine PO diphenhydramine hydrochloride + placebo	Nasal airway resistance	Combination of diphenhydramine-cimetidine was more effective in reducing the nasal resistance to topical histamine than diphenhydramine alone ($p < 0.001$) Diphenhydramine increased the resistance of the unprovoked nose, whereas combined diphenhydramine-cimetidine produced no significant change
Carpenter et al.[1804]	1983	2	RCT	During allergy season medicated with: PO chlorpheniramine PO chlorpheniramine + PO cimetidine	Symptoms (rhinorrhea, sneezing, nasal congestion, nasal pruritus, eye discomfort) Rescue medication use	Reduced symptoms and medication scores in chlorpheniramine-cimetidine
Brooks et al.[1803]	1982	2	RCT	Allergy challenge with premedication: PO cimetidine Placebo	Symptoms (congestion, itch, drainage, sneeze) Nasal airway resistance Nasal secretion weight	No difference in subjective scores Increased secretion and sneeze count, no difference in nasal resistance

Abbreviations: LOE, level of evidence; PO, per os (by mouth); RCT, randomized controlled trial.

TABLE XI.B.1.c Evidence table – intranasal antihistamines for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Carr et al.[1805]	2012	2	DBRCT (post-hoc analysis)	Azelastine 0.28 mg BID Fluticasone propionate 0.1 mg spray BID	rTNSS rTOSS RQLQ	Fluticasone superior to azelastine for improving rhinorrhea; comparable symptom and QOL improvement
Han et al.[1846]	2011	2	DBRCT	Azelastine 0.1% Levocabastine hydrochloride 0.05% spray	rTNSS	Comparable symptom improvement
Howland et al.[1828]	2011	2	DBRCT	Azelastine 0.82 mg BID Placebo	rTNSS rTOSS RQLQ	Azelastine superior to placebo for nasal and eye symptoms and QOL
Meltzer et al.[1829]	2011	2	DBRCT	Olopatadine 1.33 mg BID Placebo	rTNSS rTOSS PRQLQ CGTSQ-AR	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers
Kalpaklioglu and Kavut[1806]	2010	2	Single-blind RCT	Azelastine 0.56 mg BID Triamcinolone acetonide 0.22 mg spray QD	TNSS PNIF ESS SF-36 mRQLQ	Comparable improvement in nasal symptoms, PNIF, ESS and QOL; azelastine superior for ocular symptoms
Berger et al.[1830]	2009	2	DBRCT	Olopatadine 1.33 mg BID Olopatadine 2.66 mg BID Placebo	TNSS TOSS PRQLQ CGTSQ-AR SGA	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers
Bernstein et al.[1831]	2009	2	DBRCT	Azelastine 0.28 mg BID Reformulated azelastine 0.28 mg BID Azelastine 0.56 mg BID Reformulated azelastine 0.56 mg BID Placebo 2 sprays	TNSS	Both azelastine spray formulations superior to placebo; dose–response effect was seen; no difference in bitter taste between formulations
Kaliner et al.[1807]	2009	2	DBRCT	Olopatadine 2.66 mg BID Fluticasone 0.2 mg spray QD	rTNSS rTOSS	Both treatments improve symptoms; faster onset for olopatadine
Shah et al.[1832]	2009	2	DBRCT	Azelastine 0.82 mg BID Azelastine 0.56 mg BID Placebo	TNSS	Both azelastine doses superior to placebo; greater improvement with higher dose
Shah et al.[1833]	2009	2	DBRCT	Olopatadine 2.66 mg BID Azelastine 0.56 mg BID Placebo	TNSS	Both treatments superior to placebo; no difference between treatments; less bitter taste with olopatadine

(Continues)

TABLE XI.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
van Bavel et al.[1834]	2009	2	DBRCT	Azelastine 0.82 mg QD Placebo	TNSS	Azelastine superior to placebo
Meltzer et al.[1847]	2008	2	DBRCT	Olopatadine 2.66 mg BID Azelastine 0.56 mg BID	Sensory perception	Olopatadine favored for taste, aftertaste, and likelihood of use
Pipkorn et al.[1835]	2008	2	DBRCT	Olopatadine 0.1% Olopatadine 0.2% Azelastine 0.1% Placebo	4-item symptom score Nasal lavage	Both olopatadine doses superior to placebo for reducing symptoms; higher concentration inhibits mast cell degranulation
Lumry et al.[1836]	2007	2	DBRCT	Azelastine 0.28 mg QD Azelastine 0.28 mg BID Placebo	TNSS	Azelastine both doses superior to placebo
Patel et al.[1808]	2007	2	DBRCT	Azelastine 0.56 mg QD Mometasone furoate 0.2 mg spray QD Placebo	TNSS	Azelastine superior to mometasone and placebo
Patel et al.[1809]	2007	2	DBRCT	Olopatadine 2.66 mg QD Mometasone furoate 0.2 mg spray QD Placebo	TNSS Patient satisfaction	Olopatadine superior to placebo and mometasone in reducing symptoms; faster onset for olopatadine
Berger et al.[1810]	2006	2	DBRCT	Azelastine 0.56 mg BID Cetirizine 10 mg tablet QD	TNSS RQLQ	Azelastine superior for sneezing and nasal congestion; azelastine superior for QOL
Hampel et al.[1837]	2006	2	DBRCT	Olopatadine 2.66 mg BID Olopatadine 1.77 mg BID Placebo	Total symptom score RQLQ	Olopatadine (both doses) superior to placebo in majority of domains for QOL improvement
Horak et al.[1479]	2006	2	DBRCT	Azelastine 0.4 mg QD Desloratadine 5 mg tablet QD Placebo spray	TNSS	Azelastine superior to desloratadine and placebo
Corren et al.[1811]	2005	2	DBRCT	Azelastine 0.56 mg BID Cetirizine 10 mg tablet QD	TNSS RQLQ	Azelastine superior cetirizine for symptoms and QOL
Meltzer et al,[1838]	2005	2	DBRCT	Olopatadine 2.66 mg BID Olopatadine 1.77 mg BID Placebo	TNSS RQLQ	Olopatadine (both doses) superior to placebo for symptoms and QOL improvement

(Continues)

TABLE XI.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ratner et al.[1839]	2005	2	DBRCT	Olopatadine 2.66 mg BID Olopatadine 1.77 mg BID Placebo	TNSS	Olopatadine (both doses) superior to placebo
LaForce et al.[1812]	2004	2	DBRCT	Azelastine 0.56 mg BID Azelastine 0.56 mg BID + fexofenadine 60 mg tablet BID Placebo spray + placebo tablet	TNSS	Azelastine superior to placebo; no additional benefit of adding oral fexofenadine to azelastine monotherapy
Berger et al.[1813]	2003	2	DBRCT	Azelastine 0.56 mg BID Azelastine 0.56 mg BID + loratadine 10 mg tablet Desloratadine 5 mg tablet + placebo spray Placebo spray + placebo tablet	TNSS	All treatments superior to placebo; azelastine at least as effective as desloratadine; no additional benefit of adding oral loratadine to azelastine monotherapy
Saengpanich et al.[1840]	2002	2	DBRCT	Azelastine 0.28 mg BID Placebo	TNSS Nasal lavage Response to methacholine challenge	Azelastine superior to placebo for symptoms; no effect on nasal eosinophils or cytokines; azelastine inhibits methacholine response
Falser et al.[1848]	2001	2	DBRCT	Azelastine 0.56 mg BID Levocabastine 0.2 mg spray BID	10-item symptom score Global assessment	Azelastine superior to levocabastine
Berlin et al.[1814]	2000	2	DBRCT	Azelastine 0.56 mg BID Flunisolide 0.116 mg spray BID Placebo	9-item symptom score	Flunisolide superior to azelastine; both treatments superior to placebo
Golden et al.[1841]	2000	2	DBRCT	Azelastine 0.56 mg BID Placebo	RSS ESS	Azelastine superior to placebo for improving rhinorrhea and sleep quality
Berger et al.[1815]	1999	2	DBRCT	Azelastine 0.56 mg BID Loratadine 10 mg tablet QD + beclomethasone dipropionate 0.168 mg spray BID	5-item symptom score Global evaluation	Azelastine at least as effective as combination therapy with loratadine plus beclomethasone spray
Stern et al.[1816]	1998	2	DBRCT	Azelastine 0.28 mg BID Budesonide 0.256 mg spray QD Placebo	3-item symptom score	Budesonide superior to azelastine; both treatments superior to placebo

(Continues)

TABLE XI.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Herman et al.[1842]	1997	2	DBRCT	Azelastine 0.28 mg BID Placebo	TNSS	Azelastine superior to placebo for children
Newson-Smith et al.[1843]	1997	2	DBRCT	Azelastine 0.56 mg BID Beclomethasone 0.2 mg spray BID Placebo	6-item symptom score	Beclomethasone superior to azelastine for long-term symptom improvement; both treatments superior to placebo; azelastine more rapid onset
Weiler and Meltzer[1844]	1997	2	DBRCT	Azelastine 0.56 mg spray BID + azelastine 0.5 mg tablet BID Placebo spray + azelastine 0.5 mg tablet BID	13-item symptom score	Azelastine spray showed limited benefit over placebo in patients already treated with systemic azelastine
LaForce et al.[1818]	1996	2	DBRCT	Azelastine 0.56 mg QD Azelastine 0.56 mg BID Chlorpheniramine 12 mg tablet BID Placebo	8-item symptom score	Azelastine superior to placebo at both doses; no comparison with chlorpheniramine
Charpin et al.[1819]	1995	2	DBRCT	Azelastine 0.28 mg BID Cetirizine 10 mg tablet QD	8-item symptom score	Azelastine superior for nasal stuffiness and rhinorrhea; no difference in other symptoms
Pelucchi et al.[1820]	1995	2	DBRCT	Azelastine 0.28 mg BID Beclomethasone dipropionate 0.1 mg spray BID Placebo	8-item symptom score Nasal lavage Response to methacholine challenge	Azelastine superior to placebo and comparable to beclomethasone for symptom improvement; neither treatment prevented bronchial responsiveness; no effect of azelastine on eosinophils
Gastpar et al.[1821]	1994	2	DBRCT	Azelastine 0.28 mg QD Terfenadine 60 mg tablet QD	13-item symptom score	Comparable symptom improvement
Meltzer et al.[1822]	1994	2	DBRCT	Azelastine 0.28 mg QD Azelastine 0.28 mg BID Chlorpheniramine 12 mg tablet BID Placebo	11-item symptom score	Azelastine comparable to chlorpheniramine and superior to placebo at both doses

(Continues)

TABLE XI.B.1.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Passali and Piragine[1823]	1994	2	DBRCT	Azelastine 0.28 mg BID Cetirizine 10 mg tablet QD	13-item symptom score	Azelastine at least as effective as cetirizine
Ratner et al.[1845]	1994	2	DBRCT	Azelastine 0.28 mg QD Azelastine 0.28 mg BID Placebo	8-item symptom score	Azelastine twice-daily superior to placebo
Davies et al.[1824]	1993	2	DBRCT	Azelastine 0.28 mg BID Beclomethasone dipropionate 0.1 mg spray BID Placebo	TNSS Rhinomanometry	Azelastine superior to beclomethasone and placebo for symptoms; no change in airway resistance with either treatment
Dorow et al.[1825]	1993	2	DBRCT	Azelastine 0.28 mg BID Budesonide 0.10 mg spray BID Placebo	13-item symptom score	Azelastine comparable to budesonide for nasal symptoms and superior for ocular symptoms; both treatments superior to placebo
Gambardella[1826]	1993	2	DBRCT	Azelastine 0.28 mg BID Loratadine 10 mg tablet QD	12-item symptom score Global assessment	Azelastine at least as effective as loratadine
Gastpar et al.[1827]	1993	2	DBRCT	Azelastine 0.28 mg BID Budesonide 0.10 mg spray BID	10-item symptom score Nasal flow rate	Azelastine at least as effective as budesonide for symptoms; flow rate improved in both treatment groups

Abbreviations: BID, twice daily; CGTSQ-AR, Caregiver Treatment Satisfaction Questionnaire for Allergic Rhinitis; DBRCT, double-blind randomized controlled trial; ESS, Epworth Sleepiness Scale; LOE, level of evidence; mRQLQ, mini-Rhinoconjunctivitis Quality of Life Questionnaire; PNIF, peak nasal inspiratory flow; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; QD, daily; QOL, quality of life; r, reflective; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SF-36, 36-item Short Form Survey; SGA, Subject Global Assessment; TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score.

Score (TOSS, five studies), the Caregiver Treatment Satisfaction Questionnaire (two studies), the Pediatric RQLQ (one study), the SF-36 (one study), the ESS (one study), the Rhinitis Severity Score (one study), and a Subjective Global Assessment (one study). Multiple studies, particularly those published more than 20 years ago, relied upon arbitrary, non-validated symptom scores for reporting treatment outcomes (19 studies). A minority of studies included objective measures such as nasal lavage (three studies), response to methacholine challenge (two studies), nasal flow rate (two studies), and rhinomanometry (one study).

The most frequent treatment duration was 14 days in the included studies, with a range from 2 days to 8 weeks. Study enrollment ranged from 20 to 1188 subjects. In the 29 studies using placebo as a comparison group,[1808,1809,1812–1814,1816,1818,1820,1822,1824,1825,1828–1845] intranasal antihistamine showed superiority for the primary outcome of nasal symptom improvement. An active treatment comparator of a different medication was used in 24 studies.[1479,1805–1827] The intranasal antihistamine spray treatment group consistently had a more rapid onset of action than the treatment comparator, occurring as early as 15 min after administration, although this was not reported in all studies. Azelastine and olopatadine were directly compared in three studies, with no significant difference in symptom relief between agents.[1833,1835,1847] Azelastine was compared with an experimental formulation of intranasal levocabastine in two additional studies, with either comparable or superior results for azelastine.[1846,1848] Levocabastine is not available as a commercial product.

The active treatment comparators utilized in 24 studies consisted of an INCS or oral antihistamine. Twelve studies compared intranasal antihistamine with INCS, with the primary outcome of nasal symptom improvement favoring antihistamine in two studies,[1808,1809] INCS in three studies,[1814,1816,1843] and showing equivalency in seven studies.[1805–1807,1820,1824,1825,1827] Superiority of the antihistamine for treating ocular symptoms was found in two studies, one of which was nearly 30 years old.[1806,1825] The three studies showing superiority of INCS were over 20 years old and reported outcomes using heterogeneous non-validated symptom scores.

Intranasal antihistamine was compared to oral antihistamine monotherapy in eight studies, with superiority of intranasal antihistamine in three studies,[1810,1811,1819] and equivalency in five studies.[1813,1821–1823,1826] One study included a treatment arm with oral chlorpheniramine as a positive control without intent to compare efficacy with azelastine.[1818] Azelastine monotherapy was at least as effective as combination therapy in a single study comparing azelastine spray versus oral loratadine plus intranasal beclomethasone.[1815] Combination therapy with intranasal azelastine plus oral antihistamine was not found to confer additional benefit in two studies compared to intranasal azelastine monotherapy.[1812,1813] An overall dose–response relationship was found in 11 studies that included comparison of multiple dose concentrations of intranasal antihistamine.[1818,1822,1830–1832,1835–1839,1845]

Most of the included studies set a minimum enrollment age of 12 years or older. Three studies that included children aged between 6 and 12 years old found superiority of intranasal antihistamine to placebo in improving symptoms and QOL.[1829,1830,1842]

No study reported any serious adverse effects from use of an intranasal antihistamine. These formulations are noted to be generally well tolerated, with taste aversion being the most reported adverse effect. One study that compared a reformulated vehicle against the commercially available form of azelastine found no difference in taste aversion.[1831] Olopatadine was reported to have better sensory attributes than azelastine in one study.[1847] Other reported adverse effects were uncommon, with somnolence, headache, epistaxis, and nasal discomfort each occurring in less than 10% of patients treated with azelastine or olopatadine (Table II.C).

In 2021, the US FDA approved azelastine hydrochloride as an over-the-counter formulation, making intranasal antihistamines available for the first time without a prescription. This change may remove some financial barriers to patient use and improve access to this medication as a treatment option for AR.

Intranasal antihistamines

Aggregate grade of evidence: A (Level 2: 44 studies; Table XI.B.1.c)
Benefit: Rapid onset; more effective for nasal congestion than oral antihistamines; more effective for ocular symptoms than INCS; consistent reduction in symptoms and improvement in QOL in RCTs compared to placebo.
Harm: Patient tolerance, typically related to taste aversion; less effective for congestion than INCS. See Table II.C.
Cost: Low to moderate financial burden; available as prescription or nonprescription product.
Benefits-harm assessment: Preponderance of benefit over harm. Intranasal antihistamine as monotherapy is consistently more effective than placebo. Most studies show intranasal antihistamines superior to INCS for sneezing, itching, rhinorrhea, and ocular symptoms. Adverse effects are minor and infrequent. Generic prescription and over-the-counter formulations now available.
Value judgments: Extensive high-level evidence comparing intranasal antihistamine monotherapy to active and placebo controls demonstrates overall effectiveness and safety.
Policy level: Strong recommendation.
Intervention: Intranasal antihistamines may be used as first- or second-line therapy in the treatment of AR.

XI.B.2 | Corticosteroids

XI.B.2.a | *Oral corticosteroids*

Early work using the nasal challenge model has elucidated the anti-inflammatory effects of oral corticosteroids in AR. Pipkorn et al.[1849] premedicated patients with seasonal AR with either prednisone or placebo for 2 days prior to an allergen challenge. When compared to placebo, patients receiving prednisone demonstrated a significant reduction in sneezing as well as reduced levels of histamine and other mediators of vascular permeability in nasal lavages during the late phase response. Active treatment also reduced the priming response to consecutive allergen challenges. In similar placebo-controlled studies, Bascom et al.[1850,1851] demonstrated a reduction in the influx of eosinophils and levels of eosinophil mediators (MBP and eosinophil derived neurotoxin) in nasal secretions during the late phase response in patients receiving 60 mg

oral prednisone for 2 days prior to nasal challenge (Table XI.B.2.a).

The efficacy of oral corticosteroids in seasonal clinical disease has also been demonstrated with less rigorous studies that did not include a placebo control. Schwartz et al.[1852] demonstrated that 15 days of cortisone (25 mg QID [four times daily]) during the ragweed season resulted in significant relief of symptoms in 21 of 25 patients. Schiller and Lowell[1853] showed that cortisone (100 mg daily) for 4 day courses during the pollen season resulted in rhinitis symptom relief in 42 of 51 patients. Twenty of those patients had a relapse of symptoms within 7 days of cessation of therapy.[1853] Oral hydrocortisone (40–80 mg daily) has been shown to reduce symptoms of ragweed allergies.[1854] In a placebo-controlled study performed during the ragweed season, Brooks et al.[1855] compared the efficacy of methylprednisolone (6, 12, or 24 mg PO [per os, by mouth] daily for 5 days) to placebo in controlling nasal symptoms. They reported a significant reduction in congestion, postnasal drainage, and ocular symptoms compared to placebo after 6 and 12 mg doses. The higher, 24 mg, dose was more effective and resulted in a significant reduction in all symptoms queried (congestion, runny nose, sneezing, itching, postnasal drainage, and ocular symptoms) compared to placebo. Snyman et al.[1856] performed a parallel, double blind study comparing betamethasone 1 mg alone to a combination of betamethasone and loratadine and loratadine alone in patients with severe AR. The group on oral steroids had a significant improvement from baseline in total nasal symptoms and was superior to loratadine alone.

Although effective, oral corticosteroids have well recognized systemic adverse events,[152] and therefore, their use has been largely replaced by intranasal preparations (Table II.C). In a double-blind, placebo-controlled trial conducted during the ragweed season, the effect of intranasal flunisolide and its oral dose bioequivalent (an oral dose that would lead to similar systemic levels) were compared.[1857] The intranasal preparation reduced rhinitis symptoms compared to placebo whereas the oral dosing did not, suggesting that INCS achieve their benefit primarily through local activity as opposed to systemic bioavailability.

Karaki et al.[1858] compared the efficacy of INCS to systemic steroids by performing an open label, parallel, randomized trial during the cedar pollen season in Japan. Patients were randomized to receive loratadine 10 mg daily alone, loratadine with intranasal mometasone furoate (200 μg once daily), or loratadine with oral betamethasone 0.25 mg twice daily for 1 week. Participants receiving any form of steroids demonstrated significantly reduced symptoms of sneezing, rhinorrhea, and nasal obstruction compared to loratadine alone, with no significant difference between the intranasal and oral preparations noted. The oral steroid was more effective than the INCS, however, in controlling allergic eye symptoms.

In summary, oral corticosteroids are effective for the treatment of AR. However, given the significant systemic adverse effects related to using these agents for prolonged periods of time, and the availability of effective and less systemically available intranasal preparations, oral corticosteroids are not recommended for the routine treatment of AR.

Oral corticosteroids

Aggregate grade of evidence: B (Level 2: 6 studies, level 3: 1 study, level 4: 3 studies; Table XI.B.2.a)
Benefit: Oral corticosteroids can attenuate symptoms of AR and ongoing allergen induced inflammation.
Harm: Oral corticosteroids have multiple potential adverse effects, including hypothalamic-pituitary axis suppression. Prolonged use may lead to growth retardation in pediatric populations. See Table II.C.
Cost: Low.
Benefits-harm assessment: The risks of oral corticosteroids outweigh the benefits, given similar symptomatic improvement observed with the use of safer INCS.
Value judgments: In the presence of effective symptom control using INCS, the risk of adverse effects from using oral corticosteroids for AR outweighs potential benefits.
Policy level: Strong recommendation against routine use.
Intervention: Although not recommended for routine use in AR, certain clinical scenarios may warrant the use of short courses of systemic corticosteroids, following a discussion of the risks and benefits with the patient. For example, oral steroids could be considered in select patients with significant nasal obstruction that precludes adequate penetration of intranasal agents (corticosteroids or antihistamines). In these cases, a short course of systemic corticosteroids may improve congestion and facilitate access of topical medications. No evidence supports this suggestion, and thus careful clinical judgement and risk discussion are advocated.

XI.B.2.b | *Intranasal corticosteroids*

XI.B.2.b.i | *Traditional spray application.* INCS have potent anti-inflammatory properties and lead to a significant reduction in mediator and cytokine release along with a significant inhibition in the recruitment of inflammatory cells to nasal secretions and the nasal

TABLE XI.B.2.a Evidence table – oral corticosteroids for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Snyman et al.[1856]	2004	2	Parallel, double-blind, active controlled multicenter study	Patients with severe AR treated for 5–7 days ($n = 299$): Betamethasone 1.0 mg Betamethasone 1.0 mg + loratadine 10 mg Betamethasone 0.5 mg + loratadine 10 mg Loratadine 10 mg	Total symptom scores Nasal obstruction Doctor and patient perception of improvement	Regimens with oral steroids had significant improvement of total nasal symptoms better than loratadine alone
Brooks et al.[1855]	1993	2	Placebo-controlled, parallel group study	Patients with SAR during the season ($n = 31$): methyl-prednisolone 6, 12, 24 mg QD x 5 days	Symptom scores	All doses more effective than placebo in reducing symptoms; highest dose was most effective
Bascom et al.[1851]	1989	2	Placebo-controlled, crossover, nasal challenge study	SAR out of season ($n = 13$): prednisone 60 mg PO QD for 2 days	Eosinophils, levels of MBP and EDN in nasal lavages	Prednisone reduced the number of eosinophils and mediator levels after allergen challenge
Bascom et al.[1850]	1988	2	Placebo-controlled, crossover, nasal challenge study	SAR out of season ($n = 10$): prednisone 60 mg PO daily for 2 days	Neutrophils, eosinophils, and mononuclear cells in nasal lavages	Prednisone reduced the influx of eosinophils into nasal secretions after allergen challenge
Pipkorn et al.[1849]	1987	2	Placebo-controlled, crossover, nasal challenge study	SAR out of season ($n = 13$): prednisone 60 mg PO daily for 2 days	Sneezes; levels of histamine, TAME-esterase, kinins, PGD2, LTC4/D4, albumin in nasal lavages	Prednisone inhibited the late phase response to nasal allergen challenge
Kwaselow et al.[1857]	1985	2	Multicenter, randomized, double-blind, placebo-controlled	Patients with SAR during season ($n = 99$): Oral flunisolide 500 μg BID Intranasal flunisolide 50 μg per nostril BID x 4 weeks	Symptom scores	Intranasal preparation only one to show efficacy in reducing rhinitis symptoms
Karaki et al.[1858]	2013	3	Open label, parallel, randomized trial	Patients with SAR during season ($n = 72$): Loratadine 10 mg daily Loratadine + intranasal MF 200 μg QD Loratadine + PO betamethasone 0.25 mg BID	Symptom scores	Groups on steroids had lower symptoms compared to loratadine alone No significant difference between steroid groups

(Continues)

TABLE XI.B.2.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Schwartz[1854]	1954	4	Observational case series	Patients with SAR during season (n = 10): hydrocortisone 40 to 80 mg QD	Symptom relief	7/10 patients reported symptom relief
Schiller and Lowell[1853]	1953	4	Observational case series	Patients with SAR during season (n = 51): cortisone 100 mg QD x 4 days	Symptom relief	42/51 patients reported symptom relief
Schwartz et al.[1852]	1952	4	Observational case series	Patients with SAR during season (n = 25): cortisone 100 mg QD x 15 days	Symptom relief	21/25 patients reported symptom relief

Abbreviations: AR, allergic rhinitis; BID, twice daily; EDN, eosinophil derived neurotoxin; LOE, level of evidence; LTC4/D4, leukotriene C4/D4; MBP, major basic protein; MF, mometasone furoate; PGD2, prostaglandin D2; PO, per os (by mouth); QD, daily; SAR, seasonal allergic rhinitis; TAME, N-a-p-tosyl-L-arginine methyl ester.

mucosa.[255,496,1859–1861] INCS also reduce the antigen-induced hyperresponsiveness of the nasal mucosa to subsequent challenge.[255,1862,1863]

Clinical trials in adults and children have demonstrated the effectiveness of INCS in the reduction of nasal symptoms in AR.[1864–1866] INCS also significantly improve patients' QOL[1865,1867,1868] and sleep.[1053,1107,1108,1869,1870] Onset of action starts at time points ranging from 3–5 h to 60 h after dosing.[1871–1874] Although the continuous daily use of INCS is overall superior,[1875,1876] studies have demonstrated the superiority of as needed use of intranasal fluticasone propionate over placebo[1877,1878] and one study showed equivalence of as needed to continuous dosing[1879] (Table XI.B.2.b.i.-1).

INCS have beneficial effects on allergic eye symptoms,[1880–1883] secondary to a reduction in the naso-ocular reflex.[1884] This effect is not equal among preparations.[1885] Some, but not all, studies have suggested that INCS improve asthma control measures and asthma exacerbations[1886–1888] (Table XI.B.2.b.i.-2).

In comparative studies there are no significant differences in efficacy between the available agents,[1867] and one study shows an advantage of using double dosing.[1889] INCS have shown superior efficacy to H_1 antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference in the relief of ocular symptoms.[1890–1892] However, for fast relief of nasal congestion (1 h after dosing) a combination of loratadine-pseudoephedrine was superior to intranasal fluticasone propionate.[1488] INCS are more effective than LTRAs[1892–1894] (Table XI.B.2.b.i.-3).

Different preparations of INCS are comparable in efficacy, making sensory attributes an important factor in patient preference.[1895] These include aftertaste, nose runout, throat rundown, and odor; there are minor differences between preparations.[1896] Two intranasal non-aqueous preparations with hydrofluoroalkane aerosols, beclomethasone dipropionate, and ciclesonide address some of these concerns.[1097,1897–1901]

The most common side effects of INCS are a result of local irritation and include dryness, burning, stinging, blood-tinged secretions, and epistaxis (Table II.C). The incidence of epistaxis with different preparations ranges 4%–8% over short treatment periods (2–12 weeks) with no differences between placebo and active therapy.[1902,1903] In studies carried over 1 year, epistaxis is as high as 20%.[1904,1905] Septal perforations are rare complications of INCS.[82] In a systematic review of biopsy studies in patients using INCS, none of the studies that evaluated atrophy of the nasal mucosa reported any atrophy with INCS.[1906] Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis and adrenal insufficiency show no clinically relevant adverse effects.[1905,1907–1919] Although there exists a report of association between INCS use and development of posterior subcapsular cataracts,[1920] two systematic reviews of controlled trials did not demonstrate a clinically relevant impact of INCS on either ocular pressure, glaucoma, lens opacity, or cataract formation.[1921,1922] Therefore, it is reasonable to use these agents with caution in patients with increased intraocular pressure, glaucoma, or cataracts. The effect of INCS on growth in children has been investigated in controlled short-term (2–4 weeks) and long-term (12 months) studies. A meta-analysis of eight RCTs showed that in the short-term, mean growth was significantly lower among children using INCS compared to placebo in trials using knemometry (n = 4), but that in the long-term, there was no significant growth difference in studies using stadiometry (n = 4).[1923] The data suggest that INCS might have deleterious effects on short-term growth in children, but the heterogeneity of the results in the stadiometry studies (two studies show growth increase and

TABLE XI.B.2.b.i.-1 Evidence table – intranasal corticosteroids (spray) for allergic rhinitis: clinical efficacy

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Rachelefsky et al.[1868]	2013	1	Systematic review	16 trials, children 2–18 years old with AR ($n = 2290$ seasonal AR, $n = 800$ perennial AR)	Controlled studies ≥2 weeks Measures assessing impairment and/or risk of comorbidities	INCS improved risk outcomes associated with asthma and OSA
Rodrigo and Neffen[1865]	2011	1	SRMA	16 trials, $n = 5348$ patients FFNS versus placebo Seasonal AR (7 studies), perennial AR (9 studies) Adolescents and adults (13 studies, ≥12 years old), pediatric patients (3 studies)	Primary: rTNSS, iTNSS, rTOSS, iTOSS Secondary: QOL, adverse effects	FFNS significantly improved rTOSS, iTOSS, rTNSS, iTNSS versus placebo in patients with seasonal and perennial AR FFNS led to greater improvements in QOL FFNS had a favorable safety profile
Penagos et al.[1864]	2008	1	Meta-analysis of DBRCTs	16 trials, $n = 2998$ patients with AR MFNS, $n = 1534$ Placebo, $n = 1464$	TNSS Individual nasal symptoms TNNSS	MFNS significantly reduced TNSS, TNNSS, nasal stuffiness and congestion, rhinorrhea, sneezing, nasal itching
Thongngarm et al.[1879]	2021	2	RCT	Patients with perennial AR, $n = 108$, 6-week trial FFNS daily x1 week, then as needed FFNS daily x6 weeks	Primary: TNSS Secondary: PNIF, RQLQ	TNSS between the 2 groups not significant at week 6 FFNS-daily group had higher mean change in PNIF than FFNS-as-needed group at week 6 Both groups had similar improvement in RQLQ
Urdaneta et al.[1866]	2019	2	Post-hoc analysis of two RCTs	Patients with seasonal AR and moderate–severe nasal congestion, $n = 684$ MFNS versus placebo x15 days	Change from baseline in morning and evening reflective nasal congestion scores	MFNS had significantly more patients who experienced >30% and >50% response in nasal congestion In MFNS group, response greater during second week of treatment versus first
Yamada et al.[1053]	2012	2	DBRCT, crossover	Patients with perennial AR, $n = 57$ MFNS versus placebo x14 days	Nasal symptom scores QOL Sleep quality ESS	MFNS significantly improved nasal symptoms, QOL, sleep quality Significant reduction of ESS observed in the MFNS group with high sleep disturbance

(Continues)

TABLE XI.B.2.b.i.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Meltzer et al.[1870]	2010	2	DBRCT, parallel group	Adults with moderate perennial AR & disturbed sleep, $n = 30$ MFNS 200 μg daily versus placebo x4 weeks	Primary: AHI Secondary: TNSS, nighttime symptom score, daytime PNIF, nighttime flow limitation index, RQLQ, ESS, WPAI-AS	AHI was not significantly different between groups MFNS significantly improved morning & evening TNSS, nasal obstruction/blockage/congestion, daily PNIF, ESS, RQLQ, and two of five WPAI-AS domains
Kaiser et al.[1873]	2007	2	DBRCT, parallel group	Patients ≥12 years old with fall seasonal AR, $n = 299$ FFNS 110 μg daily versus placebo	Nasal and ocular symptoms rTNSS, iTNSS, rTOSS	FFNS produced significantly greater improvements in daily rTNSS and rTOSS, morning pre-dose iTNSS, and patient-rated overall response to therapy
Craig et al.[1869]	2003	2	DBRCT	Patients with perennial AR, $n = 32$ Fluticasone NS 100 μg per nostril daily versus placebo	Questionnaires, QOL instruments, daily diary, ESS, polysomnography	Fluticasone improved subjective sleep versus placebo No difference in the AHI in treated subjects
Dykewicz et al.[1878]	2003	2	DBRCT	Patients ≥12 years old with seasonal AR in the fall, $n = 241$ FPNS 200 μg as needed x4 weeks	TNSS	FPNS group had significantly greater reduction in TNSS and individual symptoms
Hughes et al.[1107]	2003	2	DBRCT, crossover	Patients with perennial AR, $n = 22$ Budesonide 128 μg/day versus placebo x8 weeks	ESS; Functional Outcomes of Sleep Questionnaire; RQLQ; diary of nasal symptoms, sleep problems, daytime fatigue	Budesonide significantly improved daytime fatigue, somnolence, and quality of sleep versus placebo
Fokkens et al.[1872]	2002	2	DBRCT, parallel group	Patients 6–16 years old with perennial AR, $n = 202$ BANS 128 μg daily versus placebo	Daily PNIF, nasal symptom scores, overall evaluation of treatment efficacy Subset of patients ($n = 76$), QOL measured by validated questionnaires	BANS significantly more effective than placebo in improving PNIF, nasal symptoms, and overall evaluation of treatment efficacy Onset within 12 h for symptoms and within 48 h for PNIF
Day et al.[1871]	2000	2	DBRCT, parallel group	Ragweed-sensitive subjects, $n = 217$ BANS (64 and 256 μg) versus placebo Allergen challenge model in environmental exposure unit	Combined nasal score, individual nasal symptoms, overall evaluation of treatment efficacy reported by participants, PNIF	At 7–12 h, BANS better than placebo in reducing combined nasal and blocked nose symptoms For PNIF, time to onset of action was shortest for BANS 256 μg

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TABLE XI.B.2.b.i.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jen et al.[1877]	2000	2	DBRCT parallel group	Adults with seasonal AR to ragweed, n = 52 FPNS or placebo as-needed Study conducted in season	Nasal symptom score, QOL, number of eosinophils and level of eosinophilic cationic protein in nasal lavage	Nasal symptom score reduced and QOL improved with FPNS versus placebo Eosinophil number significantly lower with FPNS versus placebo at final visit
Craig et al.[1108]	1998	2	DBRCT	Patients with perennial AR treated with INCS versus placebo, n = 20	Daily symptom diary focused on nasal symptoms, sleep, and daytime sleepiness	Nasal congestion and subjective sleep improved significantly in INCS group
Day and Carrillo[1874]	1998	2	DBRCT, parallel group	Adults with perennial AR, n = 273 BANS FPNS Placebo 8–14 days (baseline), 6 weeks (treatment)	Mean combined nasal symptom scores (nasal blockage, runny nose, and sneezing)	BANS decreased nasal symptoms more than FPNS Both treatments decreased nasal symptoms versus placebo Adverse events were mild and transient
Juniper et al.[1875]	1990	2	DBRCT, parallel group	Ragweed-sensitive adults, n = 60 Aqueous BDNS 200 μg BID Aqueous BDNS 100 μg as needed, up to 400 μg daily	Sneezing, stuffy nose, rhinorrhea, measured by a daily diary QOL questionnaires Rescue medication use (terfenadine)	Nasal symptoms, QOL, and rescue medication use significantly better in the regular-treated group versus to the as-needed group
Herman[1867]	2007	3	Review of RCTs	14 studies Patients with seasonal and perennial AR Treated with once-daily BANS, MFNS, FPNS, or TANS	Different endpoints for different studies	All four INCSs administered once daily were effective and well tolerated in adult patients Similar efficacy and adverse event profiles Based on sensory attributes, patients preferred BANS and TANS
Juniper et al.[1876]	1993	3	Unblinded RCT, parallel group	Adults with ragweed pollen-induced rhinitis, n = 60 BDNS 400 μg daily BDNS as-needed Study performed in-season	Daily symptoms and medication use QOL Patient satisfaction with symptom control	27% of patients in as-needed group reported unsatisfactory symptom control, worse QOL, increased medication use No obvious predictors of unsatisfactory control identified Patients who achieved satisfactory control in as-needed group had similar symptom and QOL scores to daily use group

Abbreviations: AHI, apnea-hypopnea index; AR, allergic rhinitis; BANS, budesonide aqueous nasal spray; BDNS, beclomethasone dipropionate nasal spray; BID, twice daily; DBRCT, double-blind randomized controlled trial; ESS, Epworth Sleepiness Scale; FFNS, fluticasone furoate nasal spray; FPNS, fluticasone propionate nasal spray; i, instantaneous; INCS, intranasal corticosteroid; LOE, level of evidence; MFNS, mometasone furoate nasal spray; OSA, obstructive sleep apnea; PNIF, peak nasal inspiratory flow; QOL, quality of life; r, reflective; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SRMA, systematic review and meta-analysis; TANS, triamcinolone aqueous nasal spray; TNSS, Total Nasal Symptom Score; TNNSS, Total Non-Nasal Symptom Score; TOSS, Total Ocular Symptom Score; WPAI-AS, Work Productivity and Activity Impairment-Allergy Specific.

TABLE XI.B.2.b.i.-2 Evidence table – intranasal corticosteroids (spray) for allergic rhinitis: effect on comorbidities (ocular symptoms and asthma)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bielory et al.[1883]	2020	1	Meta-analysis of 8 RCTs	Patients with seasonal AR ($n = 1727$) treated for ≥2 weeks: TANS 220 μg daily, $n = 859$ FPNS 200 μg daily, $n = 327$ Placebo, $n = 541$	Mean change in total or individual (tearing, redness, and itching) eye symptoms	Total eye symptom reduction greater with TANS than placebo Significant reductions in tearing, but not itching or redness, observed with TANS versus placebo No significant difference between TANS and FPNS for total ocular symptoms
Lohia et al.[1887]	2013	1	SRMA	Patients with AR and asthma, 18 trials, $n = 2162$ patients	Pulmonary function, bronchial reactivity, asthma symptom scores, asthma specific QOL, rescue medication use	INCS spray significantly improved FEV_1, bronchial challenge, asthma symptom scores, morning/evening peak expiratory flow, and rescue medication use No significant changes in asthma outcomes with addition of INCS spray to orally inhaled corticosteroids
Bielory et al.[1881]	2011	1	Meta-analysis of 10 RCTs	Patients with seasonal AR (6 studies) and perennial AR (4 studies), $n = 3132$ MFNS 200 μg daily	Severity of reflective ocular symptoms (itching/burning, redness, and tearing/watering)	Overall treatment effect was significant for all three individual ocular symptoms in the seasonal and perennial AR studies
DeWester et al.[1880]	2003	1	Pooled data from 7 multicenter DBRCTs	Each study evaluated the efficacy of FPNS 200 μg daily in the treatment of nasal and ocular symptoms in patients with seasonal AR	Clinician-rated TOSS (itching, tearing, redness, and puffiness) at 7 and 14 days of therapy	FPNS group had significantly greater mean change in the TOSS and all four individual symptom scores versus placebo at both time points
Taramarcaz et al.[1886]	2003	1	Meta-analysis of RCTs	Subjects with asthma and AR, 14 trials, $n = 477$ INCS versus placebo or traditional asthma treatments	Asthma outcomes: symptoms, FEV_1, peak expiratory flow, methacholine test	Meta-analysis for asthma outcomes failed to show a statistically significant benefit of INCS
Ratner et al.[1882]	2015	2	DBRCT	Patients with seasonal AR, $n = 614$ FPNS 200 μg x14 days Placebo	rTOSS	FPNS more efficacious in reducing the ocular symptoms of AR versus placebo

(Continues)

TABLE XI.B.2.b.i.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Baroody et al.[1884]	2009	2	DBRCT	Subjects with seasonal AR outside of their allergy season, n = 20, underwent allergen challenge after 1 week of treatment FFNS 110 μg daily Placebo	Nasal and ocular symptoms after allergen challenge	Pretreatment with FFNS significantly reduced eye symptoms following nasal allergen challenge
Yu et al.[1888]	2019	3	Population-based cohort	Patients (n = 10,708; years 2000-2012) with asthma who had used asthma controller and followed for 1 year: AR, n = 5429 No AR, n = 5279	Occurrence of asthma exacerbations Medication use tracked in patients with AR	AR with INCS and/or antihistamine group (but not AR without treatment) was found to have a lower risk of asthma exacerbations than patients without AR Use of INCS and/or antihistamines was associated with significant reduction in exacerbations among AR patients aged 2–6 and 7–18 years

Abbreviations: AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; FEV_1, forced expiratory volume in one second; FFNS, fluticasone furoate nasal spray; FPNS, fluticasone propionate nasal spray; INCS, intranasal corticosteroid; LOE, level of evidence; QOL, quality of life; r, reflective; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis; TANS, triamcinolone acetonide nasal spray; TOSS, Total Ocular Symptom Score.

two show growth decrease) makes the effects on long-term growth suppression unclear. It is therefore wise to check growth periodically in children on long-term INCS (Table XI.B.2.b.i.-4).

Intranasal corticosteroid spray

Aggregate grade of evidence: A (Level 1: 18 studies, level 2: 29 studies, level 3: 3 studies; Tables XI.B.2.b.i.-1, XI.B.2.b.i.-2, XI.B.2.b.i.-3, and XI.B.2.b.i.-4)

Benefit: INCS are effective in reducing nasal and ocular symptoms of AR. Studies have demonstrated superior efficacy compared to oral antihistamines and LTRAs.

Harm: INCS sprays have undesirable local adverse effects, such as epistaxis, with increased frequency compared to placebo in prolonged administration studies. There are no apparent negative effects on the hypothalamic-pituitary axis. There might be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression. See Table II.C.

Cost: Low.

Benefits-harm assessment: The benefits of using INCS outweigh the risks when used to treat seasonal or perennial AR.

Value judgments: INCS are first line therapy for the treatment of AR by virtue of their superior efficacy in controlling nasal symptoms. Subjects with seasonal AR should start prophylactic treatment with INCS several days before the pollen season with an evaluation of the patient's response a few weeks after initiation, including a nasal exam to evaluate for local irritation or mechanical trauma. Children receiving INCS should be on the lowest effective dose to avoid negative growth effects.

Policy level: Strong recommendation.

Intervention: The demonstrated efficacy of INCS, as well as their superiority over other agents, make them first line therapy in the treatment of AR.

XI.B.2.b.ii | *Non-traditional application.* INCS are typically administered with metered devices for AR. Alternate routes of delivery (irrigation and nebulization) have been studied. Periasamy et al.[1924] conducted a prospective, single center double-blind RCT in 52 patients with AR.

TABLE XI.B.2.b.i.-3 Evidence table – intranasal corticosteroids (spray) for allergic rhinitis: comparison to other agents

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Khattiyawittayakun et al.[1889]	2019	1	SRMA	12 studies, $n = 4166$ 5 pediatric studies, $n = 1868$ 5 adult studies, $n = 1414$ 2 studies with mixed populations, $n = 884$ Double- versus standard-dose INCS	TNSS TOSS Adverse events	Adults: TNSS and TOSS scores favored double-dose INCS Pediatric: TNSS, no difference; TOSS, insufficient data for analysis
Benninger et al.[1892]	2010	1	SR of RCTs	38 studies of seasonal AR, $n = 11{,}980$ adults and 946 children 12 studies of perennial AR, $n = 3800$ adults and 366 children US medications for AR	TNSS	INCS produce the greatest improvements in nasal symptoms in patients with seasonal AR INCS effective for perennial AR, but the data were of variable quality; oral antihistamines may be equally effective for some patients
Wilson et al.[1893]	2004	1	SRMA	11 studies on seasonal AR 8 evaluating LTRA alone or with other treatments versus placebo or other treatments, $n = 3924$ 3 evaluating LTRA plus antihistamine, $n = 80$	Composite daily rhinitis symptom scores Rhinitis-specific QOL	LTRAs modestly better than placebo, and as effective as antihistamines LTRAs less effective than INCS for symptoms and QOL in patients with seasonal AR
Yanez and Rodrigo[1891]	2002	1	SR of RCTs	9 studies, AR patients, $n = 648$ INCS versus topical antihistamines	Total nasal symptoms, sneezing, rhinorrhea, itching, nasal blockage	INCS produced greater relief of nasal symptoms versus topical antihistamines No difference in relief of the ocular symptoms
Weiner et al.[1890]	1998	1	Meta-analysis of RCTs	16 trials, subjects with AR, $n = 2267$ INCS versus oral antihistamines	Nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, nasal discomfort, total nasal symptoms, nasal resistance, eye symptoms, global ratings	INCS had greater relief than oral antihistamines in nasal blockage, discharge, sneezing, nasal itch, postnasal drip, total nasal symptoms No significant differences between treatments for nasal discomfort, nasal resistance, eye symptoms

(Continues)

TABLE XI.B.2.b.i.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ng et al.[1488]	2021	2	DBRCT, crossover	Patients with ragweed AR challenged in environmental exposure chamber Randomized to receive one of four treatment sequences (loratadine 5 mg-pseudoephedrine 120 mg [LP] tablet, placebo tablet, FPNS 2 sprays in each nostril, placebo spray), n = 82	Percent change in PNIF from baseline to 4 h after dosing	Average change in PNIF was 31% with LP, significantly greater than with placebo and FPNS (12% and 15%, respectively)
Bhattachan et al.[1894]	2020	2	Prospective, randomized, parallel, cross-sectional	Patients with AR treated for 1 month, n = 126 MFNS Oral montelukast	TNSS	Significant reduction of TNSS versus baseline in both groups MFNS significantly more effective than montelukast

Abbreviations: AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; FPNS, fluticasone propionate nasal spray; INCS, intranasal corticosteroid; LOE, level of evidence; LP, loratadine-pseudoephedrine; LTRA, leukotriene receptor antagonist; MFNS, mometasone furoate nasal spray; PNIF, peak nasal inspiratory flow; RCT, randomized controlled trial; SR, systematic review; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score; US, United States.

Patients received buffered hypertonic saline nasal irrigation (60 ml each nostril twice daily) with either a placebo or a budesonide respule (0.5 mg/2 ml) for 4 weeks. Patients were assessed using the SNOT-22 questionnaire, visual analog scale (VAS) for sneezing, nasal obstruction, itching, and nasal discharge, and nasal endoscopy findings. SNOT-22, VAS, and endoscopy score improved from baseline in both groups. The group on budesonide had significantly more improvement than the saline only group in SNOT-22 and VAS but not endoscopy scores. Study results suggest a beneficial effect of saline irrigations on AR symptoms that is enhanced when steroids are added (Table XI.B.2.b.ii).

Brown et al.[1925] investigated the effect of budesonide administered by nebulization in patients with perennial AR. Patients received either budesonide (0.25 mg) or placebo (saline) delivered by nebulization once daily for 4 weeks. The patients on budesonide had significant increases in PNIF, decreases in symptoms and improvement in QOL compared to baseline but the changes were not significantly different from placebo.

Some studies evaluated the effect of corticosteroids in patients with both asthma and AR. Profita et al.[1926] randomized children with rhinitis and asthma to either nebulized beclomethasone (administered via face mask breathing through mouth and nose) or placebo twice daily for 4 weeks. Compared to baseline, concentrations of nasal IL-5 were significantly decreased, and nasal pH levels were significantly increased after beclomethasone treatment. Nasal symptom scores showed a significant reduction in obstruction, sneezing, and rhinorrhea after treatment with beclomethasone dipropionate, but no change after placebo. When the data were compared between beclomethasone and placebo groups, there were significant differences in favor of beclomethasone in nasal IL-5 and pH but not symptom scores. The significance of nasal pH increase is not clear but could lead to better mucociliary function.[1927] Active treatment did improve FEV_1 and asthma symptoms. In a similar study, Camargos et al.[1928] randomized patients with AR and asthma to either fluticasone propionate hydrofluoroalkane (FP-HFA) (100–150 μg) inhaled through the nose (mouth closed) using a large volume spacer attached to a face mask or a nasal spray of isotonic saline plus oral inhalation of FP-HFA through a mouthpiece attached to the same spacer. After 8 weeks of treatment, there was a significant improvement in AR scores and nasal peak flow in the group who received FP-HFA through the nose compared to the group who received FP by mouth inhalation. There was a significant reduction in asthma scores and increase in FEV_1 values in both groups. Shaikh[1929] performed an open, parallel crossover trial in patients with asthma and rhinitis and compared budesonide administered inhaled/intranasal to budesonide inhaler alone, exhaled through the nose. When exhaled through the nose,

TABLE XI.B.2.b.i.-4 Evidence table – intranasal corticosteroids (spray) for allergic rhinitis: side effects and adverse events

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Sampieri et al.[1919]	2022	1	SRMA	39 trials, $n = 1678$, years of 1946–2020 1st and 2nd generation INCS effect on adrenal insufficiency Length of use: short (<1 month), medium (1-2 months), long (>12 months)	AI (morning serum cortisol <550nmol/L and <80nmol/L, with and without adrenocorticotropic hormone stimulation)	Pooled AI 0.70% Short-term use: 0.48% Medium-term use: 1.13% Long-term use: 1.67%
Valenzuela et al.[1922]	2019	1	SRMA	10 studies for qualitative synthesis, 4 studies for meta-analysis, $n = 2226$, years of 1947–2018 INCS versus placebo for rhinitis and their effect on IOP, cataracts, or glaucoma	Increased IOP above 20 mm Hg, or formation of posterior subcapsular cataracts	RR of elevated IOP with INCS was 2.24 versus placebo, nonsignificant increase Absolute increased incidence of elevated IOP for INCS was 0.8% No cases of glaucoma in placebo or INCS at 12 months Absolute increased incidence of developing posterior subcapsular cataract was 0.02%, nonsignificant increase
Ahmadi et al.[1921]	2015	1	SR	19 studies (10 RCTs, 1 case–control, 8 case series), years of 1974–2013	IOP, lens opacity, glaucoma, or cataract incidence	In studies that reported data on glaucoma, IOP, cataracts, or lens opacity, none demonstrated changes versus control
Mener et al.[1923]	2015	1	SR of RCTs	8 studies, $n = 755$, years of 1988–2013 Knemometry, $n = 342$ Stadiometry, $n = 413$ INCS for AR in children 3–12 years old	Interval change in growth	Knemometry: mean growth significantly lower among children using INCS versus placebo Stadiometry: no significant growth difference in INCS versus placebo
Verkerk et al.[1906]	2015	1	SR	34 studies (11 RCTs, 5 cohort, 20 case series), years of 1946–2013 21 studies of rhinitis patients 13 studies of CRS patients INCS with or without control group	Histopathology assessment	No histological evidence for deleterious effects of INCS on human nasal mucosa Significant reduction in odds of developing squamous metaplasia with INCS

(Continues)

TABLE XI.B.2.b.i.-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hampel et al.[1918]	2015	2	DBRCT	Patients with perennial AR (6–11 years old) treated for 6 weeks: BDP nasal aerosol 80 μg/day, n = 67 Placebo, $n = 32$	Change from baseline in 24-h serum cortisol	No decrease in serum cortisol from baseline in either group Serum cortisol concentration–time profiles similar for placebo and BDP groups at baseline and week 6
Meltzer et al.[1903]	2009	2	Sub-analysis of three DBRCTs	Children (6–11 years old) with AR, $n = 948$ Once-daily treatment with either FFNS 55 μg, FFNS 110 μg, or placebo	Adverse event monitoring, nasal examinations, ophthalmic examinations, 24-h urine cortisol, serum cortisol	Epistaxis 4% in active and placebo groups No difference between groups for IOP No posterior subcapsular cataracts No difference in HPA measures between groups
Ratner et al.[1905]	2009	2	RCT	Children (6–11 years old) with perennial AR treated for 12 months, $n = 255$ MFNS 100 μg daily BDPNS 168 μg daily	Symptom control and safety	Appropriate symptom control in both groups Incidence of epistaxis was 12.7% with MFNS and 9.4% for BDPNS
Tripathy et al.[1917]	2009	2	DBRCT, parallel group	Children (2–11 years old) with perennial AR treated for 6 weeks, $n = 112$ FFNS 110 μg daily Placebo	24-h serum and urine cortisol	FFNS non-inferior to placebo for 24-h serum cortisol change from baseline 24-h urine cortisol excretion similar between groups
Weinstein et al.[1916]	2009	2	DBRCT, parallel group	Children (2–5 years old) with perennial AR treated for 4 weeks, $n = 474$ TANS 110 μg daily Placebo	Adverse events, morning serum cortisol, growth via stadiometry	Adverse events comparable between treatment groups No significant change from baseline in stimulated serum cortisol Distribution of children by stature-for-age percentile remained stable
Maspero et al.[1902]	2008	2	DBRCT	Children (2–11 years old) with perennial AR treated for 12 weeks, $n = 558$ FFNS 110 μg daily FFNS 55 μg daily Placebo	Nasal symptom scores Nasal and ophthalmic examinations, HPA assessments	Epistaxis 6% in all groups No significant ophthalmic or HPA related side effects in the treated subjects FFNS 55 μg reduced nasal symptoms significantly versus placebo

(Continues)

TABLE XI.B.2.b.i.-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Patel et al.[1915]	2008	2	DBRCT, parallel group	Patients (12–65 years old) with perennial AR, $n = 112$ FFNS 110 μg daily for 6 weeks Prednisone 10 mg daily for last 7 days of study Placebo	Change in 24-h serum cortisol and 24-h urine free and total cortisol, 6-beta hydroxycortisol excretion, plasma concentration of FF	FFNS noninferior to placebo for serum cortisol; prednisone significantly reduced ratio from baseline Change from baseline in 24-h urinary cortisol excretion similar in FFNS and placebo groups Plasma levels of FF undetectable after 6 weeks of treatment
Chervinsky et al.[1914]	2007	2	DBRCT	Patients (≥12 years old) with perennial AR treated up to 52 weeks, $n = 663$ Ciclesonide 200 μg daily Placebo	Adverse events and exam findings, 24-h urine free cortisol, morning plasma cortisol, IOP, lens opacification	No clinically relevant differences between ciclesonide and placebo groups
Kim et al.[1913]	2007	2	Two phase 3 RCTs, parallel group	Children (2–5 years old) with perennial AR treated for 6 or 12 weeks Ciclesonide 200 μg daily	Cortisol levels Systemic exposure of ciclesonide and its active metabolite, des-CIC, examined at end of 6-week study	Changes in plasma or urine cortisol levels with ciclesonide were not significantly different from placebo Serum concentrations of ciclesonide and des-CIC were below the lower limit of quantification in many samples
Rosenblut et al.[1904]	2007	2	DBRCT, parallel group	Patients with perennial AR treated for 12 months, $n = 806$ FFNS 110 μg Placebo	Adverse events, 24-h urine cortisol, nasal and ophthalmic examinations, electrocardiograms, clinical laboratory tests	Incidence of adverse events similar to placebo, except epistaxis (active treatment 20%) No clinically meaningful differences in ophthalmic parameters and 24-h urine cortisol excretion
Galant et al.[1912]	2003	2	DBRCT	Children (2–3 years old) with AR treated for 6 weeks, $n = 65$ FPNS 200 μg daily Placebo	12-h creatinine-corrected urine free cortisol	No significant difference between FPNS and placebo

Abbreviations: AI, adrenal insufficiency; AR, allergic rhinitis; BDPNS, beclomethasone dipropionate nasal spray; CRS, chronic rhinosinusitis; DBRCT, double-blind randomized controlled trial; FF, fluticasone furoate; FFNS, fluticasone furoate nasal spray; FPNS, fluticasone propionate; HPA, hypothalamic-pituitary axis; INCS, intranasal corticosteroids; IOP, intraocular pressure; LOE, level of evidence; MFNS, mometasone furoate nasal spray; RCT, randomized controlled trial; RR, relative risk; SR, systematic review; SRMA, systematic review and meta-analysis; TANS, triamcinolone acetonide nasal spray.

TABLE XI.B.2.b.ii Evidence table – intranasal corticosteroids (non-traditional application) for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Periasamy et al.[1924]	2020	2	DBRCT, single center	Patients with AR (n = 52) treated with BID irrigations for 4 weeks: Hypertonic saline nasal irrigation (60 ml/nostril) Hypertonic saline nasal irrigation (60 ml/nostril) with budesonide (0.5 mg/2 ml)	SNOT-22 VAS: sneezing, nasal obstruction, itching, discharge Nasal endoscopy	SNOT-22, VAS, endoscopy improved from baseline in both groups Budesonide group improved significantly over saline only group in SNOT-22 and VAS
Brown et al.[1925]	2014	2	DBRCT, parallel pilot study	Patients with perennial AR (n = 40) treated with NasoNeb daily for 26 days: Budesonide (0.25 mg) Placebo (saline)	rTNSS PNIF RQLQ Acoustic rhinometry	Improvement in TNSS and PNIF greater for budesonide group but did not reach significance RQLQ improved in both groups, no significant difference between groups Acoustic rhinometry showed no significant difference between groups
Profita et al.[1926]	2013	2	DBRCT	Children with grass AR/asthma (n = 40): Nebulized BDP (400 μg BID) Placebo *Treatment for 4 weeks after a 2-week run-in *Inhalation via nose and mouth	Nasal and oral FeNO PFTs Nasal and oral pH and IL-5 Nasal and bronchial symptom scores	Nasal IL-5 significantly reduced & nasal pH significantly increased with BDP Reduction in nasal obstruction, sneezing, rhinorrhea with BDP, no change with placebo, no significant difference between groups
Camargos et al.[1928]	2007	2	RCT	Patients with AR/asthma (n = 60, 6–18 years old) treated BID x8 weeks: FP-HFA (100–150 μg) inhaled through the nose (mouth closed) using large volume spacer attached to face mask Nasal spray isotonic saline plus oral inhalation of FP-HFA through a mouthpiece attached to the same spacer	AR scores Asthma scores PNIF FEV_1	Significant improvement in AR scores and PNIF in the nasal FP-HFA group Significant reduction in asthma scores and increase in FEV_1 in both groups

(Continues)

TABLE XI.B.2.b.ii (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Shaikh[1929]	1999	3	Open, parallel, comparative, crossover	Patients with perennial AR/asthma (n = 49): Budesonide MDI + budesonide nasal spray Budesonide inhaler alone, with instructions to exhale through the nose	Symptom scores PNIF Medication dose reduction	Budesonide inhaler exhaled through the nose resulted in improved symptoms and PNIF; these were significantly less than the group using budesonide nasal spray and MDI Exhaling budesonide through the nose resulted in a 40.1% reduction of dose requirement for budesonide nasal spray (p<0.001)

Abbreviations: AR, allergic rhinitis; BDP, beclomethasone dipropionate; BID, twice daily; DBRCT, double-blind randomized controlled trial; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FP-HFA, fluticasone propionate hydrofluoroalkane; IL, interleukin; LOE, level of evidence; MDI, metered dose inhaler; PFT, pulmonary function test; PNIF, peak nasal inspiratory flow; r, reflective; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, Sinonasal Outcome Test (22 item); TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

budesonide resulted in an improvement in nasal symptoms and nasal flow to a lesser extent than using intranasal budesonide but allowed for a significant reduction in the dose of intranasal budesonide required to improve nasal symptoms.

INCS are also used in drop form, usually for treatment of nasal polyps. In a few cases where they were used for AR, there was systemic absorption leading to unfavorable side effects such as growth inhibition and adrenal suppression[1930] or iatrogenic Cushing syndrome.[1931] In a study comparing fluticasone propionate administered as nasal drops or aqueous spray, the drops had eight times more systemic bioavailability than the spray.[1932]

Intranasal corticosteroid, non-traditional application

Aggregate grade of evidence: B (Level 2: 4 studies, level 3: 1 study; Table XI.B.2.b.ii). Some studies noted in the text were not performed in patients with AR or were case reports so are not summarized in the table.

Benefit: Nebulized steroids or those used via irrigation show some benefit in the treatment of AR in limited studies. Furthermore, steroids inhaled or exhaled through the nose in patients with asthma and rhinitis also show some benefit for rhinitis. Nasal steroid drops are not approved for treatment of rhinitis but are used in certain countries.

Harm: Nasal steroid drops have significant systemic side effects.

Cost: Low.

Benefits-harm assessment: The risks of using corticosteroid nasal drops for AR outweigh the benefits. Limited evidence suggests that nasal steroid irrigations for rhinitis lead to significant improvement of symptoms. Scarce evidence does not support routine recommendation for this route of therapy.

Value judgments: In the presence of effective symptom control using traditional spray administration for INCS, there is no solid data to support other routes of administration.

Policy level: Recommendation against routine use.

Intervention: There is some evidence that inhaled steroids, when exhaled through the nose might improve AR symptoms. Similar benefit is seen when steroids are inhaled by first passing through the nose. These routes might be useful in patients with both rhinitis and asthma.

XI.B.2.c | *Injectable corticosteroids*

Corticosteroids have been injected intramuscularly or into the turbinates for management of AR. Several early studies demonstrated significant improvement in subjective allergy symptoms after intramuscular corticosteroid injections. Four of these studies were single center RCTs with a placebo arm and modest numbers of participants[1933–1936] (Table XI.B.2.c).

TABLE XI.B.2.c Evidence table – injectable corticosteroids for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bayoumy et al.[1943]	2021	1	SR	10 RCTs of IM corticosteroid use in SAR: IM corticosteroids, $n = 387$ Non-IM corticosteroids, $n = 44$ Placebo, $n = 77$	Improvement of symptoms and/or patient satisfaction	6 studies showed superiority of IM corticosteroids versus placebo or other therapies 4 studies showed equal efficacy outcomes versus controls SR judged inconclusive because of the epidemiological high risk of bias and older studies
Yang et al.[1951]	2008	2	Randomized, placebo-controlled single-blind	Patients with perennial AR ($n = 39$) received intraturbinate injections: Botox A (25 units each turbinate) Triamcinolone (20 mg each turbinate) Isotonic saline (1 cc each turbinate)	Symptoms of rhinorrhea, nasal obstruction, sneezing, itching at 1, 4, 8, 12, 16 and 20 weeks	Botox improved nasal symptoms for the longest time post-injection Steroid injection was better than placebo but duration of action was shorter than Botox
Laursen et al.[1936]	1988	2	Double-blind, double-dummy, placebo-controlled	Patients with SAR during season ($n = 30$): Intranasal beclomethasone dipropionate (400 μg daily x4 weeks) IM injection of 2 ml betamethasone dipropionate/betamethasone disodium phosphate at beginning of season	Symptom scores (nasal blockage, rhinorrhea, sneezing, nasal itching, eye itching)	Depot injection was significantly more effective than placebo and intranasal preparation
Pichler et al.[1942]	1988	2	Double-blind, comparative	Patients with SAR ($n = 30$) treated x3 weeks: Budesonide nasal spray (400 μg/day) Methylprednisolone acetate IM 80 mg	Daily symptom scores (sneezing, nasal blockage, runny nose, itchy nose, red eyes, runny eyes, itchy eyes)	Methylprednisolone was as effective as budesonide in controlling symptoms and decreasing rescue medications Methylprednisolone-treated patients had a significantly lower cortisol value after 7 days but retained normal response to ACTH-stimulation
Borum et al.[1934]	1987	2	Double-blind, placebo-controlled, parallel	Patients with SAR during 2 consecutive allergy seasons ($n = 24$), received injections each season: Methylprednisolone IM 80 mg Placebo	Sneezing and nose blowing during the day Reflective symptom scores at end of day	Marked beneficial effect of active treatment on nasal blockage lasting >4 weeks, moderate effect on eye symptoms Effect obtained irrespective of timing of therapy Best to administer as soon as symptoms start during the season

(Continues)

TABLE XI.B.2.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Laursen et al.[1941]	1987	2	Randomized, double-blind comparative	Patients with SAR during season ($n = 37$): Oral prednisolone 7.5 mg PO daily x3 weeks Single IM injection of 2 ml betamethasone dipropionate/betamethasone disodium phosphate at start beginning of season	PNIF Symptom scores (nasal blockage, nasal running, sneezing, nasal itching, eye symptoms) ACTH at 3 weeks	Both treatments significantly reduced nasal and ocular symptoms compared to baseline, with no significant differences between groups Significant suppression of adrenal function with oral steroid treatment
Ohlander et al.[1938]	1980	2	Prospective, randomized, parallel group	Patients with SAR during season ($n = 60$) received one of three long-acting injections: Betamethasone dipropionate (5 mg) Betamethasone disodium phosphate-acetate (3–3 mg) Methylprednisolone acetate (4 mg)	Symptom scores (rhinorrhea, congestion, ocular symptoms) at 1, 2, 4 weeks Cortisol and glucose blood levels ($n = 38$)	All treatments led to significant reductions in nose and eye symptoms during season, no difference between groups All preparations suppressed endogenous cortisol, in some cases >14 days post-injection, 2/3 injections increased blood glucose
Kronholm[1937]	1979	2	Prospective, parallel, randomized, open label	Patients with SAR during season ($n = 42$), season onset injection: IM betamethasone dipropionate/betamethasone phosphate (5 and 2 mg/ml) Methylprednisolone acetate (40 mg/ml)	Weekly nasal and ocular symptoms x5 weeks	Both preparations significantly reduced nasal and ocular symptoms Betamethasone combination was more effective
Axelsson and Lindholm[1935]	1972	2	RCT	Patients with allergic and vasomotor rhinitis ($n = 38$): Triamcinolone acetonide 40 mg Placebo	Subjective nasal symptoms 10 days post-injection	Significant improvement in nasal symptoms, especially in patients with AR in the actively treated group
Hermance et al.[1939]	1969	2	Randomized trial	Patients with perennial AR ($n = 70$) given IM: Dexamethasone (8 or 16 mg) Cortisone acetate (10 mg)	Subjective symptom relief (complete, marked, moderate, slight, no relief)	More complete and marked relief with dexamethasone preparations versus cortisone acetate
Chervinsky[1940]	1968	2	Randomized, comparative	Patients with SAR ($n = 97$) poorly responsive to hyposensitization or with no previous treatment received single injection: Methylprednisone 80 mg Betamethasone phosphate-acetate (6–6 mg) Dexamethasone acetate-phosphate disodium (16–4 mg) Dexamethasone acetate 16 mg	Patient satisfaction (none, poor, fair, good, excellent) at 2 weeks	All treatments were beneficial with no difference between them

(Continues)

TABLE XI.B.2.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Brown et al.[1933]	1960	2	RCT	Adults with ragweed allergy ($n = 95$) poorly responsive to hyposensitization or with no prior treatment received 3 weekly IM injections at season start: Depo-methylprednisolone (80 mg) Cholesterol	Symptom score evaluation by patients (none, slight, moderate, severe)	Significantly more patients in the active group evaluated symptoms as none and slight, compared to placebo
Moss et al.[1956]	2015	4	Retrospective case series & literature review	Patients ($n = 78$) with chronic rhinitis or sinusitis underwent 237 intra-turbinate or intra-polyp triamcinolone acetonide injections (April 2008 to June 2013)	Patients report of clinical improvement and adverse events	84% of patients reported clinical improvement One of the intra-polyp injections resulted in a transient visual change, resolved spontaneously Literature review: 117,669 injections, three with visual complications (0.003%); all resolved spontaneously, no permanent visual deficits
Aasbjerg et al.[1945]	2013	4	Retrospective study of Danish National Registries	Patients receiving IM steroid injections in April–July or AIT to grass or birch pollen ($n =$ 47,382; 1995–2011)	Incidence and relative risk of osteoporosis, diabetes, tendon rupture, respiratory tract infection	Relative risk and incidence osteoporosis and diabetes were higher in allergic individuals receiving at least one depot corticosteroid injection during the allergy season versus those receiving AIT

Abbreviations: ACTH, adrenal corticotropic hormone; AIT, allergen immunotherapy; AR, allergic rhinitis; IM, intramuscular; LOE, level of evidence; PO, per os (by mouth); PNIF, peak nasal inspiratory flow; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis; SR, systematic review.

Studies comparing different intramuscular steroid preparations have showed improvement of symptoms with all variations but some differences in efficacy among them.[1937–1940] When compared to other agents, intramuscular corticosteroids demonstrated similar or superior efficacy in controlling symptoms of AR. Specifically, pre-seasonal betamethasone injection was as effective as daily oral prednisolone[1941] and more effective than daily intranasal beclomethasone dipropionate in controlling nasal itching, congestion, rhinorrhea and eye symptoms.[1936] In another seasonal study, a single injection of methylprednisolone was as effective as intranasal budesonide over a 3 week treatment period.[1942] Although these studies show a favorable effect of intramuscular steroids on symptoms of AR, a recent systematic review was inconclusive based on a high risk of bias of the available studies that mostly dated back to more than 30 years ago.[1943]

Injectable corticosteroid preparations have significant potential side effects which can include adrenal suppression and growth retardation[1944] (Table II.C). Injectable corticosteroids affected adrenal function in two out of four relevant studies[1938,1942] (Table XI.B.2.c). Evidence from a study of Danish National Registries shows that the relative risk and incidence of both osteoporosis and diabetes were higher in allergic individuals receiving at least one depot corticosteroid injection yearly for three consecutive years during the allergy season compared to those receiving AIT.[1945] Laursen et al.[1941] reported that ACTH testing performed at 3 weeks showed significant suppression of adrenal function in the oral steroid treatment group but no evidence of suppression after a single corticosteroid injection. This discrepancy may relate to the short-lasting adrenal suppression after a single injection of corticosteroids compared to continuous administration of the oral formulation, although Kronholm[1937] also did not

show any effect of intramuscular preparations on adrenal function.

Corticosteroid injection into the nasal turbinates has also been studied for the management of AR; however, this route is less widely utilized than previously observed. Several early reports detailed significant improvement in symptoms of AR in a large proportion of patients who received intra-turbinate injections of various steroid formulations.[1946–1950] A placebo-controlled, single-blind RCT showed that intra-turbinate injections of botulinum toxin A or triamcinolone in patients with perennial AR resulted in improved control of nasal symptoms, including nasal congestion, compared to isotonic saline, although botulinum toxin had the longest duration of clinical effect.[1951]

Enthusiasm for intra-turbinate steroid injection has been tempered by reports of orbital complications associated with intra-turbinate, but not intramuscular, deposition. Complications have included transient visual loss and diplopia[1952]; blurred vision and temporary blindness[1953]; and temporary distorted vision, decreased visual acuity, and paresis of the medial rectus.[1953] Martin reported on the rapid onset of ocular pain, blurred vision, and decreased visual acuity after an intra-turbinate injection of triamcinolone acetonide.[1954] Symptoms were caused by choroidal and retinal arterial embolization and resolved completely within 24 h. A more recent report detailed progression of glaucoma-related optic neuropathy after intra-turbinate injection associated with chorioretinal microvascular embolism.[1955] The mechanism of embolization is likely related to retrograde flow from the anterior tip of the IT to the ophthalmic artery, followed by anterograde flow with the particles lodging in the end arteries of the choroid and retinal vessels. Larger particle size steroids (e.g., methylprednisolone) are thought to present higher risk than smaller sized particles (e.g., triamcinolone).[1954] Moss et al.[1956] reported on personal experience with 152 turbinate and 85 intra-polyp injections of triamcinolone acetonide, noting one transient subjective decrease in vision after intra-polyp injection. They reviewed the literature for an estimated 117,000 individual intra-turbinate and polyp injections and reported an estimated visual complication rate of 0.003% (three instances), with a 0.00% (0 instances) rate of permanent visual complications.

Injectable corticosteroids

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 11 studies, level 4: 2 studies; Table XI.B.2.c)
Benefit: Injectable corticosteroids improved symptoms of AR in clinical studies.
Harm: Injectable corticosteroids have known undesirable adverse effects on the hypothalamic-pituitary axis, growth, osteoporosis, glycemic control, and other systemic adverse effects, for varied periods of time after injection. Intraturbinate corticosteroids have a small but potentially serious risk of ocular side effects including decline or loss of vision. See Table II.C.
Cost: Low.
Benefits-harm assessment: In routine management of AR, the risk of serious adverse effects outweighs the demonstrated clinical benefit.
Value judgments: Injectable corticosteroids are effective for the treatment of AR. However, given the risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of effective alternatives (e.g., INCS), injectable corticosteroids are not recommended for the routine treatment of AR.
Policy level: Recommendation against.
Intervention: None.

XI.B.3 | Decongestants

XI.B.3.a | *Oral decongestants*

Oral decongestants are medications that act on adrenergic receptors, which leads to vasoconstriction of small blood vessels (such as those in the nasal mucosa), resulting in relief of nasal congestion symptoms in AR patients. The most commonly used oral decongestants are pseudoephedrine and phenylephrine, which are sympathomimetic vasoconstrictors that differ in their selectivity to adrenoceptors.[1957] Due to the oral administration of pseudoephedrine and phenylephrine, both drugs act systemically and can lead to side effects such as insomnia, headache, nervousness, anxiety, tremors, palpitations, urinary retention, increased blood pressure, and other adverse effects[1005,1958–1960] (Table II.C).

Our review of the literature found 12 studies that evaluate the use of oral decongestants in AR and are summarized in Table XI.B.3.a. Individual studies evaluating the effect of oral decongestants in AR patients as monotherapy during allergy season have shown that pseudoephedrine monotherapy led to improved symptom scores (total nasal symptom and individual symptom scores) compared to baseline.[1960–1964] One study also compared pseudoephedrine monotherapy against placebo and found that pseudoephedrine monotherapy is more effective in reducing total nasal symptom and nasal stuffiness scores than placebo.[1959] With regard to the comparison of pseudoephedrine monotherapy

TABLE XI.B.3.a Evidence table – oral decongestants for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Meltzer et al.[1969]	2015	2	Open-label RCT	SAR during season (n = 539, 18–77 years old): PE HCL 10 mg PE HCL 20 mg PE HCL 30 mg PE HCL 40 mg Placebo Study protocol: every 4 h, up to 6 tablets/24 h	Daily reflective nasal congestion score	PE HCL is not significantly better than placebo at relieving nasal congestion in adults with SAR
Grubbe et al.[1962]	2009	2	DBRCT	SAR during season (n = 598, 12–76 years old): Desloratadine 2.5 mg + PSE 120 mg BID Desloratadine 5.0 mg + placebo tablet daily PSE 120 mg BID	Total symptom score (excluding nasal congestion) Nasal congestion score	Desloratadine-PSE was more effective in reducing SAR symptoms, including nasal congestion, than the individual components alone Monotherapies were equal to each other and improved symptom scores versus baseline
Mucha et al.[1965]	2006	2	DBRCT	SAR during season (n = 58, 18–45 years old): Montelukast 10 mg daily PSE HCL 240 mg sustained release daily	RQLQ Nocturnal RQLQ Total symptom score PNIF	PSE and montelukast were nearly equally effective and improved QOL scores, PNIF, symptom scores compared to baseline PSE controlled nasal congestion better than montelukast
Pleskow et al.[1970]	2005	2	DBRCT	SAR during season (n = 1047, 12–78 years old): Desloratadine 5 mg + PSE 240 mg sustained release daily Desloratadine 5 mg daily PSE 240 mg sustained release daily	Total symptom score (excluding nasal congestion) Nasal congestion score	Desloratadine-PSE provided additional benefit over individual components alone Monotherapies were equally effective and led to improved symptom scores versus baseline
Sussman et al.[1964]	1999	2	RCT	SAR during season (n = 651, 12–66 years old): Fexofenadine HCL 60 mg BID PSE HCL 120 mg BID Fexofenadine HCL 60 mg + PSE HCl 120 mg BID	Total symptom score (excluding nasal congestion) Nasal congestion score	Fexofenadine-PSE provided additional benefit over individual components alone Monotherapies were equally effective and led to improved symptom scores versus baseline
Grosclaude et al.[1960]	1997	2	DBRCT	SAR during season (n = 687, 9–66 years old): Cetirizine 5 mg BID PSE retard 120 mg BID Cetirizine 5 mg + PSE retard 120 mg BID	Patient symptom assessment: nasal obstruction, sneezing, rhinorrhea, nasal pruritus, ocular pruritus	Cetirizine-PSE provided additional benefit over individual components alone Monotherapies were equally effective and led to improved symptoms versus baseline

(Continues)

TABLE XI.B.3.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bertrand et al.[1963]	1996	2	DBRCT	Perennial AR (n = 215, 12–65 years old): Cetirizine 5 mg + PSE retard 120 mg BID Cetirizine 5 mg BID PSE retard 120 mg BID	Most severe symptom score	Cetirizine-PSE was more effective than treatment with each individual agent Cetirizine monotherapy was more effective than PSE in relieving sneezing, nasal pruritis, ocular pruritus
Dockhorn et al.[1961]	1996	2	DBRCT	SAR during season (n = 702, 12-73 years old): Acrivastine 8 mg + PSE HCL 60 mg QID Acrivastine 8 mg QID PSE HCL 60 mg QID Placebo QID	Diary symptom score Allergy symptom score Nasal congestion score	Acrivastine-PSE more effective in reducing symptom scores than treatment with each individual agent PSE more effective than acrivastine in reducing diary symptom scores and nasal symptom scores, equally effective in reducing allergy symptom score Both monotherapies were more effective than placebo
Bronsky et al.[1959]	1995	2	DBRCT	SAR season (n = 879, 12–82 years old): Loratadine 10 mg + PSE sulfate 240 mg extended release daily Loratadine 10 mg daily PSE sulfate 120 mg daily Placebo daily	Total symptoms score (nasal plus non-nasal scores)	Loratadine-PSE more effective than either of its components alone, or placebo, in treating SAR Loratadine and PSE monotherapy similarly effective Three active treatment groups had better therapeutic response than placebo
Howarth et al.[1968]	1993	2	DBRCT, crossover	Allergen challenge with premedication: *First part – AR (n = 12, 12–40 years old) PSE 60 mg Placebo, pretreatment Study protocol: 6 tablets on 2 days before challenge, 1 tablet on the morning of challenge day *Second part – perennial AR (n = 17, 19–56 years old) PSE 120 mg Terfenadine 60 mg PSE 120 mg + terfenadine 60 mg Placebo Study protocol: 5 doses of medication BID on the 2 days before challenge, 1 dose on the morning of challenge day	First part: nasal airway resistance after challenge Second part: nasal itching, sneezing, rhinorrhea, blockage	There is benefit of combination therapy (PSE-terfenadine) over each individual component when administered alone for all nasal symptoms associated with AR

(Continues)

TABLE XI.B.3.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Henauer et al.[1966]	1991	2	RCT, crossover	Allergen challenge with premedication, SAR (n = 13, mean age 13 years): Terfenadine 60 mg rapid release + PSE 120 mg controlled release Terfenadine 60 mg rapid release PSE 120 mg controlled release Placebo Study protocol: 5 doses of medication – BID dosing, on the 2 days before challenge, one dose on the morning of challenge day	Allergic reaction threshold	Terfenadine-PSE was more effective than the individual components when administered alone Terfenadine monotherapy was more effective than PSE monotherapy Both therapies were more effective than placebo
Empey et al.[1967]	1984	2	DBRCT, crossover	Allergen challenge with premedication, SAR (n = 18, 19–38 years old): Triprolidine 2.5 mg + PSE 60 mg Triprolidine 2.5 mg PSE 60 mg Placebo	Nasal airway resistance	Tripolidine-PSE and its individual components were superior to placebo in reducing the increase in nasal resistance after histamine challenge

Abbreviations: AR, allergic rhinitis; BID, twice daily; DBRCT, double-blind randomized controlled trial; HCL, hydrochloride; LOE, level of evidence; PE, phenylephrine; PNIF, peak nasal inspiratory flow; PSE, pseudoephedrine; QID, four times daily; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality of life; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis.

against the combination therapy, including an oral antihistamine and pseudoephedrine, studies have shown that pseudoephedrine monotherapy is less effective than combination therapy in treating primary outcomes such as total nasal symptom and individual symptom scores.[1959–1964]

Studies on the effectiveness of oral decongestants in AR patients as premedication monotherapy before allergy challenge have shown that pseudoephedrine is equally effective compared to montelukast[1965] and more effective than placebo[1966,1967] in treating primary outcomes. One study showed that pseudoephedrine monotherapy was less effective than a combination therapy of an oral antihistamine and pseudoephedrine,[1966] while another study showed no difference in outcome.[1967] The results in head-to-head comparisons between antihistamine and pseudoephedrine monotherapy are contradictory. While some studies showed that antihistamine monotherapy was more efficient than pseudoephedrine,[1961,1966] other studies have had different findings.[1960–1962,1964,1968] Nonetheless, either monotherapy (i.e., pseudoephedrine or antihistamine) was more effective than placebo.[1959,1961,1966,1967] Interestingly, an analysis of the effectiveness of phenylephrine compared to placebo has shown that phenylephrine (up to 40 mg six times daily) is not superior to placebo in relieving nasal congestion symptoms in AR patients.[1969]

Oral decongestants

Aggregate grade of evidence: A (Level 2: 12 studies; Table XI.B.3.a)

Benefit: Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.

Harm: Oral decongestants have known undesirable adverse effects. See Table II.C.

Cost: Low.

Benefits-harm assessment: Balance of benefit and harm for pseudoephedrine. Possible harm for phenylephrine.

Value judgments: Little evidence for benefit in controlling symptoms other than nasal congestion.

Policy level: Strong recommendation against for routine use in AR. In certain cases, combination therapy with an oral antihistamine may be beneficial to alleviate severe nasal congestion in short courses.

Intervention: Although not recommended for routine use in AR, pseudoephedrine can be effective in reducing nasal congestion in patients with AR; however, it should only be used as short-term/rescue therapy after a discussion of the risks and benefits with the patient (comorbidities) and consideration of alternative intranasal therapy options.

XI.B.3.b | *Intranasal decongestants*

INDC – oxymetazoline, xylometazoline, and phenylephrine – are α-adrenergic agonists acting as topical vasoconstrictors reducing edema/tissue thickness.[182] The highest level of evidence consists of seven RCTs[1971–1977] looking at short-term effects of INDC. There are also three RCTs[111,1978,1979] and two cohort studies[123,1980] evaluating prolonged effects of INDC.

Clinically, short-term use results in reduction of nasal congestion/blockage, with little to no effect on allergic symptoms such as sneezing, rhinorrhea, or nasal itching.[1971,1972,1974,1975] Onset of action is within 10 min,[1973] and duration of the effect lasts up to 12 h.[1977] There are also improvements in objective measures of nasal congestion/blockage, including nasal airway resistance, measures of nasal cavity volume for airflow, and PNIF.[1972–1976] Measures of nasal cavity volume for airflow exhibit a clear dose–response relationship across doses ranging from 6.25 to 50 μg, with nasal airway resistance requiring a higher threshold dose of 25 μg before significant changes in nasal patency are seen.[1974] Despite oxymetazoline's vasoconstrictive effects, it does not seem to affect histamine-induced plasma exudation.[1971] The majority of studies compared INDC to placebo,[1971–1974,1976] but Barnes et al.[1975] found that the decongestant response was stronger for intranasal xylometazoline after 15 min than daily administration of intranasal mometasone furoate after 28 days. It is worth noting that only three studies included patients with AR,[1975–1977] the remainder consisted of healthy participants.[1971–1974]

Rhinitis medicamentosa, which is a condition thought to result from prolonged usage of INDC, is characterized by an increase in symptomatic nasal congestion, thereby precluding a recommendation for long-term use of these medications. Studies to identify the duration of intranasal decongestant use that leads to rhinitis medicamentosa have shown variable results. Some studies show prolonged use (up to 6 weeks) does not produce any symptoms of rebound nasal congestion or objective markers of impaired decongestant response.[123,1978,1980] Another study, however, noted development of rhinitis medicamentosa after as little as 3 days of use.[111] This may be due to nasal hyperreactivity and mucosal swelling. Additionally, Graf et al.[1979] looked at the impact of the presence of the preservative benzalkonium chloride, which can be found in INDC sprays. Compared to oxymetazoline and placebo nasal sprays, a nasal spray with benzalkonium chloride alone induces mucosal swelling, suggesting the presence of this preservative may aggravate rhinitis medicamentosa. (See Section V.B.2 Rhinitis Medicamentosa for additional information on this topic.)

Known adverse effects of INDC include nasal discomfort/burning, dependency, dryness, increased congestion, rhinitis medicamentosa, hypertension, anxiety, and tremors (Table II.C). One study noted significantly decreased ciliary beat frequencies at 1000 μg/ml, but no significant difference at 500 μg/ml.[1981] The 500 μg/ml (0.5 mg/ml,.05%) concentration is typical for available formulations. In sum, while intranasal decongestants are effective at reducing nasal congestion, short-term use of the medication, approximately 3 days or less, is recommended to avoid the potential for rebound nasal congestion and rhinitis medicamentosa.[111]

Intranasal decongestants

Aggregate grade of evidence: B (Level 2: 10 studies, level 3: 2 studies; Table XI.B.3.b). Limitation – only 3 studies included subjects with AR.
Benefit: Reduction in symptoms of nasal congestion/blockage and corresponding objective markers with INDC compared to placebo.
Harm: Side effects include nasal discomfort/burning, dependency, dryness, hypertension, anxiety, and tremors. See Table II.C. Potential for rebound congestion with long-term use.
Cost: Low.
Benefits-harm assessment: Harm likely outweighs benefit if used long-term, with adverse effects appearing as early as 3 days.
Value judgments: INDC can be helpful for short-term relief of nasal congestion.
Policy level: Option for short-term use.
Intervention: INDC can provide effective short-term relief of nasal congestion in patients with AR during an acute flare but recommend against chronic use due to risk of rhinitis medicamentosa.

XI.B.4 | Leukotriene receptor antagonists

LTRAs have been studied in the treatment of AR. Montelukast is approved by the US FDA for the treatment of seasonal AR in adults and children over 2 years of age, and

TABLE XI.B.3.b Evidence table – intranasal decongestants for allergic rhinitis[a]

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Druce et al.[1977]	2018	2	DBRCT	Acute coryzal rhinitis ($n = 128$; 42 with concomitant AR): Intranasal oxymetazoline Isotonic saline	Subjective nasal congestion Objective nasal flow rate	Up to 12 h post-treatment, there was a significant improvement in subjective nasal congestion and objective nasal flow rate versus control
Gomez-Hervas et al.[1973]	2015	2	DBRCT, crossover	Healthy participants ($n = 8$): Intranasal oxymetazoline Placebo	PNIF during exercise Parameters of exercise performance (e.g., oxygen consumption, ventilatory pattern, efficiency)	10 min after use, nasal airflow trended toward improvement with oxymetazoline, but this did not translate to improvements in exercise performance
Pritchard et al.[1976]	2014	2	RCT	Nasal congestion due to upper respiratory infection or hay fever ($n = 21$): Intranasal oxymetazoline Placebo	Inferior turbinate total volume Middle turbinate total volume	Up to and including 12 h post-treatment, there was a significant reduction in inferior and middle turbinate volumes with oxymetazoline versus placebo
Barnes et al.[1975]	2005	2	DBRCT, crossover	AR ($n = 36$): Intranasal xylometazoline Intranasal mometasone furoate (daily x28 days)	PNIF Nasal forced inspiratory volume in 1 s Nasal blockage score	Xylometazoline 15-min response was stronger for all endpoints than mometasone furoate 28-day response
Watanabe et al.[1978]	2003	2	DBRCT	Healthy participants ($n = 30$): Intranasal oxymetazoline TID x4 weeks Placebo	Subjective nasal blockage PNIF Airway resistance Airway volume	Following 4 weeks of treatment, no significant nasal blockage or impaired decongestant response with oxymetazoline versus placebo
Bickford et al.[1972]	1999	2	DBRCT, crossover	Healthy participants ($n = 20$): Intranasal oxymetazoline Placebo	Nasal airway resistance Nasal cavity cross-sectional area and volume Subjective congestion	Up to 120 min after treatment, all endpoints were significantly improved with oxymetazoline versus placebo
Taverner et al.[1974]	1999	2	DBRCT	Healthy participants ($n = 125$): Intranasal oxymetazoline Placebo	Nasal airway resistance Nasal cavity cross-sectional area and volume Subjective congestion	Up to 120 min after treatment, all endpoints except subjective nasal congestion were significantly improved with oxymetazoline versus placebo

(Continues)

TABLE XI.B.3.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Morris et al.[111]	1997	2	DBRCT	Healthy participants ($n = 50$): Intranasal oxymetazoline daily x7 days Intranasal oxymetazoline every other day x7 days Placebo	Nasal airway resistance Subjective scaling of nasal patency Clinical visual examination	Evidence of rebound nasal congestion (higher nasal airway resistance) was found following 3 days of both daily and intermittent oxymetazoline treatment
Graf and Hallen[1979]	1996	2	DBRCT	Healthy participants ($n = 30$): Intranasal oxymetazoline TID x28 days Intranasal benzalkonium chloride TID x28 days Placebo	Nasal mucosal swelling Subjective nasal stuffiness and secretions Nasal reactivity	Following 28 days of treatment (long-term), subjective nasal stuffiness, secretions, and reactivity were greatest with oxymetazoline Increase in nasal mucosal swelling with benzalkonium chloride alone
Svensson et al.[1971]	1992	2	DBRCT, crossover	Healthy participants ($n = 12$): Intranasal oxymetazoline Placebo	Nasal symptoms (sneezing, nasal secretion, blockage) Histamine-induced plasma exudation	Up to 130 min after treatment, there was a significant decrease in nasal blockage but not any of the other endpoints
Yoo et al.[123]	1997	3	Individual cohort	Healthy participants ($n = 10$): Intranasal oxymetazoline nightly x4 weeks	Subjective history Physical exam Anterior rhinomanometry	All subjects remained responsive to oxymetazoline 4 weeks and 8 weeks after the study began
Petruson[1980]	1981	3	Individual cohort	Intranasal xylometazoline TID x6 weeks, $n = 20$	Posterior rhinomanometry	Following 6 weeks of treatment, all subjects remained responsive based on posterior rhinomanometry

Abbreviations: AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; LOE, level of evidence; PNIF, peak nasal inspiratory flow; RCT, randomized controlled trial; TID, three times daily.

[a]Limitation – only 3 of the listed studies specifically addressed the use of intranasal decongestants in patients with AR.

for perennial AR in adults and children over 6 months of age. Other LTRAs include pranlukast (approved for treatment of AR in Japan) and zafirlukast (FDA-approved for treatment of asthma).

Since the 2018 ICAR-Allergic Rhinitis consensus statement,[1] the body of evidence surrounding LTRA monotherapy has grown. A systematic search revealed 15 SRMAs of RCTs published since 2014. This gave a total of 34 studies examining the use of LTRA in AR which are considered high-level evidence (Table XI.B.4).

Most recent studies[1982–1986] demonstrate concordance with previous findings that LTRA monotherapy is superior to placebo in controlling symptoms and improving QOL in both seasonal and perennial AR, except a single RCT[1987] which showed no difference between the two. Yoshihara et al.[1988] found that LTRA showed promise as a prophylactic agent in children with seasonal AR when administered before the Japanese cedar pollen season.

However, there remains consistent evidence that LTRA is inferior to INCS in terms of symptom reduction and QOL improvement.[1894,1989,1990] In a RCT by Chen et al,[1989] LTRA was inferior to INCS in improving acoustic rhinometry readings, concentrations of inflammatory mediators in nasal secretions, and the inflammatory cell composition (Th1, Th2, Treg) from turbinate brush cytology. Dalgic et al.[1991] found

TABLE XI.B.4 Evidence table – leukotriene receptor antagonists for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Feng et al.[1992]	2021	1	SR of RCTs	LTRA OAH	Symptoms QOL Adverse events	LTRA superior for nighttime symptoms OAH superior for daytime symptoms
Meltzer et al.[1982]	2021	1	SR of RCTs	LTRA INCS OAH Intranasal antihistamine OAH + decongestant Intranasal antihistamine + INCS SLIT tablet Placebo	TNSS	Adult SAR: LTRA inferior to OAH, INCS, SLIT, combination therapy Adult perennial AR: LTRA similar to OAH, inferior to INCS and SLIT Pediatric SAR: LTRA superior to INCS, intranasal antihistamine (alone and with INCS), SLIT
Krishnamoorthy et al.[1983]	2020	1	SR of RCTs	Montelukast Montelukast + OAH INCS Placebo	Symptoms (day, night, composite)	LTRA superior to placebo OAH superior to LTRA except for nighttime symptoms INCS superior to LTRA LTRA-OAH superior to LTRA or OAH monotherapy
Durham et al.[1986]	2016	1	Pooled analysis	Montelukast OAH INCS SLIT Placebo	TNSS	LTRA superior to placebo LTRA inferior to OAH, INCS, SLIT
Wei[1985]	2016	1	Pooled analysis	Montelukast OAH Montelukast + OAH Placebo	Symptoms	LTRA superior to placebo LTRA superior to OAH for nighttime symptoms LTRA similar to OAH for composite symptoms LTRA-OAH superior to LTRA alone for nighttime symptoms
Xiao et al.[1993]	2016	1	Network meta-analysis	Montelukast OAH	Symptoms	LTRA inferior to OAH
Devillier et al.[1995]	2014	1	SR of RCTs	LTRA SLIT Placebo	Symptoms	SLIT superior to LTRA LTRA superior to placebo
Xu et al.[1994]	2014	1	SR of RCTs	Montelukast OAH	Symptoms	In SAR, OAH superior for daytime symptoms and LTRA superior for nighttime symptoms
Goodman et al.[1999]	2008	1	SR of RCTs	Montelukast Levocetirizine Desloratadine Fexofenadine	Symptoms Cost	Montelukast has higher incremental cost-effectiveness ratio than levocetirizine and desloratadine

(Continues)

TABLE XI.B.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Grainger and Drake-Lee[2000]	2006	1	SR of RCTs	Montelukast OAH INCS Placebo	Symptoms QOL	Montelukast improved symptoms and QOL compared to placebo Montelukast was inferior to OAH and INCS
Rodrigo and Yanez[2001]	2006	1	SR of RCTs	LTRA OAH INCS Placebo	Symptoms QOL	LTRA improved symptoms and QOL compared to placebo LTRA was equally effective to OAH and inferior to INCS
Wilson et al.[1893]	2004	1	SR of RCTs	Montelukast OAH INCS Placebo	Symptoms QOL	Montelukast improved QOL compared to placebo, and was inferior to OAH and INCS
Gonyeau and Partisan[2002]	2003	1	SR of RCTs	Montelukast INCS Placebo	Symptoms	Montelukast was more effective than placebo in reducing symptoms, but was inferior to INCS
Bhattachan et al.[1894]	2020	2	RCT	Montelukast INCS	TNSS	INCS superior to LTRA for symptom reduction
Li et al.[1996]	2020	2	RCT	Montelukast Chinese acupoint application Combination therapy	Symptoms Serum IL-4, IFN-γ, Th1/Th2	Combination LTRA and Chinese acupoint application superior to either therapy alone
Chen et al.[1989]	2018	2	RCT	Montelukast INCS INCS half dose + montelukast	Symptoms Acoustic rhinometry FeNO Serum ECP, histamine, cysLT, Th1/Th2	LTRA alone inferior to INCS for overall nasal symptoms Combination therapy superior to monotherapy
Hashiguchi et al.[1987]	2018	2	RCT	Montelukast Placebo	Symptoms	No difference in LTRA versus placebo
Dalgic et al.[1991]	2017	2	RCT	Montelukast INCS Montelukast + INCS	Olfactory testing	No change with LTRA monotherapy Combination therapy was superior to INCS
Okubo et al.[1984]	2017	2	RCT	ONO-4053 (anti-PGD2) Pranlukast Placebo	Symptoms	Pranlukast superior to placebo ONO-4053 superior to pranlukast
Yoshihara et al.[1988]	2017	2	RCT	Long-term pranlukast Rescue therapy with pranlukast Rescue therapy with loratadine	Symptoms	In children under 15 with asthma and SAR, long-term LTRA is superior to rescue treatment with LTRA or OAH during allergy season
Jindal et al.[1990]	2016	2	RCT	Montelukast INCS	Symptoms	INCS superior to LTRA

(Continues)

TABLE XI.B.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Endo et al.[2003]	2012	2	RCT	Pranlukast Placebo	Symptoms	Following artificial introduction of allergen, pranlukast prevented and reduced symptoms versus placebo
Wakabayashi et al.[2004]	2012	2	RCT	Pranlukast Placebo	Symptoms	Following artificial introduction of allergen in children, pranlukast prevented and reduced symptoms versus placebo
Day et al.[2005]	2008	2	RCT	Montelukast Levocetirizine Placebo	Symptoms	Both montelukast and levocetirizine improved symptoms following artificial allergen exposure Levocetirizine was more effective than montelukast
Jiang[2006]	2006	2	RCT	Zafirlukast Loratadine Loratadine + pseudoephedrine	Symptoms Acoustic rhinometry Rhinomanometry	All treatment groups had a significant reduction of pre-treatment symptoms Zafirlukast was superior at reduction of nasal congestion No difference in acoustic rhinometry or rhinomanometry among groups
Mucha et al.[1965]	2006	2	RCT	Montelukast Pseudoephedrine	Symptoms QOL PNIF	Montelukast and pseudoephedrine had equivalent improvement of symptoms (except pseudoephedrine more effective for nasal congestion), QOL, PNIF
Patel et al.[2007]	2005	2	RCT	Montelukast Placebo	Symptoms QOL	Montelukast was more effective than placebo in reducing symptoms and improving QOL in patients with perennial AR
Chervinsky et al.[2008]	2004	2	RCT	Montelukast Placebo	Symptoms Pollen count	Montelukast was more effective than placebo in reducing symptoms Effect size related to amount of pollen exposure

(Continues)

TABLE XI.B.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Philip et al.[2009]	2004	2	RCT	Montelukast Placebo	Symptoms Rhinitis QOL Asthma QOL	Montelukast improved symptoms, rhinitis QOL, and asthma QOL versus placebo in patients with SAR and asthma
Ratner et al.[2010]	2003	2	RCT	Montelukast Fluticasone	Symptoms QOL	Fluticasone was more effective than montelukast in reducing symptoms and improving QOL
van Adelsberg et al.[2011]	2003	2	RCT	Montelukast Loratadine Placebo	Symptoms QOL	Montelukast was more effective than placebo at improving symptoms and QOL Montelukast was not directly compared to loratadine
van Adelsberg et al.[2012]	2003	2	RCT	Montelukast Loratadine Placebo	Symptoms QOL	Montelukast was more effective than placebo at improving symptoms and QOL Montelukast was not directly compared to loratadine
Philip et al.[2013]	2002	2	RCT	Montelukast Loratadine Placebo	Symptoms QOL Peripheral eosinophil count	Montelukast was more effective than placebo at reducing eosinophil count, and improving symptoms and QOL Montelukast was not directly compared to loratadine
Pullerits et al.[2014]	1999	2	RCT	Zafirlukast Beclomethasone Placebo	Symptoms Tissue eosinophilia	Zafirlukast was not different from placebo in symptoms or tissue eosinophilia Both were inferior to intranasal beclomethasone

Abbreviations: AR, allergic rhinitis; cysLT, cysteinyl leukotriene; ECP, eosinophil cationic protein; FeNO, fractional exhaled nitric oxide; IFN, interferon; IL, interleukin; INCS, intranasal corticosteroid; LOE, level of evidence; LTRA, leukorience receptor antagonist; OAH, oral antihistamine; PGD2, prostaglandin D2; PNIF, peak nasal inspiratory flow; QOL, quality of life; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy; SR, systematic review; Th, T helper; TNSS, Total Nasal Symptom Score.

LTRA to be inferior to INCS in improving olfactory function in patients with seasonal AR. In comparison to oral antihistamines, there remains mixed evidence for relative efficacy,[1992–1994] with recent studies favoring oral antihistamines. Comparing diurnal symptoms of AR, Feng et al.[1992] found LTRA to be superior to oral antihistamines for controlling nighttime symptoms, but inferior for daytime symptoms. LTRA monotherapy was further compared against AIT and found to be inferior for symptom control.[1982,1995] Li et al.[1996] compared LTRA monotherapy to acupoint-application of Chinese herbal medication and found no difference in symptom control for children with perennial AR.

In March 2020, the US FDA announced a safety concern regarding montelukast and potential serious neuropsychiatric events, including suicidal thoughts. A boxed warning, the FDA's most prominent warning, was added to prescribing information. The FDA advised further that in AR,

montelukast should be reserved for patients who are not treated effectively with or cannot tolerate other allergy medications.[1997]

In their 2015 Clinical Practice Guidelines for AR, the AAO-HNSF recommended against LTRA monotherapy, as it was less effective than other first-line medications and more costly.[1005] In 2020, this guideline was endorsed by the American Academy of Family Physicians.[1998] In the same year, the Joint Task Force on Practice Parameters issued an update recommending against the selection of LTRA as initial treatment of AR.[182]

While LTRA monotherapy has been consistently shown to be superior to placebo for the treatment of AR, there is now significant evidence that alternative agents such as INCS are superior and less costly.[1] Given the increased risk profile of LTRA highlighted by the FDA boxed warning, LTRA monotherapy is not recommended as first-line therapy for patients with AR but may be considered in selected patients who have contraindications to both oral antihistamines and INCS.

Leukotriene receptor antagonists

Aggregate grade of evidence: A (Level 1: 13 studies, level 2: 21 studies; Table XI.B.4)
Benefit: Consistent reduction in symptoms and improvement in QOL compared to placebo.
Harm: FDA boxed warning regarding neuropsychiatric side effects, including suicidal ideation. Consistently inferior compared to INCS at symptom reduction and improvement in QOL. Equivalent or inferior effect compared to oral antihistamines in symptom reduction and improvement of QOL. See Table II.C.
Cost: Moderate.
Benefits-harm assessment: LTRAs are effective as monotherapy compared to placebo. However, there is a consistently inferior or equivalent effect to other, less expensive agents used as monotherapy. Also, there is an FDA boxed warning associated with LTRAs.
Value judgments: LTRAs are more effective than placebo at controlling both asthma and AR symptoms in patients with both conditions. However, in the light of significant concerns over its safety profile and the availability of effective alternatives such as INCS and oral antihistamines, evidence is lacking to recommend LTRAs as monotherapy in the management of AR.
Policy level: Recommendation against LTRAs as first-line monotherapy for patients with AR. Option for LTRA as monotherapy in patients with contraindications to other preferred treatments.
Intervention: LTRAs should not be used as monotherapy in the treatment of AR but can be considered in select situations where patients have contraindications to alternative treatments.

XI.B.5 | Intranasal cromolyn

Disodium cromoglycate (DSCG) [synonyms: cromolyn sodium, sodium cromoglycate, disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4H-chromene-2-carboxylate] is a mast cell stabilizer that inhibits the release of mast cell mediators that promote IgE-mediated inflammation.[2015,2016] DSCG is FDA-approved for adults and children (2 years and older) for the prevention and relief of nasal symptoms of AR and is available as an over-the-counter nasal spray. It has a rapid onset of action with efficacy lasting up to 8 h, taken as one spray 3-6 times daily, and is primarily used to prevent the onset of symptoms prior to allergen exposure, but it also can be used to treat symptoms once they occur.[2017–2020]

DSCG exhibits an excellent safety profile with only minor adverse effects including nasopharyngeal irritation, sneezing, rhinorrhea, and headache. There are very rare reports of immediate IgE-mediated reaction to the medication.[2021,2022] Due to its high safety profile, this medication can be considered for very young children and pregnant patients.[2023,2024]

DSCG has been shown to be more effective than placebo in patients with seasonal AR in controlling nasal symptoms of sneezing, rhinorrhea, and nasal congestion as treatment during their peak allergy season.[2025–2029] The largest double-blind placebo-controlled trial included 1150 patients with seasonal AR treated for 2 weeks (580 patients on DSCG, 570 treated with placebo).[2025] Patients received DSCG as a 4% nasal solution, one spray every 4–6 h, no more than six times per day. DSCG was significantly better than placebo in controlling overall symptoms ($p = 0.02$), sneezing ($p = 0.01$), and nasal congestion ($p = 0.03$). Studies on the superiority of DSCG versus placebo in perennial AR have been controversial and with relatively small sample sizes.[2030–2034] In the most recent study that demonstrated a benefit of DSCG in perennial AR ($n = 14$), DCSG resulted in significant improvement in the symptom scores of runny nose, nasal congestion, sneezing, and nose blowing, when compared to placebo ($p < 0.005$).[2030] Additionally, factors that were found to be associated with a good clinical response to the medication included: (1) patients with higher IgE levels, (2) patients with markedly positive skin test reactions to foods and animal dander

compared to pollen allergy, and (3) female gender[2030] (Table XI.B.5).

In a small study, DSCG demonstrated similar efficacy for controlling nasal symptoms compared to oral antihistamines and significantly reduced the number of nasal eosinophils, whereas oral antihistamines did not.[2035] When compared to intranasal antihistamines[2036,2037] and INCS,[2031,2037–2046] DSCG has been shown to be less effective in controlling nasal symptoms. Ultimately, the role of DSCG as a primary treatment for AR is limited given its lower efficacy when compared to INCS and potential compliance challenges secondary to a frequent dosing regimen. The medication can also be administered as a preventive strategy, prior to allergen exposure to reduce the development of AR symptoms.

Intranasal cromolyn

Aggregate grade of evidence: A (Level 2: 25 studies; Table XI.B.5)
Benefit: DSCG is effective in reducing sneezing, rhinorrhea, and nasal congestion.
Harm: Rare local side effects.
Cost: Low.
Benefits-harm assessment: Preponderance of mild to moderate benefit over harm. Less effective than INCS and intranasal antihistamines.
Value judgments: DSCG is useful for preventative short-term use in adult patients, children (2 years and older), and pregnant patients with known exposure risks.
Policy level: Recommendation as a second-line treatment in AR.
Intervention: DSCG may be used as a second-line treatment for AR in patients who fail INCS or intranasal antihistamines, or for short-term preventative benefit prior to allergen exposures.

XI.B.6 | Intranasal anticholinergics

IPB is a synthetic quaternary ammonium anticholinergic compound that is related to atropine. Effects of IPB have been explored prior to nasal methacholine challenge in patients with AR. It was found to reduce rhinorrhea and sneezing with no effects on nasal airway resistance.[2050,2051] In addition, administration of IPB resulted in the reduction of rhinorrhea following cold air exposure and following the ingestion of hot soup, which suggested that this type of rhinorrhea is mediated through a reflex leading to hypersecretion from nasal glands.[2052] IPB is effective in controlling anterior rhinorrhea with no effect on nasal congestion or sneezing.[2053–2058] IPB is available at 0.03% and 0.06% concentration and is effective in adults and children with perennial rhinitis (0.03%) and common cold (0.06%).[2056,2059] It has a quick onset of action and short half-life and can be administered up to six times per day, with less than 10% absorption over a range of 84–336 μg/day.[2060]

Intranasal IPB is poorly absorbed, and systemic side effects have not been observed with therapeutic dosing, as plasma concentrations of greater than 1.8 ng/ml are needed to produce systemic anticholinergic effects.[2060] However, care should be taken to avoid overdosage that could lead to high serum concentrations of ipratropium. Side effects of topical IPB are mostly local (Table II.C).

IPB is FDA-approved for the treatment of seasonal AR in both adults and children (5 years and older). IPB also controls rhinorrhea in children and adults with perennial AR.

The largest study that compared IPB to placebo was conducted on perennial AR and perennial non-allergic rhinitis in pediatric patients aged 6–18 years.[2061] A total of 204 patients were included in this double-blind RCT, divided equally between IPB and placebo subgroups. There was a significant reduction in the severity and duration of rhinorrhea and improvement in QOL in the IPB group. The effect was more pronounced in the perennial non-allergic rhinitis group compared to the perennial AR group (Table XI.B.6).

Evidence on the efficacy of IPB in seasonal AR is derived from two studies, a prospective study and a double-blind RCT. The prospective study included a total of 230 children aged 2–5 years old with seasonal or perennial AR and found that IPB was safe and effective in controlling rhinorrhea.[2059] In the double-blind crossover trial ($n = 24$), adults aged 18–49 with seasonal AR, perennial AR, and non-allergic perennial rhinitis the local pretreatment with IPB effect on methacholine challenge was studied.[2051] IPB was found to be more effective than placebo in suppressing sneezing and nasal hypersecretion with no effect on nasal airway resistance.

When compared to other medications for treating AR, IPB has been shown to be equally effective compared to INCS with respect to nasal drainage. Despite its beneficial effects on rhinorrhea and sneezing, IPB was shown to be inferior to INCS in controlling sneezing.[2062] No head-to-head studies have compared IPB to other AR medications.

TABLE XI.B.5 Evidence table – intranasal cromolyn for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lejeune et al.[2030]	2015	2	DBRCT	Adults with mild-moderate persistent AR mono-sensitized to HDM: DSCG QID, $n = 14$ Placebo, $n = 7$	Nasal symptoms	DSCG was more efficacious than placebo
Pistios et al.[2046]	2006	2	RCT	Patients with moderate–severe SAR (12–57 years old): MF 200 μg each nostril daily, $n = 34$ Nedocromil sodium 1.3 mg each nostril TID, $n = 27$	Nasal symptoms	MF was more efficacious than DSCG
Lange et al.[2037]	2005	2	RCT	Patients with SAR (18–65 years old): MF 200 μg daily, $n = 41$ Levocabastine HCL 200 μg BID, $n = 40$ DSCG 5.6 mg QID, $n = 42$	Symptom scores PNIF	MF was most efficacious Levocabastine was equivalent to DSCG, except levocabastine was more effective for daytime sneezing
Meltzer et al.[2025]	2002	2	DBRCT	Patients with SAR (>12 years old): DSCG 4%, one spray q4–6 h, $n = 580$ Placebo, $n = 570$	Nasal symptoms	DSCG was more efficacious than placebo
Fisher[2038]	1994	2	RCT, blinded	Patients with SAR (6–15 years old): DSCG six times daily (31.2 mg per day), $n = 26$ Budesonide BID (400 μg per day), $n = 30$	Nasal symptoms	Budesonide was more efficacious than DSCG
Bousquet et al.[2039]	1993	2	DBRCT No placebo	Patients with SAR: FP 200 μg QD, $n = 110$ DSCG 5.2 mg QID, $n = 108$	Nasal/ocular symptoms Rescue medication use	FP was more efficacious for all symptoms except nasal discharge No difference in rescue medication use
Orgel et al.[2035]	1991	2	DBRCT	Patients with AR (12–56 years old): DSCG 4%, one spray each nostril QID Terfenadine PO BID	Nasal symptoms	No difference between groups
Schata et al.[2036]	1991	2	DBRCT	Patients with SAR: Levocabastine HCL 0.5 mg/ml, two sprays each nostril QID, $n = 18$ DSCG 20 mg/ml, two sprays QID, $n = 19$ Placebo, $n = 20$	Nasal/ocular symptoms	Levocabastine was most efficacious

(Continues)

TABLE XI.B.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Schuller et al.[2047]	1990	2	DBRCT	Patients with SAR (12–65 years old): Nedocromil 1%, $n = 80$ DSCG 4%, one spray QID, $n = 76$ Placebo, $n = 77$	Nasal symptoms	Nedocromil and DSCG were more efficacious than placebo Nedocromil was equivalent to DSCG
Welsh et al.[2040]	1987	2	RCT	Patients with SAR (12–50 years old): BDP two sprays BID (336 μg/day), $n = 26$ Flunisolide two sprays BID (200 μg/day), $n = 26$ DSCG one spray QID (41.6 mg/day), $n = 26$ Placebo, $n = 22$	Symptom score Medication use	All active treatments were better than placebo DSCG was the least effective of the active treatments
Bjerrum and Illum[2041]	1985	2	DBRCT	Patients with SAR (15–55 years old): Budesonide 200 μg BID, $n = 22$ DSCG 5.2 mg, five times daily, $n = 21$	Nasal symptoms	Budesonide was more efficacious than DSCG
Morrow-Brown et al.[2042]	1984	2	RCT	Patients with SAR: (11–71 years old): BDP two sprays BID (400 μg/day), $n = 47$ DSCG 2.6 mg, six times daily, $n = 39$	Symptom score Medication use	BDP was more efficacious for symptoms than DSCG No difference in rescue medications between groups
Chandra et al.[2026]	1982	2	DBRCT, crossover	Patients with SAR ($n = 47$, 9–41 years old): DSCG 4%, one spray q3–4 h Placebo	Nasal symptoms Medication use	DSCG was more efficacious than placebo for all endpoints
Brown et al.[2043]	1981	2	RCT	Patients with SAR: DSCG 2.6 mg, six times daily, $n = 29$ Flunisolide spray 25 μg BID, $n = 38$	Nasal symptoms	Flunisolide was more efficacious than DSCG
Tandon and Strahan[2031]	1980	2	DBRCT, crossover	Perennial AR due to animal dander ($n = 14$, 13–45 years old): BDP 50 μg QID DSCG 10 mg QID	Nasal symptoms	BDP was more efficacious than DSCG
Craig et al.[2048]	1977	2	DBRCT	Patients with SAR: DSCG 5.2 mg, six times daily, $n = 22$ Placebo, $n = 17$	Nasal symptoms Rescue medication use	No difference between groups
Handelman et al.[2027]	1977	2	DBRCT	Patients with SAR (6–51 years old): DSCG 62.4 mg, six times daily, $n = 45$ Placebo, $n = 45$	Symptom score Rescue medication use	DSCG was more efficacious than placebo

(Continues)

TABLE XI.B.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
McDowell and Spitz[2032]	1977	2	DBRCT, crossover	Patients with perennial AR (n = 12, 17–71 years old): DSCG 2.5 mg, six times daily Placebo	Nasal symptoms Cytology	No significant difference in most patients
Nizami and Baboo[2028]	1977	2	DBRCT, crossover	Patients with SAR (n = 92, 7–59 years old): DSCG 10 mg QID Placebo	Nasal symptoms	DSCG was more efficacious than placebo
Posey and Nelson[2049]	1977	2	DBRCT	Patients with SAR (n = 32, 12–54 years old): DSCG 4%, six times daily, n = 17 Placebo, n = 15	Symptom score Rescue medication use	No difference except for in-season use of rescue medications in DSCG group
Warland and Kapstad[2033]	1977	2	DBRCT, crossover	Perennial AR (n = 17, 15–57 years old): DSCG 10 mg QID Placebo	Nasal symptoms	No difference between groups
Cohan et al.[2034]	1976	2	DBRCT, crossover	Perennial AR (n = 34, 16–37 years old): DSCG 4%, six times daily Placebo	Symptom score Rescue medication use	DSCG was more efficacious than placebo
Knight et al.[2029]	1976	2	DBRCT	Patients with SAR (10–59 years old): DSCG 10 mg QID, n = 36 Placebo, n = 41	Nasal symptoms	DSCG was more efficacious than placebo for all endpoints
Wilson and Walker[2044]	1976	2	RCT	Adults with SAR: DSCG 10 mg QID, n = 10 Beclomethasone valerate 100 μg BID, n = 10	Nasal symptoms	Beclomethasone was more efficacious than DSCG
Frankland and Walker[2045]	1975	2	DBRCT	Adults with SAR: DSCG 10 μg in each nostril QID (80 μg total daily dose), n = 14 Beclomethasone valerate 100 μg in each nostril BID (400 μg total daily dose), n = 19	Nasal symptoms PNIF	Betamethasone was more efficacious for symptom control No difference between groups for PNIF

Abbreviations: AR, allergic rhinitis; BDP, beclomethasone dipropionate; BID, twice daily; DBRCT, double-blind randomized controlled trial; DSCG, disodium cromoglycate; FP, fluticasone propionate; HCL, hydrochloride; HDM, house dust mite; LOE, level of evidence; MF, mometasone furoate; PNIF, peak nasal inspiratory flow; QID, four times daily; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis; TID, three times daily.

TABLE XI.B.6 Evidence table – ipratropium bromide for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dockhorn et al.[2063]	1999	2	DBRCT	Perennial AR (8–75 years old): IPB 0.03% (42 μg) two sprays TID + BDP 82 μg BID, $n = 109$ IPB 0.03% (42 μg) two sprays TID, $n = 222$ BDP 82 μg BID, $n = 222$ Placebo, $n = 55$	Rhinorrhea	IPB more effective than placebo Combined use of IPB with BDP more effective than either agent alone for controlling rhinorrhea
Milgrom et al.[2062]	1999	2	RCT, blinded, no placebo	Perennial AR, non-allergic perennial rhinitis (6–18 years old): IPB 0.03% (42 μg) two sprays BID, $n = 75$ BDP, $n = 71$	Nasal symptoms QOL	Equally effective in controlling rhinorrhea and improving QOL BDP more effective in controlling sneezing
Finn et al.[2064]	1998	2	DBRCT, crossover	Perennial AR, ($n = 205$, 18–75 years old): IPB 0.03% (42 μg) TID + terfenadine 60 mg PO BID Placebo + terfenadine	Nasal symptoms	Control of rhinorrhea and sneezing better in IPB-terfenadine No differences in nasal congestion
Kaiser et al.[2056]	1998	2	DBRCT	Adults with perennial AR: IPB 0.03% (42 μg) TID IPB 0.06% (84 μg) TID Placebo	Nasal symptoms	High and low dose IPB resulted in significant reduction of nasal hypersecretion
Meltzer et al.[2061]	1997	2	DBRCT	Perennial AR and non-allergic rhinitis (6–18 years old): IPB 0.03% (42 μg) two sprays BID, $n = 102$ Placebo, $n = 102$	Nasal symptoms Medication use QOL	IPB reduced symptoms, with a modest effect noted in perennial AR
Gorski et al.[2065]	1993	2	DBRCT	Perennial AR ($n = 18$, 23–33 years old): IPB 80 μg QID Placebo	Sneezing	IPB resulted in increase in nasal reactivity to histamine, increase in number of sneezes
Meltzer et al.[2066]	1992	2	DBRCT	Perennial AR (18–70 years old): IPB 21 μg ($n = 48$) or 42 μg ($n = 54$), one spray TID Placebo ($n = 53$)	Nasal symptoms	IPB effective in controlling rhinorrhea
Sanwikarja et al.[2051]	1986	2	DBRCT, crossover	Seasonal or perennial AR ($n = 14$), perennial non-allergic rhinitis ($n = 14$), 18–49 years old: IPB 80 μg QID Placebo	Nasal symptoms	IPB has suppressive effects on sneezing and hypersecretion but no influence on nasal airway resistance

(Continues)

TABLE XI.B.6 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Schultz Larsen et al.[2067]	1983	2	RCT, crossover	Perennial AR ($n = 20$, 23–84 years old): IPB 80 μg QID Placebo	Nasal symptoms	IPB effective in controlling rhinorrhea
Borum et al.[2068]	1979	2	RCT, crossover	Perennial AR ($n = 20$, 18–82 years old): IPB 20 μg, one spray QID Placebo	Nasal symptoms	Significant effect on rhinorrhea No effect on other symptoms
Kim et al.[2059]	2005	3	Prospective	Common cold, seasonal/perennial AR ($n = 230$, 2–5 years old): Allergy group – IPB 0.06% (42 μg) one spray TID for 14 days, $n = 187$	Nasal symptoms	IPB effective in controlling rhinorrhea
Kaiser et al.[2057]	1995	3	Prospective	Perennial AR ($n =$ 219, 18–75 years old): First 6 months: IPB 0.06% (84 μg) TID 6 months-1 year: lowest dose of IPB that controls rhinorrhea	Nasal symptoms Medication use QOL	IPB effective in controlling rhinorrhea, congestion, PND, sneezing Reduction in medication use, improvement in QOL

Abbreviations: AR, allergic rhinitis; BDP, beclomethasone dipropionate; BID, twice daily; DBRCT, double-blind randomized controlled trial; IPB, ipratropium bromide; LOE, level of evidence; PND, postnasal drainage; PO, per os (by mouth); QID, four times daily; QOL, quality of life; RCT, randomized controlled trial; TIC, three times daily.

Intranasal anticholinergics (ipratropium bromide)

Aggregate grade of evidence: A (Level 2: 10 studies; level 3: 2 studies; Table XI.B.6)
Benefit: Reduction of rhinorrhea with topical anticholinergics.
Harm: Care should be taken to avoid overdosage leading to systemic side effects. See Table II.C.
Cost: Low.
Benefits-harm assessment: Preponderance of benefit over harm in AR patients with rhinorrhea.
Value judgments: Benefits limited to controlling rhinorrhea. Can be used as add on treatment for AR patients with persistent rhinorrhea despite first line medical management.
Policy level: Option.
Intervention: IPB nasal spray may be used as an adjunct medication to INCS in AR patients with persistent rhinorrhea.

XI.B.7 | Biologics

The biologics investigated for treating allergic conditions include omalizumab, mepolizumab, dupilumab, benralizumab, and reslizumab.[2069] These compounds work by targeting specific components of the pathways involved in type 2 inflammation. Omalizumab acts on IgE; dupilumab on the IL-4 receptor α subunit (recognized by IL-4 and IL-13); and mepolizumab, benralizumab, and reslizumab on IL-5 or its receptor.[2069] Only omalizumab and dupilumab have been studied specifically for AR. Biologics are currently FDA approved for the treatment of moderate to severe persistent asthma, AD, CRSwNP, chronic idiopathic urticaria, and eosinophilic esophagitis (EoE), but not for AR.[2070]

Omalizumab interferes with the allergic cascade by binding the serum free IgE molecules and preventing them from attaching to mast cells and basophils.[2071] Trials using omalizumab as a monotherapy in treating AR have been favorable (Table XI.B.7.-1). Two systematic reviews demonstrated decreased use of rescue medication, improvement of overall symptoms and QOL in patients treated with

TABLE XI.B.7.-1 Evidence table – omalizumab for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yu et al.[2073]	2020	1	SRMA	Omalizumab Placebo $n = 3458$	Symptoms Rescue medication QOL	Omalizumab superior to placebo Generally well tolerated
Tsabouri et al.[2072]	2014	1	SRMA	Omalizumab Placebo $n = 2870$	Symptoms Rescue medication QOL	Omalizumab superior to placebo Generally well tolerated
Casale et al.[2087]	2006	2	RCT	Omalizumab Placebo	Symptoms Adverse events	Omalizumab superior to placebo Well tolerated
Okubo et al.[2078]	2006	2	RCT	Omalizumab Placebo	Symptoms Rescue medication	Omalizumab effective and well tolerated in cedar pollen AR
Chervinsky et al.[2077]	2003	2	RCT	Omalizumab Placebo	Symptoms Rescue medication QOL	Omalizumab effective and well tolerated in perennial AR
Kuehr et al.[2088]	2002	2	RCT	Omalizumab Placebo	Symptoms Rescue medication Adverse events	Omalizumab superior to placebo Well tolerated
Casale et al.[2076]	2001	2	RCT	Omalizumab Placebo	Symptoms Rescue medication QOL	Dose-finding trial, 300 mg dose effective in improving symptoms and QOL versus placebo
Adelroth et al.[2075]	2000	2	RCT	Omalizumab Placebo	Symptoms Rescue medication QOL	Omalizumab superior to placebo in improving symptoms and QOL Well tolerated
Casale et al.[2074]	1997	2	RCT	Omalizumab Placebo	Symptoms Rescue medication QOL	First dose-finding study Safety confirmed

Abbreviations: AR, allergic rhinitis; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis.

omalizumab.[2072,2073] The effectiveness of omalizumab monotherapy was assessed for both seasonal and perennial AR.[2074–2078] Omalizumab monotherapy achieved significant improvement of nasal symptom score, ocular symptom score, medication symptom score, and QOL with the corresponding reduction of emergency drug use and serum IgE levels. Together with the marked reduction of free serum IgE level, there was notable inhibition of specific inflammatory mediators tryptase and ECP in the nasal secretions.[2079,2080] When compared to suplatast tosilate, a selective Th2 cytokine inhibitor (a drug sometimes used as a prophylaxis for atopic asthma), omalizumab was superior in treating patients with seasonal AR.[2081]

Studies showed favorable safety profiles with adverse events such as local injection site reactions and anaphylaxis, with no significant difference observed compared to placebo. The dosing is based on the serum tIgE level (IU/ml) and the body weight (kg) prior to the initiation of treatment where most studies used dosing from 75 to 375 mg of omalizumab administered every 2–4 weeks and mean duration of treatment of 16 weeks. Given the weight-based dosing regimen, cost of treatment with omalizumab varies between $10,000 and $32,000 per year.[2082]

Omalizumab has been evaluated as a combination therapy with AIT. This is addressed in Section XI.D.10. Combination Biologic Therapy and Subcutaneous Immunotherapy.

Another biologic investigated for the treatment of allergic airway diseases is dupilumab, which works through binding of IL-4Rα to inhibit IL-4 and IL-13.[2083] Dupilumab was shown to be effective when administered as an adjunct treatment in patients with uncontrolled persistent asthma and comorbid AR.[2084] Similar findings were observed in a post hoc analysis of patients having uncontrolled moderate-to-severe asthma and comorbid perennial AR receiving add on dupilumab therapy.[2085] In another multicenter trial, combination therapy did not significantly improve total symptom score but it resulted in better tolerance to AIT with less withdrawal and fewer requirement of rescue medicine.[2086] These results suggest dupilumab

TABLE XI.B.7.-2 Evidence table – dupilumab for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corren et al.[2086]	2021	2	Phase 2a RCT	SCIT + dupilumab SCIT Placebo $n = 103$	TNSS	No difference between SCIT-dupilumab versus SCIT alone for TNSS Reduction of rescue treatment with SCIT-dupilumab versus SCIT alone
Busse et al.[2085]	2020	3	Post hoc analysis of phase 3 study	Add on therapy with dupilumab 200 mg or 300 mg Placebo $n = 814$	RQLQ Total and sIgE	Both dupilumab doses superior to placebo
Weinstein et al.[2084]	2018	3	Post hoc analysis of phase 2b study	Dupilumab 200 mg or 300 mg Placebo $n = 392$	SNOT-22	Dupilumab 300 mg superior to placebo No difference between dupilumab 200 mg and placebo Generally well tolerated

Abbreviations: LOE, level of evidence; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SCIT, subcutaneous immunotherapy; sIgE, allergen-specific immunoglobulin E; SNOT-22, Sinonasal Outcome Test (22 item); TNSS, Total Nasal Symptom Score.

may have a role in treating AR, at the time of this writing it is not FDA approved for this indication (Table XI.B.7.-2).

In treating refractory AR that has failed optimal pharmacological treatment, biologics show promising results. Omalizumab has been the most studied and appears to be efficacious in symptom reduction, medicine use, and improvement in QOL with favorable safety profile. Current limitations in the widespread use of biologics for the treatment of AR are related mostly to the high cost of treatment and lack of FDA approval. In addition, it is foreseeable that the use of biologics will be long-term and once discontinued the symptoms may recur. Although there is no subgroup analysis to determine the efficacy of biologics in AR with comorbid bronchial asthma, the cost to benefit analysis is expected to improve considerably in such cases.[2072]

Biologics

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 8 studies, level 3: 2 studies; Tables XI.B.7.-1 and XI.B.7.-2)
Benefit: Omalizumab treatment resulted in improvement of symptoms, rescue medication and QOL as a monotherapy. Dupilumab data is less robust and needs further investigation.
Harm: Local reaction at injection site and risk of anaphylaxis.
Cost: High.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Biologic therapies show promise as a treatment option for AR; however, no biologic therapies have been approved by the US FDA for this indication.
Policy level: Option based upon published evidence, although not currently approved for this indication.
Intervention: Monoclonal antibody (biologic) therapies are not currently approved for the treatment of AR.

XI.B.8 | Intranasal saline

Nasal saline is a frequently utilized therapy in the treatment of AR. The term "nasal saline," however, encompasses a wide variety of therapeutic regimens. These can include differences in solution characteristics, such as salinity (hypertonic versus isotonic/normal saline) and buffering (buffered versus non-buffered), and differences in frequency, volume, and mode of administration.

This review included only level 1 and 2 evidence published in the English language evaluating nasal saline in the treatment of AR. Search methodologies identified nine RCTs in adults[2089–2097] (Table XI.B.8.-1) and one systematic review[2098] and eight RCTs[2099–2106] in children (Table XI.B.8.-2). Three SRMAs[2107–2109] have been performed including both adults and children

TABLE XI.B.8.-1 Evidence table – nasal saline for allergic rhinitis in adults

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yata et al.[2097]	2021	2	DBRCT	Patients with AR: 3% saline irrigations BID 0.9% saline irrigations BID *All groups received oral antihistamine	VAS: nasal congestion, rhinorrhea Inferior turbinate size Peak nasal expiratory flow	At 2 weeks, no significant differences in any of the outcomes between groups
Sansila et al.[2095]	2020	2	SBRCT	Patients with AR: 1.8% self-prepared hypertonic saline irrigations BID 0.9% commercial isotonic saline irrigation BID *All groups continued to use medications for control	QOL (Rcq-36) TNSS	At 4 weeks, 1.8% saline group had significantly better QOL and congestion symptom scores versus 0.9% saline formula
Di Berardino et al.[2094]	2017	2	RCT, no blinding	Patients with SAR: Hypertonic saline spray TID No local or intranasal treatment	Symptom score Oral antihistamine use Mucociliary clearance time	Symptoms, oral antihistamine use, mucociliary clearance times significantly better in hypertonic saline group
Lin et al.[2096]	2017	2	RCT, no blinding	Patients with persistent AR: Saline irrigation BID INCS BID	Nasal symptom score mini-RQLQ	After 30 days, nasal symptom scores similar RQLQ significantly better with INCS versus saline irrigation
Chusakul et al.[2093]	2013	2	DBRCT, crossover	Patients with AR: Nonbuffered isotonic saline irrigations BID (pH 6.2–6.4) Buffered isotonic saline irrigations with mild alkalinity BID (pH 7.2–7.4) Buffered isotonic saline irrigations with alkalinity BID (pH 8.2–8.4)	Nasal symptom score Mucociliary clearance time Nasal patency Patient preference	After 10 days, nasal symptoms improved from baseline only by buffered isotonic saline with mild alkalinity, which was significantly preferred by patients
Garavello et al.[2092]	2010	2	RCT, no blinding	Pregnant women with SAR: Hypertonic saline irrigations TID No local therapy	Nasal symptom score Oral antihistamine use Nasal resistance	Over 6 weeks, hypertonic saline irrigations improved nasal symptoms, oral antihistamine use, and nasal resistance, versus no local therapy
Ural et al.[2091]	2009	2	RCT, no blinding	Patients with perennial AR: Hypertonic saline irrigations BID Isotonic saline irrigations BID	Mucociliary clearance time	After 10 days, isotonic saline significantly improved mucociliary clearance times; hypertonic saline did not

(Continues)

TABLE XI.B.8.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Cordray et al.[2089]	2005	2	SBRCT	Patients with SAR: Dead Sea saline spray TID Aqueous triamcinolone spray daily Placebo nasal saline spray TID	RQLQ	After 7 days, Dead Sea saline group had clinically and statistically significant overall improvement from baseline but not as pronounced as the triamcinolone group, no improvement in the placebo group
Rogkakou et al.[2090]	2005	2	RCT, no blinding	Patients with persistent AR: Hypertonic saline spray QID No saline *All groups received cetirizine	Nasal symptoms RHINASTHMA Questionnaire	Addition of hypertonic saline resulted in a significant improvement in nasal symptoms and QOL

Abbreviations: AR, allergic rhinitis; BID, twice daily; DBRCT, double-blind randomized controlled trial; INCS, intranasal corticosteroid; LOE, level of evidence; QID, four times daily; QOL, quality of life; Rcq-36, Rhinoconjunctivitis Quality of Life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SBRCT, single-blind randomized controlled trial; TID, three times daily; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

(Table XI.B.8.-3). Compared to no irrigations, all found symptoms and patient-reported disease severity were significantly better in the saline irrigation group.[2107–2109] Hermelingmeier et al.[2107] also identified a 24%–100% reduction in medication usage, as well as an improvement of 30%–37% in QOL, and suggested that children may benefit less than adults.

Adult population. All studies found improvements in clinical outcomes with the utilization of nasal saline, with formulas varying in salinity, buffering, and frequency, volume, and mode of administration. Studies also varied in the types of AR evaluated.[2089–2097] Compared to no intranasal treatment, hypertonic saline was found to significantly improve outcomes, including nasal symptoms, QOL, and oral antihistamine use.[2090,2092,2094] Ural et al.[2091] further compared hypertonic and isotonic saline irrigations, finding improved mucociliary clearance with the isotonic solution only. Looking at subjective outcomes with hypertonic versus isotonic solutions, however, Cordray et al.[2089] and Sansila et al.[2095] found QOL and symptom score were better with hypertonic solutions. Finally, Yata et al.[2097] evaluated both subjective and objective outcomes and found no difference between hypertonic and isotonic saline irrigations. Focusing on isotonic saline with various degrees of buffering, Chusakul et al.[2093] found that after 10 days buffered isotonic saline with mild alkalinity had the greatest impact on reducing nasal symptom scores and was preferred by most patients. Both Cordray et al.[2089] and Lin et al.[2096] found INCS had similar efficacy in improving nasal symptoms but showed statistically significant improvement in QOL outcomes compared to saline spray.

Pediatric population. All studies found an improvement in clinical outcomes with the incorporation of nasal saline.[2098–2106] Compared to no irrigations, hypertonic and isotonic saline were found to improve outcomes, including nasal symptoms, oral antihistamine use, and QOL.[2100,2101,2106] Supporting these findings, a 2019 SRMA found significantly better nasal symptom scores and a lower rate of rescue antihistamine use with hypertonic saline irrigations compared to the control group (isotonic saline and no irrigations).[2098] Further, studies have shown that that hypertonic saline irrigations resulted in a greater improvement in nasal symptom scores in children than isotonic saline.[2102,2103,2105] Finally, Li et al.[2099] and Chen et al.[2104] found an additive effect in the utilization of nasal saline spray as an adjunct to INCS when compared to either therapy independently.

Overall, there is substantial evidence to support the use of nasal saline in the treatment of AR. In adults, the data is conflicting regarding optimal salinity of the solution. In children, there is some data to support a hypertonic solution being more effective. Although nasal saline demonstrates improvement in symptoms and QOL outcomes when used alone, it is often implemented with other therapies, such as INCS, intranasal antihistamines, or oral antihistamines. In both adults and children, nasal saline appears to have an additive effect when used in

TABLE XI.B.8.-2 Evidence table – nasal saline for allergic rhinitis in children

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Li et al.[2098]	2019	1	SRMA	Patients with AR: Hypertonic saline irrigations Control (isotonic saline, no irrigations)	Nasal symptom score Rescue antihistamine use	Hypertonic saline group had significantly better nasal symptom scores and a lower rate of rescue antihistamine use versus control group
Jung et al.[2106]	2020	2	RCT, no blinding	Patients with AR: Isotonic saline irrigations daily No irrigations *All groups received montelukast, levocetirizine, inhaled glucocorticoid	PC20 QOL scores (Asthma Control Test, Questionnaire for Quality-of-Life Specific to Allergic Rhinitis in Korean Children) FeNO	After 12 weeks, PC20 and QOL scores significantly improved in irrigation group versus baseline No significant change differences in any endpoints between groups
Malizia et al.[2105]	2017	2	RCT, no blinding	Patients with AR: Buffered hypertonic saline spray BID Normal saline spray BID	Total 5 symptom score Nasal cytology Pediatric RQLQ Pittsburgh Sleep Quality Index	After 21 days, symptom scores significantly better in the buffered hypertonic group versus normal saline group
Chen et al.[2104]	2014	2	RCT, no blinding	Patients with persistent AR: INCS daily Seawater spray daily Both	Nasal symptom score Nasal signs	After 3 months, all groups improved Combination therapy group had more significant improvements than other arms
Marchisio et al.[2102]	2012	2	SBRCT	Patients with SAR: Hypertonic saline irrigations BID Normal saline irrigations BID No irrigations	Nasal symptom score Turbinate, adenoid hypertrophy, middle ear effusion Oral antihistamine use	After 4 weeks, hypertonic saline significantly better in improving all endpoints Nasal symptom score significantly improved in normal saline versus control group
Satdhabudha and Poachan-ukoon[2103]	2012	2	DBRCT	Patients with AR: Buffered hypertonic saline BID Normal saline irrigations BID *All groups allowed to continue to use previous medications for control	Saccharin clearance time TNSS QOL score (Rcq-36) Oral antihistamine use	Over 4 weeks, greater improvement in saccharin clearance time and symptoms with buffered hypertonic saline No significant difference in QOL or antihistamine use
Li et al.[2099]	2009	2	RCT, no blinding	Persistent AR: INCS daily Isotonic saline irrigations BID Both *All groups received oral antihistamine	Nasal symptom score Mucociliary clearance Nasal secretions	After 12 weeks, all groups improved Combination therapy group had more significant improvement than other arms

(Continues)

TABLE XI.B.8.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Garavello et al.[2101]	2005	2	RCT, no blinding	Patients with SAR: Hypertonic saline irrigations TID No irrigations	Nasal symptom score Oral antihistamine use	After 7 weeks, hypertonic saline irrigations during pollen season had a significant improvement in nasal symptoms and oral antihistamine versus no therapy
Garavello et al.[2100]	2003	2	RCT, no blinding	Patients with SAR: Hypertonic saline irrigations TID No irrigations	Nasal symptom score Oral antihistamine use	Over 5 weeks, hypertonic saline irrigations during pollen season had a significant improvement in nasal symptoms and oral antihistamine use versus no therapy

Abbreviations: AR, allergic rhinitis; BID, twice daily; DBRCT, double-blind randomized controlled trial; FeNO, fractional exhaled nitric oxide; INCS, intranasal corticosteroid; LOE, level of evidence; PC20, provocative concentrations of methacholine causing a 20% decrease in FEV_1; QOL, quality of life; Rcq-36, Rhinoconjunctivitis Quality of Life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SBRCT, single-blind randomized controlled trial; SRMA, systematic review and meta-analysis; TID, three times daily; TNSS, Total Nasal Symptom Score.

TABLE XI.B.8.-3 Evidence table – nasal saline for allergic rhinitis in adults and children

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wang et al.[2109]	2020	1	SRMA	Patients with AR, multiple comparisons: Saline versus no irrigations Saline irrigation versus INCS Hypertonic versus isotonic saline	Nasal symptom score	Symptom scores significantly better with saline irrigation versus no irrigation in adults and children INCS was superior to saline irrigation in adults but similar in children Hypertonic saline was superior in efficacy to isotonic saline
Head et al.[2108]	2018	1	SRMA	Patients with AR: Saline irrigations No irrigations	Patient-reported disease severity Common adverse events	Saline irrigations may reduce patient-reported disease severity versus no saline irrigation at up to 3 months in adults and children, with no reported adverse effects
Hermeling-meier et al.[2107]	2012	1	SRMA	Patients with AR: Saline irrigations No irrigations	Nasal symptom score Medicine use Mucociliary clearance QOL	Up to 7 weeks, saline irrigations improve nasal symptoms, medicine use, and mucociliary clearance time, versus no therapy Children benefit less than adults

Abbreviations: AR, allergic rhinitis; INCS, intranasal corticosteroid; LOE, level of evidence; QOL, quality of life; SRMA, systematic review and meta-analysis.

combination with other standard AR treatments. Further, nasal saline is of relatively low cost and has an excellent safety profile. While adverse effects are rare, they can include nasal irritation, sneezing, cough, and ear fullness (Table II.C).

Intranasal saline

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 17 studies; Tables XI.B.8.-1, XI.B.8.-2, and XI.B.8.-3)
Benefit: Improved nasal symptoms and QOL, reduction in oral antihistamine use, and improved mucociliary clearance. Well-tolerated with excellent safety profile.
Harm: Nasal irritation, sneezing, cough, and ear fullness. See Table II.C.
Cost: Minimal.
Benefits-harm assessment: Preponderance of benefit over harm.
Value judgments: Nasal saline can and should be used as a first line treatment in patients with AR, either alone or combined with other pharmacologic treatments as evidence supports an additive effect. Hypertonic saline may be more effective in children. Data is otherwise inconclusive on optimal salinity, buffering, and frequency and volume of administration.
Policy level: Strong recommendation.
Intervention: Nasal saline is strongly recommended as part of the treatment strategy for AR.

XI.B.9 | Probiotics

The relationship between the microbiome and the development of atopy is complex and incompletely understood. The hygiene hypothesis theorizes that modern sanitized living conditions reduce microbial exposure resulting in inadequate immune priming. Low biodiversity in early life affects the immune system and can result in a pro-inflammatory response, including allergic oversensitization. Conversely, appropriate microbial exposure in infancy influences gut biodiversity, thereby increasing regulatory T cell action and immune tolerance. (See Section VI.J. Microbiome and Section VIII.C.3. Hygiene Hypothesis for additional information on this topic.)

Probiotics induce immunomodulatory effects on gut-associated lymphoid tissue. The gut microbiome and the immune system interact via dendritic cells, regulatory T cells, bacterial metabolites, and cytokines. Probiotic exposure induces a Th1 response via IL-12, IFN-γ, with upregulation of Treg cells via IL-10 and TGF-β. Furthermore, the allergy-associated Th2 pathway is suppressed through downregulation of IL-4, tIgE, IgG1, and IgA.[2110]

Numerous RCTs have examined the therapeutic role of probiotic administration for the control of AR symptoms. Several high-quality meta-analyses have been performed on aggregate data from RCTs. Results in children and adults have been mixed.

Guvenc et al.[2111] performed a meta-analysis of 22 RCTs comprising 2242 patient aged 2–65 years with seasonal or perennial AR who were treated with daily probiotic or placebo in addition to standard allergy therapies for 4 weeks to 12 months. The primary outcomes of the study were nasal/ocular symptom scores and QOL. Seventeen trials demonstrated clinical benefit of probiotics with improvement in nasal symptoms (standardized mean difference [SMD)] −1.23, $p < 0.001$), ocular symptoms (SMD −1.84, $p < 0.001$), total QOL (SMD −1.84, $p < 0.001$), nasal QOL (SMD −2.30, $p = 0.006$), and ocular QOL (SMD −3.11, $p = 0.005$).

Zajac et al.[2112] performed a meta-analysis of 21 RCTs and two randomized crossover studies that included 1919 adult and pediatric patients with seasonal or perennial AR. Patients were treated with 3 weeks to 12 months of probiotic or placebo. The primary outcomes were validated QOL, symptom scores, and immunologic variables. Seventeen studies demonstrated clinical benefit of probiotics for AR. Meta-analysis demonstrated improvement in RQLQ global score (SMD −2.23, $p = 0.02$) and RQLQ nasal symptom score (SMD −1.21, $p < 0.00001$). No effect of probiotic administration was found for Rhinitis Total Symptom Score, tIgE, or sIgE.

Du et al.[2113] published a meta-analysis of 19 RCTs comprising a total of 5264 healthy children treated with at least 6 months of probiotic or placebo. Ten RCTs reported no difference in the risk of developing AR (RR 1.03; $p = 0.83$) or a positive SPT (RR 0.74; $p = 0.13$) after administration of oral probiotics.

Zuccotti et al.[2114] reported a meta-analysis of 17 RCTs comparing probiotics versus placebo in 4755 children. The primary endpoint was to determine if supplementation of probiotics in pregnancy or early infancy reduced the relative risk of eczema, asthma, wheezing, and rhinoconjunctivitis. No significant difference in terms of prevention of asthma, wheezing or rhinoconjunctivitis was noted (RR 0.91; $p = 0.53$), whereas the relative risk of eczema in the treatment group was significantly lower than controls (RR = 0.78; $p = 0.0003$).

Probiotics are inexpensive and well tolerated in patients with minimal side effects (e.g., flatulence, diarrhea, and abdominal pain). The data from meta-analyses and RCTs suggests a potential benefit of probiotics in reduction of symptoms of seasonal and perennial AR in both adults and children but interpretation is limited by the heterogeneity of age, diagnosis, interventions, and outcomes included in the studies. The current data indicate that administration of probiotics in infancy does not reduce the diagnosis of most atopic diseases, with exception of eczema.

Probiotics

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 5 studies; Table XI.B.9)
Benefit: Improved nasal/ocular symptoms or QOL in most studies.
Harm: Mild gastrointestinal side effects.
Cost: Low.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Minimal harm associated with probiotics. Heterogeneity across studies makes magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific recommendations for treatment.
Policy level: Option.
Intervention: Consider adjuvant use of probiotics for patients with symptomatic seasonal or perennial AR.

XI.B.10 | Combination therapy

XI.B.10.a | *Oral antihistamine and oral decongestant*

Oral antihistamines, commonly used for treatment of AR, target the H_1 histamine receptor, block histamine receptor binding, and prevent histamine-mediated symptoms of AR such as pruritus, sneezing, vasodilation, and flushing. The effect of oral antihistamines on nasal obstruction in AR may be less pronounced. Oral decongestants such as phenylephrine or pseudoephedrine, which are typically sympathomimetic drugs that target α-1 receptors causing blood vessel constriction, cause more pronounced nasal decongestion. Oral antihistamines can thus be combined with oral decongestants to reduce histamine-mediated symptoms of AR while concomitantly improving nasal airflow.[296,1488,2120,2121]

RCTs have demonstrated that combination antihistamine-decongestant medications including fexofenadine-pseudoephedrine, desloratadine-pseudoephedrine, cetirizine-pseudoephedrine, loratadine-pseudoephedrine, and others reduce AR symptoms including rhinorrhea, nasal congestion, nasal itching, and sneezing when compared to placebo.[1477,1492,1959,1960,1962–1964,1968,1970,2121–2130] Combination oral antihistamine-oral decongestant medications have also been shown to reduce nasal congestion symptoms versus oral antihistamine alone or versus oral decongestant alone.[1477,1492,1959,1960,1962–1964,1968,1970,2121–2130] Studies have also demonstrated that once daily dosing of combination oral antihistamine-oral decongestant medications are statistically equivalent to twice daily dosing with regard to symptom relief[2131,2132] and that different antihistamine-decongestant combinations are statistically equivalent in improving symptom scores.[2132–2136] In some studies, oral antihistamine-oral decongestant combination medications are reported to be superior to INCS with regard to improving AR symptoms, particularly nasal congestion.[1488,2137,2138] In contrast, cetirizine-pseudoephedrine was not superior to xylometazoline nasal decongestant spray alone in improving nasal airflow and nasal obstruction symptoms[2139] (Table XI.B.10.a).

Oral antihistamines may cause sedation and dry mouth, especially in the case of first-generation antihistamines such as doxylamine and diphenhydramine; oral antihistamines may also cause urinary retention.[296,2120] Oral decongestants, through their actions on α-1 receptors may cause palpitations, insomnia, jitteriness, and dry mouth. Oral decongestants or oral antihistamine-decongestant combinations are typically not recommended by their manufacturers in patients under 12 years old, while oral antihistamines other than cetirizine are typically not recommended in patients under age 2.[296,2120] Over-the-counter sales of oral decongestants and oral antihistamine-oral decongestant combinations are typically monitored or restricted given their potential use in the illicit manufacture of methamphetamines. Oral decongestants should be used with caution in pregnant patients and patients with cardiac arrythmias, hypertension, or benign prostatic hypertrophy. Oral antihistamines should be used with caution in patients with preexisting cardiac conditions, patients taking monoamine oxidase inhibitors, narcotic pain medications or other sedating medications, and some antiseizure medications[296,2120] (Table II.C).

TABLE XI.B.9 Evidence table – probiotics for allergic rhinitis

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Du et al.[2113]	2019	1	SRMA	17 RCTs, 5264 children	Clinical diagnosis of asthma, wheeze, AR, positive SPT	No reduction of asthma, wheeze, AR, or positive SPT with probiotic
Zuccotti et al.[2114]	2016	1	SRMA	17 RCTs: Probiotic, $n = 2381$ Control, $n = 2374$	Eczema, prevention of asthma and rhinoconjunctivitis	Lower relative risk for eczema with probiotic versus control No significant difference in prevention of asthma or rhinoconjunctivitis
Guvenc et al.[2111]	2015	1	SRMA	22 DBRCTs, 2242 patients	Total nasal and ocular symptom scores QOL	Probiotics showed significant reduction of nasal and ocular symptom scores versus placebo
Zajac et al.[2112]	2015	1	SRMA	21 RCTs, two crossover studies, 1919 patients	RQLQ RTSS Total IgE	Improvement in RQLQ with probiotic versus placebo No effect on RTSS or total IgE
Anania et al.[2115]	2021	2	RCT	250 children with AR on conventional therapy: Probiotic Placebo	Nasal symptom score	Probiotic group had significant reduction in nasal symptom score
Jalali et al.[2116]	2019	2	Randomized, crossover	152 patients with persistent AR	SF-36 SNOT-22 CARAT	SF-36 improved versus baseline in both groups Probiotic group showed more reduction in SNOT-22 and CARAT
Sumadiono et al.[2117]	2018	2	RCT	Three groups: Cetirizine, $n = 15$ Cetirizine + Protexin probiotic, $n = 26$ Cetirizine + AIT, $n = 23$	Symptoms of AR (sneezing, rhinorrhea, itchy nose)	Certizine-probiotic had significant improvement in AR symptoms versus cetirizine alone
Dennis-Wall et al.[2118]	2017	2	DBRCT	$n = 173$ participants: probiotic versus placebo for 8 weeks	mRQLQ scores Changes in immune markers (IgE and IL-10)	Probiotic group reported an improvement in the mRQLQ
Miraglia Del Giudice et al.[2119]	2017	2	RCT	Probiotic versus placebo, $n = 40$ children	Total symptom score mRQLQ	Improvement in AR symptoms and QOL with probiotic

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; CARAT, Control of Allergic Rhinitis and Asthma Test; DBRCT, double-blind randomized controlled trial; IgE, immunoglobulin E; IL, interleukin; LOE, level of evidence; mRQLQ, mini Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, Rhinitis Total Symptom Score; SF-36, 36-item Short Form Survey; SNOT-22, Sinonasal Outcome Test (22 item); SPT, skin prick test; SRMA, systematic review and meta-analysis.

[a]Relevant prior studies included in SRMAs.

TABLE XI.B.10.a Evidence table – combination therapy: oral antihistamine and oral decongestant

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ng et al.[1488]	2021	2	RCT	Loratadine-PSE Placebo tablet Fluticasone propionate nasal spray Placebo nasal spray ($n = 82$)	TSS PNIF	Loratadine-PSE improved PNIF versus placebo tablet and versus fluticasone nasal spray PNIF was not significantly different for fluticasone versus placebo nasal spray
North et al.[2121]	2014	2	RCT	PF-03654764 (histamine receptor-3 antagonist) + fexofenadine Fexofenadine-PSE Placebo ($n = 80$)	TNSS Nasal congestion	PF-03654764-fexofenadine did not significantly reduce nasal congestion or TNSS versus fexofenadine-PSE Fexofenadine-PSE significantly reduced congestion and TNSS versus placebo PF-03654764-fexofenadine significantly improved TNSS, but not congestion versus placebo
Grubbe et al.[1962]	2009	2	RCT	Desloratadine-PSE Desloratadine + placebo tablet PSE ($n = 598$)	TSS (without nasal congestion) Nasal congestion	Desloratadine-PSE significantly reduced TSS and nasal congestion versus desloratadine-placebo and versus PSE
Chen et al.[2131]	2007	2	RCT	Loratadine-PSE Qday Loratadine-PSE BID ($n = 48$)	TSS	TSS improved in both groups with no statistically significant difference
Chiang et al.[2132]	2006	2	RCT	Cetirizine-PSE Loratadine-PSE ($n = 51$)	TNSS	Both groups statistically equivalent in symptom scores
Nathan et al.[2122]	2006	2	RCT	Cetirizine-PSE Placebo ($n = 274$)	Total and asthma symptoms PFTs Asthma QOL	Cetirizine-PSE significantly reduced seasonal AR symptoms and asthma symptom/QOL scores
Chervinsky et al.[2123]	2005	2	RCT	Desloratadine-PSE Desloratadine PSE ($n = 650$)	TSS	Desloratadine-PSE significantly reduced TSS and non-nasal symptom scores versus desloratadine or PSE alone
Pleskow et al.[1970]	2005	2	RCT	Desloratadine-PSE Desloratadine PSE ($n = 1047$)	TSS Morning instantaneous TSS Nasal congestion score	Desloratadine-PSE superior to desloratadine or PSE in reducing TSS and nasal congestion

(Continues)

TABLE XI.B.10.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zieglmayer et al.[2137]	2005	2	RCT	Cetirizine-prolonged-release PSE Budesonide nasal spray ($n = 36$)	Nasal congestion Rhinomanometry Nasal cavity images	Cetirizine-PSE more effective than budesonide in reducing nasal congestion during house dust mite exposure
Moinuddin et al.[2133]	2004	2	RCT	Fexofenadine-PSE Loratadine-montelukast ($n = 72$)	RQLQ Nasal symptoms PNIF	Fexofenadine-PSE and loratadine-montelukast equivalent in improving RQLQ, total symptom PNIF Loratadine-montelukast superior in improving sleep
Meltzer et al.[2124]	2003	2	RCT	Clemastine-PSE-acetaminophen PSE-acetaminophen Placebo ($n = 298$)	Major symptom complex score	Clemastine-PSE-acetaminophen significantly reduced major symptom complex score versus PSE-acetaminophen or placebo
Berkowitz et al.[1477]	2002	2	RCT	Fexofenadine-PSE Placebo ($n = 298$)	Major symptom complex score Total symptom complex score Individual symptoms	Fexofenadine-PSE significantly improved all symptoms following allergen exposure
Stübner et al.[2139]	2001	2	RCT	Cetirizine-prolonged-release PSE Xylometazoline nasal spray ($n = 36$)	Nasal congestion Nasal cavity photographs Nasal airflow Nasal secretions Nasal and ocular symptoms	Cetirizine-PSE was not superior to xylometazoline in nasal cavity appearance or nasal airflow Cetirizine-PSE significantly improved nasal secretions and ocular symptoms but not nasal obstruction versus xylometazoline
McFadden et al.[2125]	2000	2	RCT	Loratadine-PSE Placebo ($n = 20$)	Acoustic rhinometry QOL Inferior turbinate photographs	Loratadine-PSE significantly improved nasal edema, nasal secretions, nasal and ocular symptoms, and rhinoconjunctivitis versus placebo
Sussman et al.[1964]	1999	2	RCT	Fexofenadine-PSE Fexofenadine PSE ($n = 651$)	TSS Nasal congestion	Fexofenadine-PSE significantly improved TSS and nasal congestion symptoms versus fexofenadine or PSE alone Fexofenadine-PSE improved daily activities and work productivity versus fexofenadine or PSE

(Continues)

TABLE XI.B.10.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Horak et al.[1492]	1998	2	RCT	Cetirizine-PSE Placebo ($n = 24$)	Nasal obstruction Nasal patency/airflow	Cetirizine-PSE significantly improved nasal airflow and nasal obstruction symptoms versus placebo
Kaiser et al.[2140]	1998	2	RCT	Loratadine-PSE Qday Loratadine-PSE BID Placebo ($n = 469$)	Total nasal and non-nasal symptom scores	Loratadine-PSE daily or BID was superior to placebo in reducing symptom scores
Serra et al.[2126]	1998	2	RCT	Loratadine-PSE Placebo ($n = 40$)	Nasal symptoms/signs TSS	Loratadine-PSE significantly improved signs and TSS versus placebo Both placebo and loratadine-PSE improved nasal symptoms
Corren et al.[2127]	1997	2	RCT	Loratadine-PSE Placebo ($n = 193$)	Nasal and pulmonary symptoms Albuterol use PEF, FEV_1	Loratadine-PSE significantly reduced symptoms and improved PEF and FEV_1 versus placebo
Grosclaude et al.[1960]	1997	2	RCT	Cetirizine-PSE Cetirizine PSE ($n = 687$)	Daily congestion, sneezing, rhinorrhea, nasal itching, ocular itching	Cetirizine-PSE significantly improved symptoms versus cetirizine or PSE alone
Bertrand et al.[1963]	1996	2	RCT	Cetirizine-PSE Cetirizine PSE ($n = 210$)	Daily symptom scores	Cetirizine-PSE significantly reduced symptoms and increased symptom-free days versus cetirizine or PSE alone
Simola et al.[2134]	1996	2	RCT	Astemizole-PSE Brompheniramine-phenylpropanolamine ($n = 64$)	Nasal and eye symptoms	Astemizole-PSE equivalent to brompheniramine for nasal obstruction symptoms Brompheniramine-phenylpropranolamine superior to astemizole-PSE for rhinorrhea and itchy eyes
Williams et al.[2128]	1996	2	RCT	Acrivastine-PSE Acrivastine PSE Placebo ($n = 676$)	TSS	Acrivastine-PSE significantly more effective than acrivastine, PSE, and placebo in reducing AR symptoms

(Continues)

TABLE XI.B.10.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bronsky et al.[1959]	1995	2	RCT	Loratadine-PSE Loratadine PSE Placebo ($n = 874$)	Total, nasal, and non-nasal symptom scores	Loratadine-PSE superior to loratadine, PSE, and placebo in improving symptom scores
Negrini et al.[2138]	1995	2	RCT	Astemizole-PSE Beclomethasone nasal spray ($n = 204$)	TNSS VAS	Astemizole-PSE more effective than beclomethasone nasal spray in reducing ocular symptoms and reduced need for rescue vasoconstrictor eyedrops
Prevost et al.[2135]	1994	2	RCT	Loratadine-PSE Chlorpheniramine-PSE ($n = 131$)	TSS	Loratadine-PSE was equally effective versus chlorpheniramine-PSE in improving TSS
Howarth et al.[1968]	1993	2	RCT	Terfenadine-PSE Terfenadine PSE Placebo ($n = 14$)	TSS	Terfenadine-PSE significantly improved all symptoms versus placebo
Segal et al.[2136]	1993	2	RCT	Terfenadine-PSE Clemastine-phenylpropanolamine Placebo ($n = 178$)	TSS	Terfenadine-PSE and clemastine-phenylpropanolamine equally effective in improving TSS, both superior to placebo
Grossman et al.[2129]	1989	2	RCT	Loratadine-PSE Placebo ($n = 264$)	Nasal and non-nasal symptoms	Loratadine-PSE significantly reduced nasal and non-nasal symptoms scores versus placebo
Storms et al.[2130]	1989	2	RCT	Loratadine-PSE Loratadine PSE Placebo ($n = 435$)	TSS	Loratadine-PSE more effective than loratadine, PSE, or placebo in reducing TSS

Abbreviations: BID, twice daily; FEV_1, forced expiratory volume in 1 second; LOE, level of evidence; PEF, peak expiratory flow; PFT, pulmonary function test; PNIF, peak nasal inspiratory flow; PSE; pseudoephedrine; Qday, daily; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, Total Nasal Symptom Score; TSS, total symptom score; VAS, visual analog scale.;

Combination oral antihistamine and oral decongestant

Aggregate grade of evidence: A (Level 2: 30 studies; Table XI.B.10.a)

Benefit: Improved nasal congestion and total symptom scores (TSS) with combination oral antihistamine-oral decongestants.

Harm: Oral decongestants can cause adverse events in patients with cardiac conditions, hypertension, or benign prostatic hypertrophy and are not indicated in patients under age 12 or pregnant patients. Oral antihistamines are not indicated in patients under 2 years of age, and caution should be exercised in patients aged 2–5 years old. See Table II.C.

Cost: Low.

Benefits-harm assessment: Combination oral antihistamine-oral decongestant medications carry relatively low risks of adverse events when used as needed for episodic AR symptoms in well-selected patients. Risk may be higher if used daily or in patients with certain comorbidities.

There is not a preponderance of benefit or harm when used appropriately as a treatment option.
Value judgments: Oral antihistamine-oral decongestants may be an effective option for acute AR symptoms such as nasal congestion and sneezing. Caution should be exercised with long-term use.
Policy level: Option for episodic or acute AR symptoms.
Intervention: Combination oral antihistamine-oral decongestant medications may provide effective relief of nasal symptoms of AR on an episodic basis. Caution should be exercised in chronic or long-term use as the adverse effect profile of oral decongestants is greater for chronic use.

XI.B.10.b | *Oral antihistamine and intranasal corticosteroid*

A combination of an oral antihistamine with INCS is a commonly used treatment option for patients with AR. First-generation antihistamines include diphenhydramine, chlorpheniramine, and hydroxyzine, while newer second-generation medications include cetirizine, levocetirizine, fexofenadine, loratadine, and desloratadine. Typically, second-generation antihistamines are preferred given their improved safety profile compared to first-generation antihistamines. INCS reduce inflammatory mediator and cytokine release; decrease the recruitment of nasal eosinophils, neutrophils, basophils, lymphocytes, monocytes, and macrophages; and can decrease hyperresponsive effects to antigen challenge. INCS have an excellent safety profile and low systemic absorption.

There have been several RCTs examining the use of oral antihistamine-INCS combinations in the treatments of AR. Pinar et al.[2141] used TNSS, rhinoconjunctivitis scores, and PNIF to compare 4 groups: (1) intranasal mometasone-oral desloratadine, (2) intranasal mometasone-oral montelukast, (3) intranasal mometasone alone, and (4) placebo. This study found that intranasal mometasone with desloratadine or montelukast was superior to intranasal mometasone alone or placebo for improving TNSS and QOL (Table XI.B.10.b).

Anolik[2142] examined TNSS and TSS in patients treated with intranasal mometasone-oral loratadine, intranasal mometasone alone, oral loratadine alone, or placebo. This study noted that intranasal mometasone plus loratadine and intranasal nasal mometasone alone were statistically equivalent for TNSS and TSS. All treatment groups were superior to placebo in improving TNSS and TSS. The study also reported that intranasal mometasone and mometasone-loratadine were superior to loratadine alone or placebo for TNSS and TSS, while loratadine alone was superior to placebo for TNSS.[2142]

Barnes et al.[2143] compared RQLQ scores, PNIF, TNSS, and nNO in patients treated with intranasal fluticasone-oral cetirizine versus intranasal fluticasone-oral placebo. Their study found that nasal symptom score was statistically equivalent for cetirizine-fluticasone patients versus fluticasone-placebo patients.

Di Lorenzo et al.[2144] evaluated five groups: (1) oral cetirizine-intranasal fluticasone, (2) oral montelukast-intranasal fluticasone, (3) intranasal fluticasone alone, (4) oral cetirizine-oral montelukast, or (5) placebo. This study reported that all treatment groups were superior to the placebo group in improving TSS and rhinorrhea, sneezing, and nasal itching scores. They also noted that the fluticasone alone and fluticasone-cetirizine groups were superior to placebo or cetirizine-montelukast in improving TSS, nasal congestion on waking, and daily nasal congestion.

Ratner et al.[2145] examined intranasal fluticasone-oral loratadine versus fluticasone alone, loratadine alone, or placebo. They found that fluticasone and fluticasone-loratadine were superior to loratadine only and placebo groups for clinician and patient total and individual nasal symptom scores, and that loratadine alone was equivalent to placebo for nasal symptom score. QOL improvement was greater for fluticasone and fluticasone-loratadine compared to loratadine alone or placebo. QOL improvement was statistically equivalent for fluticasone-loratadine versus fluticasone.

A SRMA in 2018 by Seresirikachorn et al.[2146] showed no added benefit for oral antihistamines plus INCS. This is in contrast to intranasal antihistamines plus INCS, which did show additional benefit. Potential side effects of oral antihistamine with INCS combinations are typically low and are included in the combined table of AR treatment side effects (Table II.C).

Combination oral antihistamine and intranasal corticosteroid

Aggregate grade of evidence: A (Level 1: 1 study, level 2: 12 studies; Table XI.B.10.b)
Benefit: The addition of oral antihistamine to INCS has not consistently demonstrated a benefit over INCS alone for symptoms of AR.
Harm: Oral antihistamines generally not recommended in patients under 2 years old, and attention to dosing is necessary in patients 2–12 years old. See Table II.C.
Cost: Low.
Benefits-harm assessment: Benefit likely outweighs potential harms in patients with significant nasal congestion symptoms in addition to symptoms such as sneezing and ocular itching. Addition of an INCS may be limited benefit versus potential harm

in patients without significant nasal congestion symptoms.
Value judgments: Adding oral antihistamine to INCS spray has not been demonstrated to confer additional benefit over INCS spray alone. INCS improves congestion with or without oral antihistamine.
Policy level: Option.
Intervention: Current evidence is mixed to support antihistamines as an additive therapy to INCS, as several randomized trials have not demonstrated a benefit over INCS alone for symptoms of AR.

XI.B.10.c | *Oral antihistamine and leukotriene receptor antagonist*

The combination of oral antihistamine-LTRA in the treatment of AR was reviewed as a therapeutic option in the previous ICAR-Allergic Rhinitis 2018 consensus statement.[1] An updated systematic search revealed three additional systematic reviews and two RCTs,[1983,1985,2153–2155] giving a total of 17 studies meeting criteria for level 1 or 2 evidence (Table XI.B.10.c).

Combination oral antihistamine-LTRA has been shown to be superior to placebo in multiple RCTs. Recent studies have sought to clarify the comparative efficacy of combination therapy against monotherapy with LTRA or oral antihistamines, which was previously unclear. Compared to LTRA alone, Kim et al.[2153] found that oral antihistamine-LTRA therapy was superior in reducing nasal symptoms. However, in asthmatic patients, no difference was reported between the two treatment arms in improving spirometry readings or Asthma Control Test scores.

Krishnamoorthy et al.[1983] found that oral antihistamine-LTRA therapy was superior to monotherapy with either LTRA or oral antihistamines in improving daytime and nighttime symptoms of AR, as well as ocular symptoms. Additional systematic reviews by Liu et al.[2154] and Wei[1985] are concordant with these findings.

There have been no new studies comparing combination oral antihistamine-LTRA therapy to monotherapy with INCS. Previous evidence suggests that combination therapy is equivalent to, or less effective than INCS alone for reduction of symptoms and nasal eosinophil counts.[1893,2144,2156,2157] Comparing different antihistamines with LTRA, Mahatme et al.[2155] found that fexofenadine added to LTRA led to a greater decrease in symptoms, although the combination with levocetirizine was more cost-effective.

Regarding objective measures, there is mixed evidence for the use of combination oral antihistamine-LTRA. Cingi et al.[2158] found that combination oral antihistamine-LTRA was superior to oral antihistamines alone in reducing nasal resistance on rhinomanometric testing, and Li et al.[2159] found that the former was superior to the latter in increasing nasal volume as measured by acoustic rhinometry. However, Moinuddin et al.[2133] found that there was no significant difference in PNIF values between the two. Combination oral antihistamine-LTRA was superior to placebo in reducing peripheral and nasal eosinophil counts, but inferior to INCS[2144] and equivalent to oral antihistamines alone.[2153]

It is important to note that in the Joint Task Force Practice Parameters,[182] INCS were recommended when symptoms were not controlled with an oral antihistamine alone. Although the combination of LTRA and oral antihistamines was previously found to be well tolerated with minimal concerns for drug interactions,[1] recent concerns regarding the safety of LTRA have been raised, with the US FDA now requiring a boxed warning for serious neuropsychiatric events on montelukast.[1997]

Overall, the combination of oral antihistamine-LTRA is an effective therapy option when compared to placebo. However, in view of the adverse effect profile of montelukast, we recommend the consideration of other efficacious agents such as INCS which have been shown to result in superior symptom control, and that combination oral antihistamine-LTRA therapy be reserved for rare patients with contraindications to alternative treatments.

Combination oral antihistamine and leukotriene receptor antagonist

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 13 studies; Table XI.B.10.c)
Benefit: Combination oral antihistamine-LTRA was superior in symptom reduction and QOL improvement versus placebo and versus either agent as monotherapy.
Harm: Boxed warning due to risks of mental health side effects limiting use for AR. See Table II.C.
Cost: Generic montelukast added to generic loratadine or cetirizine is more expensive per month than generic fluticasone furoate nasal sprays, according to National Average Drug Acquisition Cost data provided by the Centers for Medicare and Medicaid Services.
Benefits-harm assessment: Combination LTRA and oral antihistamine is superior to placebo, and superior to either agent as monotherapy. However, there is an inferior effect versus INCS, which is also less costly. In addition, there is a boxed warning associated with montelukast.
Value judgments: Combination therapy of LTRA and oral antihistamines is effective, but in light

of concerns over the safety profile of montelukast, and the availability of effective alternatives such as INCS, evidence is lacking to recommend combination therapy in the management of AR.

Policy level: Recommendation against as first line therapy.

Intervention: Combination LTRA and oral antihistamines should not be used as first line therapy for AR but can be considered in patients with contraindications to other alternatives. This combination should be used judiciously after carefully weighing potential risks and benefits.

XI.B.10.d | *Intranasal corticosteroid and intranasal antihistamine*

Combination therapy of INCS plus intranasal antihistamine spray is available for the treatment of AR. One combined formulation is currently available in North America for intranasal use as a combination of azelastine hydrochloride and fluticasone propionate (AzeFlu). This agent is alternatively designated in the literature as MP-AzeFlu or MP29-02 and is marketed in the US under the trade name Dymista (Viatris, Canonsburg, PA). A second combination of olopatadine and mometasone (OloMom) was FDA approved in January 2022 and is marketed in the US under the trade name Ryaltris (Glenmark Pharmaceuticals, Mahwah, NJ).

A systematic review of the English-language literature was performed for clinical trials of combination INCS and intranasal antihistamine for the treatment of AR. A total of 18 RCTs (16 double-blind, two non-blinded) evaluated the efficacy of combination therapy against either placebo or active control.[1071,1480,2165–2180] An additional three observational studies reported outcomes of AzeFlu as a single treatment arm.[2181–2183] This evidence has been summarized in two previous systematic reviews[2146,2184] (Table XI.B.10.d).

Patient-reported symptom scores and QOL assessments are the most commonly reported outcome measures. The most common outcome measure was the TNSS (16 studies), which records the severity of runny nose, sneezing, itching, and congestion. Other outcome measures included the TOSS Score (eight studies), VAS (four studies), the RQLQ (seven studies), the PRQLQ (one study), and odor threshold/discrimination/identification score (one study).

The majority of included studies enrolled patients with a minimum age of 12 years or older. Most studies reported outcomes from 14 days of treatment, with the exception of two studies with a 3-month duration[2180,2183] and one study with a 52-week duration.[2180] The number of subjects in each study ranged from 47 to 3398. AzeFlu as a single formulation was compared to placebo in seven studies, with primary outcomes showing superiority to placebo in all studies.[2169–2171,2173–2176] Superiority of combination therapy with AzeFlu was also demonstrated over active treatment with fluticasone propionate monotherapy in six studies.[2172–2174,2176,2178,2180] Similarly, superiority of combination therapy with AzeFlu was demonstrated over active treatment with azelastine hydrochloride monotherapy in four studies.[2173,2174,2176,2180] A single study evaluated combination therapy with nonproprietary azelastine hydrochloride and fluticasone propionate applied using two separate spray bottles, which found superiority over either azelastine or fluticasone as monotherapy.[2178]

OloMom was compared to olopatadine or mometasone monotherapy in four studies, all of which showed superiority of the combination therapy.[2165–2168] One study comparing AzeFlu with OloMom found comparable symptom reduction.[2168] AzeFlu was directly compared to combination therapy with intranasal olopatadine and fluticasone in one study, with no significant difference in symptom relief between treatment groups.[2177] An experimental combination of solubilized azelastine and budesonide was found in a single study to be superior to either a suspension-type formulation of azelastine and budesonide or placebo.[2175] A recent meta-analysis found that intranasal antihistamines plus INCS is superior to oral antihistamines plus INCS in improving nasal symptoms in patients with AR.[2185]

Current FDA approval for the AzeFlu combined formulation extends to children ages 6 years and up, although indications for monotherapy are as low as 4 years for fluticasone and 6 months for azelastine. Children aged 6 to 12 years old were evaluated in two studies, with superiority of AzeFlu over placebo in improving symptoms and QOL.[2170,2180] Several studies reported time to onset of AzeFlu was more rapid than INCS alone.

No study reported serious adverse effects from the use of combination INCS plus intranasal antihistamine. This combination therapy was generally well tolerated, with the most common adverse effect being taste aversion. Other reported adverse effects occurred in less than 5% of cases in any study, and included somnolence, headache, epistaxis, and nasal discomfort (Table II.C). One study that compared combination therapy of fluticasone propionate with either azelastine or olopatadine reported more treatment-related events for the azelastine group than the olopatadine group.[2177] Ocular changes such as increased intraocular pressure and cataract formation are unlikely; nonetheless, caution may be warranted in patients with a history of glaucoma.[1922] Additional specific patient factors may be considered when selecting options for combination therapy.

TABLE XI.B.10.b Evidence table – combination therapy: oral antihistamine and intranasal corticosteroid

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Seresirikachorn et al.[2146]	2018	1	SRMA	ICNS alone INCS-OAH INCS-IAH	TNSS TOSS Disease specific QOL PNIF	INCS-IAH decreased TNSS and TOSS No difference in disease specific QOL, PNIF, adverse events
Wang and Zhang[2147]	2015	2	RCT	Montelukast-desloratadine-nasal budesonide Desloratadine-nasal budesonide ($n = 70$)	Nasal symptom scores RQLQ Total effective rate	Montelukast-desloratadine-budesonide superior to desloratadine-budesonide in nasal symptom improvement, improvement in RQLQ, total effective rate
Modgill et al.[2148]	2010	2	RCT	Montelukast-nasal fluticasone Cetirizine-nasal fluticasone Nasal fluticasone ($n = 90$)	Daytime and nighttime symptom scores	Montelukast-fluticasone superior to fluticasone alone and cetirizine-fluticasone for nighttime AR symptoms, and equivalent to fluticasone or cetirizine-fluticasone for TSS Fluticasone and fluticasone-cetirizine equivalent for TSS
Anolik[2142]	2008	2	RCT	Loratadine-nasal mometasone Nasal mometasone Loratadine Placebo ($n = 702$)	Daily TNSS and TSS	All treatment groups superior to placebo for TNSS and TSS Loratadine-mometasone and mometasone alone equivalent for TNSS and TSS, both superior to loratadine alone and placebo
Pinar et al.[2141]	2008	2	RCT	Montelukast-nasal mometasone Desloratadine-nasal mometasone Nasal mometasone Placebo ($n = 95$)	TNSS Rhinoconjunctivitis scores PNIF	Desloratadine-mometasone and montelukast-mometasone superior to mometasone alone or placebo for symptom scores and QOL
Barnes et al.[2143]	2006	2	RCT	Cetirizine-nasal fluticasone Placebo-nasal fluticasone ($n = 27$)	RQLQ PNIF TNSS Nasal nitric oxide	Symptom scores equivalent for cetirizine-fluticasone versus fluticasone-placebo

(Continues)

TABLE XI.B.10.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Benitez et al.[2149]	2005	2	RCT	Zafirlukast-nasal budesonide Loratadine-PSE-nasal budesonide ($n = 36$)	Rhinitis and asthma symptoms Blood eosinophils PFTs Nasal cytology	Both groups had improved nasal symptoms; zafirlukast-budesonide superior to loratadine-PSE-budesonide Both groups equivalent for bronchial symptoms, cough, wheezing, breathlessness Both groups had improved blood & nasal eosinophilia, FEV_1
Di Lorenzo et al.[2144]	2004	2	RCT	Cetirizine-nasal fluticasone Montelukast-nasal fluticasone Cetirizine-montelukast Nasal fluticasone Placebo ($n = 100$)	Symptoms Eosinophil count ECP in nasal lavage	All treatment groups superior to placebo in improving symptoms, rhinorrhea, sneezing, nasal itching scores Groups treated with fluticasone alone or as combination therapy superior to placebo or cetirizine-montelukast for TSS, nasal congestion on waking, daily nasal congestion Combination of cetirizine-fluticasone showed no added benefit versus fluticasone alone for TSS
Lanier et al.[2150]	2002	2	RCT	Fexofenadine-nasal fluticasone Nasal fluticasone-olopatadine Placebo ($n = 80$)	Ocular itching Ocular redness Nasal symptoms	Fluticasone-olopatadine improved ocular itching versus fexofenadine-fluticasone Ocular redness scores similar for fluticasone-olopatadine versus fexofenadine-fluticasone Both treatment groups improved ocular redness versus placebo and had similar efficacy for TNSS
Wilson et al.[2151]	2000	2	RCT	Cetirizine-nasal mometasone Cetirizine-montelukast Cetirizine ($n = 38$)	PNIF Symptom diary	Cetirizine-mometasone statistically equivalent to cetirizine alone for PNIF and seasonal AR symptoms

(Continues)

TABLE XI.B.10.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Berger et al.[1815]	1999	2	RCT	Loratadine-nasal beclomethasone Nasal azelastine ($n = 3210$)	Physician assessment of need for rescue mediation Patient global evaluation	Need for rescue medication and the patient assessment of efficacy statistically equivalent for both groups
Ratner et al.[2145]	1998	2	RCT	Loratadine-nasal fluticasone Nasal fluticasone Loratadine Placebo ($n = 600$)	Clinician- and patient-rated total and individual nasal symptom scores RQLQ	Fluticasone and loratadine-fluticasone superior to loratadine alone and placebo for clinician and patient total and individual NSS Loratadine alone equivalent to placebo for NSS RQLQ improvement greater for fluticasone and loratadine-fluticasone versus loratadine alone or placebo RQLQ improvement statistically equivalent for loratadine-fluticasone versus fluticasone No significant benefit of loratadine-fluticasone over fluticasone alone
Juniper et al.[2152]	1989	2	RCT	Astemizole-nasal beclomethasone Nasal beclomethasone Astemizole ($n = 90$)	Nasal and ocular daily symptoms Use of rescue nasal steroid spray or antihistamine-decongestant eye drops	Sneezing, nasal obstruction, rhinorrhea significantly improved, and less rescue nasal spray needed with beclomethasone alone versus astemizole alone Astemizole-beclomethasone equivalent to beclomethasone alone for rhinitis symptoms Eye symptoms and eye drop use improved for patients taking astemizole-beclomethasone or astemizole alone versus beclomethasone alone

Abbreviations: AR, allergic rhinitis; ECP, eosinophil cationic protein; FEV_1, forced expiratory volume in 1 second; IAH, intranasal antihistamine; INCS, intranasal corticosteroid; LOE, level of evidence; NSS, nasal symptom score; OAH, oral antihistamine; PFT, pulmonary function test; PNIF, peak nasal inspiratory flow; PSE, pseudoephedrine; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score; TSS, total symptom score.

TABLE XI.B.10.c Evidence table – combination therapy: oral antihistamine and leukotriene receptor antagonist

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Krishnamoorthy et al.[1983]	2020	1	SR of RCTs	Montelukast-OAH Montelukast INCS Placebo	Symptoms (day, night, composite)	LTRA superior to placebo OAH superior to LTRA except for night symptoms INCS superior to LTRA LTRA-OAH superior to LTRA or OAH monotherapy
Liu et al.[2154]	2018	1	SR of RCTs	Montelukast-OAH OAH	Symptoms	LTRA-OAH superior to OAH alone
Wei[1985]	2016	1	SR of RCTs	Montelukast-OAH Montelukast OAH Placebo	Symptoms	LTRA superior to placebo LTRA superior to OAH for night symptoms LTRA similar to OAH for composite symptoms LTRA-OAH superior to LTRA alone for night symptoms No difference for composite
Wilson et al.[1893]	2004	1	SR of RCTs	LTRA-OAH LTRA OAH INCS	Symptoms QOL	Combination therapy improved symptoms versus LTRA or OAH alone No difference in standardized QOL measures No difference in symptoms for combination therapy versus INCS
Kim et al.[2153]	2018	2	RCT	Montelukast-cetirizine Montelukast	Symptoms Asthma Control Test Spirometry	Combination therapy superior to LTRA alone for nasal symptoms No difference in Asthma Control Test or spirometry
Mahatme et al.[2155]	2016	2	RCT	Montelukast-levocetirizine Montelukast-fexofenadine	Symptoms	Both reduced symptoms LTRA-fexofenadine greater decrease in symptoms LTRA-levocetirizine more cost effective
Ciebiada et al.[2160]	2013	2	RCT	Montelukast-OAH Montelukast OAH Placebo	Symptoms ICAM-1 levels Nasal eosinophilia	All active treatments superior to placebo at reducing symptoms, ICAM-1 levels, eosinophilia Active treatments not statistically different from each other

(Continues)

TABLE XI.B.10.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yamamoto et al.[2161]	2012	2	RCT	Montelukast-loratadine Montelukast-placebo	Symptoms	Active combination therapy with improved total symptom score, and specifically sneezing and rhinorrhea
Cingi et al.[2158]	2010	2	RCT	Fexofenadine-montelukast Fexofenadine-placebo Fexofenadine	Symptoms Rhinomanometry	Combination therapy improved symptoms and decreased nasal resistance compared to fexofenadine alone or with placebo
Li et al.[2159]	2009	2	RCT	Fexofenadine-montelukast Fexofenadine	Symptoms Acoustic rhinometry Cytokine levels	Combination therapy improved symptoms, increased nasal volume by acoustic rhinometry No difference in cytokine levels
Lu et al.[2156]	2009	2	RCT	Montelukast-loratadine INCS Montelukast Loratadine Placebo	Symptoms QOL	Combination therapy improved symptoms more than placebo and montelukast alone No difference compared to loratadine alone Combination therapy inferior to intranasal beclomethasone
Watanasomsiri et al.[2162]	2008	2	RCT	Montelukast-loratadine Loratadine-placebo	Symptoms Turbinate hypertrophy	No difference in symptoms in children treated with combination therapy or antihistamine alone Turbinate swelling significantly reduced in combination therapy arm
Di Lorenzo et al.[2144]	2004	2	RCT	Montelukast-cetirizine Fluticasone Fluticasone-cetirizine Fluticasone-montelukast Placebo	Symptoms Peripheral eosinophilia Nasal eosinophil counts	Montelukast-cetirizine improved symptoms and decreased nasal eosinophil counts compared to placebo Generally inferior to fluticasone alone or in combination
Moinuddin et al.[2133]	2004	2	RCT	Montelukast-loratadine Fexofenadine-pseudoephedrine	Symptoms QOL PNIF	No significant difference between treatment groups for symptoms, QOL, PNIF Montelukast-loratadine reduced sleep domain symptoms

(Continues)

TABLE XI.B.10.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Saengpanich et al.[2157]	2003	2	RCT	Montelukast-loratadine Fluticasone	Symptoms Nasal eosinophil count Nasal ECP level	No difference in total symptom score, although nasal symptoms were reduced in fluticasone group Decreased eosinophil cell count and ECP level in fluticasone group
Nayak et al.[2163]	2002	2	RCT	Montelukast-loratadine Montelukast Loratadine Placebo	Symptoms QOL Peripheral eosinophilia	Combination therapy decreased symptoms and improved QOL versus placebo Effect did not reach statistical significance versus monotherapy Combination therapy decreased peripheral eosinophilia versus placebo and loratadine alone
Meltzer et al.[2164]	2000	2	RCT	Montelukast-loratadine Montelukast Loratadine Placebo	Symptoms QOL	Combination therapy improved symptoms and QOL versus placebo Combination therapy not directly compared to monotherapy

Abbreviations: ECP, eosinophil cationic protein; ICAM, intercellular adhesion molecule; INCS, intranasal corticosteroid; LOE, level of evidence; LTRA, leukotriene receptor antagonist; OAH, oral antihistamine; PNIF, peak nasal inspiratory flow; QOL, quality of life; RCT, randomized controlled trial; SR, systematic review.

Combination intranasal corticosteroid and intranasal antihistamine

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 18 studies, level 4: 3 studies; Table XI.B.10.d)

Benefit: Rapid onset; more effective for relief of multiple symptoms than either INCS or intranasal antihistamine alone.

Harm: Patient tolerance, especially due to taste. See Table II.C.

Cost: Moderate financial burden for combined formulation. Concurrent use of individual intranasal antihistamine and corticosteroid sprays is likely a more economical option.

Benefits-harm assessment: Preponderance of benefit over harm. Combination therapy with intranasal antihistamine and INCS is consistently more effective than placebo or monotherapy. Low risk of non-serious adverse effects.

Value judgments: High-level evidence demonstrates that combination spray therapy with INCS plus intranasal antihistamine is more effective than monotherapy or placebo, as well as more effective than combination of INCS plus oral antihistamine. The increased financial cost and need for prescription limit the value of combination therapy as a routine first-line treatment for AR. When a combined formulation is financially prohibitive, the concurrent use of two separate formulations (antihistamine and corticosteroid) is an alternative option.

Policy level: Strong recommendation for the treatment of AR when monotherapy fails to control symptoms.

Intervention: Combination therapy with INCS and intranasal antihistamine may be used as second-line therapy in the treatment of AR when initial monotherapy with either INCS or antihistamine does not provide adequate control.

TABLE XI.B.10.d Evidence table – combination therapy: intranasal corticosteroid and intranasal antihistamine

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Debbaneh et al.[2184]	2019	1	SR	AzeFlu Azelastine FP Placebo	TNSS	AzeFlu superior to either spray alone for symptom improvement
Seresirikachorn et al.[2146]	2018	1	SR	Antihistamine-INCS INCS	TNSS TOSS RQLQ	Antihistamine-INCS superior to INCS for nasal and ocular symptom improvement No difference in QOL improvement
Andrews et al.[2165]	2020	2	DBRCT	OloMom Olopatadine Mometasone Placebo	rTNSS rTOSS RQLQ	OloMom superior to monotherapy or placebo for symptom and QOL improvement
Gross et al.[2167]	2019	2	DBRCT	OloMom Olopatadine Mometasone Placebo	rTNSS iTNSS PNSS RQLQ RCAT	OloMom superior to monotherapy or placebo for symptom and QOL improvement
Hampel et al.[2166]	2019	2	DBRCT	OloMom Olopatadine Mometasone Placebo	rTNSS rTOSS PNSS RQLQ	OloMom superior to olopatadine or placebo for symptom and QOL improvement OloMom superior to mometasone for QOL improvement
Ilyina et al.[2179]	2019	2	Nonblinded RCT	AzeFlu Azelastine	rTNSS rTOSS RQLQ EQ-5D	AzeFlu superior to azelastine for moderate-to-severe symptom and QOL improvement
Patel et al.[2168]	2019	2	DBRCT	OloMom AzeFlu Olopatadine Placebo	iTNSS	OloMom superior to olopatadine or placebo for symptom improvement AzeFlu also superior to olopatadine or placebo
Segall et al.[1071]	2019	2	DBRCT	OloMom Placebo	rTNSS PNSS RQLQ	OloMom superior to placebo for symptom and QOL improvement
Bousquet et al.[1480]	2018	2	DBRCT	AzeFlu Loratadine-FP	TNSS TOSS VAS	AzeFlu superior to loratadine-FP, more rapid onset of action
Kortekaas Krohn et al.[2169]	2018	2	DBRCT	AzeFlu Placebo	Nasal airflow Substance P level β-hexamidase level	AzeFlu superior to placebo for reducing inflammatory mediators and nasal hyperreactivity
Berger et al.[2170]	2016	2	DBRCT	AzeFlu Placebo	rTNSS rTOSS PRQLQ	AzeFlu superior to placebo for symptoms and QOL improvement in children Symptoms improved when children self-rate

(Continues)

TABLE XI.B.10.d (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Berger et al.[2180]	2016	2	Nonblinded RCT	AzeFlu FP	Total symptom score	AzeFlu superior to fluticasone for children; faster onset
Meltzer et al.[2171]	2013	2	DBRCT	AzeFlu Placebo	rTNSS rTOSS	AzeFlu superior to placebo for all symptoms
Price et al.[2172]	2013	2	DBRCT	AzeFlu FP	rTNSS Symptom-free days	AzeFlu superior to fluticasone for symptom reduction; faster onset
Carr et al.[2173]	2012	2	DBRCT	AzeFlu Azelastine FP Placebo	rTNSS rTOSS RQLQ	AzeFlu superior to either spray alone for symptom and QOL improvement; faster onset
Meltzer et al.[2174]	2012	2	DBRCT	AzeFlu Azelastine FP Placebo	rTNSS rTOSS RQLQ	AzeFlu superior to either spray alone for symptom and QOL improvement
Salapatek et al.[2175]	2011	2	DBRCT	Solubilized azelastine-budesonide (CDX-313) Azelastine-budesonide suspension Placebo	TNSS	Both treatments superior to placebo CDX-313 superior to suspension-type spray for symptoms and speed of onset
Hampel et al.[2176]	2010	2	DBRCT	AzeFlu Azelastine FP Placebo	TNSS	AzeFlu superior to either spray alone, all treatments superior to placebo
LaForce et al.[2177]	2010	2	DBRCT	AzeFlu Olopatadine-FP	TNSS	No difference between treatments
Ratner et al.[2178]	2008	2	DBRCT	Azelastine-FP Azelastine FP	TNSS	Combination superior to either agent alone
Klimek et al.[2183]	2017	4	Prospective observational	AzeFlu	TDI score VAS symptoms	Olfactory function improved after 1 month
Klimek et al.[2181]	2016	4	Prospective observational	AzeFlu	VAS	76% of subjects had symptom control after 14 days; significant improvement from baseline
Klimek et al.[2182]	2015	4	Prospective observational	AzeFlu	VAS	Rapid symptom relief across all age groups

Abbreviations: AzeFlu, azelastine-fluticasone; DBRCT, double-blind randomized controlled trial; EQ-5D, Euro-QOL 5-dimension questionnaire; FP, fluticasone propionate; i, instantaneous; INCS, intranasal corticosteroid; LOE, level of evidence; OloMom, olopatadine mometasone; PNSS, physician-assessed nasal symptom score; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality of life; r, reflective; RCAT, Rhinitis Control Assessment Test; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SR, systematic review; TDI, threshold/discrimination/identification; TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score; VAS, visual analog scale.

TABLE XI.B.10.e Evidence table – combination therapy: intranasal corticosteroid and leukotriene receptor antagonist

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Seresirikachorn et al.[2186]	2021	1	Meta-analysis	Montelukast-fluticasone INCS Montelukast-budesonide INCS	Nasal symptoms Ocular symptoms QOL	No additional benefit to add-on montelukast except for improvement in ocular symptom scores
Chen et al.[2187]	2021	2	RCT	Montelukast-budesonide INCS Budesonide INCS	Symptoms Nasal cavity volume FeNO	Combination therapy had superior improvement
Chen et al.[1989]	2018	2	RCT	Montelukast-budesonide INCS Budesonide INCS	Symptoms Nasal cavity volume FeNO	Combination therapy had superior improvement
Dalgic et al.[1991]	2017	2	RCT	Montelukast-mometasone INCS Montelukast	Olfactory function	No additional benefit to add-on montelukast
Florincescu-Gheorghe et al.[2190]	2014	2	RCT	Montelukast-mometasone INCS Desloratadine-mometasone INCS Mometasone INCS	Symptoms Immune markers	No additional benefit to add-on montelukast
Goh et al.[2188]	2014	2	RCT	Montelukast-fluticasone INCS Fluticasone INCS	Symptoms QOL	Combination therapy had superior improvement
Esteitie et al.[2189]	2010	2	RCT	Montelukast-fluticasone INCS Fluticasone INCS	Symptoms QOL	No additional benefit to add-on montelukast
Pinar et al.[2141]	2008	2	RCT	Montelukast-mometasone INCS Desloratadine-mometasone INCS Mometasone INCS	Symptoms QOL Nasal peak flow	Add-on montelukast had superior improvement in symptoms and QOL at 1 month, but at 3 months all active treatment groups were equivalent
Di Lorenzo et al.[2144]	2004	2	RCT	Montelukast-cetirizine Montelukast-fluticasone INCS Cetirizine-fluticasone INCS Fluticasone	Symptoms Immune markers	No additional benefit to add-on montelukast

Abbreviations: FeNO, fractional exhaled nitric oxide; INCS, intranasal corticosteroid; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial.

XI.B.10.e | *Intranasal corticosteroid and leukotriene receptor antagonist*

LTRAs have been studied in conjunction with INCS for the treatment of AR. Montelukast is the only LTRA approved by the FDA for the treatment of seasonal AR in adults and children over 2 years of age, and for perennial AR in adults and children over 6 months of age. However, a boxed warning from the FDA in 2020 advises restricting use of montelukast for AR due to serious neuropsychiatric events, ranging from behavioral changes to suicidal thoughts or behavior.[1997] For patients with both asthma and AR, LTRAs may be considered with awareness of the mental health risks.

Montelukast has been studied in combination with INCS to determine if add-on therapy to INCS provides improved outcomes. Nasal symptoms, olfaction, QOL, nasal airflow measures, and immunologic markers have been used to compare combination therapy with LTRA and INCS to INCS monotherapy for AR – with conflicting results reported in controlled trials. There is one meta-analysis[2186] and eight controlled trials[1989,1991,2141,2144,2187–2190] where montelukast was

studied as add-on therapy to INCS. The meta-analysis included four studies that used fluticasone propionate and one that used budesonide as the INCS; all used oral montelukast as the LTRA. No difference was demonstrated in nasal symptoms, disease specific QOL, or adverse effects, when comparing combination therapy with LTRA and INCS to INCS as monotherapy.[2186] However, significant improvement in ocular symptoms with combination therapy was reported in one RCT included in the meta-analysis (Table XI.B.10.e).

Four trials demonstrated benefit with LTRA added to INCS.[1989,2141,2187,2188] Chen et al.[1989] studied budesonide alone or in combination with montelukast. Outcome measures of symptoms, nasal cavity volume, and expired NO all demonstrated improvement in with combination therapy. A follow-up study by Chen et al.[2187] showed similar favorable outcomes in all three outcomes categories for combination therapy. Goh et al.[2188] reported an RCT with fluticasone propionate compared to montelukast-fluticasone propionate; combination therapy demonstrated improvement in symptom scores and QOL. Pinar et al.[2141] reported a trial with mometasone alone or in combination with desloratadine or montelukast. Add-on montelukast had superior improvement in symptoms and QOL compared to all other active treatment groups after 1 month of treatment but not at 3 months (when all active treatment groups showed comparable efficacy).

Four other studies did not show additional benefit with add-on montelukast.[1991,2144,2189,2190] Di Lorenzo et al.[2144] studied symptoms and eosinophil-specific inflammatory markers in four cohorts: fluticasone propionate alone, cetirizine-fluticasone propionate, montelukast-fluticasone propionate, and cetirizine-montelukast. There was no additional benefit to add-on montelukast besides a decrease in nasal itching with the combination therapy of montelukast-fluticasone propionate compared to fluticasone propionate alone. Inflammatory markers were not different when LTRA was added to INCS.

Esteitie et al.[2189] studied symptoms and QOL in patients on fluticasone propionate compared to montelukast-fluticasone propionate. There was no additional benefit to add-on montelukast for nasal symptom scores and QOL measures.

Dalgic et al.[1991] studied objective measures of olfactory function in patients on mometasone furoate, montelukast, or montelukast-mometasone. They found no difference in olfactory function with combination therapy. Florincescu-Gheorghe et al.[2190] studied eosinophils in nasal secretions and symptoms in patients on mometasone furoate, desloratadine-mometasone furoate, and montelukast-mometasone furoate. There was no additional benefit to adding montelukast to mometasone furoate for all outcomes measured.

Overall, there are varying outcomes from trials reporting combination therapy with LTRA and INCS. Differences in the corticosteroid preparation may affect study findings – two studies with budesonide had favorable outcomes, whereas those with fluticasone propionate and mometasone furoate had variable outcomes. There was heterogeneity between the studies with variations in allergy sensitizations and seasonal symptoms, and the studies had modest sample sizes. Given the FDA boxed warning[1997] and variable study outcomes, use of LTRA with INCS should primarily be considered for patients with comorbid asthma, rather than AR alone. Proper counselling regarding mental health risks to patients and families, highlighting the importance of monitoring for any neuropsychiatric symptoms regardless of prior history of psychiatric disorders.

Combination intranasal corticosteroid and leukotriene receptor antagonist

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 8 studies; Table XI.B.10.e)
Benefit: Some studies demonstrate improvement of symptoms and QOL with combination therapy. One meta-analysis did not show benefit with the exception of ocular itching.
Harm: Boxed warning due to risks of serious neuropsychiatric events limiting use for AR. See Table II.C.
Cost: Low.
Benefits-harm assessment: Boxed warning for AR limits use. If comorbid asthma and AR, treatment is an option with consideration of mental health risks.
Value judgments: Possibly useful for symptom control, especially in patients with comorbid asthma, however, boxed warning limits use in AR without asthma.
Policy level: Option as combination therapy if comorbid asthma present and mental health risks are considered. Not recommended for AR alone.
Intervention: Consider use in patients with AR and asthma, after weighing therapeutic benefits against risks of mental health adverse effects.

XI.B.10.f | *Intranasal corticosteroid and intranasal decongestant*

Combination therapy of INCS and INDC is used less frequently in clinical practice for the treatment of refrac-

tory AR. Most INDC (e.g., oxymetazoline, phenylephrine, and xylometazoline) are α-receptor agonists, and decrease nasal congestion by reducing nasal mucosal volume through sympathomimetic vasoconstriction of mucosal blood vessels.[2191] Prolonged use of INDCs alone has been shown to cause rhinitis medicamentosa,[114] or rebound rhinitis symptoms that respond increasingly poorly to INDCs. INCSs, on the other hand, as detailed in the preceding sections, have been widely validated and shown to be safe and effective in the first-line treatment of AR.

In patients refractory to first-line therapy, several RCTs have examined combination therapy using INCS and INDC. Five RCTs, varying in size from 23 to 705 participants, showed that combination therapy with INCS and INDC was significantly more effective in improving nasal symptom scores compared to INCS alone.[2192–2196] Three of these studies also reported no rhinitis medicamentosa in patients receiving combination therapy.[2193,2194,2196] In contrast, Baroody et al,[2197] in a 2011 randomized cohort with refractory AR, showed that TNSS improved with fluticasone-oxymetazoline compared to placebo or oxymetazoline alone, but not over fluticasone alone. Additionally, while Meltzer et al.[2194] showed combination therapy to be superior to mometasone alone in their AR cohort, they did not demonstrate a dose-dependent relationship of oxymetazoline as part of the combination therapy in reducing nasal congestion (Table XI.B.10.f).

This controversy extends to higher level evidence as well. A 2018 SRMA of two studies by Khattiyawittayakun et al.[2198] determined that there was no demonstrable benefit to the addition of an INDC to INCS, and an IT reduction should be recommended in AR patients refractory to first-line therapy with INCS. Several limitations in the current data exist that make comparing published RCTs challenging, including heterogeneity of methods and medications used, inconsistency between studies in their cohort construction (some including seasonal and perennial AR and others including non-allergic rhinitis), and differences in antihistamine use in various trials. This is reflected in the measured statements issued in current guidelines. The 2020 Joint Task Force Practice Parameter on Rhinitis suggests that combination therapy of INCS-INDC can be offered for up to 4 weeks to patients with nasal congestion unresponsive to INCS or INCS-intranasal antihistamine combination therapy.[182] The 2015 AAO-HNSF Clinical Practice Guideline for AR cautions that such combination therapy with INDC should be limited to a few days to prevent rebound congestion.[1005]

Combination intranasal corticosteroid and intranasal decongestant

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 5 studies, level 3: 1 study; Table XI.B.10.f)
Benefit: Some evidence in randomized studies of benefit from addition of INDC to INCS therapy in refractory AR patients. The evidence regarding the magnitude of effect is unclear, and a meta-analysis that tried to estimate this effect was significantly limited by study heterogeneity and low sample size (two trials).
Harm: See Table II.C.
Cost: Low.
Benefits-harm assessment: Balance of benefit and harm with current evidence base.
Value judgments: While combination therapy of INDC and INCS is superior to INCS therapy alone with low risk of tachyphylaxis in patients with refractory AR, the magnitude of effect is still unclear. There may be a role in patients with AR refractory to INCS and intranasal antihistamine combination therapy prior to consideration of surgery or in patients uninterested in surgery.
Policy level: Option.
Intervention: Short-term combination therapy with INCS and INDC may be considered in patients with AR refractory to combination therapy with INCS and intranasal antihistamine prior to consideration of IT reduction or in patients declining surgery.

XI.B.10.g | *Intranasal corticosteroid and intranasal ipratropium*

Current treatment algorithms for children[2199,2200] and adult patients[182,1005] with moderate to severe AR with insufficient symptom control or treatment failure with INCS monotherapy uniformly recommend adding nasal IPB to the established INCS therapy if one of the main symptoms is predominant or refractory rhinorrhea. Although most guidelines recommend the combined use of both INCS and IPB in those patients, only one study assessed the effectiveness of this combination therapy in AR patients. Dockhorn et al.[2063] conducted a double-blind RCT in patients with AR and non-allergic rhinitis and demonstrated that the combination therapy of 14 days of IPB 0.03%, 42 μg per nostril TID and beclomethasone dipropionate, 84 μg per nostril BID was superior

TABLE XI.B.10.f Evidence table – combination therapy: intranasal corticosteroid and intranasal decongestant

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Khattiyawitta-yakun et al.[2198]	2018	1	SRMA	Six RCTs: INCS-INDC INCS	TNSS, rhinorrhea, itching, sneezing	Two studies in meta-analysis Combination therapy did not show benefit over INCS alone
Kirtsreesakul et al.[2192]	2016	2	RCT	68 participants: Mometasone furoate-oxymetazoline nasal spray Mometasone furoate-placebo nasal spray	TNSS, PNIF, nasal mucociliary clearance time, total nasal polyp score	Combination therapy significantly more effective in improving blocked nose, hyposmia, mucociliary clearance, and total nasal polyp score
Thongngarm et al.[2196]	2016	2	RCT	50 participants: Budesonide-oxymetazoline nasal spray-oral cetirizine Budesonide-placebo nasal spray-oral cetirizine	Nasal symptom score, PNIF, RQLQ	Combination therapy significantly more effective than budesonide-cetirizine, particularly in AR subgroup
Meltzer et al.[2194]	2013	2	RCT	705 participants: Mometasone-oxymetazoline (3 sprays pn Qday) nasal spray Mometasone-oxymetazoline (1 spray pn Qday) nasal spray Mometasone nasal spray Oxymetazoline (2 sprays pn BID) nasal spray Placebo	TNSS	Combination therapy significantly more effective in improving nasal congestion than mometasone alone, oxymetazoline alone, and placebo No dose-dependent relationship seen with oxymetazoline in combination therapy
Matreja et al.[2193]	2012	2	RCT	123 participants: Fluticasone nasal spray Fluticasone-oxymetazoline nasal spray	Nasal symptom score (daytime, nighttime, composite)	Combination therapy significantly more effective in improving daytime, nighttime, and composite nasal symptoms versus fluticasone alone
Baroody et al.[2197]	2011	2	RCT	60 participants: Fluticasone nasal spray Oxymetazoline nasal spray Fluticasone-oxymetazoline nasal spray Placebo	TNSS, acoustic rhinometry, PNIF	Combination therapy significantly more effective in improving nasal congestion than placebo or oxymetazoline alone No significant improvement over fluticasone alone
Rael et al.[2195]	2011	3[a]	RCT	23 participants: Mometasone nasal spray Mometasone-oxymetazoline nasal spray	Mini-RQLQ	Combination therapy significantly more effective in improving nasal congestion than mometasone alone No rhinitis medicamentosa observed

Abbreviations: AR, allergic rhinitis; BID, twice daily; INCS, intranasal corticosteroid; INDC, intranasal decongestant; LOE, level of evidence; pn, per nostril; PNIF, peak nasal inspiratory flow; Qday, daily; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SRMA, systematic review and meta-analysis; TNSS, Total Nasal Symptom Score.

[a]Downgraded LOE due to very small size of RCT and lack of AR/non-allergic rhinitis subgroup analysis.

TABLE XI.B.10.g Evidence table – combination therapy: intranasal corticosteroid and intranasal ipratropium

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dockhorn et al.[2063]	1999	2	DBRCT	Perennial AR (n = 279), non-allergic rhinitis (n = 274); 8–74 years old: IPB 0.03% [42 μg pn TID] + BDP [84 μg pn BID], (n = 207) IPB 0.03% [42 μg pn TID] + placebo, (n = 103) BDP [84 μg pn BID] + placebo, (n = 109) Placebo, (n = 106)	Severity and duration of rhinorrhea (patient-perceived)	Combining IPB with BDP is more effective than either agent alone for the treatment of rhinorrhea

Abbreviations: AR, allergic rhinitis; BDP, beclomethasone dipropionate; BID, twice daily; DBRCT, double-blind randomized controlled trial; IPB, ipratropium bromide; LOE, level of evidence; pn, per nostril; TID, three times daily.

to either agent alone, or placebo, in reducing the severity and duration of rhinorrhea. The combination therapy resulted in a clinically relevant reduction in severity and duration of rhinorrhea in 74% and 66% of patients, respectively, compared to 57% and 50% for IPB monotherapy, 64% and 54% for beclomethasone dipropionate monotherapy, and 47% and 38% for placebo. Of note, in evaluation of nasal congestion alone, combination therapy was more effective than IBP monotherapy or placebo, but not statistically better than beclomethasone dipropionate alone. Similarly, better improvements in QOL PROMs, including the SF-36 Health Survey and the RQLQ, were seen in the combination therapy group relative to monotherapy or placebo. The QOL effects of the combination therapy were most pronounced on the three RQLQ questions that focus on rhinorrhea. A clinically relevant improvement from: "somewhat troubled-extremely troubled" at baseline to "not troubled-hardly troubled" after 2 weeks of treatment was found in 48.8% of patients with the combined treatment compared to 38.9%, 25.2%, and 16% in the IPB, beclomethasone dipropionate, and placebo groups. The combination therapy was generally well tolerated. The most reported adverse effects included nasal dryness, epistaxis, blood-streaked sputum, nasal irritation, and congestion (Table II.C). Interestingly, the percentage of patients reporting these adverse events was comparable to the treatment groups receiving monotherapy. Of note, this study population included patients with both AR and non-allergic rhinitis and therefore these conclusions may only apply to this combination population. Nonetheless, as there is only evidence that the combination therapy effectively controls rhinorrhea, add-on IPB should only be prescribed if one of the predominant refractory symptoms is rhinorrhea (Table XI.B.10.g).

Combination intranasal corticosteroid and intranasal ipratropium

Aggregate grade of evidence: Unable to determine based on one study. (Level 2: 1 study; Table XI.B.10.g)

Benefit: Reduction of rhinorrhea in INCS-treatment-refractory AR.

Harm: Usually no systemic anticholinergic activity if administered intranasally in the recommended doses. See Table II.C.

Cost: Low.

Benefits-harm assessment: Benefit for combined INCS and IPB therapy in patients with treatment refractory AR and the main symptom of rhinorrhea.

Value judgments: No evidence for benefit in controlling symptoms other than rhinorrhea. Evidence is limited, but results are encouraging for patients with persistent rhinorrhea.

Policy level: Option.

Intervention: Combining IPB with beclomethasone dipropionate can be more effective than either agent alone for the treatment of rhinorrhea in refractory AR in children and adults. Although multiple consensus guidelines have recommended, and there is evidence to support this recommendation, it is important to note that there has only been one RCT to study the efficacy of combined INCS and IPB therapy compared to either agent alone, and this study was performed in a combined population of patients with AR and non-allergic rhinitis.

XI.B.11 | Non-traditional and alternative therapies

XI.B.11.a | *Acupuncture*

Since the 5th century BC, acupuncture has been used as a therapeutic modality for otolaryngologic disorders.[2201] A central tenet of Traditional Chinese Medicine (TCM) is the concept of *qi*, which represents the body's vital energy and flows through a network of meridians beneath the skin.[2202] Acupuncture involves insertion of thin needles at specific acupoints located along these meridians with the goal of achieving a therapeutic "*de qi*" effect.[2203] Studies have shown that acupuncture may potentially reset the Th2-Th1 imbalance by modulating IgE and IL-10 levels in patients with AR significantly more than controls.[2204,2205] Acupuncture has an excellent safety profile with only mild reported adverse effects.[2205,2206]

Several SRMAs have been performed on acupuncture for the treatment of AR. In 2008, Roberts et al.[2206] reviewed seven RCTs and found a high degree of heterogeneity between studies with most studies being of low quality. No overall effects of acupuncture on AR symptom scores or use of relief medications were identified. In 2009, Lee et al.[2207] performed a systematic review with pooled analysis of 152 patients demonstrating that the results of acupuncture for AR are mixed – with acupuncture superior to sham acupuncture in symptom scores for perennial AR, but not for seasonal AR. In 2015, a meta-analysis by Feng et al.[2205], which included 13 studies, showed a significant improvement of nasal symptoms, RQLQ scores, and use of rescue medications in the group receiving acupuncture. This meta-analysis included data from a large multicenter RCT ($n = 422$) demonstrating improvement of seasonal AR with true acupuncture.[2208] In 2020, a systematic review by Wu et al.[2209] analyzed 15 RCTs and found acupuncture as a useful adjunct to allopathic standard of care or as monotherapy for AR. Yin et al.[2210] reviewed 39 studies, which included several studies from China and a meta-analysis showing that acupuncture was superior to sham acupuncture with improvement in nasal symptom and RQLQ scores (Table XI.B.11.a).

Most important to note is the paucity of trials with head-to-head comparisons between acupuncture and standard conventional AR medication, with most RCTs using medication primarily as rescue treatment. The uncontrolled use of AR medications can significantly impact outcomes and underscores the critical need for comparative effectiveness research, as prioritized by the National Academy of Medicine.[2211]

Acupuncture

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 1 study; Table XI.B.11.a)

Benefit: Improvement of QOL and symptoms. Fairly well tolerated with no systemic adverse effects.

Harm: Needle sticks associated with minor adverse events including skin irritation, erythema, subcutaneous hemorrhage, pruritus, numbness, fainting, and headache. Electroacupuncture can interfere with pacemakers and other implantable devices. Caution is recommended in pregnant patients as some acupoints can theoretically induce labor. Need for multiple treatments and possible ongoing treatment to maintain any benefit gained. Relatively long treatment period.

Cost: Moderate-high. Cost and time associated with acupuncture treatment; multiple treatments required.

Benefits-harm assessment: Balance of benefit and harm.

Value judgments: The evidence is generally supportive of acupuncture. Acupuncture may be appropriate for some patients to consider as an adjunct/alternative therapy.

Policy level: Option.

Intervention: In patients who are interested in avoiding medications, acupuncture can be suggested as a possible therapeutic adjunct.

XI.B.11.b | *Other complementary modalities*

Several SRMAs and RCTs have been performed on complementary interventions other than traditional acupuncture. These include: (1) ear acupressure[2212]; (2) acupoint catgut implantation[2213]; (3) acupoint herbal patching[2214]; (4) sphenopalatine ganglion acupuncture – a modern version of acupuncture developed by a Chinese otolaryngologist in the 1960s and first reported in 1990 for the treatment of AR[2215–2218]; and (5) moxibustion/thunder fire moxibustion – a therapy based upon TCM theory that entails the burning of mugwort leaves as a warming treatment to promote circulation of qi.[2210,2219,2220] SRMA results are mixed, with several of the SRMAs including studies of low methodological quality or high risk of bias (Table XI.B.11.b).

TABLE XI.B.11.a Evidence table – acupuncture for allergic rhinitis

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wu et al.[2209]	2020	1	SR	Acupuncture Sham acupuncture No acupuncture Conventional medication (1 RCT)	Nasal symptom scores RQLQ	Significant efficacy in traditional acupuncture groups Acupuncture and loratadine both had significant improvement in symptoms Acupuncture had lasting improvement after 10 weeks
Feng et al.[2205]	2015	1	SRMA	Acupuncture Sham acupuncture	Nasal symptom scores RQLQ Rescue medication use	Significant reduction in nasal symptoms, improvement in RQLQ scores and use of rescue medications with acupuncture
Lee et al.[2207]	2009	1	SR	Acupuncture Sham acupuncture Conventional medication (2 RCTs)	Nasal symptom scores RQLQ Rescue medication use	Favorable effects of acupuncture on symptom scores for perennial AR, but not for seasonal AR
Roberts et al.[2206]	2008	1	SRMA	Acupuncture Sham acupuncture	AR symptom scores Rescue medication use	No overall effect on AR symptom scores or need for rescue medications
Yin et al.[2210]	2020	2[b]	SRMA (including Chinese databases)	Acupuncture Sham acupuncture Moxibustion Electroacupuncture Conventional medication	Nasal symptom scores RQLQ	All acupuncture methods superior to sham acupuncture for nasal symptoms and RQLQ

Abbreviations: AR, allergic rhinitis; LOE, level of evidence; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SR, systematic review; SRMA, systematic review and meta-analysis.

[a]Relevant prior studies are included in the SRMAs.

[b]LOE downgraded due to unclear risk of bias for allocation concealment; insufficient blinding of participants, personnel, and outcome assessments; short treatment duration (most studies 2–4 weeks) and lack of follow up.

Other complementary modalities

Aggregate grade of evidence: Uncertain. Various complementary modalities assessed. Studies included in several SRMAs had poor methodological quality or high risk of bias.
Benefit: Unclear but some of these complementary therapies may be able to provide symptomatic relief.
Harm: Minimal side effects reported.
Cost: Moderate-high cost of therapies with multiple treatments required.
Benefits-harm assessment: Unknown.
Value judgments: There is lack of sufficient evidence to recommend the use of these interventions in AR.
Policy level: No recommendation.
Intervention: None.

XI.B.11.c | *Honey*

A long-held belief has been that honey is effective in treating symptoms of AR; however, evidence for this is scarce. It is postulated that environmental antigens contained within locally produced honey could, when ingested regularly, lead to the development of tolerance in a manner similar to SLIT.[1246] Primary sources of antigens can include pollen and microflora from the digestive tract of

TABLE XI.B.11.b Evidence table – other complementary medicine treatments for allergic rhinitis

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yin et al.[2210]	2020	2[b]	SRMA (including Chinese databases)	Acupuncture Sham acupuncture Moxibustion Electroacupuncture Conventional medication	Nasal symptom scores RQLQ	All acupuncture methods superior to sham acupuncture for nasal symptoms and RQLQ Moxibustion or manual acupuncture plus conventional medicine most effective for AR
Fu et al.[2215]	2019	2[c]	SRMA (including Chinese databases)	Acupuncture of SGA acupoint Sham acupuncture Acupuncture of other acupoints Conventional medicine	TNSS RQLQ VAS Total effective rate Improvement of disease classification	Acupuncture to the SGA alone was more effective than control groups
Yuan et al.[2220]	2020	3[d]	SRMA	TFM alone TFM + conventional therapy Sham TFM No treatment Placebo	TNSS VAS Secondary outcomes: TNNSS, RQLQ, VAS	TFM showed a significant difference in symptom score All included studies had low methodological quality
Zhou et al.[2214]	2015	3[e]	SRMA	Acupoint herbal patching + conventional medicine Acupoint herbal patching Conventional medicine Placebo No treatment	Recurrence rate of AR Symptoms RQLQ SF-36	Acupoint herbal patching effective, both alone and with Western medicine, more than placebo and Western medicine alone No adverse reactions High risk of bias
Zhang et al.[2218]	2020	4[d]	SRMA (including Chinese databases)	Acupuncture of SGA acupoint Manual acupuncture Appoint catgut embedding Acupoint herb application Western medicine	Nasal symptoms (3-point Likert scale) Global AR symptoms (binary assessment)	Acupuncture of SGA acupoint had the highest improvement of global AR symptoms Most studies had extremely low methodological quality
Li et al.[2213]	2014	4[f]	SR	Catgut implantation at acupoints Conventional medicine Moxibustion in mid-summer	Improvement in AR symptom Clinical efficacy rate	No conclusion could be made due to several methodological shortcomings and risk of bias for one included trial

(Continues)

TABLE XI.B.11.b (Continued)

Study[a]	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Zhang et al.[2212]	2010	4[g]	SR	Ear acupressure Body acupuncture Sham acupuncture Chinese herbal medicine Conventional medication No intervention	% effectiveness Total symptom severity score (1 study)	No conclusion could be made due to low methodological quality of included studies

Abbreviations: AR, allergic rhinitis; LOE, level of evidence; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SF-36, 36-item Short Form Survey; SGA, sphenopalatine ganglion acupuncture; SR, systematic review; SRMA, systematic review and meta-analysis; TFM, thunder fire moxibustion; TNNSS, Total Non-Nasal Symptom Score; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

[a]Relevant prior studies are included in the SRMAs.

[b]LOE downgraded due to unclear risk of bias for allocation concealment; insufficient blinding of participants, personnel, and outcome assessments; short treatment duration (most studies were 2–4 weeks) and lack of follow up.

[c]LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation concealment; attrition bias with incomplete outcome data.

[d]LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation concealment; selective reporting bias.

[e]LOE downgraded due to high risk of bias, including lack of details about randomization, allocation concealment, no intention-to-treat analysis, proper blinding in the majority of included studies, and heterogeneity of study subjects with AR.

[f]LOE downgraded since only one RCT met inclusion criteria for SR, with high risk of bias due to lack of validated outcome measure, details about randomization, allocation concealment, blinding of participants and personnel, selective reporting bias, and no intention-to-treat analysis.

[g]LOE downgraded due to lack of validated outcome measure, details about randomization, no blinding of participants in all 5 studies included in SR, and no intention-to-treat analysis.

honeybees, which typically contains microorganisms present in dust, air, and flowers.[2221] It is important to note, however, that heavy insect-borne pollens do not meet Thomen's postulates, as they are not airborne and hence should not be able to induce allergic sensitivity. Studies in animals have demonstrated the ability of honey to suppress IgE antibody responses against different allergens and to inhibit IgE-mediated mast cell activation,[2222–2224] while studies in humans have demonstrated various anti-inflammatory properties of honey.[2225,2226]

There have been three RCTs looking at honey in the treatment of AR. The studies all differed on geographic location, length of treatment, dose of honey, and timing with respect to specific allergy seasons. One double-blind RCT[2227] and an additional RCT[2228] showed a significant decrease in total symptoms scores in the treatment group compared to control. In contrast, another double-blind RCT[2229] found no benefit of honey ingestion for the relief of AR symptoms compared to controls (Table XI.B.11.c).

Of note, it has been reported that higher doses (50–80 g daily intake) of honey are required to achieve health benefits from honey,[2230] and only the trial by Asha'ari et al.[2227] dosed patients at that level. In addition, the benefit of birch pollen honey in the trial by Saarinen et al.[2228] might be explained by a specific immunotolerance developed during oral intake of birch pollen with honey acting as a vehicle.

Honey

Aggregate grade of evidence: D (Level 2: 3 studies, conflicting evidence; Table XI.B.11.c)
Benefit: Unclear as studies have shown differing results and include different preparations of honey in the trials. Local honey may be able to modulate symptoms and decrease need for antihistamines.
Harm: Potential compliance issues with patients not tolerating the level of sweetness. Potential risk of allergic reaction and rarely anaphylaxis. Caution should be exercised in in pre-diabetics and diabetics for concern of elevated blood glucose levels.
Cost: Cost of honey and associated healthcare costs with increased consumption.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: More studies are required before honey intake can be widely recommended.
Policy level: No recommendation.
Intervention: None.

XI.B.11.d | *Herbal therapies*

There are a vast number of studies looking at the effectiveness of various herbs and supplements in the treatment of AR; however, most are small and of poor quality. Herbal

TABLE XI.B.11.c Evidence table – honey for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Asha'ari et al.[2227]	2013	2	DBRCT	Honey Placebo	AR symptom scores	Improvement in overall and individual AR symptoms with honey
Saarinen et al.[2228]	2011	2	RCT	Birch pollen honey Regular honey No honey	Daily AR symptoms Number of asymptomatic days Rescue medication use	Birch pollen honey significantly lowered total symptom score and decreased use of rescue medications Honey groups had significantly more asymptomatic days
Rajan et al.[2229]	2002	2	DBRCT	Locally collected, unpasteurized, unfiltered honey Nationally collected, pasteurized, filtered honey Placebo	Daily AR symptoms Rescue medication use	No significant difference in AR symptoms or need for rescue medication

Abbreviations: AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; LOE, level of evidence; RCT, randomized controlled trial.

remedies that have been subjected to more rigorous study are summarized in Table XI.B.11.d.

Herbs often contain active pharmacologic ingredients, which can be difficult to measure clinically.[2231] Given the lack of robust and repeated large double-blind placebo-controlled RCTs for any particular herbal remedy, further research is needed before recommendations can be made regarding routine use of any particular herb or supplement.

Herbal therapies

Aggregate grade of evidence: Uncertain.
Benefit: Unclear, but some herbs may be able to provide symptomatic relief.
Harm: Some herbs are associated with mild side effects. Also, the safety, quality and standardization of herbal remedies and supplements are unclear.
Cost: Cost of herbal supplements.
Benefits-harm assessment: Unknown.
Value judgments: There is a lack of sufficient evidence to recommend the use of herbal supplements in AR.
Policy level: No recommendation.
Intervention: None.

XI.B.11.e | *Guideline summary recommendations for non-traditional and alternative therapies*

See Table XI.B.11.e. for a summary of current guideline recommendations for non-traditional and alternative therapies for AR.

XI.C | Intranasal procedural interventions

Although medical therapy has largely been considered the cornerstone of treatment for AR, surgical/procedural management may play a role when patients are refractory to medical treatment. In these instances, surgery aims to improve structural problems that may lead to nasal obstruction/congestion, or to directly address physiologic causes of symptoms (e.g., rhinorrhea, mucosal swelling).

The literature surrounding the role of septoplasty/septorhinoplasty as a structural treatment for AR has expanded recently. While early evidence suggested that AR patients may benefit less from septoplasty/septorhinoplasty than non-AR counterparts,[2285–2287] most of the recent literature suggests the contrary,[1093,2288–2296] with overall low complication rates.[2297,2298] Kim et al.[2299] found that AR patients with septal deviation that underwent septoplasty with turbinoplasty had greater improvement in nasal obstruction than those that who underwent turbinoplasty alone. Nevertheless, the evidence is low-quality overall, with a preponderance of retrospective case series and no RCTs.

TABLE XI.B.11.d Herbs and supplements used in the treatment of allergic rhinitis

Herb	Mechanism of action	Evidence[a]	Side effects
Apple polyphenols	Inhibits release of histamine from mast cells and basophils	DBRPCT investigated drinking apple polyphenols (50 or 200 mg daily); improvement in sneezing, nasal discharge, turbinate swelling[2232]	Rash, soft stool, headache, changes in hematocrit, increased uric acid levels
Astragalus membranaceus	Unknown	DBRPCT comparing 80 mg daily x6 weeks; improvement in rhinorrhea, TSS, QOL[2233]	Pharyngitis, rhinosinusitis
Aller-7	Possible antioxidant and anti-inflammatory pathways[2234–2236]	Two DBRPCTs showed some relief of symptoms with Aller-7, but some contradictory findings present[2237]	Dry mouth, gastric discomfort
Benifuuki green tea	Catechins, EGCG and polyphenols inhibit type I and type IV hypersensitivity reactions[2238,2239]	DBRPCT showed 700 ml Benifuuki green tea daily significantly reduced AR symptoms, improved QOL, suppressed peripheral eosinophils[2240]	None reported
Biminne	Unknown	DBRPCT showed 12 weeks of Biminne significantly reduced sneezing[2241]	None reported
Butterbur (*Petasites hybridus*)	Inhibits leukotriene/histamine synthesis and mast cell degranulation[2242]	Three DBRPCTs showed Butterbur was effective in alleviating symptoms, attenuating PNIF recovery, and reducing maximum % PNIF decrease from baseline after adenosine monophosphate challenge; two clinical trials showed butterbur was similar to antihistamine for improving QOL and symptom relief;[2231,2237] one DBRPCT demonstrated no benefit for PNIF, symptoms, QOL[2237] Six RCTs reviewed: five compared butterbur to placebo; four found butterbur to be superior to placebo. Three RCTs compared butterbur to antihistamines with no difference found between groups[2209]	Hepatic toxicity, headache, gastric upset, headache, itchy eyes, diarrhea, fatigue, drowsiness
Capsaicin	Thought to desensitize and deplete sensory C-fibers and myelinated A-δ fibers, acting as a blocking agent of neuropeptides[2243–2245]	No evidence of a therapeutic effect of intranasal capsaicin in AR[1090,2209,2245]	Mucosal irritation, burning, lacrimation, coughing
Chlorophyll c2 (*Sargassum horneri*)	Possibly inhibits degranulation of mast cells and basophils	DBRPCT showed 0.7 mg Chlorophyll c2 daily significantly decreased the need for rescue medications after 8 weeks, but no difference in QOL[2246]	None reported
Cinnamon bark, Spanish needle, acerola (ClearGuard)	Inhibits production of prostaglandin D2[2247]	DBRPCT showed 450 mg CG TID comparable to loratadine 10 mg in symptom reduction; CG prevented increase in prostaglandin D2 release following nasal allergen challenge[2247]	None reported
Conjugated linoleic acid	Immune-modulating effects of humoral and cellular immune responses, decreased in vitro production of TNF-α, IFN-γ, IL-5	DBRPCT showed that consuming 2 g conjugated linoleic acid daily before and during birch pollen season improves sneezing and wellbeing[2248]	None reported

(Continues)

TABLE XI.B.11.d (Continued)

Herb	Mechanism of action	Evidence[a]	Side effects
Grapeseed extract	Unknown	DBRPCT showed no benefit of 100 mg grapeseed extract BID on nasal symptoms, need for rescue medications, QOL[2249]	None reported
Isoquercitrin	Flavonoid with anti-allergic and antioxidant effects	DBRPCT demonstrated 100 mg Isoquercitrin significantly improved ocular symptoms but not nasal symptoms[2250,2251]	None reported
Ginger	Anti-allergic activity, suppression of mast cell infiltration and release of IgE	DBRPCT showed significant improvement of symptom and RQLQ scores for both ginger extract (500 mg) and loratadine, but there was no significant difference between them[2252]	Eructation, dry mouth and throat
Methylsulfonyl-methane	Organosulfur compound with anti-inflammatory properties and reported to block the formation of inflammasomes	DBRPCT demonstrated that 3 g daily for 2 weeks provided significant relief of AR symptoms and objective nasal obstruction measurements[2253]	None reported
Nigella sativa (Black seed)	Inhibits histamine release from rat macrophages[2254] Thymoquinone may inhibit Th2 cytokines and eosinophil infiltration in airways[2255]	*N. sativa* capsules (two DBRPCTs) and *N. sativa* nasal drops (one DBRPCT) improve AR symptoms[2256–2258]; one DBRPCT did not find significant differences between treatment and placebo[2256]	Gastrointestinal complaints with oral intake, nasal dryness with topical drops
Perilla frutescens	Polyphenolic phytochemicals such as rosmarinic acid inhibit inflammatory processes and the allergic reaction[2259–2262]	DBRPCT showed 50 mg or 200 mg *P. fruescens* enriched for rosmarinic acid did not significantly improve symptom scores[2263]	None reported
Probiotics	Downregulation of IL-5 and allergen-specific IgG4[2264,2265]	See Section XI.B.9. Probiotics for additional information on this topic	
RCM-101	Inhibits histamine release and prostaglandin E2 production[2266,2267]	DBRPCT showed 4 tablets of RCM-101 TID for 8 weeks significantly improved symptom scores and RQLQ[2268]	Mild gastrointestinal side effects
Spirulina	Reduces IL-4 levels, inhibits histamine release from mast cells[2269] Enhanced IgA levels and IFN-y, natural killer cell damage were increased[2270]	DBRPCT showed 2000 mg daily Spirulina significantly improved sneezing, rhinorrhea, congestion, and nasal itching[2271]	None reported
Ten-Cha (*Rubus suavissimus*)	Inhibits cyclooxygenase activity and histamine release by mast cells[2272]	DBRPCT showed no significant improvement in symptom scores, RQLQ, or need for antihistamine with 400 mg daily of Ten-Cha extract[2273]	None reported
TJ-19[b]	Inhibits histamine signaling and IL-4 and IL-5 expression in a rat model[2274]	DBRPCT showed 3g TJ-19 TID significantly improved sneezing, stuffy nose and rhinorrhea[2275]	None reported
Tinofend (*Tinospora cordifolia*)	Possibly through anti-inflammatory effects[2276]	DBRPCT showed 300 mg Tinofend x8 weeks significantly improved AR symptoms, also decreased eosinophils, neutrophils, goblet cells on nasal smear[2276]	Leukocytosis

(Continues)

TABLE XI.B.11.d (Continued)

Herb	Mechanism of action	Evidence[a]	Side effects
Tomato extract	Possibly inhibits histamine release	DBRPCT showed 360 mg Tomato extract daily x8 weeks decreased sneezing score, rhinorrhea, nasal obstruction[2277]	None reported
Urtica dioica (stinging nettle)	In vitro: antagonist/negative agonist activity against histamine-1 receptor, inhibits mast cell tryptase, prevents mast cell degranulation, inhibits prostaglandin formation[2278]	DBRPCT showed symptom improvement over placebo at 1 h[2279] One systematic review showed no significant intergroup differences[2237]	None reported
Vitamin C (ascorbic acid)	Acts as a water-soluble antioxidant with immune modulating effects[2280]	DBRPCT showed that 2-week nasal application of ascorbic acid reduced nasal edema, mucus secretion, nasal obstruction[2280]	Diarrhea and abdominal distention
Vitamin D	Thought to have immunomodulatory effects	DBRPCT demonstrated that 5 months of vitamin D 1000 IU daily in children with grass pollen-related AR had a significant reduction in symptom and medication scores; however, study had significant bias[621] See Section VI.H. Vitamin D for additional information on this topic	None reported
Vitamin E	Unknown	One DBRPCT showed that 800 mg per day of vitamin E had no effect on ocular symptoms but improved nasal symptoms; no reduction in medications reported[2281] Another DBRPCT showed 400 IU per day of vitamin E had no effect on nasal symptoms or IgE levels[2282]	None reported

Abbreviations: AR, allergic rhinitis; BID, twice daily; DBRPCT, double-blind randomized placebo-controlled trial; EGCG, epigallocatechin-3-O-gallate; IFN, interferon; Ig, immunoglobulin; IL, interleukin; PNIF, peak nasal inspiratory flow; QOL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; Th2, T helper 2; TID, three times daily; TNF, tumor necrosis factor; TSS, Total Symptom Score.

[a]All listed studies LOE 2.

[b]Not available in US; contains ephedra.

Furthermore, many applicable studies did not directly evaluate the role of septoplasty/septorhinoplasty in AR, but instead include it peripherally in the analysis. Therefore, in the properly selected patient, septoplasty/septorhinoplasty may represent an option at best (Table XI.C.-1).

IT surgery can improve symptoms by structurally reducing nasal obstruction/congestion caused by enlarged turbinates, reducing volume of mucosal tissue that reacts with allergens, and allow improved accommodation of AR-induced turbinate swelling.[2300] Inferior turbinoplasty is done via various surgical techniques: (1) bony lateral outfracture; (2) energy-related submucous reduction techniques (e.g., radiofrequency ablation, electrocautery, coblation, laser-assisted); (3) microdebrider-assisted submucous reduction, and (4) bony and submucosal resection, including medial flap turbinoplasty.[2301] Total turbinectomy or turbinate resection was not covered as part of this review as they are typically not performed for inflammatory disease.

There are numerous studies investigating the efficacy of IT surgery for AR. Bony outfracture, the most atraumatic and conservative IT surgery,[2301] can reduce the distance between IT and lateral nasal wall and enlarge the dimensions of the nasal airway when performed alone[2302,2303] or in conjunction with other techniques.[2304,2305] IT surgery via energy-related techniques[2304–2363] and via direct tissue removal[1093,2296,2299,2303,2307,2310,2331,2332,2335,2336,2338,2344,2364–2376] have both been extensively studied, with reported high efficacy in reducing symptoms and increasing nasal volume and airflow with minimal complications. Of note, botulinum toxin injection[2377–2379] and high-intensity focused ultrasound may also provide symptomatic relief,[2380,2381] though there remains limited evidence for

TABLE XI.B.11.e Summary of clinical practice guideline recommendations for non-traditional and alternative therapies for allergic rhinitis

Organization	Year	Statement	Guideline methodology
American Academy of Otolaryngology – Head and Neck Surgery Foundation[1005]	2015	Acupuncture: Clinicians may offer acupuncture as an option, or refer to a clinician who can offer acupuncture, for patients with AR who are interested in nonpharmacologic therapy Herbal Therapy: No recommendation regarding the use of herbal therapy for patients with AR	Systematic review of several EBM databases, with supplementation from journal article reference lists Guideline Implementability Appraisal and Extractor methodological standard AAP method for recommendation development Grading based upon Oxford Centre for EBM
Chinese Society of Allergy Guidelines[2283]	2018	Acupuncture is a safe treatment option, and most of the acupuncture methods employed can improvement AR symptoms Chinese herbal medicine needs to be assessed and confirmed by larger well-controlled multicenter trials	Lack of description regarding guideline methodology, EBM review and literature search process
China Association of Acupuncture and Moxibustion[2284]	2021	Acupuncture can be recommended for distinct types or phases of AR but attention should be paid to the selection of acupoints Moxibustion was found suitable for the distinct types or phases of AR	Lack of description regarding EBM literature review and search process (unable to find referenced appendices) Guideline primarily discusses TCM pattern differentiation and associated acupoints for treatment GRADE methodology Expert consensus panel of acupuncturists

Abbreviations: AAP, American Academy of Pediatrics; AR, allergic rhinitis; EBM, evidence-based medicine; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; TCM, Traditional Chinese Medicine.

their utility. As such, the current literature suggests that, in the properly selected AR patient with concomitant IT hypertrophy, IT surgery is an effective and safe treatment to reduce symptoms and improve QOL. More rigorous studies are warranted to directly compare various IT reduction techniques for optimal and durable outcomes (Table XI.C.-2).

Another structural target is the nasoseptal swell body, with newer interventions directed toward volumetric reduction to improve airflow. Though ablation of the swell body (whether through radiofrequency, laser, or coblation) has shown promise in reducing symptoms,[2382–2386] its effectiveness has yet to be tested with an AR-specific cohort. However, the advent of devices intended for office use (e.g., Vivaer, Aerin Medical, Sunnyvale, CA) may provide opportunities for further study.

Rhinorrhea, as part of both AR and non-allergic rhinitis, may arise from overactivity of parasympathetic nerve fibers originating from the vidian nerve. A vidian neurectomy with permanent sectioning of the most proximally accessible nerve segment is a potential surgical approach to reduce rhinorrhea in these patients.[2386] Evidence published from 2011 onwards provides support regarding its use in AR patients. Observational studies and a non-randomized controlled trial found that AR patients experienced improvements in sneezing, nasal discharge, obstruction, itching, and QOL.[2375,2387–2390] An RCT and another non-randomized controlled trial of patients with both AR and CRSwNP found similar results, as well as improvement on pulmonary functions tests.[2391,2392] There remains some concern that symptom recurrence may be high based on earlier studies,[2393] especially with longer-term follow up, though this remains in contention and recent series have reported durable outcomes. Additionally, vidian neurectomy also carries the risk of dry eye due to the rami lacrimales that diverge from the nerve.[2394] Though recent evidence suggests that the properly selected patient does not experience symptomatic dry eye postoperatively,[2395] newer, more directed techniques targeting distal nerve segments have been developed. Specifically, the PNN, a branch of the vidian, appears to be an appropriate target given its specific nasal innervation. Though there is no study that evaluates vidian and PNN neurectomy head-to-head in AR

TABLE XI.C.-1 Evidence table – septoplasty/septorhinoplasty in patients with allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Gillman et al.[1093]	2019	3	Prospective cohort	Septoplasty and turbinate reduction patients: With AR Without AR	NOSE Ease-of-Breathing Likert scale mini-RQLQ	Both groups improved in all three endpoints post-operatively, no statistical difference in degree of improvement for both cohorts
Sokoya et al.[2292]	2018	4	Retrospective case series	Open septorhinoplasty patients: With AR Without AR	NOSE	No difference in post-operative NOSE scores between AR and non-AR groups
Kim et al.[2299]	2011	4	Prospective case–control	Patients with AR: Septoplasty + turbinoplasty Turbinoplasty alone	VAS: nasal obstruction, rhinorrhea, sneezing, itching Rescue medication use Rhinasthma Questionnaire	More improvement in nasal obstruction and Rhinasthma score for those that also underwent septoplasty No difference in rescue med use
Karatzanis et al.[2286]	2009	4	Prospective case series	Septoplasty patients: With AR Without AR	NOSE Active anterior rhinomanometry	Non-AR subjects showed more improvement than AR subjects in both endpoints
Eren et al.[2298]	2022	5[a]	Retrospective case series	Heterogenous case series of patients undergoing septoplasty or septorhinoplasty ± turbinoplasty, including those with AR	Septal perforation rates	No AR patient had a septal perforation
Kim et al.[2295]	2021	5[b]	Prospective case series	Heterogenous case series of OSA patients undergoing septoplasty + IT reduction, including those with AR	Successful intervention defined as post-op AHI of <20/h and reduction of ≥50%	Patients with AR had a statistically higher rate of success, though total sample was only 35 patients, and success seen in only 5
Gerecci et al.[2294]	2019	5[a]	Retrospective case series	Heterogenous case series of patients undergoing septorhinoplasty, including those with AR	NOSE	Post-operative NOSE scores for the AR group not significantly greater than non-AR group
Kokubo et al.[2293]	2019	5[a]	Prospective case series	Heterogenous case series of patients undergoing septorhinoplasty, including those with AR	UPSIT VAS for smell perception	AR did not affect improvement in either endpoint VAS improved post-operatively No improvement in UPSIT
Manteghi et al.[2291]	2018	5[a]	Prospective case series	Heterogenous pediatrics case series of patients undergoing functional septorhinoplasty or septoplasty, including those with AR	NOSE	AR did not independently affect change in NOSE scores in children

(Continues)

TABLE XI.C.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bugten et al.[2290]	2016	5[a]	Prospective case–control	Patients undergoing septoplasty ± turbinate reduction, including those with AR Healthy controls	SNOT-20 VAS Patient satisfaction with surgery	SNOT-20 scores did not differ between AR and non-AR patients post-operatively AR patients were still bothered by nasal blockage and facial pressure more often
Mondina et al.[2287]	2012	5[a]	Prospective case series	Heterogenous case series of patients undergoing septoplasty over a 1-year period, including those with AR	NOSE RhinoQOL	Improvement in NOSE and RhinoQOL with septoplasty AR associated with decreased improvement
Topal et al.[2297]	2011	5[c]	Retrospective case series	Heterogenous case series of patients undergoing septoplasty over a 3-year period, including those with AR	Septal perforation rate	Septal perforation rates are low, and comparable between those with and without AR
Stewart et al.[2289]	2004	5[a]	Prospective case series	Heterogenous case series of patients undergoing septoplasty, including those with AR	NOSE	AR did not independently affect change in NOSE scores
Fjermedal et al.[2285]	1988	5[a]	Retrospective case series	Heterogenous case series of patients undergoing septoplasty or submucous resection, including those with AR	Patient satisfaction Symptom questionnaire	AR patients were less satisfied post-operatively compared to non-AR patients, and had unchanged nasal secretion
Stoksted and Gutierrez[2288]	1983	5[a]	Retrospective case series	Heterogenous case series of patients undergoing septorhinoplasty, including those with AR	Evaluation of normal nasal passages	Patients with AR reached post-operative normal nasal passages at lower rates

Abbreviations: AHI, apnea hypopnea index; AR, allergic rhinitis; IT, inferior turbinate; LOE, level of evidence; NOSE, Nasal Obstruction Symptom Evaluation; OSA, obstructive sleep apnea; RhinoQOL, Rhinosinusitis Quality of Life Survey; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-20, Sinonasal Outcome Test (20 items); UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

[a]LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR patients.

[b]LOE downgraded due to inclusion criteria of a unique population and low sample size.

[c]LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR patients, as well as low number in the outcome of interest.

patients, PNN neurectomy has been similarly shown to be effective for reducing symptoms,[229,2374,2396–2401] though one non-randomized controlled trial did not find a benefit to adding PNN neurectomy to microdebrider-assisted turbinoplasty.[2402] Given the evidence, neurectomy is an option for treating refractory rhinorrhea following failed medical management (Tables XI.C.-3 and XI.C.-4).

Alternatively, energy-based ablation of the PNN (RhinAer, Aerin Medical, Sunnyvale, CA) utilizing radiofrequency or cryotherapy (ClariFix, Stryker, Kalamazoo, MI) are office-based alternatives to direct nerve section. The earliest report of utilizing cryotherapy for this indication was by Terao et al.[2403] in 1983. Studies utilizing cryoablation, including a randomized, sham-controlled trial, have shown improvement in symptoms and QOL.[275,2404–2409] Though no study specifically evaluated an AR-specific cohort, many performed subgroup analysis (which showed similar improvement) or controlled for the presence of AR (which showed that AR did not modify outcomes). Similar results were seen with radiofrequency ablation, also in the form of a randomized, sham-controlled trial.[2410,2411] In-office endoscopic laser ablation of the PNN has also been reported with positive improvement.[2412] These procedures seem to be

well-tolerated, with minimal complication risk.[2413] There is also evidence to suggest that appropriate response to IPB nasal spray seems to correlate with improved cryotherapy treatment response.[2409] Ultimately, as the current evidence is largely based on industry-sponsored studies with limited long-term data, these interventions remain an option for properly selected patients (Table XI.C.-5).

Septoplasty/septorhinoplasty

Aggregate grade of evidence: C (Level 3: 1 study, level 4: 3 studies, level 5: 11 studies; Table XI.C.-1)
Benefit: Improved postoperative symptoms and nasal airway.
Harm: Risk of complications (e.g., septal hematoma or perforation, nasal dryness, cerebrospinal fluid leak, epistaxis, unfavorable aesthetic change); persistent obstruction.
Cost: Surgical/procedural costs, time off from work.
Benefits-harm assessment: Potential benefit must be weighed against low risk of harm and cost of procedure.
Value judgments: Properly selected patients with septal deviation impacting their nasal patency can experience improved nasal obstruction symptoms.
Policy level: Option for those with obstructive septal deviation.
Intervention: Septoplasty/septorhinoplasty may be considered in AR patients that have failed medical management and who have anatomic, obstructive features that may benefit from this intervention.

Inferior turbinate surgery

Aggregate grade of evidence: B (Level 1: 4 studies, level 2: 13 studies, level 3: 18 studies, level 4: 50 studies*; Table XI.C.-2)
*Level 1, 2, and 3 studies are listed in the table; level 4 studies are referenced.
Benefit: Improvement in rhinitis symptoms including nasal breathing, congestion, sneezing, and itching. Improved nasal cavity area via objective measures, as well as increased QOL via subjective measures.
Harm: Risk of complications (e.g., swelling, crusting, empty nose syndrome, epistaxis).
Cost: Surgical/procedural costs, potential time off from work.
Benefits-harm assessment: Potential benefit outweighs low risk of harm.
Value judgments: Current evidence suggests that patients with AR who suffer from IT hypertrophy will likely experience improvement in symptoms, nasal patency, and QOL.
Policy level: Recommendation in patients with medically refractory nasal obstruction.
Intervention: In AR patients with IT hypertrophy that have failed medical management, IT reduction is a safe and effective treatment to reduce symptoms and improve nasal function. More studies are warranted to directly compare IT surgery methods (e.g., radiofrequency ablation, laser-assisted, microdebrider-assisted) for the most efficacious and long-lasting outcome.

Neurectomy (vidian neurectomy, posterior nasal neurectomy)

Aggregate grade of evidence: B (Level 2: 3 studies, level 3: 5 studies, level 4: 7 studies, level 5: 2 studies; Tables XI.C.-3 and XI.C.-4)
Benefit: Improvement in rhinorrhea.
Harm: Risk of complications (e.g., dry eye and decreased lacrimation, numbness in lip/palate, nasal dryness, damage to other nerves).
Cost: Surgical/procedural costs, potential time off from work.
Benefits-harm assessment: Potential benefit must be balanced with low risk of harm but consider that long-term results may be limited.
Value judgments: Patients may experience an improvement in symptoms.
Policy level: Option.
Intervention: Vidian neurectomy or PNN neurectomy may be considered in AR patients that have failed medical management, particularly for rhinorrhea.

Cryotherapy/radiofrequency ablation of the posterior nasal nerve

Aggregate grade of evidence: C (Level 3: 2 studies, level 4: 4 studies, level 5: 5 studies; Table XI.C.-5)
Benefit: Improvement in rhinorrhea.

Harm: Risk of complications (e.g., epistaxis, temporary facial pain and swelling, and headaches), limited long-term results.
Cost: Surgical/procedural costs, cost of device, potential time off from work.
Benefits-harm assessment: Potential benefit must be balanced with low risk of harm, especially considering limited long-term results.
Value judgments: Patients may experience an improvement in symptoms
Policy level: Option.
Intervention: Cryoablation and radiofrequency ablation of the PNN may be considered in AR patients that have failed medical management, particularly for rhinorrhea.

XI.D | Immunotherapy

XI.D.1 | Allergen immunotherapy candidacy

Of the three primary modalities used to manage AR – allergen avoidance, pharmacotherapy, and AIT – immunotherapy is the only treatment that that has a disease-modifying effect through induction of immunologic tolerance.[2418] AIT may be considered when a patient has an IgE-positive skin or in vitro test to an allergen that can be correlated with a patient's exposures and symptoms. The presence of sIgE antibodies alone indicates sensitivity to the allergen but may not result in clinically significant allergic symptoms.

Most position papers on AIT recommend its use in patients with moderate to severe symptoms that are not controlled with avoidance and/or pharmacotherapy.[2418,2419] However, there is evidence that SCIT is at least as potent as pharmacotherapy in controlling symptoms of seasonal AR as early as the first season after initiating treatment.[2420] Although there is no direct evidence that AIT is as effective as pharmacotherapy as a primary treatment for AR, most RCTs evaluating the efficacy of SLIT or SCIT showed improvement in symptoms and/or medication requirement compared to placebo. One caveat to these studies is the fact that patients in the placebo groups were allowed to use allergy medications and were essentially a pharmacotherapy treatment group rather than a true placebo group.[2421,2422]

Patients who have adverse reactions to traditional pharmacotherapy or decline long-term medication use are also excellent candidates for AIT. There is strong evidence of decreased medication use up to 3 years after stopping both SCIT and SLIT.[2423–2425] In a double-blind, placebo-controlled RCT, there was no difference in symptom scores in patients who discontinued AIT after 4 years of use and those who continued it.[2423]

One perceived benefit, and perhaps indication, for AIT has been the long-held theory that it may prevent or reduce the development of new allergic disease. However, a recent meta-analysis of 32 studies found no conclusive evidence that AIT reduced the risk of long-term new allergic disease and sensitizations both in the pediatric and adult population.[2426] This study did find a reduction in short-term risk of developing asthma in patients with diagnosed AR (RR 0.4; 95% CI 0.30–0.54). There is evidence from other studies indicating that AIT helps reduce the risk of development of asthma.[2427,2428] In a double-blind RCT of 812 children (5–12 years old) with clinically relevant AR and no history of asthma, patients were treated with 3 years of grass SLIT versus placebo with 2 years of follow-up. The SLIT group had a significantly reduced risk of experiencing asthma symptoms or using asthma medication during the treatment and at the end of the 5-year period.[2429]

Clinicians should be aware that there is a subset of patients for whom AIT is not an option. Absolute and relative contraindications for AIT are addressed in Section XI.D.3 Contraindications to Allergen Immunotherapy.

There is limited evidence for the efficacy of AIT for the treatment of AR in children younger than 5. However, there is data to show the efficacy and safety of both SLIT and SCIT in children 5 years and older.[2430,2431] Patient adherence with AIT can be challenging, so consideration of risks and benefits, QOL impairment, financial concerns, and patient preference are important in treatment selection.

XI.D.2 | Benefits of allergen immunotherapy for allergic rhinitis

SCIT is the best studied form of AIT and is effective for AR and rhinoconjunctivitis, allergic asthma, and Hymenoptera venom allergy.[2432] SCIT has been practiced for over a century using aqueous extracts of the naturally occurring allergens; its effectiveness and safety have improved over time with the advent of extract standardization and research into mechanisms of action.[2433] SCIT involves the repeated subcutaneous injection of the allergen extract in question, beginning with very small doses of allergen and gradually increasing to higher doses. This is followed by repeated injections of the highest or maintenance dose for periods of 3–5 years to reduce symptoms upon exposure to that allergen. Clinical and physiological improvement can be demonstrated shortly after the patient reaches a maintenance dose.[2419] AIT can also be provided

TABLE XI.C.-2 Evidence table – inferior turbinate reduction/surgery in patients with allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Sinno et al.[2335]	2016	1	SR	Total turbinectomy Partial turbinectomy Manual submucous resection Microdebrider submucous resection Electrocautery Laser Cryotherapy RFA Turbinate outfracture	Change in nasal airflow or conductance Nasal resistance Nasal volume Symptoms	Turbinectomy (partial/total) and submucosal resection had increased crusting and epistaxis More conservative treatments such as cryotherapy and submucous diathermy failed to provide long-term results Submucous resection and RFA decreased nasal resistance and preserved mucosal function No support for outfracture alone
Acevedo et al.[2331]	2015	1	SRMA	RFA turbinoplasty Microdebrider-assisted turbinoplasty	Nasal obstruction, nasal airflow, volume, resistance	Positive short-term improvement for both techniques, with no difference between them
Jose and Coates-worth[2414]	2010	1	Cochrane review	Isolated IT surgery using any technique	Improvement in subjective sensation of nasal patency	No studies met inclusion criteria No conclusions due to insufficient data
Hytonen et al.[2311]	2009	1	SR	RFA turbinoplasty	Symptom questionnaires Acoustic rhinometry Rhinomanometry	Nasal RFA reduced IT mucous membrane volume and may decrease subjective symptoms and nasal blockage, with only minor discomfort and side effects
Ghosh et al.[2296]	2021	2	Prospective randomized	Septoplasty with bilateral microdebrider inferior turbinoplasty Septoplasty alone	Nasal obstruction NOSE score Subjective performance parameters Overall satisfaction	Greater improvement in NOSE scores in group with septum and turbinate surgery Greater improvement in overall satisfaction at 3 months but not subsequently Similar change in subjective performance parameters
Kang et al.[2341]	2019	2	Prospective RCT	Septoplasty with sham turbinate surgery Septoplasty with RFA turbinoplasty	Systemic scores for AR NOSE	Both scores improved in the two groups, with no difference between the groups
de Moura et al.[2371]	2018	2	RCT	Septorhinoplasty ± partial inferior turbinectomy	NOSE QOL Rhinoplasty outcome evaluation	Both groups had significant but comparable improvement in NOSE score, QOL, rhinoplasty outcome domains

(Continues)

TABLE XI.C.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Banhiran et al.[2334]	2015	2	Prospective randomized	RFA turbinoplasty Bipolar radiofrequency turbinoplasty	Nasal obstruction severity/frequency Nasal discharge Sneezing Hyposmia Postnasal drip Acoustic rhinometry	Similar subjective and objective outcomes between groups
Kaymakci et al.[2304]	2014	2	Prospective randomized	RFA turbinoplasty with lateral displacement RFA turbinoplasty alone	Severity/frequency of nasal obstruction	Post-operative nasal obstruction frequency/severity were significantly lower in RFA with lateral turbinate displacement versus RFA alone
Abtahi et al.[2378]	2013	2	Open label, randomized	Botox injections into: Septum IT	AR symptoms QOL	Both groups experienced significant but comparable improvements in symptoms More adverse events in IT group
Lavinsky-Wolff et al.[2323]	2013	2	RCT	Primary septorhinoplasty ± IT reduction via submucosal diathermy	Nasal obstruction Rhinoplasty outcome evaluation NOSE QOL	Both groups had significant symptomatic improvement, regardless of IT reduction
Lee[2364]	2013	2	Prospective randomized	Microdebrider-assisted inferior turbinoplasty: Intraturbinate Extraturbinate	Nasal obstruction, rhinorrhea, sneezing, nasal itching, postnasal drip Acoustic rhinometry	Symptomatic improvement significantly higher with extraturbinate treatment Acoustic rhinometry showed significant but comparable improvement in both groups
Wei et al.[2380]	2013	2	Cohort	Regular dose high-intensity focused ultrasound Increased dose	Nasal obstruction, sneezing, rhinorrhea Patient satisfaction	Symptoms significantly improved at 3 months and 1 year Patients receiving increased dose were more satisfied and had less eosinophils and submucous glands
Chusakul et al.[2352]	2011	2	Prospective RCT	INCS KTP-laser IT surgery	Histopathologic evaluation	Significant reduction in eosinophil influx after nasal challenge only seen with KTP laser IT surgery
Gunhan et al.[2316]	2011	2	Prospective randomized	INCS RFA turbinoplasty	Anterior rhinomanometry Nasal congestion QOL	RFA turbinoplasty provided more reduction in nasal congestion QOL scores improved in both groups
Liu et al.[2310]	2009	2	RCT	Microdebrider-assisted turbinoplasty RFA inferior turbinoplasty	Nasal obstruction, sneezing, rhinorrhea, snoring Anterior rhinomanometry Saccharin transit time	Microdebrider-assisted inferior turbinoplasty was more effective than RFA in decreasing nasal symptoms 1–3 years postoperatively

(Continues)

TABLE XI.C.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Unal et al.[2379]	2003	2	RCT	Turbinate injections: Low dose Botox Medium dose Botox Isotonic saline	AR symptoms Rhinoscopy exam	Rhinorrhea, nasal obstruction, sneezing improved significantly with low and medium dose Botox
Whelan et al.[2344]	2021	3	Prospective cohort	IT reduction in AR and non-allergic rhinitis patients via submucosal: Coblation Microdebrider	NOSE Nasal breathing	No difference in daily medications between the techniques NOSE score decreased regardless of technique
Gillman et al.[1093]	2019	3	Prospective cohort	IT reduction (via microdebrider) with septoplasty in AR and non-allergic rhinitis patients	NOSE QOL Ease of breathing	Both groups had significant improvement in NOSE score, QOL, and ease of breathing, with comparable change between groups
Suzuki et al.[2372]	2019	3	Case–control	Submucosal turbinoplasty with resection of PNN branches in IT Submucosal turbinoplasty alone	Nasal obstruction, sneezing, nose blowing, mouth breathing, hyposmia	Rhinorrhea severity, detection threshold, and recognition threshold significantly lower after resection of the PNN with turbinoplasty
Zhong et al[2340]	2019	3	Case–control	High-intensity focused ultrasound Plasma RFA	Nasal obstruction, nasal discharge, sneezing, pain QOL Nasal endoscopy	Compared to plasma RFA, high-intensity focused ultrasound significantly reduces nasal symptoms and improves QOL
Parthasarathi et al.[2365]	2017	3	Case–control	Microdebrider IT surgery with or without septoplasty in: AR Non-allergic rhinitis	SNOT-22 Nasal obstruction Global nasal function Nasal airflow	Nasal obstruction, SNOT-22, global nasal function, rhinitis/facial symptoms, sleep, psychological function improved in both groups Global nasal function greater in AR group
Hamerschmidt et al.[2376]	2016	3	Prospective cohort	Inferior turbinoplasty via turbinectomy scissors: AR No AR	Nasal obstruction, snoring, facial pressure, smell alteration, sneezing, nasal itching, runny nose	Nasal obstruction, snoring, facial pressure, sneezing, nasal itching, runny nose, and smell improved, with no reported difference between the groups
Shah et al.[2333]	2015	3	Prospective cohort	Radiofrequency coblation Intramural bipolar cautery	Nasal obstruction, pain Acoustic rhinometry Nasal endoscopy	Radiofrequency coblation significantly less painful with less crusting Both had similar improvement in nasal obstruction symptom and rhinometry
Di Rienzo Businco et al.[2317]	2014	3	Prospective case–control	RFA IT reduction with medical therapy Medical therapy only	Nasal obstruction, hydrorhinorrhea, sneezing, itching Rhinomanometry	Greater efficacy achieved in RFA group, especially in reducing turbinate volume

(Continues)

TABLE XI.C.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tan et al.[2375]	2012	3	Prospective cohort	Vidian neurectomy Turbinectomy and/or septoplasty Medical management	QOL	Significant improvement in all groups, with highest improvement in vidian neurectomy group
Langille and El-Hakim[2415]	2011	3	Retrospective cohort	Inferior turbinoplasty ± adenoidectomy	Glasgow children's benefit inventory	QOL improvement in both groups regardless of adenoidectomy
Di Rienzo Businco et al.[2416]	2010	3	Prospective cohort	RFA IT reduction with medical therapy Medical therapy only	Nasal obstruction, itching, rhinorrhea, sneezing Rhinoendoscopy Rhinomanometry	RFA group had more improvement in rhinoendoscopy clinical score
Chen et al.[2369]	2008	3	Retrospective cohort	Microdebrider inferior turbinoplasty with lateralization IT submucous resection	VAS Anterior rhinomanometry Saccharin test	Both groups experienced significant improvement in nasal obstruction, sneezing, rhinorrhea, snoring, rhinomanometric score, saccharin transit time No differences between groups
Tani et al.[2309]	2008	3	Case–control	Coblation-assisted versus laser-assisted inferior turbinoplasty	Nasal symptoms	Both groups had symptom improvement at one month, but only coblation group had persistent improvement at 1–2 years
Sroka et al.[2351]	2007	3	Retrospective case–control	Ho:YAG laser Diode laser	Nasal obstruction, rhinorrhea, olfaction, sneezing, itching of nose and eyes, headache Quality of life Anterior rhinomanometry	Both groups had significant increase in nasal airflow at 6 months, but only Diode laser had persistent symptomatic relief at 3 years
Ding et al.[2349]	2005	3	Case–control	Septoplasty or nasal polypectomy ± RFA turbinoplasty	Nasal obstruction, rhinitis symptoms via Haikou standard	First group (with RFA) had significantly higher improvement in nasal obstruction
Takeno et al.[2360]	2003	3	Prospective cohort	CO_2 laser on AR allergic to house dust mites and Japanese cedar pollen versus house dust mites only	Rhinorrhea, sneezing, nasal obstruction Acoustic rhinometry	Significant reduction in symptoms and increase in nasal cavity volume in both groups, less pronounced in pollen group
Janda et al.[2358]	2002	3	Case–control	Ho:YAG laser Diode laser	Rhinitis symptoms Allergy test Rhinomanometry Acoustic rhinometry	Significant but comparable improvement of nasal airflow in both groups Patients with vasomotor rhinitis had better outcomes than AR

(Continues)

TABLE XI.C.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Passali et al.[2307]	1999	3	Retrospective cohort	Electrocautery versus cryotherapy versus laser versus submucosal resection (± lateral displacement) Turbinectomy	Rhinomanometry Acoustic rhinometry Mucociliary transport time Secretory IgA Symptoms	Submucosal resection with lateral displacement of the IT had the greatest improvement in nasal respiratory function with the lowest long-term complications
LOE 4[a] studies[2302,2303,2305,2306,2308,2312–2315,2318–2322,2324–2330,2332,2336–2339,2342,2343,2345–2348,2350,2353–2357,2359,2361–2363,2366–2368,2370,2373,2374,2377,2381]						

Abbreviations: AR, allergic rhinitis; INCS, intranasal corticosteroid; IT, inferior turbinate; LOE, level of evidence; NOSE, Nasal Obstruction Symptom Evaluation; PNN, posterior nasal nerve; QOL, quality of life; RCT, randomized controlled trial; RFA, radiofrequency ablation; SNOT-22, Sinonasal Outcome Test (22 item); SR, systematic review; SRMA, systematic review and meta-analysis; VAS, visual analog scale.

[a]LOE 4 studies referenced due to extensive number of studies in this group and multiple higher LOE studies included in the table.

in the sublingual form [SLIT]; dissolvable tablets are FDA approved for a limited number of allergens.[2434]

In contrast to other treatment options for allergic disease, AIT helps achieve sustained immunological changes, by altering the immune system's response and inducing long-lasting immune tolerance to allergens. Despite extensive experience with this therapy and decades of research, the mechanisms underlying clinical improvement have not been fully elucidated. Although less mechanistic research exists for SLIT compared with SCIT, data suggest that both forms of AIT induce similar immunologic changes. These include a reduction in mast cell and basophil degranulation; an initial increase then decrease in sIgE and increase in allergen-specific IgG (sIgG) blocking antibodies; generation of allergen-specific regulatory T and B cells and suppression of allergen-specific effector T cell subsets and ILCs; and reduction in tissue mast cells and eosinophils accompanied by a decrease in type I skin test reactivity.[2435,2436] The clinically evident changes occur earlier with SCIT, and more pronounced sIgG4 responses are observed compared with SLIT.[2437]

The effectiveness of AIT for the treatment of AR is supported by an extensive body of evidence and is generally measured via improvement in allergy symptoms and reduction in allergy medication use.[2438–2440] Although meta-analyses conclude that AIT is effective, this positive judgment of efficacy (and safety) should be limited to products tested in the clinical trials. It is incorrect to make a general assumption that all forms of AIT are effective since this may lead to the clinical use of products that have not been properly studied.[1]

The severity and duration of AR symptoms, as well as coexisting medical conditions such as asthma, should be considered in assessing the need for AIT.[2419] The decision to initiate AIT depends on a number of factors, including but not limited to patient's preference, adherence, response to avoidance measures, medication requirements, and adverse effects of medications. Patients should be evaluated at least every 12 months while receiving AIT.[182] While many patients experience sustained clinical remission of their allergic disease after discontinuing AIT, others may relapse. A decision about continuation of effective AIT should generally be made after the initial period of 3–5 years of treatment.[182]

As noted in the preceding section, a 2017 meta-analysis evaluating the preventative effects of AIT (SCIT and SLIT) found evidence of a reduction in the short-term (<2 years) risk of developing asthma among patients with AR.[2426] The analysis also examined the longer term risk of asthma development, as well as the ability of AIT to prevent the occurrence of a first allergic disease in sensitized but asymptomatic individuals or to prevent sensitization to new allergens. There were trends toward benefit but inconclusive findings regarding these measures.

XI.D.3 | Contraindications to allergen immunotherapy

Contraindications to AIT are uncommon but must be reviewed in all patients prior to initiating treatment. For both SLIT and SCIT, the adverse event of greatest severity is anaphylaxis. Therefore, many of the absolute and relative contraindications to AIT are directly related to this risk, including uncontrolled asthma, concomitant β-blocker use, contraindication to injectable epinephrine, and pregnancy.

Uncontrolled asthma may be the single most important risk factor. There were fewer severe injection reactions reported among practices that routinely screened for and withheld injections from patients with asthma that was not controlled.[2441] Most fatal reactions were associated with bronchospasm and/or respiratory failure.[2441,2442]

Due to the inability to engage the β-adrenergic receptor with injectable epinephrine, β-blocker use is considered a relative contraindication for AIT. Since approximately 0.1%

TABLE XI.C.-3 Evidence table – vidian neurectomy in patients with allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Maimaitiaili et al.[2391]	2020	2	RCT	Patients with AR + CRSwNP who underwent nasal polypectomy, sinus surgery, and septoplasty (when indicated): No further treatment Vidian neurectomy	VAS: nasal symptoms TNSS PFT, methacholine challenge	Vidian neurectomy group had greater improvement in VAS nasal obstruction & rhinorrhea, but not sneezing or itching TNSS was significantly improved in vidian neurectomy group versus controls Number of patients with PFT impairment reduced more significantly in vidian neurectomy group
Qi et al.[2392]	2021	3	Non-randomized controlled trial	Patients with AR + CRSwNP underwent nasal polypectomies and inferior turbinate submucosal ablation and septoplasty (when indicated): No further treatment Selective vidian neurectomy (posterior nasal nerve and pharyngeal branch)	VAS: nasal symptoms Lund–Kennedy scores Lund–Mackay scores	All endpoints were significantly more improved in neurectomy cohort, with no increase in complications Cure/recovery rate significantly higher in neurectomy group
Tan et al.[2375]	2012	3	Non-randomized controlled trial	AR patients chose to undergo one of the following: Bilateral endoscopic vidian neurectomy Partial inferior turbinectomy and/or septoplasty Conservative treatment	RQLQ VAS for QOL Patient-reported improvement in symptoms	Both the neurectomy and septoplasty/turbinectomy group experienced improvement in RQLQ and VAS post-op Neurectomy group showed significantly greater improvement than septoplasty/turbinectomy Similar results were reported with symptom assessment
Shen et al.[2390]	2021	4	Retrospective cohort	AR patients who underwent: Bilateral endoscopic vidian neurectomy Subcutaneous immunotherapy	VAS for nasal and ocular symptoms RQLQ	Both groups showed improvement in VAS; neurectomy showed higher clinical impact in improving nasal obstruction, rhinorrhea, eye itching, lacrimation Both groups experienced significantly improved RQLQ score No difference in improvement at 4 months, but there was a statistically significant difference at 12 months, neurectomy showed greater improvement

(Continues)

TABLE XI.C.-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ai et al.[2389]	2018	4	Retrospective cohort	Patient with AR and asthma who has received: Conservative medical treatment Bilateral endoscopic vidian neurectomy	RQLQ VAS TASS AQLQ Medication scores	Neurectomy group experienced significant improvement in RQLQ, VAS, AQLQ, and medication scores versus medical management No difference in pre- and post-treatment TASS was noted in either group
Su et al.[2388]	2011	4	Retrospective case series	AR patients who underwent endoscopic vidian neurectomies	VAS: sneezing, nasal discharge, nasal obstruction, itchy eyes/nose, postnasal drip	Significant improvement in all symptoms
Lai et al.[2387]	2017	5	Retrospective cohort	Rhinitis patients (including those with AR) who underwent vidian neurectomy via: Cold instrumentation Laser ablation	VAS: nasal obstruction, itching, sneezing, rhinorrhea	Both groups experienced improvement No comparison of results between groups No AR-specific subgroup analysis

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; LOE, level of evidence; PFT, pulmonary function test; QOL, quality of life; RCT, randomized controlled trial; TASS, Total Asthma Symptom Score; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

of allergy injections may lead to systemic symptoms, and 0.003% can be considered severe, the ability to emergently treat these reactions with epinephrine when indicated is essential.[2443] β-blocker use does not appear to increase the likelihood of systemic reactions but, although not consistently observed, may be associated with higher anaphylaxis severity.[2444,2445] Thus, the lack of effect of typical subcutaneous epinephrine dosing in a β-blocked patient creates the treatment dilemma.

Although there is some variability, some guidelines consider active systemic autoimmune diseases and active malignancy as contraindications to AIT.[2446] This is based on case reports and case series and generally lower quality evidence that the risk of anaphylaxis from AIT is greater in patients with these conditions or that the immunomodulatory effect might negatively affect the underlying disease process. Successful AIT has been reported in several patients with malignancy.[2447] Similarly, the theoretical concerns in autoimmune disease are offset by several case series demonstrating relative safety and effectiveness.[2448] Furthermore, in a large observational study of 1888 patients, there was no increase in the development of autoimmune disease in AR treated with AIT over a 20 year observation period.[2449]

Initiating AIT during pregnancy is contraindicated although most consensus documents state that continuing maintenance immunotherapy during pregnancy is not contraindicated.[2418,2419] Avoiding the initiation of AIT is presumably based on the concern that severe anaphylaxis is more likely to occur during buildup immunotherapy and that anaphylaxis, or treatment thereof, could harm the developing fetus. There are limited data to guide decision making, but in a cohort of 102 pregnancies during AIT, there were no increased fetal complications compared with untreated pregnancies. Three patients had systemic reactions requiring epinephrine – none resulting in pregnancy complication.[2450] A more recent study demonstrated the relative safety of SLIT initiated during pregnancy.[2451]

SLIT is available for several allergens as an FDA approved tablet. Contraindications for this therapy include unstable or uncontrolled asthma. Therapy should not be initiated in a patient with a medical condition impairing recovery from anaphylaxis, or in those for whom epinephrine or β-agonist therapy might be less effective.[2452] SLIT tablets are also contraindicated in patients with EoE.[2452–2455]

There are a variety of relative contraindications that merit shared decision making. Cardiovascular disease, systemic autoimmune diseases in remission, severe psychiatric disorders, poor adherence, primary and secondary immunodeficiencies, and a history of serious systemic reactions to AIT have all been considered as relative contraindications. A 2019 EAACI task force summary also reviews some additional considerations. ACEI therapy in

TABLE XI.C.-4 Evidence table – posterior nasal neurectomy in patients with allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hua et al.[2397]	2022	2	RCT	AR patients that underwent either: PNN neurectomy PNN neurectomy + pharyngeal branch neurectomy	VAS: rhinorrhea, nasal obstruction, sneezing, nasal itching RQLQ Asthma control Chronic cough	VAS, RQLQ, asthma control improved significantly in both cohorts, but no difference between cohorts Chronic cough significantly improved in PNN + pharyngeal branch neurectomy versus PNN alone
Marshak et al.[229]	2016	2	SR	8 studies with pre-post-intervention comparisons, $n = 529$ patients who underwent vidian or PNN neurectomy for AR or non-allergic rhinitis	Multiple endpoints	SNOT-22 and sinus symptom questionnaire improved (1 study) RQLQ improved (2 studies) Nasal obstruction improved (5 of 7 studies) Sneezing improved (4 of 6 studies) Itching improved (2 of 3 studies) Post-nasal drip improved (1 of 4 studies) No AR-specific subgroup analysis
Li et al.[2399]	2019	3	Non-randomized controlled trial	AR patients with CRSwNP: FESS FESS + PNN neurectomy	VAS RQLQ SNOT-22	All endpoints significantly improved for both groups Sneezing- and rhinorrhea-specific VAS scores significantly more improved with FESS + PNN neurectomy
Albu et al.[2402]	2014	3	Non-randomized controlled trial	AR patients that underwent: Endoscopic microdebrider-assisted inferior turbinoplasty Endoscopic microdebrider-assisted inferior turbinoplasty + PNN neurectomy	VAS: nasal obstruction, rhinorrhea, sneezing, snoring RQLQ Nasal mucociliary transport	Both groups improved in VAS and RQLQ Mucociliary clearance decreased significantly in both groups No significant difference between groups
Kobayashi et al.[2417]	2012	3	Non-randomized controlled trial	AR patients that underwent: Selective resection of peripheral branches of PNN via submucous turbinectomy (local anesthesia) Total resection of PNN + submucous turbinectomy (general anesthesia)	Subjective patient ratings of sneezing, rhinorrhea, and nasal obstruction	Both groups experienced significant improvements in all symptoms No significant difference between the two groups (may be secondary to low sample size)

(Continues)

TABLE XI.C.-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wang et al.[2398]	2020	4	Prospective case series	AR patients that underwent endoscopic PNN neurectomy	VAS for rhinorrhea and sneezing	Significant improvements in rhinorrhea and sneezing
Ogi et al.[2401]	2019	4	Retrospective case series	AR patients that underwent endoscopic submucous inferior turbinectomy and PNN neurectomy	Symptoms: sneezing, rhinorrhea, nasal obstruction	Significant improvement in all symptoms up to 3 years post-treatment
Takahara et al.[2400]	2017	4	Retrospective case series	AR patients that underwent PNN neurectomy after submucous inferior turbinectomy	TNSS	TNSS significantly improved
Ogawa et al.[2374]	2007	4	Retrospective case series	AR patients with inferior turbinate hypertrophy that underwent submucous turbinectomy combined with PNN neurectomy	Symptoms (sneezing, rhinorrhea, nasal obstruction, severity), as classified by Okuda's criteria Cytokine levels and histopathology	Significant improvement in all symptoms Many cytokines (e.g., IL-5) significantly decreased and inflammatory cells decreased
Makihara et al.[2396]	2021	5	Retrospective case series	AR patients that underwent: PNN trunk resection in an underwater environment Resection of peripheral branches of PNN *All patients also underwent submucous inferior turbinectomy	Subjective symptoms (rhinorrhea, sneezing, nasal obstruction) Medication use	All symptoms and medication scores improved in both groups PNN trunk resection showed significantly greater improvement in medication scores, sneezing symptoms, and rhinorrhea symptoms (but not nasal obstruction)

Abbreviations: AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; FESS, functional endoscopic sinus surgery; LOE, level of evidence; PNN, posterior nasal nerve; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, Sinonasal Outcome Test (22 item); SR, systematic review; TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

venom immunotherapy is a relative contraindication, but not for aeroallergen immunotherapy.[2446] Inability to communicate symptoms that might herald the beginning of anaphylaxis are a potential contraindication and might be especially challenging in very young children (less than 5 years old). Human immunodeficiency virus (HIV) is usually not considered a contraindication unless the patient has acquired immunodeficiency syndrome (AIDS). This and other chronic infections should be factored into the overall risk/benefit evaluation.

XI.D.4 | Allergen extracts

XI.D.4.a | *Overview, units, and standardization*

Overview. Allergy testing began with pollen grains placed on the conjunctiva.[2456,2457] As skin testing and SCIT evolved, injectable allergen extracts were required. Inhaled allergenic particles are composed of a heterogeneous mixture of allergenic and non-allergenic proteins and macromolecules. Allergen extracts are created by refining raw materials and extracting proteins in a solution.[2458]

There are multiple sources of variance in allergen extracts. The composition of allergenic proteins can vary, conferring different degrees of total antigenicity through genetic or epigenetic mechanisms.[2459,2460] Impurities in the source materials, such as mold growing on pollen granules or bacteria on cat pelts, may affect immunogenicity.[2461] Variation also occurs in the raw material collection[2460] and in the extraction process.[2458,2459,2462,2463] Additionally, there is biologic variation in individual sensitizations to major and minor allergens within a source. Only a very small fraction of the proteins extracted are allergenic.[2458] Given that the antigenic

TABLE XI.C.-5 Evidence table – cryotherapy/radiofrequency ablation of the posterior nasal nerves in patients with allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Del Signore et al.[2405]	2022	3	Randomized, sham-controlled trial	Chronic rhinitis patients, including AR: Cryotherapy of PNN Sham procedure	rTNSS (responders: ≥30% improvement) RQLQ (responders: ≥0.5-point improvement) NOSE (responders: ≥20% improvement in at least one category)	Cryotherapy had significantly greater improvement in all three categories versus sham surgery Presence of AR did not affect whether cryotherapy led to improvement
Ehmer et al.[2410]	2022	4	Prospective case series	Heterogenous group undergoing radiofrequency neurolysis of PNN, including those with AR	rTNSS	Significant improvement in TNSS, with 100% of patients improving at least 1 point at 52 weeks AR subgroup analysis revealed improvement
Stolovitzky et al.[2411]	2021	3	Randomized, sham-controlled trial	Chronic rhinitis patients, including AR: Radiofrequency neurolysis of PNN Sham procedure	rTNSS (responders: ≥30% improvement)	Radiofrequency neurolysis led to statistically higher response rate versus sham surgery No subgroup analysis on AR patients
Ow et al.[2406]	2021	4	Prospective case series	Heterogenous group undergoing cryotherapy of PNN, including those with AR	rTNSS RQLQ Physician-derived CGI-I	Statistical improvement in rTNSS and RQLQ Physicians deemed improvement in 80% of patients Results did not differ when stratified by presence of AR
Chang et al.[2408]	2020	4	Prospective case series	Heterogenous group undergoing cryotherapy of PNN, including those with AR	rTNSS RQLQ	rTNSS and RQLQ significantly improved Subgroup analysis of AR patients revealed improvement
Hwang et al.[275]	2017	4	Prospective case series	Heterogenous group undergoing cryotherapy of PNN, including those with AR	TNSS	Significantly improved TNSS scores Subgroup analysis of AR patients revealed improvement as well
Gerka Stuyt et al.[2407]	2021	5[a]	Prospective case series	Heterogenous group undergoing cryotherapy of PNN, including those with AR	TNSS	TNSS significantly improved Results improved, but did not reach statistical significance, within AR subgroup (sample size was only 3 for this subgroup)
Krespi et al.[2412]	2020	5[a]	Prospective case series	Heterogenous group undergoing in-office endoscopic laser ablation of PNN, including those with AR	TNSS	Significantly improved TNSS scores No score breakdown for AR patients specifically

(Continues)

TABLE XI.C.-5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yen et al.[2404]	2020	5[a]	Prospective case series	Heterogenous group undergoing cryotherapy of PNN at middle and inferior meatus, including those with AR	rTNSS NOSE SNOT-22 VAS for rhinorrhea, congestion mini-RQLQ Physician-derived CGI-I Endoscopic images	Significant improvements in all surveys Physicians deemed improvement in 89.7% of patients 36% of inferior turbinates had reduced congestion on endoscopy No subgroup analysis of AR patients
Yoo et al.[2409]	2020	5[a]	Retrospective case series	Heterogenous group undergoing cryotherapy of PNN after failure of ipratropium, including those with AR	Runny nose score from SNOT-22	Runny nose score significantly improved Presence of AR did not affect the odds of improvement
Terao et al.[2403]	1983	5[a]	Prospective case series	Patients with vasomotor rhinitis (including AR patients) who underwent cryotherapy of PNN via a self-made device	Symptoms	Excellent-to-good result in 75.5% of subjects No subgroup analysis for AR patients

Abbreviations: AR, allergic rhinitis; CGI-I, Clinical Global Impressions-Improvement Scale; LOE, level of evidence; NOSE, Nasal Obstruction Symptom Evaluation; PNN, posterior nasal nerve; r, reflective; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22, Sinonasal Outcome Test (22 item); TNSS, Total Nasal Symptom Score; VAS, visual analog scale.

[a]LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR patients.

composition of allergen extracts is not uniformly assessed, assuring extracts are both safe and effective is challenging.

Units and potency. Allergen extracts are labeled with a variety of units, many of which do not convey information about allergenic content or allergenic potency. Potency can refer to the qualitative allergenicity of a source material's proteins or the quantitative concentration of allergens in an extract. Measures of an allergen extract may refer to quantity of extracted material in the solution (a concentration) or be standardized to the biologic activity in allergic individuals. The different techniques of assessing allergen extracts lead to multiple types of units, which can be grouped into non-standardized, standardized, and proprietary.

Non-standardized allergen extracts. The majority of allergen extracts available in the US are non-standardized. Allergen extracts are regulated by the Center for Biologics Evaluation and Research (CBER) under the US FDA.[2464] The FDA requires that allergen extracts list the biologic source, a potency unit, and an expiration date. This labeling allows for significant variation between manufacturers and between lots produced by the same manufacturer.

There are two US non-standardized units, weight/volume (w/v) and protein nitrogen units (PNU). Weight/volume refers to the ratio of grams of dry raw material to milliliters of extract solvent. An allergen extract labeled 1:20 w/v indicates for every 1 g of raw material (e.g., pollen) 20 ml of extract solvent was used. This does not provide direct information about the amount of allergenic protein in the extract nor its reactivity in allergic individuals. However, it implies a reproducible extraction methodology was employed.[2458] PNU is the second most common non-standardized unit currently used in the US. PNU refers to an assay of the precipitable protein nitrogen by phosphotungstic acid that correlates with the total protein in the extract. While most of the protein is non-allergenic, the total protein is another method to quantitate an allergen extract's content.[2458]

In Europe, many manufacturers use proprietary units and internal quality controls which must utilize a validated assay.[2459] This European manufacturer based quality control is known as "In House Reference Preparation" or "IHRP."[2460] However, the European Medical Agency has been developing a standardized framework based on protein homology rather than source species.[2465] The

European Union is also developing additional allergen standards with the WHO starting with Bet v 1 and Phl p 5a.[2465] Extract units in Europe, the US, and other countries vary without agreed upon references available for conversion.

Standardized allergen extracts. Standardized allergen extracts in the US are tested by the manufacturers to be within a reference range (70%–140%) when compared to a standard provided by the FDA's CBER. Standardized inhalant allergens within the US include cat, *Dermatophatoides pteronyssinus*, *Dermatophagoides farinae*, short ragweed, and multiple grass species.[2465]

The CBER creates the reference standardized extract through skin testing in known "highly allergic" individuals. They use serial intradermal skin testing with three-fold titrations and measure potency by how many dilutions are needed to produce a flare reaction measured by adding the largest diameter and its 90° (orthogonal) diameter. The orthogonal sums are plotted for each dilution and a best-fit line drawn. The concentration that corresponds to where the orthogonal sum of the flare totals 50 mm (ID_{50}EAL) determines the units listed in either allergy units (AU) or biologic allergy units (BAU). AU is used for HDM historically. A mean ID_{50}EAL of fourteen three-fold dilutions is defined as 100,000 BAUs/ml and 12 three-fold dilutions 10,000 BAUs/ml.[2465] Manufacturers then compare their extract lots to the CBER allergen standard through competition ELISA using pooled serum IgE from known allergic subjects.

The process is different for extracts where the major allergen reactivity strongly correlates with overall allergen reactivity (cat and ragweed). A major allergen is defined as a specific protein that elicits an allergic reaction in more than 50% of individuals allergic to that species. If there is a major allergen that correlates strongly with the population's clinical reactivity, the manufacturer compares their extract to the CBER's standard by gel electrophoresis employing monoclonal IgG antibodies to the major allergen protein.[2464] When standardized by major allergen, the units are listed in μg/ml (Fel d 1 for cat; Antigen E or Amb a 1 for ragweed). For cat extracts, the presence of Fel d 2 is also required. Also, cat extract with 10–19.9 Fed d 1 U/ml is designated as 10,000 BAU/ml. Short ragweed extract of 350 Amb a 1 U/ml is designated as 100,000 BAU/ml.[2461]

Some allergen extracts in Europe use the Nordic method where 10,000 biologically standardized units/ml is comparable to a SPT response elicited by 10 mg/ml of histamine.[2465] Most allergen extracts in Europe are proprietary; however, the European effort to develop cross-product comparability is summarized nicely by Zimmer et al.[2461] The WHO has identified allergen standardization as a problem and the European Union funds a project known as CREATE to "develop certified reference materials for allergenic products and validation of methods for their quantification."[2466,2467]

In summary, there is not an international consensus on allergen units or standardization for allergen extracts. While cross-manufacturer standardization and biologic potency labeling increase manufacturing costs, it is widely agreed that greater standardization would benefit patient efficacy and safety. Variations in allergen extracts between manufacturers may discourage medical providers from changing vendors, thus reducing competition's effect on price. Non-standardized and proprietary units also complicate the interpretation of published efficacy and safety studies. As of 2022, multiple opaquely referenced allergen units remain in use worldwide. (See Section XI.D.11.a.i. Allergen Standardization and Heterogeneity for additional information on this topic.)

XI.D.4.b | *Allergen extract adjuvants*

Although AIT is an effective treatment for AR, it is not without limitations including cumbersome-up-dosing regimens, systemic reactions, and variable efficacy.[1668] Adjuvants are chemicals and proteins that may enhance the safety, convenience, and immunological effects of AIT.[2468–2474] Effective AIT attenuates pro-inflammatory Th2 responses in favor of tolerogenic Treg responses. This immunological transformation can be enhanced with adjuvants that are subdivided into several broad categories (Table XI.D.4.b).

Of the potential adjuvants listed, several have reached Phase 1 or Phase 2 clinical trials for treating AR. Some have already received FDA approval for use in modern infectious disease vaccines. Next generation AIT products may very well incorporate adjuvants in combination with peptides and other allergenic molecules. A few adjuvants deserve specific mention.

Mineral salts and crystalline molecules. Alum (aluminum hyroxide salt) was the first adjuvant to be tested in AIT and has recently been considered for COVID-19 vaccines.[2475,2476] Early studies with alum-precipitated extracts demonstrated an augmented immunologic response but with some undesirable IgE-mediated response that hindered its therapeutic application.[2475,2477] Microcrystalline tyrosine has been tested as an alternative with less IgE production.[2470,2476] Alum formulations are currently being considered for certain allergen peptide vaccines.

Toll like receptor constructs. It has been proposed that danger signal molecules synthesized from virus, parasites, and bacteria and used in combination with allergens could help induce tolerance by augmenting TLR mediated innate immune responses.[2473,2478–2480] Tversky et al.[2481,2482] showed that traditional SCIT alone results in

TABLE XI.D.4.b Potential adjuvants for allergen immunotherapy

Category	Adjuvant	Examples and comments
Salts and crystals	Aluminum hydroxide (Alum)	Early studies showed augmented immune responses
	Calcium phosphate	Shown to have some immunogenicity enhancement with less IgE stimulation
	Microcrystalline structures	Microcrystalline tyrosine
Transfer vehicles	Liposomes	Oligo mannose-coated liposomes
	Nanoparticles	Poly lactose co-glycolide, many others
	Carbohydrate particles	Chitosan
	Amino acid particles	Cationic peptides, protamine
	Dendrimers	Highly ordered synthetic molecules that are typically spherical and can be made to be water soluble
	Oil-in-water emulsion	Oil emulsions such as MF59, AS03, CAF01, and Montanide ISA induce local inflammation while simultaneously acting as a long-term depot agent to prolong the distribution of allergen
Immunostimulatory	TLR-9 agonists	CpG oligodeoxynucleotide (CpG-ODN) has been employed in several direct disease modifying and allergen immunotherapy approaches by increasing tolerogenic cytokines including interferons. QbG10 is a synthetic virus like particle derived from bacterial DNA
	TLR-7 agonists	Virus like particles; single stranded viral RNA stimulates TLR-7 and stimulates the production of type I interferons can be used singly or in combination with allergens
	TLR-4 agonists	Monophosphoryl Lipid A fraction derived from bacterial lipopolysaccharide works as a TLR-4 agonist. Monophosphoryl lipid derived from bacterial DNA or RNA stimulate dendritic cells and other antigen-presenting cells to increase Th1 cytokines
	C-type lectin receptors	Mannan mannose polysaccharide that acts as C-type hectic ligand to enhance antigen presentation and increase tolerogenic cytokines
	DNA and mRNA vaccines	DNA and mRNA vaccines such as COVID-19 vaccine can be engineered to encode allergenic proteins but often are composed of CpG repeats that can also simultaneously induce TLR responses
	Imidazoquinones	Acts as functional adjuvant for TSLP mediated allergic T cell responses
	Heat killed bacteria	Heat killed mycobacteria, heat killed *E. coli*, heat killed *Listeria monocytogenes*
Natural derived	Probiotics	Ingested microbial products have shown some limited benefit in reducing eczema and other atopic disease. Microbial adjuncts proposed to enhance the efficacy of food allergen immunotherapy
	Vitamin D	Vitamin D3 has been shown to reduce effector T cell stimulation and cytokine production and promote the effect of allergoid in mice
	Amino acids	L-tyrosine bound to allergen acts a short-depot forming adjuvant and indirectly increases IgG production
	Chinese herbs	ASHMI

Abbreviations: ASHMI, Anti-Asthma Simplified Herbal Medicine Intervention; Ig, immunoglobulin; TLR, toll-like receptor; TSLP, thymic stromal lymphopoietin.

a partial restoration in the impaired TLR function demonstrated among AR sufferers and that this effect could potentially be augmented with certain adjuvants.

Among the specific TLR targeted clinical studies, Creticos et al.[2483] first reported a study using synthetic bacterial derived DNA (CpG oligodeoxynucleotide) bound to ragweed protein Amb a 1 designed to upregulate the immunostimulatory responses via TLR-9. This TLR-9 agonist bound to Amb a 1 (Tolamba) was administered in a double-blind, placebo-controlled study of ragweed-allergic subjects with a single season 6-injection regimen. Efficacy was observed over two ragweed seasons indicating that the vaccine conferred some clinical tolerance. A follow-up study did not reach statistical significance.[2484] In 2021, Leonard et al.[2485] reported on the use of CpG and a Fel d 1 specific mouse immunotherapy model to elucidate important signaling elements that may be capitalized upon moving forward.

CYT003-QbG10 is another TLR targeted immunotherapeutic product in development for the treatment of AR and asthma. It is based on Cytos Biotechnology's modified Immunodrug platform, which incorporates virus-like particle Qb, a TLR-9 immunostimulatory DNA sequence to induce targeted T cell responses. In a Phase 2b double-blind, placebo-controlled study of 300 patients with allergic rhinoconjunctivitis, QbG10 was shown to be safe, well-tolerated and efficacious.[2486]

A TLR-4 adjuvant has also been in clinical development (Pollinex Quattro, Allergy Therapeutics).[2487] This construct is comprised of monophosphoryl lipid A and formulated with pollen allergoids. A large grass study showed significant improvement in symptom and medication scores versus placebo.[2488] A brief ragweed trial also showed positive clinical effect.[1517]

Nanoparticle based constructs. Synthetic nanoparticles have been proffered since 1959 to deliver a host physiologically active substances including vaccines.[2489,2490] A successful recent example of this is the use of liposomes to deliver mRNA encoded spike protein instructions in the Pfizer and Moderna COVID-19 vaccines. This same approach has been proposed to deliver genetic instructions encoding allergenic proteins for immunotherapy. These so-called allergen "vaccines" have the potential to synergistically activate TLR receptors while simultaneously encoding allergenic proteins.

Naturally occurring adjuvants. Certain naturally occurring immune modulators have been shown to act as potential adjuvants. Nutritional compounds and probiotics may be ingested directly or administered subcutaneously in tandem with allergen.[2491,2492] One example is VD3 which has been shown to reduce effector T cell stimulation and cytokine production and promote the effect of AIT in both mice and humans.[2493–2495] One mouse immunotherapy study successfully employed the use of Fel d 1 covalently bound to VD3.[2496] (See Section VI.H. Vitamin D for additional information on this topic.)

Components isolated from Ganoderma Lucidum, a Chinese herb contained in Anti-Asthma Simplified Herbal Medicine Intervention (ASHMI), induce levels of IL-10, IFN-γ, and Foxp3 in response to environmental allergens.[2497] Like TLR ligands, ASHMI has shown some limited effectiveness in treating certain allergic diseases by itself without the presence of an allergen.[2498] However, because of its unique tolerogenic cytokine profile, ASHMI and other naturally occurring herb combinations may also prove to be advantageous when used as an adjuvant for AIT.

In summary, various adjuvants have been proposed and studied in animal models and tested in humans, but there is currently no adjuvant FDA approved for use in AIT. Improving the immunologic profiles of immunotherapies while maintaining safety standards remains challenging. Recent Phase 1 and Phase 2 studies have been reported for select adjuvants, and there is promise for future AIT protocols to incorporate adjuvants which outperform traditional therapies.

XI.D.4.c | *Modified allergen extracts*

Traditionally the disease-modifying capability and potential for long-lasting therapeutic effect of AIT has been accomplished via SCIT or SLIT with native, unmodified extracts. However, reliance on native extracts has limitations for widespread use including production costs and availability, as well as consistency and comparability among extracts.[2499] Furthermore, while generally safe, AIT with natural extracts has the potential for inducing hypersensitivity reactions that can rarely be life-threatening. The use of modified allergen extracts has been studied as an alternative to native extracts as a means of providing improved AIT efficacy, safety, and reliability. This section discussed several approaches of modified allergen extracts.

Recombinant allergen extracts. Recombinant-derived allergens rely on recombinant DNA technology to produce clones of natural allergens in the case of wild type recombinant allergens, or clones of partial allergen sequences in hypoallergenic recombinant allergens. For wild type recombinant allergens, this technique produces consistent structures that preserve allergenic epitopes and potencies.[2500] However, the disadvantage is that as a clone, there is potential for inducing hypersensitivity reactions. Hypoallergenic recombinant extracts, on the other hand, maintain certain T cell epitopes but may induce less IgE driven responses.[2501] Immunotherapy trials using recombinant birch and Timothy grass allergens have been reported. Timothy grass AIT with recombinant allergen induced immunologic changes, including increased IgG4 and down trending sIgE while decreasing symptoms and medication use compared to placebo.[2502,2503] Similarly for birch AIT, recombinant allergen use resulted in reduced rhinoconjunctivitis symptoms and rescue medication use, with symptom improvement similar to treatment with natural extract; immunological changes included increased IgG levels compared to placebo.[2504,2505] Together, these studies show potential for comparable performance of recombinant allergen extracts, with the advantage over natural extract of using a more consistent, pure allergen that could be precisely dosed.

Synthetic peptides. These are linear fragments of amino acids derived from T cell epitopes of allergens. Peptides do not induce early phase responses because they lack the conformational structure to bind to IgE receptors. When used for AIT, they do not generate a

robust blocking IgG but do have the capability of inducing immunologic T cell changes. AIT with synthetic peptides has been studied for several allergens including cat, grass, HDM, ragweed, and birch with somewhat inconsistent efficacy. Grass allergen peptides were effective in reducing rhinoconjunctivitis symptom scores when injected at 2-week intervals over a brief trial,[1511] and ragweed peptide therapy improved symptom scores compared to natural extract and placebo.[2506] Birch pollen pre-seasonal treatment induced immunologic changes, but clinical symptoms were not significantly improved.[2507] Cat peptide AIT in particular had promising initial results reducing symptoms in sensitized individuals, but Phase 3 data of one product did not significantly outperform the placebo group.[1516,2508–2510] Longer sequences, termed contiguous overlapping peptides, have been alternatively used in an attempt to generate a more robust immunogenic response; birch AIT resulted in improved symptom scores and medication use as well as induction of IgG antibodies.[2511–2513]

Allergoids. These involve native allergens that have been modified or denatured with the use of additional chemical agents, such as aldehydes and polyethylene glycol. These modified structures have the potential to retain immunogenicity, largely via T cell responses, but also decrease the risk for IgE-mediated reactions. In addition to improved safety, this may offer ability to decrease the number of injections required during a build-up period.[2514] While immediate hypersensitivity reactions are reduced, late phase adverse reactions can still occur.[2515] Allergoid preparations have been evaluated to several different allergens. Initially utilized in ragweed allergic patients, allergoid preparations reduced symptom scores and increased blocking antibodies.[2516,2517] Subsequent studies with grass pollen allergoid also showed effectiveness in reducing clinical symptom scores and medication use.[2477,2518,2519] Allergoids in HDM allergic patients also demonstrated improved symptom scores, in both subcutaneous and sublingual routes.[2520,2521] More recently, in an open label study a glutaraldehyde-modified allergoid in birch pollen allergic patients induced initial humoral responses as well as T cell augmentation of IL-10 production.[2522] While allergoids are commercially available in Europe, standardization criteria have been a limiting factor in receiving regulatory approval in the US.

Encapsulated allergens. Encapsulation of allergens involves use of nanoparticles or microparticles to envelop allergens of interest which can then be injected or ingested orally. This process has the potential to decrease the dose required for immunologic responses, protect the allergen from degradation, and improve uptake of allergen while limiting adverse reactions.[2523] Encapsulation can be accomplished with biodegradable nanoparticles including synthetic or natural polymers, liposomes, and virus-like particles, or with nonbiodegradable nanoparticles such as dendrimers or carbon-based particles.[2524] Most of the research involving encapsulated allergens has yet to be evaluated in human trials.[2469] In one study, a liposome encapsulated HDM extract was evaluated in patients with asthma, who had improved symptom scores over a 12-month period compared to placebo.[2525] Separately, an oral microencapsulated form of Timothy grass allergen was used to treat patients with AR over a period of 10 weeks; patients in the active treatment group experienced decreased symptom scores compared to placebo.[2526] Limited human trial data suggest that encapsulated allergens may induce immune responses but further understanding of their role in AIT is needed.[2474]

Overall, a variety of modified allergen extracts hold promising clinical and immunologic findings. Further research is needed involving larger clinical groups to study the efficacy and safety of these agents as compared to the native allergen extracts.

XI.D.5 | Subcutaneous immunotherapy for allergic rhinitis

XI.D.5.a | *Conventional subcutaneous immunotherapy for allergic rhinitis*

Efficacy. Over the past 68 years,[2527] multiple RCTs have supported the therapeutic efficacy of SCIT for AR.[2419] SCIT efficacy is contingent upon an appropriate treatment duration and dose, with an optimal target maintenance dose between 5 and 20 μg of major allergen for each clinically relevant aeroallergen.[2419] SCIT has been associated with effective symptom amelioration and potential disease modification that can persist after stopping treatment.[2419]

Evidence suggests that a SCIT treatment duration of 3–5 years is appropriate.[2419] A clinically significant relapse rate has been observed with SCIT discontinuation prior to 3 years.[2528] Currently, there are no validated biomarkers to reliably identify when SCIT can be discontinued and clinical remission sustained. The determination to discontinue SCIT in patients who have responded should balance the potential for benefit with the potential for harm and burden, in an open discussion with patient participation in the medical decision-making process.

High-quality data have substantiated the therapeutic utility of SCIT for AR patients with particular aeroallergens and certain formulations. Therefore, SCIT efficacy for AR treatment is contextual, and should not be interpreted as an "umbrella" description based on favorable outcomes observed in RCTs focused on a limited number of products.[2529]

SCIT is efficacious for AR sensitive to pollen, mold, HDM, and animal allergens.[1206,2419,2529–2534] Such efficacy has been demonstrated based on rigorous RCTs for pollens (e.g., ragweed, grass, and birch), cat, and HDM (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), where a standardized extract target concentration is available and was studied. However, these data cannot be interpreted as a "class effect" that necessarily extends to other aeroallergens. Data supporting the SCIT efficacy for dog, cockroach, and mold spores (particularly *Alternaria* and *Cladosporium*) are encouraging, but limited, and additional studies are needed to substantiate the therapeutic efficacy of SCIT for AR related to these inhalant allergens.[1206,2419,2530–2533]

The majority of RCTs supporting SCIT for AR have been studies of single aeroallergens.[2419] There have been very few studies of multi-allergen SCIT, which are heterogeneous and suffer from methodological shortcomings. While multi-allergen SCIT is a mainstay of clinical practice in the US, and patients report favorable treatment benefits, additional high-quality studies are needed to provide rigorous support for the efficacy of multi-allergen SCIT in treating AR.

Safety. SCIT is associated with localized reactions occurring in the majority of patients.[2419] Evidence indicates local reactions do not reliably predict occurrence of subsequent systemic reactions; dosage adjustment is not typically required after their occurrence.[2419] While there is a low risk for systemic reactions from SCIT, potentially life-threatening and fatal reactions may occur. Non-fatal systemic reactions occur at a rate of approximately 2 per 1000 injections in patients receiving SCIT.[2419] Severe grade 4 anaphylactic reactions occur in approximately 1 per million injections, and fatal reactions in approximately 1 in 23 million injection visits.[2535,2536]

Risk factors for systemic reactions from SCIT include poorly controlled asthma, exquisite aeroallergen sensitivity, concomitant β-blocker use, rush SCIT protocols, prior systemic reaction, high dose SCIT, injection from a new SCIT vial (i.e., higher potency), and dosing error.[2419,2535–2537] A recent decline in fatal systemic reaction rate has been observed, which has been attributed to greater awareness and identification of patients with risk factors.[2536]

Cost-effectiveness. Data support SCIT as a cost-effective intervention, in large part due to the potential for reductions in long-term symptom burden, disease complications, disease progression, and medication costs. US studies demonstrate SCIT superiority over alternative approaches – providing clinical benefit while improving health outcomes.[2538,2539] However, practice variation may produce cost disparities. As an example, some physicians may require SCIT patients to be provided a self-injectable epinephrine prescription, which has not been shown to be cost-effective (incremental cost-effectiveness ratio $669,327,730 per QALY [quality adjusted life year]).[2540]

Evidence. Dhami et al.[2438] undertook a systematic review appraising SCIT efficacy for AR, with 61 robustly conducted double-blind RCTs of SCIT satisfying inclusion criteria (Table XI.D.5.a). Study quality was high, with the majority of RCTs having low risk of bias. Significant improvements were seen in symptom scores (standardized mean difference [SMD] −0.65 [95% CI −0.86, −0.43]), medication use (SMD −0.52 [95% CI −0.75, −0.29]), combined symptom/medication score (SMD −0.51 [95% CI −0.77, −0.26]), and QOL (SMD −0.35 [95% CI −0.74, −0.04]; six trials). Analysis of safety was obfuscated by variation in reporting of adverse effects. In 19 RCTs, the overall relative risk of adverse events was 1.58 (95% CI 1.13, 2.20). Local adverse event relative risk was 2.21 (95% CI 1.43–3.41, nine RCTs). Systemic adverse event relative risk was 1.15 (95% CI 0.67–2.00, 15 RCTs). This systematic review provides evidence for short-term benefit in symptoms and medication reliance, as well as a limited effect on disease specific QOL.

Several studies imply SCIT for AR is associated with continued benefit after stopping treatment, including a reduced risk for developing asthma[2541,2542] and new allergen sensitivities.[2543,2544] However, data meta-analyzed by Dhami et al.[2438] are more limited in terms of persistence of benefit in symptoms scores after treatment discontinuation. Additional studies are required to support this important and desirable outcome of SCIT treatment.

An updated systematic review of RCTs of SCIT for AR was performed from January 1, 2015, through October 1, 2021. All studies did not evaluate clinical endpoints, heterogeneity between studies was significant, and there was variable risk of bias. In general, studies demonstrated significant SCIT treatment benefit across age groups.[1671,2545,2546] Arroabarren et al.[2425] evaluated children 5–15 years old in a prospective study comparing a 3-year versus a 5-year course of SCIT, demonstrating a 44% reduction in symptom and medication scores from baseline after 3 years of therapy ($p = 0.002$) and a 50% decrease after 5 years of therapy ($p = 0.001$). Wang and Shi[2547] reported 77% reduction in TNSS in children with a similar decrease in medication scores. In an elderly cohort, Bozek et al.[2548] evaluated subjects 65–75 years old with moderate or severe intermittent AR, comparing 3 years of grass SCIT to placebo and finding a 41% decrease in combined symptom and medication scores versus baseline ($p = 0.004$).

Recent evidence demonstrates SCIT benefit for HDM and grass allergens.[1403,1510,2425,2548–2550] Kim et al.[2550] demonstrated through network meta-analysis that efficacy of SCIT for HDM was greater than SLIT drops or tablets.

Recent studies support the safety of SCIT; however, the rate of SCIT-associated hypersensitivity reactions has shown a wide range. In the study by Arroabarren et al.,[2425]

TABLE XI.D.5.a Evidence table – subcutaneous immunotherapy for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim et al.[2550]	2021	1	Network meta-analysis	SCIT SLIT	Symptoms Medication use	All forms of AIT were effective, with SCIT providing greater benefit
Dhami et al.[2438]	2017	1	SRMA	SCIT Comparator	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Corren et al.[2086]	2021	2	DBRCT	Pollen SCIT Pollen SLIT + dupilumab Dupilumab Placebo	Symptom scores following nasal challenge	Dupilumab did not provide additional symptom benefit to SCIT Fewer dupilumab patients required epinephrine
Shamji et al.[2552]	2021	2	DBRCT	Timothy grass pollen SCIT Timothy grass pollen SLIT Placebo	Combined symptom and medication scores sIgA and sIgG	AIT groups had improvement in symptom scores that did not persist after treatment discontinuation
Xian et al.[2546]	2020	2	DBRCT	HDM SCIT HDM SLIT Placebo	Combined symptom and medication scores	Patients receiving SCIT experienced improvement in symptoms and medications versus placebo
Worm et al.[2545]	2019	2	DBRCT	Birch pollen SCIT Placebo	Combined symptom and medication scores	Overall, SCIT group had improvement in symptom and medication scores that was not statistically significant For subjects residing in high pollen count areas, a statistically significant benefit was recorded
Bozek et al.[2549]	2017	2	DBRCT	HDM SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Pfaar et al.[1510]	2017	2	Dose-finding DBRCT	Grass pollen SCIT Placebo	Combined symptom scores Skin testing	SCIT group had improvement in symptom and medication scores
Scadding et al.[1671]	2017	2	DBRCT	Grass pollen SCIT Grass pollen SLIT Placebo	Symptom scores	AIT group had improvement in symptom scores, but this did not reach statistical significance
Rondon et al.[2553]	2016	2	DBRCT	HDM SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kleine-Tebbe et al.[2554]	2014	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT did not result in a statistically significant improvement in symptoms or medications
Klimek et al.[2555]	2014	2	DBRCT	Grass pollen SCIT Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Patel et al.[1516]	2013	2	DBRCT	Fel d 1 antigen SCIT Placebo	Symptom scores	SCIT group had improvement in symptom scores
Tworek et al.[2556]	2013	2	DBRCT	Perennial SCIT Pre-seasonal SCIT	Combined symptoms and medication scores	Perennial SCIT was more effective than pre-seasonal SCIT in reducing symptom and medication scores
James et al.[2557]	2011	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptoms
Kuna et al.[2558]	2011	2	DBRCT	*Alternaria* SCIT Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Hoiby et al.[1059]	2010	2	DBRCT	Birch pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Pfaar et al.[2559]	2010	2	DBRCT	Tree pollen SCIT Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Riechelmann et al.[2520]	2010	2	DBRCT	Glutaraldehyde-modified HDM SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Tabar et al.[2560]	2008	2	DBRCT	*Alternaria* SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Charpin et al.[2561]	2007	2	DBRCT	Tree pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Powell et al.[2562]	2007	2	DBRCT	Grass pollen immunotherapy Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Colas et al.[1061]	2006	2	DBRCT	Tree pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Alvarez-Cuesta et al.[2563]	2005	2	RCT	Pollen SCIT Placebo	QOL Skin test response	Symptom scores and medication scores were significantly reduced, QOL improved

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corrigan et al.[2477]	2005	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use sIgG	SCIT group had improvement in symptom and medication scores
Dokic et al.[2564]	2005	2	DBRCT	HDM SCIT Placebo	Symptoms Medication use Nasal challenge SPT sIgG4	SCIT group had improvement in symptom and medication scores
Ferrer et al.[2565]	2005	2	DBRCT	Parietaria pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Tabar et al.[2566]	2005	2	DBRCT	Cluster HDM SCIT Conventional HDM SCIT	Symptoms Medication use	Cluster and conventional SCIT schedule resulted in similar symptom and medication scores
Crimi et al.[2567]	2004	2	DBRCT	Parietaria pollen SCIT Placebo	Symptoms Medication use Methacholine responsiveness Eosinophilia and sputum cytokines	SCIT group had improvement in symptom and medication scores SCIT may decrease asthma progression
Mirone et al.[2568]	2004	2	DBRCT	Ambrosia pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Radcliffe et al.[1089]	2003	2	DBRCT	Enzyme potentiated mixed inhalant extract Placebo	Symptoms QOL Skin testing	SCIT group had no significant improvement over placebo with two injections of enzyme potentiated desensitization
Varney et al.[2569]	2003	2	DBRCT	HDM SCIT Placebo	Symptoms Medication use Skin test reactivity	SCIT group had improvement in symptom and medication scores
Arvidsson et al.[2570]	2002	2	DBRCT	Birch pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Bodtger et al.[2571]	2002	2	DBRCT	Birch pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Drachenberg et al.[2572]	2002	2	DBRCT	Tree pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Drachenberg et al.[2478]	2001	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use Skin testing IgG	SCIT group had improvement in symptom and medication scores

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Leynadier et al.[2573]	2001	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Walker et al.[2574]	2001	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Durham et al.[2423]	1999	2	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use Conjunctival response Immediate and late skin test response	SCIT group had improvement in symptom and medication scores
Balda et al.[2575]	1998	2	DBRCT	Tree pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Zenner et al.[2576]	1997	2	DBRCT	Pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Olsen et al.[2577]	1995	2	DBRCT	Pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Ortolani et al.[2578]	1994	2	DBRCT	Parietaria pollen SCIT Placebo	Combined symptom and medication scores Skin, nasal, and conjunctival provocation	SCIT group had improvement in symptom and medication scores
Pastorello et al.[2579]	1992	2	DBRCT	Grass pollen SCIT Placebo	Combined symptom and medication scores Nasal provocation	SCIT group had improvement in symptom and medication scores
Varney et al.[2580]	1991	2	DBRCT	Pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Grammer et al.[2581]	1983	2	DBRCT	Grass pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Grammer et al.[2517]	1982	2	DBRCT	Ragweed pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Weyer et al.[2582]	1981	2	DBRCT	Grass pollen SCIT Placebo	Combined symptoms and medication scores	SCIT group had improvement in symptom and medication scores
Schmid et al.[1403]	2021	3	Placebo-controlled study	Grass pollen SCIT Placebo	Combined symptom and medication scores Nasal challenge Basophil sensitivity	Decrease in basophil sensitivity after 3 weeks predicted improvement in symptom and medication scores

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wang and Shi[2547]	2017	3	Randomized prospective trial	Multi-allergen SCIT HDM SLIT	Symptoms Medication use	Patients receiving SCIT had improvement in symptoms and medications compared to baseline
Bozek et al.[2548]	2016	3	RCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Moreno et al.[2583]	2016	3	Double-blind, randomized dose-range study	HDM SCIT regimens, 5 dosing groups	Nasal provocation	A dose-response in allergen concentration needed to induce nasal provocation was observed
Arroabarren et al.[2425]	2015	3	Randomized comparative trial	HDM SCIT x3 years HDM SCIT x5 years	Symptoms Medication use	Symptom and medication scores improved in both groups
Pfaar et al.[2584]	2012	3[a]	DBRCT	Grass pollen SCIT Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
DuBuske et al.[2585]	2011	3	Placebo-controlled study	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Ceuppens et al.[2586]	2009	3[a]	DBRCT	Birch pollen SCIT Placebo	Symptoms sIgG	SCIT group had reduced symptom scores
Pauli et al.[2504]	2008	3[a]	DBRCT	Birch pollen SCIT Placebo	Symptoms Medication use Skin testing	SCIT group had improvement in symptom and medication scores
Chakraborty et al.[2587]	2006	3[a]	DBRCT	Pollen SCIT Placebo	Symptoms Medication use sIgE and IgG, total IgE Skin test response FEV_1	SCIT group had improvement in symptom and medication scores
Frew et al.[2588]	2006	3[a]	DBRCT	Pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Jutel et al.[2502]	2005	3[a]	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Rak et al.[2589]	2001	3[a]	DBRCT	Pollen SCIT Nasal steroid	Symptoms Medication use	Nasal steroid was more effective than a short course of pre-seasonal SCIT in improving symptoms

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ariano et al.[2590]	1999	3	Double blind, observational	Parietaria pollen SCIT Placebo	Clinical effectiveness	Significant reduction of symptoms and medications was noted during pollen seasons in patients receiving SCIT
Tari et al.[2591]	1997	3[a]	DBRCT	Parietaria pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Dolz et al.[2592]	1996	3[a]	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use Conjunctival and bronchial challenge End-point cutaneous tests sIg	SCIT group had improvement in symptom and medication scores
Brunet et al.[2593]	1992	3[a]	DBRCT	Ragweed pollen SCIT Placebo	Symptoms Nasal provocation sIgE and sIgG Basophil histamine release	SCIT group had reduced symptom scores
Bousquet et al.[2594]	1991	3[a]	DBRCT	Pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Iliopoulos et al.[2595]	1991	3[a]	DBRCT	Pollen SCIT Placebo	Symptoms Medication use sIgE and sIgG	SCIT group had improvement in symptoms, but epinephrine was used in 19% of subjects
Bousquet et al.[2518]	1990	3[a]	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Fell and Brostoff[2596]	1990	3[a]	DBRCT	Pollen SCIT Placebo	Symptoms Nasal challenge	SCIT group had improvement in symptom scores
Horst et al.[2597]	1990	3[a]	DBRCT	*Alternaria* SCIT Placebo	Global symptom and medication scores Skin tests sIgG	SCIT group had improvement in symptom and medication scores
Juniper et al.[2598]	1990	3[a]	DBRCT	Pollen SCIT Nasal steroid	Symptoms Medication use	SCIT group had less improvement than the nasal steroid group, but the duration of SCIT was only 6 weeks before and during the pollen season
Bousquet et al.[2519]	1989	3[a]	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had reduced symptoms and decreased medications but a higher rate of adverse reactions

(Continues)

TABLE XI.D.5.a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ewan et al.[2599]	1988	3[a]	DBRCT	HDM SCIT Placebo	Symptoms Nasal challenge Skin test response	SCIT group had improvement in symptom scores
Bousquet et al.[2600]	1987	3[a]	DBRCT	Grass pollen SCIT Placebo	Symptoms Medication use	SCIT group had reduced symptoms and decreased medications but a higher rate of adverse reactions
Grammer et al.[2601]	1987	3[a]	DBRCT	Ragweed pollen SCIT Placebo	Symptoms Medication use	SCIT group had improvement in symptom and medication scores
Grammer et al.[2602]	1984	3	Placebo-controlled study	Ragweed pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptoms
Metzger et al.[2603]	1981	3[a]	DBRCT	Ragweed pollen SCIT Placebo	Clinical symptoms	SCIT group had improvement in symptoms

Abbreviations: AIT, allergen immunotherapy; DBRCT, double-blind randomized controlled trial; FEV_1, forced expiratory volume in 1 second; HDM, house dust mite; Ig, immunoglobulin; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial; s, allergen-specific; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SRMA, systematic review and meta-analysis.

[a]LOE downgraded for placebo- or comparator-controlled studies due to loss to follow-up, insufficient description of blinding or protocol adherence, selective outcome reporting, use of unvalidated outcome measures, selective recruitment, or indirectness of outcome measures

systemic adverse effects were noted in 2.5% of patients overall, while Scadding et al.[1671] reported hypersensitivity events (mostly mild) in 47.2% of subjects with grade 3 systemic reactions in 5.5%.

Values and preferences. While the recommendation for AIT is strong with high certainty evidence, given the potential for harm associated with potentially life-threatening anaphylaxis (with very rare SCIT associated fatality), and the burden associated with receiving SCIT, patient preference is important. Comparatively, the potential for harm and burden associated with medications is lower; the potential for benefit is also lower, with no potential for disease-modifying immunomodulation. Some patients may prefer safety and a reduced risk of therapy-associated anaphylaxis, despite reduced therapeutic efficacy. Patient motivation and choice are important considerations in AR treatment.

Summary. ICAR-Allergic Rhinitis 2018[1] recommended SCIT for AR with an Aggregate Grade of Evidence "A." Recently, evidence has continued to accrue in support of the therapeutic efficacy of SCIT in properly selected patients with AR, across age ranges and with selected standardized allergens. SCIT carries a strong recommendation and high certainty of evidence. The data concerning safety support a favorable potential for benefit with SCIT in patients with AR compared with the potential for harm or burden, though patients started and continued on SCIT must be counseled on the risk of anaphylaxis and potential fatality and presented treatment alternatives that may be safer though less efficacious. It should be noted that while SCIT remains the predominant method for AIT administration in the US, in the past two decades SLIT became the dominant approach for AIT in several European countries[2551]; recommendations for SLIT in Europe include tablet formulations and sublingual drops.[2418] Additional studies are required to substantiate the long-term effectiveness of SCIT for AR, including its potential for reducing risk for future development of asthma and sensitization to novel antigens in monosensitized patients treated with SCIT, and the safety and efficacy of multi-allergen SCIT.

Conventional subcutaneous immunotherapy

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 46 studies, level 3: 29 studies; Table XI.D.5.a)

Benefit: SCIT reduces symptom and medication use, as demonstrated in multiple high-quality studies.

Harm: Risks of SCIT include frequent local reactions and rare systemic reactions, which may be severe and potentially fatal if not managed appro-

priately. This risk must be discussed with patients prior to initiation of therapy. See Table II.C.

Cost: SCIT is cost-effective, with some studies demonstrating value that dominates the alternative strategy with improved health outcomes at lower cost. Direct and indirect costs of AIT vary based on the third-party payer, the office/region, co-payment responsibilities, and travel/opportunity related costs in being able to adhere to the frequency of office visits required.

Benefits-harm assessment: For patients with symptoms lasting longer than a few weeks per year and for those who cannot obtain adequate relief with symptomatic treatment or who prefer an immunomodulation option, benefits of SCIT outweigh harm. The potential benefit of secondary disease-modifying effects, especially in children and adolescents, should be considered.

Value judgments: A patient preference-sensitive approach to therapy is needed. Comparatively, the potential for harm and burden associated with medications are significantly lower, although the potential for benefit is also lower (with no potential for any disease-modifying effect or long-term benefit) as medications do not induce immunomodulation. Logistical issues surrounding time commitment involved with AIT may be prohibitive for some patients. The strength of evidence for SCIT efficacy, along with the benefit relative to cost, would support coverage by third party payers.

Policy level: Strong recommendation for SCIT as a patient preference-sensitive option for the treatment of AR.

Strong recommendation for SCIT over no therapy for the treatment of AR.

Option for SCIT over SLIT for the treatment of AR.

Intervention: SCIT is an appropriate treatment consideration for patients who have not obtained adequate relief with symptomatic therapy or who prefer this therapy as a primary management option, require prolonged weeks of treatment during the year, and/or wish to start treatment for the benefit of the potential secondary disease-modifying effects of SCIT.

XI.D.5.b | *Rush subcutaneous immunotherapy for allergic rhinitis*

Rush SCIT rapidly reaches the target therapeutic dose by administering incremental allergen doses over a much shorter period compared to conventional SCIT. Rush SCIT has successfully been implemented for venom immunotherapy.[2604] Evaluating rush SCIT for aeroallergen immunotherapy is difficult due to study heterogeneity with escalation protocols, target doses, premedication regimens, and extracts utilized. Furthermore, there remains a lack of standardization of what constitutes rush SCIT versus other immunotherapy protocols.

The main benefit of rush SCIT is the expedited build-up phase, decreasing the time to reach maintenance dosing and office visits required. Patient convenience is improved, but evidence has not yet determined if the expedited process leads to more rapid clinical improvement. Potential disadvantages include increased risk of systemic reactions, higher staff/resource utilization, and decreased long-term compliance with one study at a military medical center citing a decrease from 80% (conventional schedule) to 48% (rush schedule).[2605]

Efficacy and safety. Aeroallergen rush SCIT has demonstrated effectiveness for AR and asthma.[2604] The majority of double-blind RCTs utilized single-allergen extracts, primarily grass pollen.[2584,2592,2600,2606] Other allergens investigated include ragweed, various tree pollens, *Alternaria*, cat, dog, and HDM.[2087,2594,2597,2607–2611] These studies report significant benefit over placebo in clinical outcomes (most commonly reported with combined symptom-medication scores), SPT, and provocation challenges (Table XI.D.5.b).

Safety remains a limiting factor for aeroallergen rush SCIT due to a greater risk of systemic reactions, which range 15%–100% of patients without premedication for standardized extracts, depot preparations, and allergoids.[2604] This improves to 12%–38% when using routine premedication.[2612] Depigmented-polymerized extracts have a significantly better safety profile with systemic reactions occurring in less than 2% of patients.[2584,2606,2608,2613] Local reactions do not appear to predict systemic reactions and delayed systemic reactions are reported rarely with rush SCIT.[2608] Only one double-blind RCT specifically evaluated safety and efficacy of rush versus conventional SCIT.[2609] In this small Der p 1 trial ($n = 18$), the efficacy was similar, but the rush SCIT group had significantly higher side effect scores without any severe systemic reactions. One retrospective observational study found an increase in systemic reactions on subsequent doses following initial rush SCIT, although additional studies are needed due to the variability in rush SCIT protocols.[2614]

Rush, ultra-rush, and modified rush. Rush SCIT has traditionally been defined as achieving target therapeutic dose within 1–3 days[1,2419]; however, lack of universal standardization has led to variations of rush SCIT schedules. Modified rush designates accelerated SCIT protocols that reach a target dose within 3 days, then follow a more conventional build-up to reach maintenance. Ultra-rush

TABLE XI.D.5.b Evidence table – rush subcutaneous immunotherapy for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Pfaar et al.[2606]	2013	2	DBRCT	Rush SCIT: Pre-seasonal depigmented-polymerized birch and grass pollen extract Placebo	Combined symptom and medication score	Significantly improved combined scores in peak season at year 2 versus placebo Higher rates of mild SRs in therapy arm but none required specific treatment
Pfaar et al.[2584]	2012	2	DBRCT	Rush SCIT: Pre-seasonal depigmented polymerized grass pollen Placebo	Combined symptom and medication score	Significantly improved combined scores in peak season at year 2 versus placebo Higher rates of mild SRs in treatment arm but no grade 3 or 4 reactions
Klunker et al.[2607]	2007	2	DBRCT	Rush SCIT: Ragweed SCIT + anti-IgE mAb Placebo SCIT + anti-IgE mAb Ragweed SCIT + placebo anti-IgE mAb Placebo SCIT + placebo anti-IgE mAb	Ragweed hypersensitivity via IgE-facilitated allergen binding assay sIgG4	Combination therapy enhanced the inhibition of sIgE binding for 42 weeks after discontinuation
Casale et al.[2087]	2006	2	DBRCT	Rush SCIT: Ragweed SCIT + anti-IgE mAb Placebo SCIT + anti-IgE mAb Ragweed SCIT + placebo anti-IgE mAb Placebo SCIT + placebo anti-IgE mAb	Daily allergy symptom scores Adverse events	Pretreatment with omalizumab resulted in a five-fold decrease in risk of rush SCIT associated anaphylaxis Combination therapy associated with significant reduction in symptom severity versus AIT alone
Cox[2604]	2006	2	Systematic review	AR, asthma, Hymenoptera, imported fire ant Adults and children RCTs, observational cohorts, case series	Combined symptom-medication score SR rate Cutaneous testing Provocation challenges sIgE and sIgG	SR rate significantly higher for rush SCIT (27%–100%) Baseline FEV_1 <80% and high skin test reactivity are predictive of SR Premedication reduced risk of SRs with rush SCIT
Akmanlar et al.[2609]	2000	2	RCT	Der p 1 rush SCIT Der p 1 conventional SCIT	Combined symptom and medication score Lung function Side effect score Cutaneous testing Bronchial provocation sIgE and sIgG4	Similar efficacy between rush and conventional SCIT Significantly higher side effect score was seen in the rush SCIT group Three had mild SRs No severe reactions

(Continues)

TABLE XI.D.5.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dolz et al.[2592]	1996	2	DBRCT	Grass pollen rush SCIT Placebo	End-point cutaneous testing Conjunctival and bronchial provocation Adverse reactions Symptom scores	Significant improvement in all clinical outcomes for treatment group but 7/15 (46.7%) had mild to moderate SRs during build-up requiring epinephrine
Portnoy et al.[2615]	1994	2	DBRCT	Combination H_1 and H_2 antihistamines and prednisone capsule premedication for rush SCIT Lactose capsule (placebo) for rush SCIT	SR rate and severity	Significant decline in SRs in premedication group from 73% to 27%
Bousquet et al.[2594]	1991	2	DBRCT	Placebo-grass pollen rush SCIT Placebo-multiple pollens rush SCIT Grass pollen rush SCIT Multiple pollens rush SCIT	Combined symptom-medication scores Nasal provocation challenge	Only monosensitized patients receiving grass pollen extract showed significant improvement over placebo Polysensitized patients had a nonsignificant improvement
Horst et al.[2597]	1990	2	DBRCT	*Alternaria* rush SCIT Placebo	Symptom-medication scores Nasal provocation challenge Skin end-point titration *Alternaria* sIgE and sIgG	Rush SCIT with *Alternaria* showed a significant benefit in all clinical outcome measures 15.4% of patients developed SRs in the treatment group versus 0 in the placebo arm
Lilja et al.[2610]	1989	2	DBRCT	Animal-dander rush SCIT Placebo (transferred to active arm after 1 year)	Skin prick test Allergen and histamine bronchial challenges	Improvement in skin prick test and bronchial challenges for treatment group at 1 and 2 year follow-up periods
Bousquet et al.[2600]	1987	2	DBRCT	Six-mixed grass pollen allergoid prepared by mild formalinization rush SCIT Standard orchard grass pollen extract rush SCIT Placebo	Symptom scores Skin test titration sIgE and sIgG	Rush SCIT with both formalinized allergoid and standardized allergen extract showed significant improvement versus placebo Nearly 2-fold increase in SRs for patients treated with allergoid

(Continues)

TABLE XI.D.5.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Morais-Almeida et al.[2608]	2016	3	Observational cohort	Children with AR	Local and systemic reaction rate	Depigmented-polymerized extracts are safe in children utilizing an ultra-rush protocol without premedication Two cases of mild SRs out of 100 patients
Casanovas et al.[2613]	2006	3	Observational cohort	Rhinoconjunctivitis and/or asthma patients sensitized to HDM and/or pollen	Local and systemic reaction rate	Depigmented and polymerized allergen extracts can be safely administered via an ultra-rush schedule, reaching the maximum dose within two injections on day 1 without the need for premedication
Hejjaoui et al.[2616]	1990	3	Non-randomized, controlled cohort	Rush SCIT without preventive measures Rush SCIT + premedication Rush SCIT + premedication + preventive measures Rush SCIT step protocol + premedication + preventive measures	SR rate and severity	Premedication with methylprednisolone, ketotifen and theophylline decreased SRs by 55% for HDM rush SCIT Further improvements occurred with dose adjustments for large local reactions
Bousquet et al.[2611]	1989	3	Observational cohort	HDM-allergic patients with asthma Adults and children	SR rate and severity	38% SRs in cohort with eight cases of anaphylactic shock
Cook et al.[2614]	2017	4	Case series	Rush SCIT	SR rate	Increased rate of SRs on subsequent doses after initial rush SCIT
Winslow et al.[2612]	2016	4	Case series	AR and asthma Adults and children	SR rate and severity	Per-patient incidence of SRs was four-fold higher in rush SCIT patients compared to conventional and cluster protocols despite premedication use
Cox et al.[2419]	2011	4[a]	Evidence-based search	AIT RCTs, observational cohorts, case series	Not applicable	Rush schedules can achieve maintenance dose more quickly than conventional SCIT Rush schedules with inhalant allergens associated with increased risk of systemic reactions

(Continues)

TABLE XI.D.5.b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
More et al.[2605]	2002	4	Case series	Adults with AR	Compliance rate	Patients receiving conventional SCIT were more compliant than those on rush SCIT, 80.0% versus 48.4%, respectively

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; FEV_1, forced expiratory volume in 1 second; HDM, house dust mite; IgE, immunoglobulin E; IgG, immunoglobulin G; LOE, level of evidence; mAb, monoclonal antibody; s, allergen-specific; SCIT, subcutaneous immunotherapy; SR, systemic reaction; RCT, randomized controlled trial.

[a]Upgraded from LOE 5 due to established methodology, several rounds of review, long history of evidence-based guideline development.

classifies those that attain maintenance dose within several hours.

Due to the increased risk of systemic reactions with ultra-rush, traditional extracts have not generally been used. Depigmented-polymerized extracts, which are approved and commercially available in several regions of Europe, have been utilized via an ultra-rush protocol with good efficacy in adults and children.[2584,2606,2608,2613] Local reactions occurred in 21%–70.4% of patients, while systemic reactions ranged 2%–12.7%; all considered non-severe (no grade 3 or 4 reactions).

Pre-medication for rush SCIT. Limited studies specifically evaluated the effects of premedication on aeroallergen rush SCIT.[2615,2616] Premedication regimens varied, including H_1 and H_2 histamine antagonists, systemic steroids, theophylline, and anti-IgE monoclonal antibodies.

In one double-blind, placebo-controlled study of 22 children undergoing multiallergen rush SCIT over 1.5 days, a significant reduction in systemic reactions was observed in those receiving pretreatment with astemizole, ranitidine, and prednisone versus placebo (27% vs. 73%, respectively).[2615] A larger non-randomized study involving children and adults undergoing rush SCIT to *Dermatophagoides pteronyssinus* evaluated the effects of premedication (methylprednisolone, ketotifen, and theophylline) and preventive measures (modifying dosing schedule after local reactions of >10 cm) on systemic reaction rates.[2616] The systemic reaction rate declined from 36% of patients with rush SCIT alone to 16% of patients that received premedication. This further declined to 7.3% when preventive measures were added to the premedication regimen.

Omalizumab has also been investigated as part of a 9-week pretreatment regimen for ragweed rush SCIT.[2087,2607] A five-fold reduction in anaphylaxis was reported for the omalizumab-premedicated group compared to the placebo-premedicated group. Combination omalizumab and rush SCIT also led to lower symptom severity scores compared to either intervention alone.

In summary, rush SCIT has increasing availability globally with moderate evidence demonstrating improvement in clinical/immunologic outcomes versus placebo. The lack of SRMAs is notable and a key research need. There is also insufficient data directly comparing rush to conventional SCIT. Systemic reactions are a limiting factor but can be mitigated with premedication, use of depigmented-polymerized extracts, and careful patient selection. Due to the heterogeneity of rush SCIT protocols, extract types, and premedication regimens, studying rush SCIT remains challenging.

Rush subcutaneous immunotherapy

Aggregate grade of evidence: B (Level 2: 12 studies, level 3: 4 studies, level 4: 4 studies; Table XI.D.5.b)
Benefit: Accelerates the time to reach therapeutic dosing which may improve compliance, lead to earlier clinical benefit, and be more convenient for the patient. Improvement of symptoms and decreased need for rescue medication.
Harm: Higher rates of local and systemic reactions with rush SCIT protocols compared to conventional and cluster SCIT. Inconvenience of visits to a medical facility to receive injections.
Cost: Direct costs may be similar or slightly less compared to conventional SCIT, which includes cost of extract preparation and injection visits. Indirect costs are improved due to the reduced number of appointment visits, which reduces work and school absenteeism.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Careful patient selection and shared decision making would reduce risks. Heterogeneity of protocols, extract types, and dosing across studies makes quantification of risk difficult.

Policy level: Option.
Intervention: Aeroallergen rush SCIT is an option for AR in appropriately selected patients that do not have adequate control of their symptoms with symptomatic therapies. If available at practice location, the use of depigmented-polymerized allergen extracts for rush SCIT has a better safety profile compared with standard extracts.

XI.D.5.c | *Cluster subcutaneous immunotherapy for allergic rhinitis*

Cluster SCIT is a method to shorten the build-up phase for SCIT. Cluster schedules entail two or more injections during each visit on non-consecutive days. Typically, target maintenance dosing can be reached in 4–8 weeks. This improves convenience for patients and may lead to more rapid symptom improvement, without a significant rise in systemic reactions when premedication is used.[2617–2619]

Efficacy and safety. Like rush SCIT, cluster SCIT is difficult to study due to the heterogenicity of study protocols, extract types, target maintenance dosing, and premedication regimens. One SRMA evaluated the cluster SCIT efficacy for single allergen extracts and included eight RCTs comparing cluster SCIT to conventional SCIT or placebo.[2617] While no differences were found between cluster SCIT and placebo for symptom and medication scores, the high level of heterogenicity between the studies creates difficulty with interpretation. Several individual RCTs showed benefit in symptom, medication, and QOL benefit, consistent with other forms of SCIT.[2620,2621] Two additional RCTs not included in the meta-analysis show improvement in symptom/medication scores for cluster SCIT over placebo using depot or polymerized pollen extracts.[2555,2571] Compared to conventional SCIT, cluster SCIT demonstrates similar efficacy for multiple extracts including pollens and HDM.[2566,2617,2622–2624] Cluster and rush SCIT have not been directly compared in RCTs (Table XI.D.5.c).

Two meta-analyses of RCTs and observational studies have assessed cluster SCIT safety.[2617,2618] When evaluating for local and systemic adverse reactions by number of patients, no difference was found with cluster versus conventional SCIT. The meta-analysis by Jiang et al.[2618] showed a lower rate of grade 1 systemic and local adverse reactions if analysis is done per injection. Additional studies are needed to further explore these findings, as non-randomized studies may favor inclusion of less vulnerable patient populations in the cluster cohort. High heterogeneity was noted which limits study conclusions.

A more recent RCT from China and large retrospective study of a multiple-physician practice in the US with over 2.5 million injections given during the study period showed no difference in systemic reactions between cluster and conventional SCIT on a per-patient basis, but the retrospective trial did show a slightly increased risk on a per-injection basis.[2612,2623] Minimal data is available on delayed reactions with cluster SCIT and no conclusions can be drawn.[2618,2625]

Factors that affect systemic reactions with cluster SCIT. Only one RCT specifically assessed the use of premedication in cluster SCIT with standardized pollen extracts.[2626] Use of loratadine prior to cluster dosing showed a decline in systemic reactions from 79% of patients to 33% for the study duration.[2626] While no life-threatening systemic reactions occurred, there was a reduction in severity of systemic reactions with premedication. Other RCTs and observational studies had high variability in premedication regimens (e.g., oral antihistamines, oral systemic steroids, and leukotriene modifying agents) and most do not provide relevant information. Timing of the premedication has not been directly studied.[2604]

Other factors may affect the frequency and severity of systemic reactions during cluster SCIT including dosing frequency, extract formulation (standardized, depot, polymerized), number of injections administered during a cluster session, and number of clusters given to reach maintenance.[2604] Currently there is insufficient data to draw any conclusions, but this should be an area of emphasis for future research.

In summary, cluster SCIT has a similar safety profile as conventional SCIT and fewer systemic reactions than rush SCIT.[2612,2618,2622] Importantly, the safety of cluster SCIT is comparable to standard regimens overall because the number of injections required for buildup can be less, not because the per injection risk is necessarily lower. Additionally, premedication use appears to be necessary to reach this comparable safety profile for cluster SCIT. Some practices may translate this as the need to observe patients during cluster sessions more closely and for longer periods. Efficacy remains difficult to investigate due to the significant study heterogeneity but does appear to be similar to conventional SCIT, which is strongly recommended to manage refractory AR. Standardization of cluster protocols through additional large-scale RCTs should be a key area of research as there remain many understudied topics including dosing frequency, number of injections per visit, and the optimal duration of the build-up phase.

TABLE XI.D.5.c Evidence table – cluster subcutaneous immunotherapy for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jiang et al.[2618]	2019	1	SRMA	Relationship of cluster SCIT and adverse reactions	Not applicable	Rates of local and systemic reactions are similar or slightly better for cluster versus conventional SCIT
Yu et al.[2622]	2021	2	RCT	Children and adults Mixed allergen conventional SCIT Mixed allergen cluster SCIT	Symptom scores SPT Adverse reactions	Conventional and cluster SCIT have similar efficacies and no significant difference in SRs
Fan et al.[2619]	2017	2	RCT	HDM cluster SCIT HDM conventional SCIT	Nasal mucosa scores Local reactions SRs	Cluster SCIT group had improvement of symptoms at 6 weeks versus conventional SCIT No conclusive difference in SR rate
Feng et al.[2617]	2014	2[a]	SRMA	Efficacy and safety of cluster SCIT versus conventional SCIT or placebo	Not applicable	Similar efficacy and safety of cluster SCIT versus conventional SCIT Improved QOL for cluster SCIT versus placebo Nonsignificant trend for improved symptom and medication scores
Klimek et al.[2555]	2014	2	DBRCT	Cluster SCIT with grass/rye polymerized antigen Placebo	Combined symptom and medication score Rescue medication use Total rhinoconjunctivitis symptom score	Improvement in symptoms and medication usage versus placebo
Wang et al.[2624]	2011	2	RCT	HDM cluster SCIT HDM conventional SCIT	Symptom and medication scores Local reactions SRs HDM-specific IgE and IgG4	Cluster group achieved clinical efficacy with improved symptom and medication scores earlier than conventional SCIT group with similar safety profiles
Zhang et al.[2623]	2009	2	RCT	HDM cluster SCIT HDM conventional SCIT	QOL Cutaneous reactivity sIgE to Der p	Time to maintenance decreased by 57% with cluster SCIT, more rapid improvement of clinical symptoms and medication use Adverse reactions were similar in the two groups
Subiza et al.[2621]	2008	2	RCT	Grass mix cluster SCIT Placebo	Nasal provocation test	Significant increase in threshold concentration for positive provocation

(Continues)

TABLE XI.D.5.c (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Cox[2604]	2006	2[b]	Systematic review	Adults and children AR, asthma, Hymenoptera, imported fire ant RCTs, observation cohorts, case series	Combined symptom-medication score SR rate Cutaneous testing Provocation challenges sIgE and sIgG	Similar risk of SRs for cluster SCIT versus conventional SCIT
Tabar et al.[2566]	2005	2	DBRCT	Der p cluster SCIT Der p conventional SCIT	Adverse reactions Symptom-medication scores Peak flow SPT sIgE	Reduction in time to maintenance dose by 47% using cluster SCIT Similar efficacy and SR rate in both groups
Nanda et al.[2620]	2004	2	DBRCT	Cat hair and dander: Cluster SCIT 0.6 μg Fel d 1 Cluster SCIT 3 μg Fel d 1 Cluster SCIT 15 μg Fel d 1 Placebo	Skin prick test Titrated nasal challenge sIgE and sIgG4 Intranasal cytokines (TGF-β, IL-10, IFN-γ, IL-4, and IL-5)	Significant and dose-dependent differences were seen with total symptom scores on nasal challenge and SPT with cat extract
Bodtger et al.[2571]	2002	2	DBRCT	Depot birch extract: Cluster SCIT Placebo	Symptom score Medication score Conjunctival sensitivity SPT SRs	Treatment group showed improvement in all categories versus placebo, with similar rates of adverse events
Nielsen et al[2626]	1996	2	DBRCT	Birch or grass cluster SCIT + loratadine Birch or grass cluster SCIT + placebo	Rate of SRs	Pretreatment with loratadine decreased frequency and severity of SRs
Cook et al.[2625]	2017	4	Case series	Timing of SRs to aeroallergen immunotherapy	Rate of SRs	52.8% of SRs occurred after at least 30 min from the injection time
Winslow et al.[2612]	2016	4	Case series	AR and asthma Adults and children	SR rate and severity	Per-patient incidence of SRs was four-fold higher in rush SCIT patients compared to conventional and cluster SCIT protocols, despite premedication use

Abbreviations: AR, allergic rhinitis; DBRCT, double-blind randomized controlled trial; HDM, house dust mite; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial; s, allergen-specific; SCIT, subcutaneous immunotherapy; SPT, skin prick test; SR, systemic reaction; SRMA, systematic review and meta-analysis; TGF, transforming growth factor.

[a]LOE downgraded due to heterogenicity of included studies included.

[b]LOE downgraded due to inconsistency of results.

Cluster subcutaneous immunotherapy

Aggregate grade of evidence: B (Level 1: 1 study, level 2: 12 studies, level 4: 2 studies; Table XI.D.5.c)
Benefit: Accelerates the time to reach therapeutic dosing which may improve compliance, lead to earlier clinical benefit, and be more convenient for the patient. Improvement of symptoms and decreased need for rescue medication. Similar safety profile compared to conventional SCIT.
Harm: Minimal harm with occasional, but mild, local adverse events, and rare systemic adverse events when premedication is used. Inconvenience of visits to a medical facility to receive injections.
Cost: Direct costs may be similar, slightly more, or slightly less compared to conventional SCIT, depending on how the practicing provider bills for the services. This includes cost of extract preparation, injection visits, and possibly rapid desensitization codes. Indirect costs are lower due to the reduced number of appointment visits, which reduces work and school absenteeism.
Benefits-harm assessment: Preponderance of benefit over harm for patients that cannot achieve adequate relief with symptomatic management. Balance of benefit and harm compared to conventional SCIT but in slight favor of cluster SCIT due to convenience.
Value judgments: Careful patient selection and shared decision making would reduce risks. Heterogeneity of protocols, extract types, and dosing across studies makes risk quantification difficult.
Policy level: Option.
Intervention: Cluster SCIT can be safely implemented in clinical practice and offered to those patients eligible for SCIT that may prefer this protocol compared to conventional build-up protocols due to convenience. Premedication should be strongly considered.

XI.D.6 | Sublingual immunotherapy for allergic rhinitis

XI.D.6.a | *Sublingual immunotherapy for allergic rhinitis – general efficacy*

While SCIT was first practiced over a century ago by Noon et al.,[2457,2627] the first double-blind placebo-controlled trial of SLIT dates from 1986 by Scadding and Brostoff.[2628] Over the next two decades several small trials were conducted. From 2006 onward, the "big trials" finally demonstrated the clinical efficacy and safety of SLIT.[2629,2630] Since then, a wealth of high-quality SLIT trials have been conducted.[2631]

In ICAR-Allergic Rhinitis 2018,[1] the joint outcomes of the best quality trials gathered in over two dozen SRMAs on SLIT were presented. Since then, further trials have been conducted taking better care to define the exact dosing, focus on specific allergens, and separate the two different sublingual administration routes: aqueous or tablets. In this section, evidence for SLIT efficacy in general is reviewed, and subsections on aqueous and tablet SLIT follow. SRMAs were primarily analyzed. Several RCTs that have been published since ICAR-Allergic Rhinitis 2018 were added as well. For the interpretation of the SMD of meta-analyses, an effect size 0.3-0.5 indicates a mild effect, 0.5-0.8 indicates a moderate effect, and above 0.8 indicates a large effect the intervention on the disease.[2632]

Table XI.D.6.a.-1 shows the cumulative recent evidence from SRMAs, primarily over the past 5 years. Additional notable studies prior to ICAR-Allergic Rhinitis 2018 are also listed. Combined evidence previously published in ICAR-Allergic Rhinitis 2018 is presented in Table XI.D.6.a.-2 for an Aggregate Grade of Evidence of SLIT efficacy in general.

Efficacy in adults. The majority of the SRMAs show mild-to-moderate symptom and medication reduction in patients on SLIT compared to placebo. Symptom score improvements have also been demonstrated to be higher with longer treatment duration (greater than 12 months treatment, SMD = 0.70).[2421] All subjects, both those in the SLIT and in the placebo arms, had open access to rescue medication. As such, symptom reduction with SLIT comes on top of the symptom improvement obtained with rescue medication. SLIT efficacy in adults is judged to be grade A, with mild-to-moderate impact.

Efficacy in children. Studies on SLIT efficacy in children were previously limited by the heterogeneity of trials and the considerable risk of bias.[2633] In addition to the ICAR-Allergic Rhinitis 2018 evidence demonstrating moderate efficacy for symptom relief in pollen and HDM liquid SLIT[2634] and grass pollen tablet SLIT,[2635] there is additional evidence for a moderate reduction in symptoms and medication scores in pediatric perennial AR.[2636,2637] SLIT efficacy in children is judged to be grade A, with moderate impact.

Efficacy of SLIT over pharmacotherapy. For perennial AR, HDM SLIT tablets are more effective than antihistamines, LTRAs, and INCS. For seasonal AR, grass pollen and ragweed tablet SLIT are almost as effective as INCS and more effective than the other pharmacotherapies.[1986] An additional study showed that the 5-grass tablet had the highest relative clinical impact on symptom score over all

TABLE XI.D.6.a.-1 Evidence table – recent high-level studies of sublingual immunotherapy for allergic rhinitis (aqueous and tablet formulations)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Aqueous and tablet SLIT reported together						
Kim et al.[2661]	2021	1	SR	SLIT aqueous and tablet HDM for mono- or poly-sensitized AR 9 RCTs	Primary: symptoms Secondary: QOL, medication scores	Effective in mono- and poly-sensitized subjects No significant difference in efficacy of single allergen SLIT for mono- versus poly-sensitized AR
Chen et al.[2636]	2020	1	SRMA	SLIT for HDM tablet versus placebo in children with perennial AR 16 RCTs	Symptoms Medication use Adverse events	Improved symptom ($p = 0.0001$) and medication ($p < 0.00001$) scores More frequent adverse events (1.08–1.68 times more)
Dhami et al.[2438]	2017	1	SRMA	AIT for AR and ARC Antigens versus placebo or other comparator 61 SCIT trials, 71 SLIT (aqueous and tablet) trials	Primary: symptoms, medication use Secondary: cost-effectiveness, safety	Improved symptom scores: SMD −0.48 [−0.61, −0.36] Improved medication scores: SMD −0.31 [−0.44, −0.18] Risk for bias present (For aqueous and tablet separately, see below)
Feng et al.[2637]	2017	1	MA of 26 RCTs	Pediatric AR SCIT and SLIT, all allergens Tablets included 26 RCTs	Symptoms Medication use Adverse events	Improved symptom scores: SMD −0.55 [−0.86, −0.25] Improved medication scores: SMD −0.67 [−0.96, −0.38] No significant difference between pre-co-seasonal and continuous SLIT for seasonal AR Similar adverse events in SLIT and placebo (1167 versus 1025), oral pruritis most common
Kristiansen et al.[2426]	2017	1	SRMA	SLIT, SCIT, oral AIT Numerous antigens versus placebo 17 RCTs, 15 controlled before-after for prevention of allergy	Development of asthma Development of new sensitizations	No significant reduction for AIT to prevent new sensitizations Long-term (≥2 years): inconclusive evidence for the prevention outcomes Short-term (<2 years post-treatment) prevention: SLIT reduces the risk of those with AR developing asthma (RR 0.40; 95% CI 0.30–0.54)
Boldovjáková et al.[2662]	2021	2	SRMA	AR in adults Grass pollen SLIT versus placebo 6 RCTs	Symptoms QOL Adverse events	SLIT improved symptoms ($p < 0.05$) in 5/6 studies and QOL ($p < 0.05$) in 4/6 studies SLIT demonstrated safety High risk of bias in 50% of studies

(Continues)

TABLE XI.D.6.a.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ji et al.[2644]	2019	2	SRMA	SCIT versus SLIT for AR 20 RCTs	Symptoms VAS Adverse events	Nasal symptoms, VAS, compliance: no significant difference between SCIT and SLIT Adverse reactions lower with SLIT (RR 1.79; 95% CI 1.42–2.26, $p < 0.05$)
Blanco et al.[2663]	2018	2	SR	Pediatric and adult DBRCT SLIT for respiratory allergy 112 RCTs	Symptoms Medication use	SLIT effective for HDM and grass pollen Disease modifying effect lasts 2 years after 3-year course Preventive effect reducing asthma incidence in AR patients No major safety concerns
Aqueous and tablet SLIT reported separately						
Kim et al.[2550]	2021	1	SRMA, network MA	HDM AIT for AR	Symptoms Medication use	HDM SCIT and SLIT Aqueous: symptoms SMD −0.461 (95% CI −0.795, −0.127) Tablet: symptoms −0.329 (95% CI −0.426, −0.231) In network MA SCIT more effective than aqueous SLIT and tablets
Dhami et al.[2438]	2017	1	SRMA	AIT for AR and ARC Antigens versus placebo or other comparator 61 SCIT trials, 71 SLIT (aqueous and tablet) trials	Primary: symptoms, medication use Secondary: cost-effectiveness, safety	Symptoms: Aqueous: SMD −0.42 (95% CI −0.68, −0.15) Tablets: SMD −0.53 (95% CI −0.73, −0.34) Medication: Aqueous: SMD −0.42 (95% CI −0.68, −0.15) Tablets: SMD −0.53 (95% CI −0.73, −0.34) SLIT is likely to be cost-effective
Nelson et al.[2639]	2015	1	Network meta-analysis of RCTs	Grass pollen allergy: SLIT tablets versus placebo SLIT aqueous versus placebo SCIT versus placebo	ARC symptoms and medication use	Symptom and medication scores with SCIT, SLIT aqueous, and tablets all reduced versus placebo, except for symptom score with SLIT aqueous
Di Bona et al.[2638]	2012	1	MA-based comparison	Grass pollen seasonal AR: SCIT versus placebo SLIT versus placebo	Symptoms Medication use	Indirect modest evidence that SCIT is more effective for seasonal AR than SLIT (aqueous) and SLIT (tablet) for symptom and medication score reduction

(Continues)

TABLE XI.D.6.a.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Radulovic et al.[2664]	2011	1	SR of RCTs	SLIT for AR	Symptoms Medication use	Symptoms: Aqueous: SMD −0.35 (95% CI −0.42, −0.28) Tablets: SMD −0.48 (95% CI −0.58, −0.38) Medication: Aqueous: SMD −0.01 (CI −0.05, 0.4) Tablets: SMD −0.33 (95% CI −0.46, −0.2) SLIT appears safe for AR
Di Bona et al.[2665]	2010	1	MA of RCTs	Grass pollen: SLIT versus placebo	Symptoms Medication use	Symptoms: Aqueous: median SMD −0.11 Tablets: median SMD −0.43 Medication: Aqueous: median SMD −0.28 Tablets: median SMD −0.30
Aqueous alone						
Lin et al.[2666]	2013	1	SR of RCTs	Aqueous SLIT for ARC and asthma	Symptoms Medication use	Moderate evidence of aqueous SLIT improving rhinitis symptom score and medication usage
Ortiz et al.[2667]	2018	2	RCT	Single or multiple allergen aqueous SLIT for polysensitized AR	Symptoms Medication use	Significant improvement in symptom scores for all treatment group No significant difference between treatment groups
Li et al.[2668]	2014	2	RCT	SLIT for mono- or poly-sensitized HDM AR	Symptoms Medication use	Significant benefit of SLIT over placebo in mono- and poly-sensitized HDM AR without significant difference in symptom or medication scores
Kim et al.[2634]	2013	2	SR of RCTs	SCIT and SLIT in the treatment of pediatric asthma and ARC	Symptoms Medication use	Moderate-strength evidence that aqueous SLIT improves rhinitis symptoms and decreases medication usage
Amar et al.[2669]	2009	2	RCT	Single- or multiple-allergen SLIT for Timothy grass pollen AR	Symptoms Medication use Inflammatory markers	No significant difference in medication or symptom scores in either treatment group versus placebo Significant improvement in inflammatory markers in monotherapy group
Moreno-Ancillo et al.[2670]	2007	2	RCT	Single- or multiple-allergen SLIT for polysensitized AR and asthma	Symptoms Medication use PFTs Inflammatory markers	Improvement in clinical symptoms and inflammation significantly greater in multi- versus single-allergen group

(Continues)

TABLE XI.D.6.a.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lee et al.[2671]	2011	4	Case series	SLIT for mono- or poly-sensitized HDM AR	Symptoms Medication use	Significant benefit of SLIT over placebo in mono- and poly-sensitized HDM AR without significant difference in symptom or medication scores
Tablet alone						
Meltzer et al.[1982]	2021	1	SRMA of DBRCT	Seasonal or perennial AR in adults and adolescents: INCS INCS + INAH Oral AH LTRA Tablet-SLIT Placebo	TNSS Random effect MA versus placebo	Seasonal AR: TNSS reduction (95% CI; *T* = number of trials) INCS 1.38 (1.18–1.58; T39) INCS-INAH 1.34 (1.15–1.54; T4) INAH 0.72 (0.56–0.89; T13) Oral AH 0.62 (0.35–0.90; T18) SLIT tablets 0.57 (0.41–0.73; T4) LTRA 0.48 (0.36–0.60; T10) Perennial AR: TNSS reduction (95% CI; *T* = number of trials) INCS 0.82 (0.66–0.97; T14) SLIT tablet 0.65 (0.42–0.88; T3) Oral AH 0.27 (0.11–0.42; T3)
Chen et al.[2636]	2020	1	SRMA	SLIT for HDM Children with perennial AR 16 RCTs 2 tablets	TNSS TMS Adverse events	Subgroup analyses showed only tablet studies improved ocular symptoms (See aqueous and tablet SLIT reported together)
Li et al.[2672]	2018	1	SRMA	SLIT in adults with AR 7 RCTs, 5 evaluated in MA	Symptoms QOL IgE levels	SLIT tablets decrease rhinitis symptoms IgE levels unchanged
Di Bona et al.[2646]	2015	1	MA of RCTs	Seasonal AR: Grass pollen SLIT tablets versus placebo	Symptoms Medication use	Small improvement in symptom and medication scores versus placebo: SMD −0.28 (−0.37, −0.19; $p < 0.001$) and SMD −0.24 (−0.31, −0.17; $p < 0.001$) 7/2259 SLIT patients were given epinephrine for adverse events
Devillier et al.[1995]	2014	1	MA of RCTs	Pollen SLIT versus pharmacotherapy versus placebo for seasonal AR	Relative clinical impact	Clinical impact: 5-grass tablet > INCS > Timothy grass tablet > montelukast > antihistamines
Nelson[2532]	2018	2[a]	SR of 15 DBRCTs	HDM SCIT (3 trials) SLIT tablets (12 trials)	Symptoms Medication use	Effectiveness of SCIT and SLIT tablets established

(Continues)

TABLE XI.D.6.a.-1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Durham et al.[1986]	2016	2	Pooled analysis from RCTs	Seasonal AR: grass or ragweed SLIT tablet versus pharmacotherapy[b] Perennial AR: HDM SLIT tablet versus pharmacotherapy[b]	TNSS versus placebo	Seasonal AR: SLIT numerically greater than montelukast and AH; almost equal to MFNS Perennial AR: SLIT effect numerically greater than all pharmacotherapy
Maloney et al.[2651]	2015	2	Pooled analysis from RCTs	Grass SLIT tablet versus placebo Grass SLIT in AR patients with (24%) and without (76%) mild asthma	TEAEs Local and systemic allergic reactions Asthma related TRAEs	Severe asthma-related TRAE in 6/120 SLIT and 2/60 placebo No difference in TRAE in SLIT-treated with or without asthma Adults and children were included
Dranitsaris and Ellis[2640]	2014	2	SR of RCTs	Grass pollen for seasonal AR: Tablet (Timothy only) Tablet (5-grass) SCIT Placebo Indirect comparison	Efficacy Safety Cost for Canadian setting	Symptoms: All AIT treatments < placebo Costs for 5-grass tablet < costs Timothy grass tablet and SCIT

Abbreviations: AH, antihistamine; AIT, allergen immunotherapy; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; CI, confidence interval; DBRCT, double-blind randomized controlled trial; HDM, house dust mite; IAH, intranasal antihistamine; IgE, immunoglobulin E; INCS, intranasal corticosteroid; LOE, level of evidence; LTRA, leukotriene receptor antagonist; MA, meta-analysis; MFNS, mometasone furoate nasal spray; PFT, pulmonary function test; QOL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMD, standardized mean difference; SR, systematic review; SRMA, systematic review and meta-analysis; TEAS, treatment emergent adverse events; TMS, Total Medication Score; TNSS, Total Nasal Symptom Score; TRAE, treatment related adverse event; VAS, visual analog scale.

[a]LOE downgraded due to no meta-analysis, not limited to SLIT or AR alone.

[b]Antihistamines, montelukast, mometasone furoate nasal spray.

other pharmacotherapy treatments.[1995] SLIT efficacy over pharmacotherapy is judged to be grade B.

Efficacy of SLIT compared to SCIT. Several investigators have tried to compare the efficacy of SLIT against that of SCIT.[2638–2643] Most meta-analyses show superiority of SCIT over SLIT, but they are of low grade evidence as they are based on indirect comparisons.[2644] There are very few direct head-to-head randomized trials comparing both treatments. One recent head-to-head study was powered for the comparison against the placebo-group, but not for SCIT versus SLIT.[1671] In children, SCIT seems more effective than SLIT, but the quality of evidence is low.[2634] SLIT efficacy compared to SCIT is judged to be grade B, with low grade evidence of SCIT superiority.

Short-term preventative effects of SLIT. There is moderate grade evidence for a high impact of SLIT in patients with AR to prevent them from developing asthma, during three years of treatment and within the first 2 years off-treatment.[2426] However, there is no evidence for primary prevention with SLIT, nor for long-term secondary preventive effects. For the development of new sensitizations, there are a few systematic reviews. The most comprehensive meta-analysis showed only a tendency for SLIT, and the effect did not withstand the sensitivity analysis,[2426] while another systematic review found only low-grade evidence.[2645] Evidence for short-term preventative effects of SLIT is judged to be grade B.

SLIT safety. Rare systemic and serious adverse events have been reported with SLIT. In general, meta-analyses, including the most recent in 2019,[2644] found SLIT to be safer than SCIT. In the complete dataset of systemic reviews, there were seven reports of the use of epinephrine in the SLIT group.[2646] There was no administration of epinephrine in trials outside of the US. There were several reports of symptoms suggestive of anaphylaxis with the first grass pollen tablet[2647,2648] and three with the first HDM tablet; this supports the recommendation in the package insert for administration under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and observation in the office for at least 30 min following the initial dose.[2649] Starting SLIT in-season seemed to be safe. Although

TABLE XI.D.6.a.-2 Established aggregate grade of evidence from ICAR-Allergic Rhinitis 2018[1]

	Aggregate grade of evidence	Direction of impact	Magnitude of impact[a]	Recommendation, accounting for harm (minimal) and cost (moderate)
SLIT is effective for the reduction of symptoms of AR in adults	A	Yes	Low impact	Strong recommendation
	Lin,[2666] Radulovic,[2664] Di Bona,[2646,2665] Nelson,[2639] Calderon[2643]			
SLIT is effective for the reduction of symptoms of AR in children	B	Yes	Low impact	Recommendation
	Kim,[2634] Larenas-Linnemann[2635]; not enough evidence: Roder[2673]			
SLIT is safe for the treatment of AR in adults	A	Yes	–	Safety profile is very good
	Many of the systematic reviews included safety evaluation Makatsori[2652] – same drop-out rates SLIT versus placebo			
SLIT is safe for the treatment of AR in children	B	Yes	–	Safety profile is very good
	Systematic reviews (Kim,[2634] Larenas-Linnemann,[2635] Roder[2673]) all included safety evaluation Makatsori[2652] – same drop-out rates SLIT versus placebo			
SCIT is more effective than SLIT	A	Yes	Weak evidence	Recommendation
	Chelladurai,[2641] Dretzke,[2674] Calderon (HDM),[2643] Kim (children)[2634] Grass pollen tablets/drops versus SCIT: Di Bona[2638] SCIT equivalent to grass pollen tablets only, drops less effective: Nelson[2639]			
SLIT is safer than SCIT	B	Yes	Weak evidence	Recommendation
	Aasbjerg[2642]			
Total cost of SLIT is less than SCIT	A	Yes	Moderate evidence	Recommendation
	Meadows (UK setting),[2657] Dranitsaris (Canadian setting)[2640]			
It is safe to continue SLIT during pregnancy	B	No added risk	Moderate evidence	Recommendation
	Oykhman[2654]			
It is safe to start SLIT during the season	B	Sightly added risk	Moderate evidence	Option
	Creticos[2650]			
Tablet SLIT is more effective than pharmacotherapy	A	Yes	Moderate: antihistamines, montelukast Weak: INCS	Recommendation
	Devillier (pollen tablet SLIT),[1995] Durham (grass pollen or ragweed tablet SLIT)[1986] Exception: in seasonal AR; INCS as efficacious as tablet SLIT			
SLIT is cost-effective in the first year	B	No	Moderate evidence	Option (considering its long-term benefit)
	Meadows,[2657] Dranitsaris[2640]			
SLIT is cost-effective after several years of treatment	B	Yes	Weak-moderate evidence	Recommendation
	Meadows,[2657] Dranitsaris[2640]			
SLIT has a long-term effect beyond 3-years' application	B	Yes	Moderate evidence	Recommendation
	Durham,[2675] Didier[2676]			
SLIT has a preventive effect; reduces the development of asthma in patients with AR 2 years after a 3-year treatment course	B	Yes	Weak effect	Recommendation
	Kristiansen[2426] (New evidence since ICAR-Allergic Rhinitis 2018)			

(Continues)

TABLE XI.D.6.a.-2 (Continued)

	Aggregate grade of evidence	Direction of impact	Magnitude of impact[a]	Recommendation, accounting for harm (minimal) and cost (moderate)
SLIT with grass pollen is effective for seasonal AR	A	Yes	Low impact	Strong recommendation[b]
	Di Bona,[2646,2665] Nelson,[2639] Durham[1986]			
SLIT with tree pollen is effective for seasonal AR	A	Yes	Moderate effect	Strong recommendation[b]
	Valovirta[2677]			
SLIT with ragweed pollen is effective for seasonal AR	A	Yes	Moderate effect	Strong recommendation[b]
	Durham,[1986] Nolte,[2678] Creticos,[2679] Skoner[2680]			
SLIT with HDM is effective for AR	A	Yes	Low impact	Strong recommendation[b]
	Nolte,[1515] Bergmann,[2681] Mosbech,[1673] Calderon[2643]			
SLIT with animals is effective for AR	X	No data	No data	Option
	No separate data in SRMAs; no recent trials			
SLIT with fungi is effective for AR	B	Yes	Weak evidence	Option
	No separate data in SRMAs; Cortellini[2682]			

Abbreviations: AR, allergic rhinitis; HDM, house dust mite; INCS, intranasal corticosteroid; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SRMA, systematic review and meta-analysis.

[a]For those variables with meta-analysis: according to Cohen's classification: low impact SMD 0.2–0.5, moderate 0.5–0.8, high above 0.8. For those with only systematic review: strength of evidence.

[b]Considering the added long-term post-treatment effect and the possible preventive effects on the development of asthma and new sensitizations.

there were two serious treatment related adverse events with co-seasonal SLIT initiation, none needed epinephrine administration.[2650]

Grass pollen SLIT tablets were noted to be equally safe in AR patients with and without mild asthma.[2651] Dropout rates have been raised as a concern for trial safety, but there is no evidence of differences in drop-out rates between SLIT and placebo groups.[2652] There have been a few case-reports of EoE after a course of grass pollen SLIT tablets.[2653] Continuing SLIT during pregnancy did not increase the incidence of adverse outcomes during delivery nor alter the risk of developing atopic disease in the offspring. However, there is insufficient data to draw conclusions about safety and efficacy in pregnant women.[2654]

Evidence that SLIT is generally safe is judged to be grade A. Evidence that SLIT is safer than SCIT is judged to be grade B.

Cost-effectiveness of SLIT. The meta-analysis comparing the efficacy and cost-savings of the 5-grass SLIT tablet versus the Timothy grass tablet has several flaws, making direct comparison of outcomes not possible.[2655,2656] The 5-grass tablet was associated with cost savings against year-round SCIT, seasonal SCIT, and the Timothy grass tablet during the first year of therapy, which persisted during the second and third year of treatment. The higher costs for SCIT were due to elevated indirect costs from missing working hours and transportation costs related to in-office SCIT administration. The higher costs for the Timothy grass tablet are due to the year-round dosing versus the pre- and co-seasonal 6-month total dosing of the 5-grass tablet.

After a previous positive UK meta-analysis on costs,[2657] a more recent one also concluded that the body of evidence suggests that SLIT and SCIT could be considered cost-effective using the National Institute for Health and Clinical Excellence cost-effectiveness threshold of £20,000 per QALY.[2658]

Additional data not included in systematic reviews. Investigators showed after a 3-year course of Japanese cedar pollen tablet SLIT, there was a reduction in symptom-medication score of 45.3% one year post-treatment and 34.0% two years post-treatment ($p < 0.001$).[2659] A post-hoc analysis demonstrated symptom and medication reduction with the birch SLIT tablet during the oak pollen season in adults with allergic rhinoconjunctivitis.[2660]

There have been several studies on immunologic changes and biomarkers for AIT. There seems to be a differential induction of allergen-specific antibody responses after grass pollen AIT, with SCIT primarily inducing sIgG4 and SLIT inducing sIgA.[2552]

Sublingual immunotherapy – general

Aggregate grade of evidence for SLIT overall: A (Level 1: 17 studies, level 2: 12 studies, level 4: 1 study; Tables XI.D.6.a.-1 and XI.D.6.a.-2)
Due to heterogeneity of SLIT study reporting, it is difficult to separate out overall versus aqueous SLIT versus tablet SLIT.
Benefit: SLIT improves patient symptom scores, even as add-on treatment with rescue medication. SLIT reduces medication use. The effect of SLIT lasts for at least 2 years after a 3-year course of therapy. In AR patients, there is some evidence that SLIT reduces the frequency of onset of asthma and the development of new sensitizations up to 2 years after treatment termination. Benefit is generally higher than with single-drug pharmacotherapy; however, it may be less than with SCIT (low quality evidence).
Harm: Minimal harm with very frequent, but mild local adverse events, and very rare systemic adverse events. SLIT seems to be safer than SCIT. See Table II.C.
Cost: Intermediate. SLIT becomes cost-effective compared to pharmacotherapy after several years of administration. Total costs seem to be lower than with SCIT.
Benefits-harm assessment: Benefit of treatment over placebo is small but tangible and occurs in addition to improvement with medication. There is a lasting effect at least 2 years off treatment. Minimal harm with SLIT, greater risk for SCIT.
Value judgments: SLIT improved patient symptoms with low risk for adverse events.
Policy level: Strong recommendation for use of SLIT grass pollen tablet, ragweed tablet, HDM tablet, and tree pollen aqueous solution. Recommendation for SLIT for *Alternaria* allergy. Option for SLIT for animal allergy. Recommendation for dual-therapy SLIT in bi-allergic patients.
Intervention: Recommend tablet or aqueous SLIT in patients (adults and children) with seasonal and/or perennial AR who wish to reduce their symptoms and medication use, as well as possibly reduce the propensity to develop asthma or new allergen sensitizations.

XI.D.6.b | *Sublingual immunotherapy for allergic rhinitis – tablets*

SLIT tablets have been studied for HDM, as well as short ragweed, grass, birch, and Japanese cedar pollens. US FDA-approved tablets encompass Timothy grass, short ragweed, a 5-grass combination, and HDM allergens. Administration schedules and age ranges of approved use vary based on the specific tablet prescribed.

Since 2017, numerous SRMAs were identified for SLIT tablets (Table XI.D.6.a.-1). Eight reported both aqueous and tablet SLIT,[2426,2438,2636,2637,2644,2661–2663] six presented aqueous and tablet SLIT separately,[2438,2550,2638,2639,2664,2665] and nine reported on tablet SLIT alone.[1982,1986,1995,2532,2636,2640,2646,2651,2672] All studies reported outcomes for HDM, grass pollen, and/or ragweed pollen. There were no SRMAs for birch or Japanese cedar pollen tablets. Studies focusing only on SLIT tablets demonstrated safety and efficacy for HDM, grass pollen, and ragweed pollen. Improvement in symptom scores, medication scores, and QOL metrics are evident with minimal adverse reactions.

Meltzer et al.[1982] published a meta-analysis evaluating the efficacy of pharmacotherapies and SLIT tablets versus placebo on nasal symptoms in seasonal and perennial AR. Active treatments significantly improved nasal symptoms versus placebo. Trial heterogeneity and publication bias limited comparison of treatment classes. Of note, comparison groups were not equally matched. SLIT is generally used for pharmacotherapy-recalcitrant patients, resulting in a more severe group using SLIT. Additionally, patients often use supplement SLIT with rescue medications, confounding individual comparison of medical treatments.

Analysis of pediatric studies demonstrated that HDM SLIT reduced symptoms and medication scores versus placebo, with a slight increase in adverse reactions.[2636] A similar study of HDM SLIT tablets in adults[2672] showed improvement in symptom scores and QOL compared to placebo. Nelson et al.[2532] published a systematic review of 12 double-blind RCTs for HDM SLIT tablets and concluded that efficacy was established with all 12 studies, with statistically significant symptom score improvement.

SRMAs including SLIT tablet and aqueous preparations also reported favorable outcomes for symptoms scores, medications, and QOL. Findings for aqueous SLIT are discussed in the next section.

Examples of dose–response studies for grass pollen and HDM tablets include those by Didier et al.,[2630] Horak et al.,[2683] Malling et al.,[2684] and Bergmann et al.[2681] Dose-finding studies aim to identify effective therapeutic doses while minimizing adverse effects.

The efficacy findings from 2017 to 2022 SLIT tablet studies are consistent with the findings reported in the first ICAR-Allergic Rhinitis 2018.[1] The majority of the SRMAs show mild-to-moderate efficacy of SLIT tablets over placebo. There is strong evidence that grass pollen

SLIT tablets and HDM tablets reduce symptoms of AR in children.

Rare systemic and serious adverse events have been reported with SLIT, but in general, meta-analyses found SLIT to be safer than SCIT. One study found seven of 2259 patients on grass pollen SLIT tablets were given epinephrine for treatment related adverse effects.[2646] Presence of mild asthma did not affect adverse reactions for grass pollen SLIT tablets.[2651] Starting SLIT in-season is generally deemed to be safe; although there were two serious treatment related adverse events with co-seasonal SLIT initiation, none needed epinephrine.[2650]

SLIT tablet options are limited compared to off-label aqueous SLIT extracts. Since HDM is the only tablet approved for patients with non-seasonal AR, data regarding polysensitized patients is important. Kim et al.[2661] reported a meta-analysis of HDM AIT in mono- or polysensitized patients. Nine studies, five SLIT and four SCIT, revealed no differences for nasal symptom score, medication use, and QOL scores between mono- and polysensitized patients.

The use of multiple concurrent SLIT tablets (Timothy grass and short ragweed) has been studied by Maloney et al.[2651] Simultaneous co-administration within 5 min did not result in severe swelling, systemic allergic reactions, asthma attacks, or reactions requiring epinephrine. Gotoh et al.[2685] reported the first study of dual administration of SLIT tablets for perennial and seasonal AR using HDM and Japanese cedar pollen tablets administered alone and as dual therapy. The percentage of subjects with adverse events and reactions was similar between the two groups and between the two periods of monotherapy and dual therapy. There were no serious events and immunologic marker responses were not altered by co-administration of tablets. These studies provide support for the contention that co-administration of tablets does not adversely affect the safety or efficacy of tablet SLIT.

Sublingual immunotherapy – tablets

Aggregate grade of evidence: A (Level 1: 11 studies, level 2: 4 studies; Table XI.D.6.a.-1)
Benefit: Improvement of symptoms, rescue medication, and QOL.
Harm: Local reaction at oral administration site and low risk of anaphylaxis.
Cost: Intermediate. More expensive than standard pharmacotherapy, but persistent benefit may result in cost-saving in the long-term.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Useful for patients with severe or refractory symptoms of AR.
Policy level: Strong recommendation.
Intervention: SLIT tablets are recommended for patients with severe or refractory AR. Epinephrine auto-injector is recommended in the FDA labeling for approved tablets due to the rare but serious risk of anaphylaxis. Tablets for select antigens are available in various countries.

XI.D.6.c | *Sublingual immunotherapy for allergic rhinitis – aqueous*

SLIT can be administered via tablets or aqueous drops. Like sublingual tablets, this offers easy at-home administration with a similar safety profile. While some aqueous extracts are approved for use in Europe, aqueous SLIT products are not FDA approved in the US; many providers currently use subcutaneous allergen extracts off-label for sublingual desensitization.[2686]

Aqueous SLIT has a mild to moderate effect on improving patient symptoms and reducing medication usage.[2438,2634,2638,2665,2666] Although it is difficult to compare studies due to methodologic or extract differences, improvement in symptom/medication outcomes is prevalent across most studies. The FDA has approved SLIT tablets for HDM, grass pollen, and ragweed pollen allergy – these antigens have standardized dosages; however, many allergens cannot be treated with the limited number of available tablets. Additionally, there is currently no head-to-head data comparing aqueous SLIT to tablet SLIT. Some meta-analyses have undertaken subgroup analysis between aqueous SLIT and tablet SLIT and found both to be effective without clear superiority of one over the other.[2438,2639]

Aqueous SLIT seems to be efficacious for adults and children. An earlier meta-analysis noted no significant improvement in symptom score for children treated with SLIT.[2665] However, most of the included studies had a low monthly allergen dose that has been shown to be ineffective in subsequent meta-analyses.[2438,2638,2639,2666] Lack of dosing standardization across multiple studies in different countries using extracts from various manufacturers has led to heterogeneity in aqueous SLIT data[2687] (Table XI.D.6.a.-1).

Leatherman et al.[2686] provided recommendations for effective doses of aqueous SLIT based on micrograms per day administered in RCTs that demonstrated efficacy. Published and recommended dosing ranges for common allergens are shown in Table XI.D.6.c. However, many allergens such as cat, dog, mold/fungi, and cockroach did not have enough data to provide specific recommendations.[2686] There is expert opinion that for allergens without current

TABLE XI.D.6.c Recommended SLIT dosing (μg/day)[2686]

Allergen	Published dosing range (μg/day)	Recommended daily dose range (μg/day)
D. pteronyssinus	0.32–47	16 (10–28)
D. farinae	0.07–121	16 (10–28)
Timothy grass	15–30	15–30
Bermuda grass	5–40	18
Ragweed	12–124	15–50
Pollen	5–40	18

effective ranges, daily SLIT dose equal to the monthly SCIT dose may be in the effective dose range; further studies should validate this.[2419]

While single allergen SLIT has been shown to be effective in both monosensitized and polysenstized patients,[2661,2668,2671] there is equivocal evidence on added benefit of multi-allergen immunotherapy in the polyallergic patient. This is pertinent to tablet SLIT as well because of the limited number of antigens available as tablets. Most RCTs demonstrate significant benefit over placebo with multi-allergen SLIT but have not compared monotherapy to polytherapy. One open-label, controlled trial in patients with grass and birch sensitization randomized patients to treatment with grass pollen, birch pollen, grass and birch pollen, or placebo.[2688] Monotherapy with grass or birch showed clinically significant improvement and nasal eosinophil reduction versus baseline, but polytherapy with grass and birch showed improvement over the monotherapy groups. Alternatively, comparing Timothy extract alone or with nine additional pollen extracts against a placebo group demonstrated secondary outcome efficacy (e.g., SPT reactivity, nasal challenge, sIgE) in favor of the mono-Timothy group, though neither treatment group showed symptom/medication improvement over placebo, as the grass pollen season was too mild.[2669] Another study randomized polysensitized patients to single, pauci, or multi-allergen SLIT.[2667] Symptom scores significantly improved in all groups, yet there was no significant efficacy difference shown for single versus pauci- versus multi-allergen SLIT. Of note, this study had only 16 patients total and follow up was 9 months. Further study is needed to determine the role of monotherapy or polytherapy SLIT on specific seasonal symptoms and QOL measures over several seasons.

Safety of aqueous SLIT is comparable to its SCIT and tablet SLIT counterparts. There is no standardized mechanism of reporting safety outcomes across RCTs but reported adverse outcomes have been modest. Local reactions range 0.2%–97%. Life-threatening reactions or anaphylaxis were largely absent from most meta-analyses[2664,2666] except for one meta-analysis of SCIT and SLIT for grass allergens[2638] which found one case of anaphylaxis in the SLIT group. Notably the SCIT group had 12 cases of anaphylaxis and the placebo group had two cases, suggesting that the risk of anaphylaxis in SLIT is significantly lower than in SCIT.[2638] There were no cases of anaphylaxis or life-threatening events in children[2634] (Table II.C).

Sublingual immunotherapy – aqueous

Aggregate grade of evidence: B (Level 1: 7 studies, level 2: 5 studies, level 4: 1 study; Table XI.D.6.a.-1)
Benefit: Aqueous SLIT improves patient symptom scores and decreases rescue medication use. There is some indication of less benefit from aqueous versus tablet SLIT, but the lack of standardized dosing across multiple trials does not allow for adequate comparison.
Harm: Common mild to moderate local adverse events. Very rare cases of systemic adverse events. No reported cases of life-threatening reactions. See Table II.C.
Cost: Intermediate. More expensive than standard pharmacotherapy, but there are indications of lasting benefit and cost-saving in the long-term.
Benefits-harm assessment: Appreciable benefit in patient symptoms and minimal harm.
Value judgments: Aqueous SLIT improves patient symptoms and rescue medication usage with minimal risk of serious adverse events but common local mild adverse events. Single allergen therapy has been extensively tested. Multiallergen AIT requires future studies to validate its use.
Policy level: Recommendation.
Intervention: High-dose aqueous SLIT is recommended for those patients who wish to reduce their symptoms and rescue medication use.

XI.D.7 | Subcutaneous versus sublingual allergen immunotherapy for allergic rhinitis – comparison table

Table XI.D.6.d.

XI.D.7 | Epicutaneous/transcutaneous immunotherapy

Epicutaneous or transcutaneous immunotherapy is a non-invasive form of AIT that consists of the application of allergens to the skin without involving injections.

TABLE XI.D.6.d Comparison – subcutaneous versus sublingual immunotherapy

	Subcutaneous immunotherapy	Sublingual immunotherapy
Efficacy	Significant efficacy over placebo[1517,2561,2573,2689]	Significant efficacy over placebo[1694,2690,2691]
	Both demonstrate efficacy over placebo for allergic rhinoconjunctivitis and other allergic conditions, but head-to-head data are lacking[2422,2634,2644,2674,2692–2695,a] Low grade evidence for SCIT superiority	
Side effects [Table II.C.]	Redness/swelling at injection site, large local injection site reactions, sneezing, cough, throat swelling, wheezing, chest tightness, nausea, dizziness, anaphylaxis	Lip/mouth/tongue irritation, mouth swelling, eye swelling/itching/redness, nausea, vomiting, stomach cramps, diarrhea, nasal congestion/itching, sneezing, increased mucus production, wheezing, cough, hives, skin itching, anaphylaxis, eosinophilic esophagitis
Safety	Increased risk of systemic reactions compared with SLIT Prescription of epinephrine autoinjector for delayed reactions at physician's discretion[2419]	Decreased risk of systemic reactions compared with SCIT Epinephrine autoinjector mandated in the US by the FDA for tablet SLIT[2696 b]
	At office visits, consider peak expiratory flow tests or spirometry in patients with asthma (no treatment or testing if exacerbation)[2419]	
Cost[c]	Lower direct cost to patient, but may be comparable or higher in total (e.g., indirect) costs[2640,2697,2698 d] Lower initial ICER (e.g., first 6 years)[2657]	Higher direct cost to patient, but may be comparable or lower in total (e.g., indirect) costs[2640,2697,2698 d] Higher initial ICER (e.g., first 6 years)[2657]
	Cost-effectiveness threshold: £20,000–30,000/QALY by year 6[2657,2658]	
Covered by insurance?[2697c]	Yes	Aqueous: no Tablet: yes
Convenience	Less convenient (recurring office visits for injections: weekly during build-up phase, every 2–4 weeks during maintenance phase)[2419]	More convenient (self-administered daily at home) Preferable for those opposed to injections (e.g., children)
Testing considerations	Skin allergy test or in vitro testing to determine sensitization (SPT) and possible titration of starting dose (IDT or MQT/blended techniques)	Skin allergy test or in vitro testing to determine sensitization only (SPT)
	Other laboratory tests and repeat skin tests not routinely performed[e]	
Equipment considerations[2419]	May need supplies for IDT or MQT depending on treatment paradigm Needs vial preparation supplies for serial dilutions Need injection supplies	May be performed with SPT results only Substantially more antigen needed for aqueous SLIT preparations Need antigen delivery device (dropper) For SLIT tablets essentially no administration supplies needed
	Appropriate equipment and medications for anaphylaxis treatment[f]	
Length of therapy	Longer build up phase with conventional SCIT and cluster protocols	Shorter build up phase
	Maintenance: ≥3 years, up to 5 years[2693,2699–2702]	
Adherence to therapy	More easily monitored (in office) Most common reason for discontinuation is inconvenience[2703]	Less easily monitored (at home) Adherence may be improved with more frequent clinic visits, improving therapy availability, and mitigating concerns about clinical efficacy[2704,2705]
	Overall adherence rates are similar, but conflicting data depends on how adherence is measured[2703,2706–2708 g] Patients should be re-evaluated at least every 6–12 months while receiving immunotherapy[2419 h]	

(Continues)

TABLE XI.D.6.d (Continued)

	Subcutaneous immunotherapy	Sublingual immunotherapy
Mechanism of action	Subcutaneous (systemic) injection IgG, IgG4 antibody induction[2552]	Sublingual (local) administration[2709] IgA1, IgA2 antibody induction[2552]
	Allergen extracts presented to immune system induce allergen desensitization and immunologic tolerance[2693,2699,2700]	
FDA-approved allergens[2710,2711c,i]	Animal dander (e.g., cat) Insect venom (e.g., honeybee, wasp, hornet, yellow jacket, mixed vespid) Pollen (e.g., grass, ragweed) House dust mite (*Dermatophagoides pteronyssinus*, *D. farinae*)	Pollen (grass, ragweed) House dust mite
Indications[2693,2700]	Verification of IgE-mediated sensitization (e.g., skin or in vitro testing) and bothersome symptoms upon exposure Availability of standardized or high-quality allergen extracts Proof of efficacy of planned allergen immunotherapy for the respective indication and age group Allergen avoidance not possible or inadequate	
Contraindications[2693,2700]	See below	Acute, severe inflammatory disorder of oral cavity Chronic disease of oral mucosa
	Diseases in which epinephrine is contraindicated (except insect venom allergies) Treatment with β-blockers (local or systemic) is a relative contraindication Partially controlled or uncontrolled bronchial asthma Severe autoimmune diseases, immune defects, immunodeficiencies, immune suppression Malignant neoplastic diseases with current disease relevance History of serious systemic reactions to allergen immunotherapy Insufficient adherence to therapy Acute infections (e.g., gastroenteritis) Eosinophilic esophagitis[j] Pregnancy[k] Preparation-specific contraindications (see product information leaflet)	

Abbreviations: FDA, Food and Drug Administration; IDT, intradermal dilutional test; IECR, incremental cost-effectiveness ratio; Ig, immunoglobulin; MQT, modified quantitative test; QALY, quality adjusted life year; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; US, United States.

[a]No significant difference in patient outcomes (symptom score, medication score, combined symptom-medication score, quality of life). Some studies demonstrated indirect or low-grade evidence of greater efficacy with SCIT than SLIT,[2638,2641] but the most recent meta-analyses did not demonstrate superiority of one over the other.[2422,2644] Overall there is a lack of RCTs directly comparing the efficacy of SCIT to SLIT.

[b]This is not a requirement for SLIT prescribed in Europe.[2707] Controversy exists regarding whether epinephrine autoinjectors are warranted for patients on SLIT due to factors such as the rarity of systemic allergic reactions,[2712] costs exceeding that of SLIT therapy, and poor compliance with purchasing/carrying autoinjectors.[2696,2713] Patients should be educated specifically regarding when and how to use epinephrine.

[c]May vary by geographic region. Examples provided in the table refer to the US unless otherwise stated.

[d]Indirect costs include travel expenses and loss of productivity. Some studies found that overall SLIT was more cost effective than SCIT.[2640]

[e]Some tests, such as titrated SPT, titrated nasal allergen challenge, and sIgG4 measurement, have been shown to correlate with clinical efficacy or predict future response.[2620,2714,2715]

[f]Required for all office administrations (e.g., all SCIT, first dose SLIT). Example equipment: stethoscope and sphygmomanometer; aqueous epinephrine 1:1000 weight/volume (i.e., the primary treatment for anaphylaxis); tourniquet, syringes, large bore (14 gauge) needles, and intravenous catheters; equipment to administer oxygen by mask; intravenous fluid set-up; antihistamine for injection (second-line treatment); glucocorticoids for intramuscular or intravenous administration (second-line treatment); equipment to maintain an airway appropriate for the supervising clinician's expertise and skill; glucagon kit for patients on β-blockers.

[g]Conflicting studies have shown SCIT to have higher adherence,[2716,2717] SLIT to have higher adherence,[2718,2719] or both to have comparable compliance.[2708,2720]

[h]To assess efficacy and compliance, reinforce safe administration, and determine whether treatment adjustments or discontinuations are warranted.

[i]SCIT allergens listed are standardized (compared to a US reference standard for potency). Other SCIT allergens demonstrated to be effective in placebo-controlled studies include molds (e.g., *Alternaria*, *Cladosporium*), insects (e.g., cockroach, imported fire ant), dog dander, and tree pollen.[2721,2722] May use SCIT extracts off label for SLIT.

[j]Contraindication for SLIT. Limited evidence suggests SCIT should not typically be recommended for patients with eosinophilic esophagitis. However, SCIT may benefit some patients with eosinophilic esophagitis.[2723]

[k]Considered a contraindication for initiating AIT, though it may be continued during pregnancy at stable/maintenance doses. Only in isolated cases may SCIT be initiated during pregnancy.[2419,2700]

Allergen is applied through patches kept on the skin for several hours. The epidermal barrier is usually impermeable to molecules larger than 500 Da.[2724] In order to increase/improve antigen delivery to the immune cells of the epidermis and dermis, different techniques have been used including adhesive tape stripping, abrasion of the skin, and sweat accumulation through patch application.[2469,2725] Newly engineered techniques are being evaluated for the delivery of powder-based AIT into the epidermis with minimal skin reaction, including microneedle arrays and laser-mediated microporation; these have primarily been studied in food allergy (peanut).[2726] To date, four clinical trials of aeroallergen epicutaneous AIT have been published (three of them by the same group of investigators) reporting the efficacy of grass pollen extract coated patches in varying doses, numbers of weekly patches, and duration in contact with the skin[2727] (Table XI.D.7).

The first pilot study of aeroallergen epicutaneous AIT was a monocentric, placebo-controlled, double-blind trial of 37 adults with positive SPT and nasal challenge tests to grass pollen randomized to treatment with allergen or placebo patches.[2728] Symptom scores after NPT scores showed notable reduction in the grass-treated patients, but the difference was not statistically significant. Grass-treated patients had improved subjective symptom scores, both after the pollen seasons of 2006 ($p = 0.02$) and 2007 ($p = 0.005$). Eczema at application sites was significantly higher in the treatment arm; there were no serious adverse events.

A second monocentric double-blind study randomized 15 children to grass epicutaneous AIT versus placebo.[2729] There were no significant differences in skin test wheal size between groups before and after treatment. Both groups had an increase in symptoms, but the treatment group had lower rhinorrhea, nasal obstruction, dyspnea, and ocular tearing. The treatment group had a significant reduction in antihistamine use ($p = 0.019$). There were no systemic or local reactions.

A third monocentric trial randomized 132 adults to placebo, low, medium, or high dose grass extract patches. Significant improvement in rhinoconjunctivitis symptoms was found only in the high dose treated patients one year later ($p = 0.017$).[2730] There were no differences in conjunctival provocation test, SPT, or rescue medication use. Local reactions were more frequent in high dose treated patients and decreased with subsequent applications. Systemic reactions treated with intravenous antihistamines and corticosteroids occurred in 8.3% of patients.

A fourth monocentric double-blind RCT randomized 98 adults to grass patches or placebo.[2731] There was a 48% improvement in seasonal symptom scores in the first year (placebo 10%) but no significant differences in combined treatment and medication scores. CPT scores improved after the first year in the active treatment group. Allergen-specific IgG4 was significantly increased in the active treatment group only during the first pollen season; sIgE did not show any variation. Local adverse events occurred in 18%; eight systemic reactions led to study exclusion.

A systematic review of the efficacy and safety of epicutaneous AIT for food and pollen allergy; the four clinical trials above on grass allergy were included.[2732] Given the lack of original data on means and standard deviation of symptom scores, a meta-analysis on the efficacy was not possible and the authors concluded that the effectiveness of epicutaneous AIT for grass pollen allergy is unclear. Subgroup analyses concluded that epicutaneous grass pollen AIT significantly increased the risk of local (relative risk [RR] 2.29; 95% 1.05–4.96) and systemic (RR 4.65; 95% CI 1.10–19.64) adverse reactions. It is interesting to note that the cited clinical trials were conducted more than 10 years ago suggesting little progress in this area for AR.

Epicutaneous/transcutaneous immunotherapy

Aggregate grade of evidence: B (Level 2: 5 studies; Table XI.D.7)
Benefit: Epicutaneous AIT to grass pollen resulted in limited and variable improvement in symptoms, medication use, and allergen provocation tests in patients with AR or conjunctivitis.
Harm: Epicutaneous AIT resulted in systemic and local reactions, with a RR of 4.65 and 2.29, respectively. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous AIT.
Cost: Unknown.
Benefits-harm assessment: There is limited and inconsistent data on benefit of the treatment, while there is a concerning rate of adverse effects. Three out of 4 studies on this topic were published by the same investigators from 2009 to 2015.
Value judgments: Epicutaneous AIT could offer a potential alternative to SCIT and SLIT, but further research is needed.
Policy level: Recommendation against.
Intervention: While epicutaneous AIT may potentially have a future clinical application in the treatment of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a significant rate of adverse reactions. Given the above and the availability of alternative treatments, epicutaneous AIT is not recommended at this time.

TABLE XI.D.7 Evidence table – epicutaneous/transcutaneous immunotherapy for the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Xiong et al.[2732]	2020	2[a]	SR	Grass patches, 4 studies Placebo, 4 studies	Symptom score (3 of 4 studies) Adverse events	Clinical efficacy unclear Significant increase in risk of systemic (RR 4.65) and local (RR 2.29) adverse reactions
Senti et al.[2731]	2015	2	DBRCT	Adults, 6 weekly patches kept on for 8 h: Grass patches, $n = 48$ Placebo patches, $n = 50$	Symptoms CPT	Symptom score improved in treatment arm in year 1, not significantly different from control in year 2 CPT improved in treatment group Systemic reactions occurred in seven treatment (14.6%) and one control patients
Senti et al.[2730]	2012	2	DBRCT	Adults, 6 weekly patches kept on for 8 h: Placebo patches, $n = 33$ Low dose grass patches, $n = 33$ Medium dose grass patches, $n = 33$ High dose grass patches, $n = 33$	Symptoms Medication use SPT CPT	Symptoms improved only in highest dose group No difference in medication use, SPT, or CPT Local reactions common Systemic reactions occurred in 8.3%
Agostinis et al.[2729]	2010	2	DBRCT	Children, 12 weekly patches kept on for 24 h: Grass patches, $n = 15$ Placebo patches, $n = 15$	Symptoms Antihistamine use Skin test wheal size	No difference in skin wheal size at study end Treatment group had less symptoms and antihistamine use
Senti et al.[2728]	2009	2	DBRCT	Adults, 12 weekly patches kept on for 48 h, skin stripped six times: Grass patches, $n = 21$ Placebo patches, $n = 17$	Symptoms NPT	No significant difference in NPT Subjective symptom score improved More local reactions (eczema) in treatment group

Abbreviations: CPT, conjunctival provocation test; DBRCT, double-blind randomized controlled trial; LOE, level of evidence; NPT, nasal provocation test; RR, relative risk; SR, systematic reviewSPT, skin prick test.

[a]LOE downgraded due to lack of consistency in study inclusion and heterogeneity of outcome measurements (symptom scores).

XI.D.8 | Intralymphatic immunotherapy

Notwithstanding the long-term benefits to AR patients by AIT, the recommended treatment duration of 3–5 years is time consuming, expensive, and demands strict adherence from patients.[2528] SCIT requires monthly maintenance injections, and SLIT requires daily oral intake. Intralymphatic immunotherapy (ILIT) was introduced to address these concerns. ILIT involves the application of low dose allergens via ultrasound-guided injection into the lymph nodes, mainly the inguinal nodes. The treatment protocol of ILIT has a shorter duration, usually comprising three injections over a period of 8 weeks.[2733] The cumulative dose for ILIT is dramatically lower than that used for conventional AIT and there are significantly fewer adverse events.[2734]

Thus far, two systematic reviews are available (Table XI.D.8). The first systematic review included 11 trials and two cohorts in a qualitative and quantitative analyses of 483 participants with the average age of 33 years.[2734] The

TABLE XI.D.8 Evidence table – intralymphatic immunotherapy for the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Aini et al.[2735]	2021	1	SRMA	ILIT Placebo SCIT	CSMS Symptoms Medication use Overall improvement score QOL Adverse events	No difference versus placebo Generally well-tolerated ILIT had fewer adverse events versus SCIT
Hoang et al.[2734]	2021	1	SRMA	ILIT Placebo SCIT	CSMS Symptoms Medication use VAS QOL Serum IgG4/IgE levels Adverse events	Short-term improvement in CSMS and VAS in ILIT but no long-term difference Increased IgG4 at short-term but no effect on IgE level in ILIT ILIT had fewer adverse events versus SCIT
Skaarup et al.[2744]	2021	2	RCT, blinded	Grass pollen induced AR, $n = 36$: Aluminum hydroxide adsorbed, depot pollen vaccine Placebo	CSMS Rescue medication use NPT Serum IgG4/IgE level	Reduction in CSMS and use of rescue medication No effect on nasal reactivity Increased IgG4/IgE level No effect of booster dose
Konradsen et al.[2743]	2020	2	RCT, blinded	Birch or Timothy pollen induced AR, $n = 14$: Aluminum hydroxide adsorbed, depot birch- or grass-pollen vaccine Placebo	Symptoms Medication use NPT Serum IgG4/IgE level	Reduction in symptom and medication score Reduction in nasal reactivity Increased IgG4 level No effect on IgE level
Terada et al.[2746]	2020	2	RCT, open	Japanese cedar pollinosis, $n = 12$: Aluminum hydroxide adsorbed, depot pollen vaccine Placebo	Symptom-medication score VAS NPT Serum IgG4/IgE level Adverse events	Improvement in symptoms Reduction in nasal reactivity No effect on VAS Increased IgG/IgE levels Safe and well-tolerated
Thompson et al.[2745]	2020	2	RCT, blinded	Mountain cedar pollinosis, $n = 21$: Aluminum hydroxide adsorbed, depot pollen vaccine Placebo	Total combined score Serum IgE level Adverse events	Improvement in symptoms No effect on IgE level Safe and well-tolerated
Hellkvist et al.[2742]	2018	2	RCT, blinded	Birch and grass pollen induced AR, $n = 60$: Aluminum hydroxide adsorbed, birch- or grass-pollen vaccine Placebo	Total nasal symptom score NPT Serum IgG4/IgE level Rescue medication use Adverse events	Improvement in symptoms Reduction in nasal reactivity Increased IgG4 level Transient increase in IgE level Safe to inject two different allergens concurrently

(Continues)

TABLE XI.D.8 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hylander et al.[2741]	2016	2	RCT, blinded	Birch or grass pollen induced AR, $n = 36$: Aluminum hydroxide adsorbed, depot birch- or grass-pollen vaccine Placebo	Seasonal allergic symptoms by VAS Safety of injections Nasal symptom score NPT Serum IgE and IgG4 level Rescue medication use	ILIT is effective and safe Marked reduction of seasonal allergic symptoms
Patterson et al.[2740]	2016	2	RCT, blinded	Adolescents, grass pollen induced AR, $n = 15$: Aluminum hydroxide-adsorbed grass pollen extract Placebo	Patient diary score of allergy and asthma symptoms and medication use Local and systemic symptoms score after injections	ILIT is effective and safe, with notably low adverse reactions
Hylander et al.[2736]	2013	2	Pilot study and RCT, blinded	Birch pollen/grass pollen induced AR, pilot $n = 6$, RCT $n = 15$: Three intralymphatic inguinal injections of 1000 SQU birch pollen or grass pollen Placebo	Seasonal allergic symptoms by VAS SPT Validated rhinitis QOL questionnaire	ILIT is effective and safe
Witten et al.[2739]	2013	2	RCT, blinded	Grass pollen induced AR, $n = 45$: Six injections of 1000 SQU of depot grass pollen extract at a minimal interval of 14 days Three injections of 1000 SQU followed by three injections of placebo Six injections of placebo	CSMS Global seasonal assessment RQLQ	ILIT produced immunological changes but no improvement in symptoms
Senti et al.[2738]	2012	2	RCT, blinded	Cat dander induced AR, $n = 20$: MAT-Fel d 1 Placebo (saline in alum)	Immunological parameters Systemic adverse events NPT SPT Validated rhinitis QOL questionnaire	ILIT with MAT–Fel d 1 (recombinant major cat dander allergen fused to a modular antigen transporter) was safe and induced allergen tolerance after three injections
Senti et al.[2737]	2008	2	RCT, open	Grass pollen induced AR, $n = 165$: Three 0.1-ml injections with 1000 SQU of aluminum hydroxide-adsorbed grass pollen extract injected into lymph node at day 0 and after 4 and 8 weeks 54 subcutaneous injections over 3 years (cumulative dose of 4,031,540 SQU).	Seasonal allergic symptoms by VAS Adverse events Safety of injections Rescue medication use SPT Grass-specific IgE levels	ILIT enhanced safety and efficacy of immunotherapy and reduced treatment time from 3 years to 8 weeks

(Continues)

TABLE XI.D.8 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wang et al.[2747]	2019	4	Pilot study, open, no control group	House dust mite induced AR, $n = 81$: Aluminum hydroxide adsorbed, depot birch- or grass-pollen vaccine	Symptom score QOL score Rescue medication use Adverse events	Improvement in symptoms and QOL score Decreased rescue medication use Safe and well-tolerated
Lee et al.[2748]	2017	4	Pilot study, open, no control group	House dust mite, cat, and dog induced AR, $n = 11$: Aluminum hydroxide adsorbed, *D. farinae*, *D. pteronyssinus*, cat, dog vaccine	SNOT-20 RQLQ Rescue medication use NPT Serum IgG4/IgE level Adverse events	Improvement in SNOT-20 and RQLQ Decreased rescue medication use Reduction in nasal reactivity Increased IgG4/IgE to house dust mite No effect on IgG4/IgE to cat and dog
Schmid et al.[2749]	2016	4	Pilot study, open, no control group	Grass pollen induced AR, $n = 7$: Three injections of 1000 SQU of allergen, dose interval 23–36 days	CSMS RQLQ Number of IgE+ and IgE- plasmablasts specific for grass	ILIT may induce allergen specific plasmablasts Confirms an effect on provocation of mast cells in skin and nasal mucosa during the ensuing winter

Abbreviations: AR, allergic rhinitis; CSMS, combined symptom-medication score; IgE, immunoglobulin E; IgG4, immunoglobulin G4; ILIT, intralymphatic immunotherapy; LOE, level of evidence; NPT, nasal provocation test; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SCIT, subcutaneous immunotherapy; SNOT-20, Sinonasal Outcome Test; SPT, skin prick test; SQU, standardized quality units; SRMA-systematic review and meta-analysis; VAS, visual analog scale.

second systematic review involved quantitative analysis of 11 trials with 452 participants aged 15 years and above.[2735] The outcomes assessed in both reviews include the combined symptom-medication score, symptom score, VAS, medication score, overall improvement score, medication reduction, QOL, sIgE level, sIgG level, and adverse events. The overall level of evidence of the included trials ranged from very low to moderate.

ILIT was administered by injecting aluminum hydroxide-adsorbed antigen vaccine into inguinal lymph nodes for all patients under ultrasound guidance.[2736–2746] In one pilot study, the cervical lymph nodes were used as the injected site.[2747] Single allergen was evaluated in seven trials,[2737–2740,2744–2746] two different allergens assessed simultaneously in four trials,[2736,2741–2743] and one trial assessed two different allergens individually.[2742] Grass pollen extract was injected in eight trials,[2736,2737,2739–2744] cedar pollen extract in two trials,[2745,2746] birch pollen extract in four trials,[2736,2741–2743] and cat dander allergen extract (MAT-Fel d 1) in one trial.[2738] Placebo injections were used in all but two trials[2736,2737] which used SCIT as control groups.

All trials performed three injections at 4-week intervals except for one trial which used a 2-week interval. Short-term relief of the combined symptoms and medication score was achieved in the 4-week but not for the 2-week interval.[2734] Increased sIgG4 levels have been associated with the effectiveness of AIT.[1327] While a short-term increase of sIgG4 level has been documented following ILIT, there has not been any medium-term or long-term effects.[2734] The reduction of sIgE in the short, medium, and long-term is frequently reported with SCIT; however, this has been notably absent with ILIT.[2734,2737]

ILIT was shown to confer short-term relief of AR symptoms in one review.[2734] Despite being safe and well tolerated, both meta-analyses determined that the efficacy of ILIT for long-term relief of AR symptoms was inconclusive.[2734,2735] The safety of ILIT and reported adverse events were investigated in all eleven trials. While more local reactions were noted from ILIT compared to placebo, systemic adverse events were similar in both the ILIT and placebo groups.[2734] The major advantage in favor of ILIT compared to SCIT is fewer adverse effects of local and systemic reactions[2737] compared to SCIT. At present, there is no trial comparing ILIT versus SLIT with regard to adverse effects. Overall, two anaphylactic events have been reported for ILIT but no deaths.[2748] The anaphylaxis following ILIT transpired following the first injection in one patient and following the second injection in another patient, both patients receiving non-standardized aqueous

allergen extract compared to aluminum-based extract used in most trials.

ILIT trials varied as to the dose of allergen administered and the interval between injections. Increased efficacy was associated with a 4-week (vs. 2-week) interval, and future trials should use and establish a standard treatment regimen. Another shortcoming is a lack of standardization of clinical endpoints. The use of standardized assessment such as combined symptoms-medication score could better reflect the actual potential of ILIT. The high heterogeneity among the trials could be due, in part, to the use of different allergens. The immunogenicity effect may differ between allergens when administered as a single or multiple allergens. One trial used both grass and birch allergen to treat polysensitized patients and found elevated sIgE and sIgG4 levels for grass pollen but not for birch pollen.[2742] ILIT could be beneficial as an alternative to other forms of AIT due to its shorter treatment period, reduced number of injections, and fewer adverse events; however, the long-term efficacy has to be supported by more studies prior to its incorporation into clinical practice.

Intralymphatic immunotherapy

Aggregate grade of evidence: A (Level 1: 2 studies, level 2: 11 studies, level 4: 3 studies; Table XI.D.8)
Benefit: Shorter treatment period, decreased number of injections, smaller amount of allergen, lower risk of adverse events versus SCIT.
Harm: Local reaction at injection site and risk of anaphylaxis.
Cost: Cost savings due to shorter treatment duration and fewer injections. Additional cost for training required.
Benefits-harm assessment: Benefit outweighs harm.
Value judgments: Apparent short-term favorable effect, but long-term effect is lacking.
Policy level: Option.
Intervention: More studies are essential to establish the long-term effects of ILIT.

XI.D.9 | Other forms of immunotherapy – oral, nasal, inhaled

Oral, nasal, and inhaled (intra-bronchial) routes of AIT administration have been investigated for AR to bypass some challenges of SCIT, including resource utilization and discomfort. Today, SCIT remains commonly used while these alternative techniques have been largely supplanted by SLIT and are relegated to primarily historical significance.[2419]

Oral, nasal, and inhaled AIT involve the topical absorption of allergen extracts via the oral cavity/gastrointestinal tract, nasal cavity, or bronchial mucosa, respectively. RCTs have evaluated oral/gastrointestinal AIT for the treatment of birch,[2750] cat,[2751] and ragweed[2752] allergy without a significant decline in nasal symptoms, improvement in provocation testing, or reduction in medication utilization. Moreover, oral/gastrointestinal allergen administration requires extract concentrations approaching 200-times greater than SCIT, and is associated with adverse gastrointestinal side effects.[2419,2751] In contrast to AR, the efficacy of oral/gastrointestinal immunotherapy has been demonstrated for the treatment of food hypersensitivity[2753] (Table XI.D.9).

Oral mucosal immunotherapy (OMIT) is an alternative form of AIT distinct from both SLIT and oral/gastrointestinal administration. OMIT utilizes a glycerin-based toothpaste vehicle to introduce antigen to high-density antigen processing oral Langerhans cells in the oral vestibular and buccal mucosa.[2754] Theoretical benefits include induction of immune tolerance using lower antigen concentrations, decreased local side effects, and higher adherence versus SLIT.[2755] Currently, OMIT has been investigated in a single pilot study versus SLIT with findings of clinically significant improvements in disease specific QOL measures and a significant rise in specific IgG4 over the first 6 months of treatment.[2756] No adverse events were reported, and there were no significant differences between outcome measures for both treatment arms.[2756] Further study is needed to define the role of OMIT in the treatment of AR.

Local nasal AIT has been established as an effective and well-tolerated approach for the treatment of pollen and HDM hypersensitivity in adults.[2757,2758] However, high rates of local adverse reactions have been identified in pediatric patients and may limit patient compliance, with one study finding that 43.9% of children abandoned this treatment option within the first year of therapy.[2716] No high quality studies of inhaled/intra-bronchial AIT exist for the treatment of AR, with current studies limited to the treatment of allergic asthma.[2759]

Current evidence suggests limited utility of oral/gastrointestinal, nasal, and inhaled AIT in the treatment of AR due to limited efficacy, increased adverse events, and poor treatment compliance. However, OMIT

TABLE XI.D.9 Evidence table – oral, nasal, and inhaled immunotherapy for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Van Deusen et al.[2752]	1997	2	RCT	Ragweed induced AR: Oral AIT Placebo	Symptoms Medication use NPT sIgE sIgG sIgG4	Oral AIT demonstrated serologic response to therapy No significant differences in symptom or medication scores versus placebo
Oppenheimer et al.[2751]	1994	2	RCT	Patients with cat allergy: Oral AIT Placebo	Symptoms SPT sIgE sIgG	Oral AIT is not effective for cat allergy No significant differences in outcome measures versus placebo
Taudorf et al.[2750]	1987	2	RCT	Birch pollen induced AR: Oral AIT Placebo	Symptoms Medication use SPT NPT CPT	Oral AIT for birch pollen allergy demonstrated significant improvement in SPT, CPT and eye symptoms; non-significant improvement in NPT and nasal symptoms
Reisacher et al.[2756]	2016	3	Cohort	AR patients: OMIT SLIT	Symptoms Medication use QOL SPT Total IgE sIgE sIgG4	OMIT and SLIT produced similar changes in symptom, medication, and QOL scores Similar improvements in SPT and serologic response
Passalacqua et al.[2757]	1995	3[a]	RCT	Parietaria induced allergy: Local nasal AIT Placebo	Symptoms Inflammatory cell infiltration on nasal scrapings following NPT sIgE sIgG Soluble ICAM-1 Soluble ECP	Local nasal AIT reduced eosinophilic and neutrophilic mucosal infiltration following NPT Soluble ICAM-1 levels significantly reduced versus placebo Symptom scores were significantly reduced with local nasal AIT
Andri et al.[2758]	1993	3[a]	RCT	Dermatophagoides induced allergy: Local nasal AIT (powdered antigen) Placebo	Symptoms Medication use SPT NPT sIgE	Local nasal AIT significantly reduced total symptom scores, nasal symptom scores, and medication scores after 26 weeks of therapy No significant differences identified in SPT or sIgE

Abbreviations: AIT, allergen-specific immunotherapy; AR, allergic rhinitis; CPT, conjunctival provocation test; ECP, eosinophil cationic protein; IgE, immunoglobulin E; ICAM, intercellular adhesion molecule; LOE, level of evidence; NPT, nasal provocation test; OMIT, oral mucosal immunotherapy; QOL, quality of life; RCT, randomized controlled trial; sIgG, specific immunoglobulin G; SPT, skin prick test; sIgE, specific immunoglobulin E; SLIT, sublingual immunotherapy.
[a]LOE downgraded due to small sample size

represents a possible alternative to SCIT/SLIT warranting further study.

Other forms of immunotherapy – oral, nasal, inhaled

Aggregate grade of evidence: B (Level 2: 3 studies, level 3: 3 studies; Table XI.D.9)

Benefit: OMIT and local nasal AIT represent alternative AIT administration methods for individuals who are unable to comply with SCIT or SLIT treatment regimens. Oral AIT has not consistently shown benefit for the treatment of AR. Inhaled AIT has not demonstrated benefit for the treatment of AR.

Harm: OMIT may be associated with increased cost to patients due to non-standard preparation methods. Oral AIT is associated with increased risk of gastrointestinal side effects and treatment noncompliance and has not consistently demonstrated benefit for AR symptoms. Inhaled AIT has not shown benefit for AR.

Cost: Moderate.

Benefits-harm assessment: OMIT equivocal to SLIT; possible benefit for local nasal AIT with low risk for harm; balance of harm over benefit for oral AIT and inhaled AIT.

Value judgments: While a single study has demonstrated OMIT to be non-inferior to SLIT in objective and subjective patient outcomes, further study of OMIT is needed to substantiate these results prior to widespread clinical use. Local nasal AIT may have utility for the treatment of AR not associated with additional atopic symptoms; however, further study is needed to demonstrate clinical efficacy. Oral AIT and inhaled IT do not appear to be beneficial for the treatment of AR.

Policy level: Option for OMIT as an alternative to SCIT or SLIT, pending additional studies. Local nasal AIT has not shown benefit as alternative to SCIT or SLIT at present, further study may find benefit for patients with AR without additional atopic symptoms. Recommend against oral AIT. Recommend against inhaled AIT.

Intervention: OMIT may be presented as an option for the administration of AIT in patients unable to tolerate SCIT or SLIT; further study is encouraged. Local nasal AIT has not yet shown clinical efficacy for the treatment of AR relative to conventional forms of immunotherapy; further study may yet find benefit. Oral AIT and inhaled AIT do not appear to be effective for the treatment of AR.

XI.D.10 | Combination therapy – monoclonal antibody (biologic) therapy and subcutaneous immunotherapy

There are currently six biologics/monoclonal antibodies approved by the US FDA for the treatment of asthma and allergic diseases: omalizumab (anti-IgE), mepolizumab (anti-IL5), reslizumab (anti-IL5), benralizumab (anti-IL5Rα), dupilumab (anti-IL4Rα), and tezepelumab (anti-TSLP). Omalizumab, mepolizumab, and dupilumab are also approved for the treatment of CRSwNP, and benralizumab is pending approval for this indication.[2760]

None of the six biologics are approved as an adjunctive therapy to AIT. However, there have been several studies examining the concomitant use of AIT with omalizumab. The only other biologic to be studied in this manner is dupilumab, and only in a single study. In a Phase 2a, multicenter, double-blind, placebo-controlled, parallel-group study conducted in 103 adults with grass pollen-induced seasonal AR, patients were randomized 1:1:1:1 to SCIT, dupilumab (300 mg every 2 weeks), SCIT plus dupilumab, or placebo. SCIT was administered using an 8-week cluster protocol (escalating doses of 1–3 SCIT injections weekly to approximately 20 μg Phl p 5) followed by 8 weeks of maintenance injections. The investigators found that 16 weeks of SCIT plus dupilumab may improve SCIT tolerability but did not incrementally reduce post-allergen challenge nasal symptoms compared with SCIT alone[2086] (Table XI.D.10).

The remainder of this section will focus on the efficacy and safety of the combination of omalizumab plus AIT. Prior to many of the studies examining the combination, omalizumab as a standalone therapy was shown to be effective for the treatment of seasonal and perennial AR.[2076,2077]

The first clinical trial that investigated the effects of omalizumab plus AIT was conducted by Kuehr et al.[2088] In this double-blind placebo-controlled multisite RCT, 221 patients aged 6–17 years with moderate to severe AR and sensitization to birch and grass pollen were randomized to one of four different treatments: SCIT (either grass or birch pollen), starting at least 14 weeks before the local birch pollen season and after the 12-week SCIT titration phase, and either omalizumab or placebo therapy was added. This combination therapy with SCIT and

TABLE XI.D.10 Evidence table – combination monoclonal antibody (biologic) therapy and subcutaneous immunotherapy for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corren et al.[2086]	2021	2	RCT	Adults, grass pollen induced AR: SCIT Dupilumab (300 mg every 2 weeks) SCIT + dupilumab Placebo	Change from pre-treatment baseline in AUC TNSS 0–1 h following nasal allergen challenge with Timothy grass extract	Dupilumab may improve SCIT tolerability but did not reduce post-allergen challenge nasal symptoms versus SCIT alone
Massanari et al.[2767]	2010	2	RCT	Adults, poorly controlled moderate persistent allergic asthma undergoing cluster SCIT: Omalizumab pretreatment Placebo	Incidence of systemic allergic reactions	Omalizumab pretreatment associated with a lower incidence of systemic reactions and higher likelihood of reaching maintenance SCIT dose
Kopp et al.[2765,2766]	2013 2009	2	RCT	Adults and adolescents, grass pollen induced AR/asthma undergoing depigmented grass SCIT: Omalizumab Placebo	Sum of daily scores for symptom severity and rescue medication use (symptom load)	Combination therapy of omalizumab-SCIT reduced daily symptom load, improved control of rhinoconjunctivitis and asthma, improved QOL
Casale et al.[2087]	2006	2	RCT	Adults, ragweed induced AR: Omalizumab pretreatment + rush SCIT Omalizumab pretreatment + placebo SCIT Placebo omalizumab + rush SCIT Placebo omalizumab + placebo SCIT	Daily symptom severity Incidence of adverse events	Pretreatment with omalizumab resulted in five-fold decreased risk of rush SCIT associated anaphylaxis Combination therapy associated with reduction in symptom severity versus SCIT alone
Kuehr et al.[2088]	2002	2	RCT	Children and adolescents, seasonal AR: SCIT-birch followed by omalizumab SCIT-birch followed by placebo SCIT-grass followed by omalizumab SCIT-grass followed by placebo	Daily symptom severity Rescue medication use	Combination therapy is clinically superior to either component monotherapy, with reduced symptom severity and rescue medication scores

Abbreviations: AR, allergic rhinitis; AUC, area under the curve; LOE, level of evidence; QOL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; TNSS, Total Nasal Symptom Score.

omalizumab or placebo lasted 24 weeks. Combination therapy with omalizumab reduced symptom load over the two pollen seasons (birch and grass) by 48% over SCIT alone ($p < 0.001$). Combination therapy also reduced the need for rescue medication, days with allergy symptoms, and symptom severity compared with SCIT alone ($p < 0.001$). A safety analyses of these data indicated that redness and swelling at the SCIT injection sites appeared significantly more often in the placebo group versus the omalizumab group ($p < 0.05$) suggesting a positive effect of omalizumab on local reactions induced by SCIT.[2761] Subgroup analysis of grass allergic patients confirmed the primary study results.[2762]

Because omalizumab reduces free IgE resulting in a decrease in the high affinity IgE receptor, FcεR1, pretreatment with omalizumab should allow for safer and more effective AIT.[2763,2764] Casale et al.[2087] conducted a three-center, double-blind placebo-controlled RCT in patients with ragweed-induced seasonal AR to examine whether omalizumab given 9 weeks before rush SCIT (1-day rush, maximal dose 1.2–4.0 μg Amb a 1), followed by 12 weeks of dual omalizumab and SCIT, is safer and more effective than AIT alone. Patients receiving both omalizumab and SCIT showed a significant improvement in severity scores during the ragweed season compared with those receiving SCIT alone (0.69 vs. 0.86; $p = 0.044$). Omalizumab pretreatment resulted in fewer adverse events during rush SCIT, and a post hoc analysis found a five-fold decrease in risk of anaphylaxis caused by ragweed SCIT (SCIT alone 25.6% vs. SCIT with omalizumab 5.6%; $p = 0.03$). The combination also resulted in prolonged inhibition of allergen-IgE binding compared with either treatment alone, events that might contribute to enhanced efficacy.[2607]

Kopp et al. performed a double-blind, placebo-controlled, multicenter RCT of omalizumab versus placebo in combination with depigmented SCIT during the grass pollen season in patients with seasonal AR and co-morbid seasonal allergic asthma. Omalizumab or placebo was started 2 weeks before SCIT, and the entire treatment lasted 18 weeks. Combination therapy reduced daily symptom load by 39% ($p < 0.05$), improved control of rhinoconjunctivitis and asthma, and improved QOL, but no significant improvements in SCIT safety were observed.[2765,2766]

Massanari et al.[2767] conducted a study to evaluate the efficacy of omalizumab in improving the safety and tolerability of SCIT given to a high-risk population of adults with persistent asthma uncontrolled on inhaled corticosteroids. This multicenter, double-blind, parallel-group study randomized patients to treatment with omalizumab or placebo for 8 weeks, after which they received SCIT to at least one of three perennial aeroallergens (cat, dog, HDM) according to a 4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance therapy. Use of omalizumab was associated with 50% fewer systemic allergic reactions to AIT and enabled more patients to achieve the target immunotherapy maintenance dose.

Combination biologic therapy and subcutaneous immunotherapy

Aggregate grade of evidence: B (Level 2: 5 studies; Table XI.D.10)

Benefit: Improved safety of accelerated cluster and rush SCIT protocols, with decreased symptom and rescue medication scores among a carefully selected population.

Harm: Financial cost and low risk of anaphylactic reactions to omalizumab.

Cost: Moderate to high.

Benefits-harm assessment: Preponderance of benefit over harm.

Value judgments: Combination therapy increases the safety of SCIT, with decreased systemic reactions following cluster and rush protocols. Associated treatment costs must be considered. While two high-quality RCTs have demonstrated improved symptom control with combination therapy over SCIT or anti-IgE alone, not all patients will require this approach. Rather, an individualized approach to patient management must be considered, with evaluation of alternative causes for persistent symptoms, such as unidentified allergen sensitivity. Also, the studies did not compare optimal medical treatment of AR (INCS, antihistamine, allergen avoidance measures) to combination therapy versus SCIT alone. The current evidence does not support the utilization of combination therapy for all patients failing to benefit from SCIT alone.

Policy level: Option

Intervention: Current evidence supports that anti-IgE may be beneficial as a premedication prior to induction of cluster or rush SCIT protocols, and combination therapy may be advantageous as an option for carefully selected patients with persistent symptomatic AR following AIT. However, at the time of this writing, biologic therapies are not approved by the US FDA for AR alone. An individualized approach to patient management must be considered.

XI.D.11 | Efficacy considerations for immunotherapy

XI.D.11.a | *Extract factors*

XI.D.11.a.i | *Allergen standardization and heterogeneity.* Although the efficacy of AIT is well-established, one factor that limits its widespread application is the heterogeneity of natural allergen extracts. Maintenance of product-specific standardization (or batch-to-batch consistency) and cross-product standardization (or consistency among products from different manufacturers) both pose unique challenges. This is due, in large part, to the natural origin of allergen product from biologic sources.[2460,2461]

Traditionally, the active ingredients of AIT extracts have been mixtures of crude proteins and allergens extracted from biological sources, such as pollens, animal dander, or HDM. In fact, prior to the 1970s it was common practice for allergists to manufacture their own extracts using allergen materials provided by regional suppliers.[2499] Understandably, this resulted in a high degree of variability among allergen extracts.

Even now with extraction methods subject to regulatory standards, allergen extracts remain heterogeneous. Today, allergens are still manufactured by extracting mixtures of allergen and other proteins from biological sources. Impurities in source materials may exist, and there is biologic variability in the raw material. While there is inherent variance in the product related to the sourcing and collection of allergenic materials, the extraction process has become more standardized across the industry.[2768] Extraction typically occurs using Coca solution (physiologic saline, bicarbonate buffer, and phenol) with or without glycerin. All allergen extracts must be sterilized and must contain bacteriostatic and fungistatic preservative. In the US, manufacturers typically use phenol at 0.2%–0.5% with or without 50% glycerin. These extracts may then be used unmodified, as is the case with most US extracts, or they may be treated with aldehydes and then processed with or without an adjuvant, such as aluminum hydroxide, as is the case with a majority of European SCIT extracts.[2460,2499]

In the US, the CBER is responsible for the regulation of allergenic extracts. Two important features of CBER's regulatory program have focused on the establishment of safe, consistent allergen manufacturing processes, as well as allergen standardization. The primary purpose of allergen standardization is to characterize the biologic potency of allergen extracts in a consistent manner. CBER mandates which test defines potency and the units by which potency is assigned. For example, one allergen may have potency determined by ELISA, while another may be determined by IDT ($ID_{50}EAL$). These standardization practices then result in potency measurements in either BAU or AU. This aids in decreasing variability among lots as well as across manufacturers. In the US, 19 allergen extracts are currently standardized. These include HDM, cat pelt and cat hair, grasses, ragweed, and venoms. A majority of allergens in the US remain non-standardized and carry labeled units (PNU or weight/volume) that do not correlate with biologic activity or potency.[2461] One caveat to CBER's standardization effort is the fact that potency units are typically assigned based on only one or two major allergen proteins, such as Fel d 1 for cat or Amb a 1 for ragweed. Even with strides made toward standardization, limitations persist and CBER continues to investigate novel approaches toward determining extract potency.

Further complicating efforts to minimize antigen heterogeneity and facilitate intercontinental evidence-based recommendations, US standardization efforts are difficult to compare with European and other global standardization practices. In fact, standardization in Europe is largely based on in-house references, and different units based on biological activity are utilized.[2499] Since no international consensus is established for the standardization of extracts, comparison of different products is difficult, and this variability interferes with intelligent interpretation of published studies across the continents. The CREATE project aimed to support the introduction of major allergen-based standardization using recombinant or purified natural allergens as reference materials, as well as to validate existing ELISA tests for the measurement of major allergens.[2467]

One additional evolving challenge is the practice (more widespread in Europe) of modifying aeroallergen extracts via formulation with adjuvants or allergoids, as well as the use of recombinant allergens. While these novel approaches to allergen preparation may ultimately lead to improved safety and efficacy of AIT, there is currently no sufficient evidence to show clear advantage over the use of crude allergen extract in a majority of cases.[2469] These modifications further contribute to questions regarding the impact on efficacy of AIT, as well as allergen standardization and heterogeneity. (See Section XI.D.4. Allergen Extracts for additional information on this topic.)

XI.D.11.a.ii | *Multi-allergen immunotherapy.* The approach to treatment of polysensitized patients has been the subject of international debate. In the US, it is common practice for allergists to first characterize a sensitization profile, and subsequently provide multi-allergen immunotherapy, whereby several allergen extracts are administered simultaneously throughout the treatment course. Conversely, a common practice in Europe entails identification of the most clinically problematic allergen followed by single-allergen administration.[2419,2769] If a

single allergen cannot be identified as the predominant culprit for allergic symptoms, additional extracts may be given so long as they are administered at separate sites with at least 30-min intervals.[2770,2771] The Allermix survey conducted across 16 countries in 2016 revealed that 98% of providers reported management of polyallergic patients. Approximately 58% of these providers used single-allergen immunotherapy while the remaining 42% used multi-allergen immunotherapy.[2772]

Given that polysensitized patients are not necessarily polyallergic, the overuse and efficacy of multi-allergen immunotherapy has been questioned. Skin testing or sIgE blood tests may be positive but may not correlate with clinical symptoms or disease. Furthermore, positive testing may reflect cross-reactivity with proteins within other allergens that are not associated with symptoms. CRD may play an important role in clarifying the primary sensitizations but is not widely available.[1409] The multi-allergen approach is scientifically supported by four double-blind placebo-controlled RCTs from the 1960s to 1980s (two studies with AR). These trials demonstrated significant improvement in patients who received mixtures of multiple, unrelated allergen extracts, but these studies were done prior to better standardization of extracts.[2773–2776] More recent studies based in Spain have also supported multi-allergen immunotherapy.[2777,2778] A systematic review in 2009 evaluated 13 multi-allergen immunotherapy studies (11 SCIT, one SLIT, and one both) and corroborated that co-administration of two extracts is in fact clinically effective.[2779] Nevertheless, the results were less clear when more than two extracts were administered contemporaneously, a practice often used by US allergists. In fact, a survey comprising 670 patients across six US and Canadian practices reported a mean of 18 extracts in their mixtures.[34,2780]

Although few prior studies have directly evaluated multi-allergen immunotherapy compared to single-allergen immunotherapy in polysensitized AR patients, there is growing evidence that the efficacy of these two strategies may not differ. Potential limitations in multi-allergen SLIT were highlighted in a previous double-blind placebo-controlled RCT in which efficacy outcomes were suboptimal compared to single-allergen SLIT.[2669] Ortiz et al.[2667] recently demonstrated that despite significant improvement in allergic symptoms across all subject groups, there was no significant difference observed in efficacy of single-allergen SLIT versus pauci-allergen (three to six allergens) or multi-allergen SLIT in polysensitized patients. Additionally, Wang and Shi[2547] concluded that single-allergen SLIT response is comparable to multi-allergen SCIT in children with AR secondary to HDM.[1721] On the other hand, several studies, including a meta-analysis for HDM, have substantiated comparable efficacy of single-allergen immunotherapy in monosensitized and polysensitized AR patients.[1406,2661,2668,2671,2684,2781,2782]

A clear knowledge gap is the need for further evidence to support the use of multi-allergen immunotherapy in polysensitized patients.[2769] Unfortunately, well-controlled studies in the polysensitized population are difficult to design and conduct. Sensitization profiles can vary drastically among patients, resulting in a heterogeneous population that is difficult to investigate. Moreover, comparison of single-allergen immunotherapy versus multi-allergen immunotherapy is challenging as each unique polysensitization profile contains a different single dominant allergen to target which in turn may be difficult to distinguish clinically. At the time of this writing, there were 11 active or recruiting clinical trials investigating efficacy of AIT in AR patients (five SCIT, two SLIT, one both SCIT and SLIT, and three ILIT).[2783] None of the studies compare single-allergen to multi-allergen IT.

If multi-allergen SCIT is administered, several considerations must be accounted for prior to the mixing process.[2771,2784] First, one must be careful to maintain therapeutic amounts of each allergen in the mixture. Second, the chosen preservative must be compatible with all allergens in the mixture. Moreover, attention must be paid to the proteolytic activity of fungal and some insect body extracts. When extracts with greater proteolytic activity are mixed with certain allergens susceptible to proteolysis such as pollen, mite, and animal dander allergens, the effective concentrations in the extract mixture may be reduced.[2785,2786]

Given the widely varied practice patterns and challenges inherent in the study of polysensitized individuals, the evidence supporting multi-allergen immunotherapy is not as strong as that supporting single-antigen immunotherapy strategies. Although it is difficult to directly compare multi-allergen and single-allergen treatment strategies, the literature strongly supports the efficacy of single-antigen immunotherapy even in polysensitized patients, while there remains a need for more careful analysis of the efficacy of multi-allergen immunotherapy. (See Section XI.D.11.b.ii. Polysensitization for additional information on this topic.)

XI.D.11.b | *Patient factors*

XI.D.11.b.i | *Patient age.* Patient age is not a contraindication for AIT, but unique characteristics of the extremes of age merit discussion. First, older adult patients with multiple or particular comorbidities might be regarded as having a higher risk associated with AIT. Second, immunosenescence is also a concern, as older adults may theoretically have reduced benefit due to a less plastic immune response from the intended immunomodulatory effects of AIT. Yet, multiple studies in older adults have confirmed AIT is

effective in treating clinical symptoms with associated positive effects on immunologic biomarkers. In four separate RCTs, Bozek et al. demonstrated the clinical effects of SLIT and SCIT for dust mite and grass pollen mixture in patients ranging 60–75 years of age, showing improvement in TNSS and medication usage, as well as an increase in antigen-specific IgG4 levels.[2548,2549,2690,2787] These effects remained durable 3 years after completing a 3-year course of SCIT.[299]

In children, several studies have demonstrated AIT has short-term and long-term effectiveness, including decreasing the dose of inhaled corticosteroids in asthmatic patients.[2788–2793] Literature supports the efficacy of both SCIT and SLIT in the pediatric population.[2438] There is no lower age limit delineated in the US for initiating SCIT, but FDA-approved SLIT products are only approved beginning at age 5.

Pediatric AIT may have additional benefit of prolonged disease modifying effects. In the Preventive Allergy Treatment (PAT) study, 205 children aged 5–13 with rhinoconjunctivitis to birch and/or grass pollen were randomized to AIT versus pharmacotherapy. AIT patients had less asthma symptoms, improved methacholine response, and potential for asthma prevention.[2794,2795] SLIT using a grass tablet was shown to have a similar asthma prevention effect in the Grass immunotherapy tablet Asthma Prevention (GAP) trial.[2429] Similarly, in a retrospective analysis of 1099 children with AR receiving grass pollen SLIT tablets were compared with 27,475 rhinitis-control patients only 1.8% of SLIT treated children developed asthma versus 5.3% of control patients.[2796] A meta-analysis concluded that AIT decreases the risk of neo-sensitization and asthma development in the short-term (asthma RR 0.40; neo-sensitization RR 0.72), although the long-term benefit is unclear.[2426]

Safety and tolerability are important considerations in the pediatric population. In a retrospective evaluation of systemic reactions in pediatric and adult patients, the unadjusted systemic reaction rate was higher in children (0.2%) but not when adjusted for asthma, gender and phase of SCIT.[2797] In a Chinese population, systemic reactions were more common in younger children (3.28% of injections) compared with adolescents (1.47% of injections) but were treatable without requiring hospitalization.[2798] AIT is not customarily initiated in infants and toddlers given fears of the child not being able to communicate symptoms, in particular those of systemic reactions, and concerns that injections may be poorly tolerated in very young children.[2419] Every potential pediatric AIT case merits consideration of balancing the potential benefits versus risks and inviting child and parent to participate in shared decision-making to express their values and preferences regarding the trade-offs of AIT, which are likely quite individualized. Similar processes and considerations are recommended for older adults.

XI.D.11.b.ii | *Polysensitization.* Polysensitization, or sensitization to more than one allergen, is common in the general population, and a factor which potentially challenges AIT efficacy. In an effort to identify the prevalence of sensitization in the general population, a 2010 study showed that among 11,355 participants in the first ECRHS, 57%–67.8% of the population was not sensitized to any test allergens, 16.2%–19.6% were monosensitized, and 23.8%–25.3% were polysensitized.[2799] Similarly, the National Health and Nutrition Examination Survey III (NHANES) studied skin sensitization to common aeroallergens in the US general population. Among the 10,863 participants 45.7% were not sensitized to any test allergens, 15.5% were monosensitized, and 38.8% were polysensitized.[2800] Hence, polysensitization appears to be more prevalent than monosensitization in the general population. More recent evidence suggests that polysensitization may be an entirely distinct phenotype compared to monosensitization, possibly predictive of more severe comorbid allergic disease expression.[418,2771,2801]

Once polysensitization is established via skin testing or sIgE testing, the conundrum facing allergists is whether this polysensitization represents true polyallergy. To have polyallergy, the individual must have relevant symptoms upon exposure to two or more specific, sensitizing allergens.

In some patients showing positive test responses to multiple allergens, this may be caused by cross-reactivity to highly conserved proteins, or panallergens. These related proteins, which have highly conserved sequence regions and structures, trigger IgE cross-recognition. Separating the clinical relevance of positive test responses to pollens known to demonstrate cross-reactivity can be challenging because the seasonality of symptoms may overlap.[2802] New technologies focused on CRD may prove useful in determining whether cross-reactive allergens are the cause of polysensitization, and may help to direct AIT decisions.[2803]

The issue of whether the polyallergic patient is best treated with more than one (or even several) clinically relevant allergens versus a single allergen deemed most responsible for the patient's symptoms, is a subject of debate, and one characterized by trans-continental practice variations. The predominant approach in the US is to treat the polyallergic patient with multiple allergens simultaneously, while the European approach is to focus AIT on one, or at most two, clinically significant allergens.[2769]

While the published literature comparing the efficacy of single- or multi-allergen immunotherapy in the polysensitized patient continues to evolve, there are published guidelines which can help to direct practical

decision making. Not unexpectedly, these guidelines reflect regional bias. The 2018 EAACI Guidelines on Allergen Immunotherapy specify that polysensitized patients who are monoallergic receive AIT only for the specific allergen driving their symptoms. The EAACI guidelines further specify that for the polyallergic patient sensitized to two homologous allergens (i.e., two grass pollens), a single allergen preparation or a mixture of two homologous allergens may be used, and for the polyallergic patient sensitized to allergens which are not homologous, AIT should be limited to one or two of the clinically most important allergens administered separately at distinct anatomic locations and separated by 30–60 min.[2418] Similarly, the 2010 Global Allergy and Asthma European Network (GA^{2}LEN)/EAACI pocket guide does not recommend the use of allergen mixtures in AIT.[2770] The Practice Parameter Third Update guidelines developed by the Joint Task Force[2419] acknowledges that there have been few studies investigating the efficacy of multiallergen SCIT, and that these studies have considerable heterogeneity, yielding conflicting results. The Practice Parameter emphasizes the importance of treating patients with only *relevant* allergens but does not discourage prescribing multi-allergen immunotherapy in properly selected patients. (See Section XI.D.11.a.ii. Multi-allergen Immunotherapy for additional information on this topic.)

XI.D.11.b.iii | *Adherence to therapy.* Adherence to AIT is variable and dependent upon route of administration, SLIT versus SCIT, dosing frequency/regimen, patient characteristics, and AIT-associated adverse events. A review of the literature indicates no reported prospective double-blind, placebo-controlled RCT examining and/or comparing the adherence of SLIT versus SCIT as the primary endpoint. However, there are data on the adherence of AIT in prospective double-blind, placebo-controlled RCT of clinical efficacy, but these data are somewhat artificial in that adherence is closely monitored and patients are selected based on criteria that would promote better compliance to therapy. Furthermore, since optimal efficacy of either SLIT or SCIT is not appreciated until a minimum of 2 and optimally 3 years of therapy, adherence rates must be determined over a prolonged period. AIT adherence is reported to be much lower in real-life studies versus clinical trials. For example, in an analysis of sales figures from two SLIT manufacturers in Italy that account for more than 60% of the Italian immunotherapy market, sales decreased from 100% at the start to approximately 44% in the first year, 28% in the second year, and 13% in the third year. This indicates that less than 20% of patients were adherent to the prescribed SLIT regimen.[2804]

A non-interventional, prospective, observational, multicenter, open label study examined the adherence of 399 patients (236 adults and 163 children) with moderate-to-severe grass-induced allergic rhinoconjunctivitis to a 3-year regimen of grass SLIT tablets. The authors found that only 55% of patients completed the 3-year treatment period.[2805] These data are similar to many retrospective analyses of adherence to SLIT at the end of a 3-year regimen, ranging 10%–61%[2806–2808] and illustrate that even though self-administration of AIT could be advantageous over injections requiring office visits, adherence is a significant problem.

The adherence rate to SCIT regimens have also been studied in retrospective and a few prospective uncontrolled studies. In a real-world study examining claims data, 103,207 patients were reported to have at least one AIT claim, but only approximately 44% of these patients reached maintenance AIT. There was no follow-up of these patients to determine how many of the 56% that reached maintenance continued AIT for a full 3 years.[2809] A retrospective cohort analysis of a German longitudinal prescription database indicated that at the end of 3 years, adherence to SCIT was 35%–37%, and higher than that reported for SLIT (10%–18%).[2810] A data management retrospective study compared adherence to SCIT and SLIT at the end of 3 years and found that SLIT patients had a higher dropout rate (39%) versus SCIT (32.4%).[2808] In a retrospective analysis of a community pharmacy database, only 18% of 6486 patients starting AIT reached a minimal duration of 3 years, 23% for SCIT and 7% for SLIT.[2717] A retrospective analysis compared attrition rates in patients prescribed SCIT or SLIT found at the end of the prescribed period, attrition rates were similar, 45% and 41%, respectively.[2811] Another retrospective analysis comparing SLIT versus SCIT adherence found that only about 30% of patients completed a 3-year course of either therapy.[2812]

Overall, the strength of evidence is low since most studies involved retrospective analyses and none reported efficacy outcomes. However, data strongly suggest that adherence to either regimen of AIT is very low which likely results in poorer efficacy. Reasons for the poor adherence are many and include inconvenience of taking a daily medication (SLIT) or frequent office visits (SCIT), adverse events especially during the first months of therapy, cost, and perceived lack of benefit.

XI.D.11.b.iv | *Pregnancy.* AR and asthma affect 20%–30% of women of childbearing age and are considered two of the most common medical conditions that can affect pregnancy.[2813] One-third of these women will suffer from worsening symptoms during pregnancy[2814] and up to 20% will experience exacerbations of asthma resulting in hospitalization or even death.[2815] AIT is an effective treatment option for AR, and its role in pregnancy continues to be investigated. The evidence regarding the efficacy

and safety of AIT during pregnancy is scarce with a single large-scale prospective study published to date. In the most recent Practice Parameter update, it is stated that AIT can be continued, but not initiated, in the pregnant patient. Furthermore, if pregnancy occurs during the build-up phase and the patient has not reached a therapeutic dose, discontinuation of AIT should be considered.[2419]

The first study to assess the safety of AIT in pregnancy was published in 1978 by Metzger et al.[2816] This retrospective study analyzed the incidence of prematurity, toxemia, abortion, neonatal death, and congenital malformation in 90 atopic women who received SCIT during their pregnancy compared to a group of 147 untreated atopic mothers. No significant difference in these outcomes was found between the two groups suggesting that continuation of AIT during pregnancy was safe.

Over the next 10 years questions regarding the safety of AIT during pregnancy continued. In 1993, Shaikh et al.[2450] published a retrospective study that investigated 81 atopic women who underwent SCIT during pregnancy, for a total of 109 pregnancies. Similar variables as the Metzger et al.[2816] study were analyzed, and when compared to the control group of 60 patients (82 pregnancies) who declined AIT, the incidence of prematurity, gestational hypertension, and proteinuria were actually lower. Of note, only seven of the 109 pregnancies initiated SCIT for the first-time during pregnancy. This study supported that SCIT was not only safe during pregnancy, but control of allergies and asthma during pregnancy may decrease adverse perinatal outcomes.

To date, only one RCT has been performed to demonstrate the safety of starting SLIT in the pregnant population. Shaikh et al.[2451] separated 280 atopic women (326 total pregnancies) into one of three groups: 155 patients received SLIT during 185 pregnancies (with 24 patients receiving SLIT for the first time during pregnancy). The remaining patients were separated into two control groups, receiving either daily budesonide (group A) or rescue inhaled salbutamol (group B). The study showed no significant differences in perinatal outcomes, suggesting that both initiation and continuation of SLIT was safe during pregnancy. Although this study concludes that initiation of SLIT during pregnancy is safe, it is important to note that only 24 patients, 13% of the treatment group, fell into the initiation arm of the study.

Continuation of AIT during pregnancy has not shown to be harmful to either the mother or the fetus. There is limited data, however, to draw conclusions regarding the safety of first-time initiation of AIT during pregnancy. Lastly, no conclusion can be made regarding the effects of pregnancy on efficacy of AIT due to lack of literature.[2551]

XII | PEDIATRIC CONSIDERATIONS IN ALLERGIC RHINITIS

XII.A | History and physical exam

As repeated exposure to allergens is required, AR takes a few years to develop in children. Food and indoor allergies are more common in children under the age of 3, with seasonal outdoor allergy risk increasing after the age of 3.[2817] A family history of AR, atopy, or asthma is important to assess as children may be at an increased risk of developing AR or other allergic diseases.[2818] The future development of AR should be considered in children exhibiting signs of the "allergic march".[2819] Certain risk factors may have a link to the development of AR in children. (See Sections VIII. A-B. Risk Factors for Allergic Rhinitis for additional information on this topic.)

Common findings consistent with AR in children include nasal congestion, sneezing, postnasal drip, cough, sniffling, throat clearing, palatal click, and mouth breathing.[2820–2824] Defining a seasonal timeline or triggers for symptoms can help identify a cause and help determine if rhinitis is allergic or non-allergic in nature.[2818]

Although evidence is conflicting and variable, there are several conditions possibly associated with AR in children, which should be assessed during clinical evaluation. The most common comorbidities associated with childhood AR are asthma, conjunctivitis, and AD.[2823] Other comorbidities include rhinosinusitis, SDB, ETD, otitis media, and oral allergy syndrome.[1143,2817,2825,2826] Oral allergy syndrome may be suspected in patients with mouth itching or swelling after eating raw fruits or vegetables.[2825]

There is data to suggest that AR is more common in children with otitis media with effusion (OME) than those without. While the results vary based on the age of the children studied, this highlights the importance of ear evaluation during the physical exam.[2826–2828] (See Section XIII.G.2. Otitis Media for additional information on this topic.) Similarly, the association of adenoid hypertrophy (AH) with AR is debated, but some studies have suggested the importance of the correlation between these two diseases.[1143,2826,2829–2831] (See Section XIII.F. Adenoid Hypertrophy for additional information on this topic.) This may help to explain the association between AR and OSA in children.

Diagnosing AR in the pediatric population may be challenging due to difficulty clearly communicating symptoms. There is also overlap of symptoms with frequent illnesses experienced in childhood, for example, upper respiratory infection. Diagnostic clues, which may be reported by a parent or caregiver include chapped lips from

mouth breathing, fatigue, irritability, poor appetite, and attention issues.[2818,2820]

After a complete history, there are several elements of the physical exam that may aid in diagnosis. An important aspect of the physical exam is to rule out other etiologies of nasal obstruction and rhinitis such as nasal foreign body or choanal atresia.[2818] Some physical exam findings are similar to the adult population including posterior pharyngeal cobblestoning, clear nasal drainage, serous middle ear effusions, and enlarged/boggy ITs.[2818,2820] Specifically in the pediatric population, "allergic" or "adenoid facies" may be present, characterized by mouth breathing, high-arched palate, and dental malocclusion. Additionally, the "allergic salute" is defined as repeated rubbing of the nose, which can lead to a transverse nasal crease or "allergic crease."[2832] "Allergic shiners" are caused by infraorbital venous stasis and Dennie-Morgan lines are folds below the lower eyelids suggesting allergic conjunctivitis (AC).[2818–2820,2822,2833] Voice changes including hoarseness and hyponasality are common in pediatric AR.[2821] Anterior rhinoscopy can reveal IT bogginess, paleness, and/or hypertrophy.[2818] Nasal endoscopy has been evaluated as a tool for diagnosis in pediatric AR, with IT and MT contact with other nasal structures as predictive factors for positive SPT results.[1218] There are no specific recommendations for the use of nasal endoscopy in children with suspected AR, but this assessment may be important in ruling out other, less common, causes of nasal obstruction or rhinitis.

Of note, one important goal of early diagnosis of AR is to identify young children at risk of developing other allergic disorders.[2834] Non-allergic rhinitis, viral URI, and anatomical causes of nasal obstruction should be on the differential diagnosis in children evaluated for AR.[2820]

XII.B | Diagnostic techniques

Allergy testing recommendations for the pediatric population are similar to those for adults. Allergy testing should be considered in children with insufficient response to medical treatment.[2835] The EAACI Section on Pediatrics recommends that allergy testing be considered in children presenting with AR clinical symptoms and signs in order to initiate treatment and lifestyle changes, such as avoidance of allergens. Clinical practice guidelines exclude children younger than 2 years of age as causes of rhinitis may be different in this population. However, there are no age limits for allergy testing and young children are eligible.[1005]

The diagnosis of AR in children should be based on both clinical history and testing. Allergy testing without clinical suspicion has been shown to lead to false-positive SPT results over 50% of the time.[2826] SPT is generally accepted as the preferred method of testing in children; it is faster and less painful than intradermal testing, and it is less expensive than in vitro serum testing.[2833] Although intradermal testing or SPT may be considered in the pediatric population, SPT is often considered superior due to ease, minimal discomfort, and timeliness of results. There are indications for in vitro testing in children as there are in adults, including skin disorders (e.g., dermatographism, dermatitis at the proposed testing site) and medication usage (e.g., inability to hold antihistamines for testing). It is also important to note that a positive SPT in a young child will result in a smaller wheal size than in an older child or adult due to relatively lower circulating IgE levels.[2818]

There is limited data regarding nasal eosinophil and basophil levels for the purpose of AR diagnosis. Nasal eosinophilia has been associated with AR in children but is not widely used to diagnose AR.[1371,2836–2838] Additionally, nasal basophilic metachromic cells have shown high sensitivity for AR.[2818,2839] While there is limited data on BAT in general, and it is considered an option for AR diagnosis in adults; one small pediatric study has shown that BAT has sensitivity and specificity of 90% and 73%, respectively.[1392]

XII.C | Pharmacotherapy

Most patients with symptoms of AR will use some form of pharmacotherapy for satisfactory symptom control. The specific management of each patient is influenced by the frequency and intensity of symptoms, response to treatment, the presence of comorbid conditions as well as the patient's age and preference. Current pharmacologic options in the treatment of AR include INCS, intranasal and oral antihistamines, decongestants, mast cell stabilizers, intranasal anticholinergics, and LTRAs.[182,1182,2822]

Children less than 2 years of age. In this age group AR is less prevalent, but children may have frequent bouts of allergy-type symptoms including rhinorrhea, sneezing, itchy eyes, etc. which could be due to other, more common triggers, such as recurrent viral illness, AH, or rhinosinusitis. Before treating a young child for AR, other causes should be investigated and ruled out.

The pharmacologic options for AR in children under 2 years old are limited. Second- and third-generation antihistamines such as cetirizine, levocetirizine, and desloratadine have indications down to 6 months of age and are an option in the treatment of the young patient with AR. First-generation antihistamines (diphenhydramine, chlorpheniramine) have the disadvantage of being lipophilic and cross the brain–blood barrier. Unwanted side effects of these medications make them difficult and dangerous

to use and not indicated in children less than 2 years old (Table II.C).

Children 2 years old and older. For the older child, treatment of AR is very similar to that in the adult patient and depends largely on the frequency and severity of symptoms.

Mild or episodic symptoms may be treated with medications aimed at addressing the specific symptom(s). A second- or third-generation antihistamine may be used on an as needed basis for rhinitis, sneezing, and itchy watery eyes. Intranasal antihistamine preparations are another option in children over the age of 5 (azelastine 0.1%) and 6 years old (olapatadine); benefits include targeted delivery, decreased side effects, and rapid onset of action.[182,1182,1479,2840] Intranasal antihistamines have been recommended over oral antihistamines in the appropriate patient population.[1005,1182]

For *persistent or moderate-to-severe symptoms*, INCS are recommended as the best single therapy in the treatment of allergic symptoms affecting QOL.[182,1005,1182,2822] The effectiveness of INCS in the reduction of nasal symptoms including sneezing, itching, rhinorrhea, and congestion in children with AR has been demonstrated.[1864,1865,1867,2841] INCS are usually well tolerated; however, because adverse effects are possible, growth in children using INCS should be monitored and dosages should be tapered to the lowest effective dose in all patients.

INCS preparations approved for children aged 2 years and older include mometasone furoate, triamcinolone acetonide, and fluticasone furoate. Most others are indicated for children aged 6 years and older, except for fluticasone propionate and beclomethasone dipropionate, which are indicated down to age 4 years.

When response to initial INCS is suboptimal, a second agent can be considered. Options include intranasal or oral antihistamines, combination intranasal INCS/antihistamine, or antihistamine/decongestant products. The choice should be made based on the persistent symptoms being addressed, patient preference, possible side effects and coexistent conditions (Table II.C).

LTRAs, such as montelukast, have been used in the management of AR and asthma. LTRA efficacy has been shown to be less effective than INCS, but more effective than placebo.[182,1182,2000,2001,2010,2822] Due to its potential for neuropsychiatric effects, the US FDA has recommended against the use of montelukast in patients with AR in favor of other treatment options. In the latest Clinical Practice Guideline on AR published by the AAO-HNSF, montelukast is not recommended as first line therapy.[1005]

Cromolyn nasal spray is a mast cell stabilizer that can inhibit the allergic response. It is most effective when used as a preventive measure when allergy exposure is anticipated. It has a low side effect profile (sneezing, bad taste, etc.), but due to its short half-life must be administered three to six times daily. It has been approved for use in children as young as 2 years old. Though less effective than INCS or second-generation antihistamines, some parents and clinicians prefer it due to its excellent safety profile.[182,2037,2046]

IPB nasal spray has been shown to decrease rhinorrhea. It has a quick onset of action and must be used frequently. It is not recommended as a first-line drug in AR but has had some success in patients with profuse rhinorrhea not otherwise controlled with INCS. It has been shown to be more effective when combined with a nasal steroid than when either medication is used alone in the treatment of chronic rhinitis.[2063] It is indicated down to age 5 years.

Oral decongestants are also a consideration in the treatment of AR, but due to their side effect profile and potential for central nervous system stimulation in the pediatric population, the risk/benefit ratio should be carefully considered when used in children between the ages of 2 and 6 year old.[182,2842,2843] Oral decongestants are not recommended in younger children (Table II.C).

XII.D | Immunotherapy

AIT is a treatment option when other strategies, such as avoidance and pharmacotherapy, have failed. It may also be considered for patients who cannot tolerate standard therapies, those who want to avoid prolonged used of medications, and those wishing to obtain a lasting response by modifying the immunologic process.[2419] Consideration for AIT should only be undertaken in patients with documented sIgE response to aeroallergens correlating with the patient's allergic symptoms. As long as these recommendations are followed, AIT is an option for allergic patients regardless of age. However, due to the required environmental exposure for the development of clinically relevant sensitization(s) to aeroallergens, combined with the limited evidence for the efficacy of AIT for AR in children under 5 years of age, the decision to provide AIT should consider the above factors along with a discussion with the family regarding its limitations and safety concerns.

Modalities for AIT administration include SCIT and SLIT (available in the form of a dissolvable tablet or as a liquid extract). Both options are available for adults and children, with specific age indications depending on the individual SLIT tablet. Usually patient demographics, preference, and treatment goals are used to guide the choice of AIT modality. For example, in young children who may be traumatized by or unable to tolerate repeated injections, and who may be unable to report early symptoms of an allergic reaction, SLIT may be considered due to its ease of administration and superior safety profile.[2650]

Dosing of SCIT and SLIT liquid extract is the same in the adult and pediatric populations. SLIT tablets currently available in the United States for use in children include a single grass (Timothy) tablet, a multi-grass (sweet vernal, orchard, perennial rye, Timothy, Kentucky bluegrass) tablet, and a short ragweed tablet, all indicated down to age 5 years. The HDM tablet available for adults has not received approval for pediatric use as of this writing.

Though the literature regarding efficacy of AIT is less robust in the pediatric population, it has been shown to be effective in the treatment of AR,[2666,2673,2844] and both SCIT and SLIT have resulted in improved control of comorbid conditions such as asthma and AC.[1005] Of particular interest is the research that has demonstrated that AIT has the potential added benefit of decreasing the development of asthma in pediatric patients with AR, as well as reducing the onset of new allergen sensitizations although additional studies are warranted.[2426,2845,2846]

In all populations, potential contraindications to AIT (SCIT and SLIT) include uncontrolled or poorly controlled asthma, active autoimmune disorders, and malignancy.[2847] EoE is also a contraindication to SLIT.[2452–2455] Special consideration should be given when treating patients with cardiovascular disease, those on β-blocker medications, and those with partially controlled asthma due to their impaired ability to respond to resuscitation efforts should an allergic reaction occur.[2419]

Challenges systematically being addressed in the practice of adult AIT extend to the pediatric population. These include the use of one or multiple allergens in the treatment of AR; whether mixtures of multiple allergens can compromise efficacy; the standardization of the allergen extracts for consistency, quality, and potency; and effective dose ranges for the pertinent allergens used.[2418]

XIII | ASSOCIATED CONDITIONS

XIII.A | Asthma

XIII.A.1 | Asthma definition

Asthma is a common chronic lung disease comprising a heterogeneous group of phenotypes, including allergic and non-allergic, and further subtypes based on demographic, clinical, and/or pathophysiological characteristics.[2848] The definition of asthma has appreciably changed over time.[2849] The latest Global Initiative for Asthma (GINA) Guidelines define asthma as "*a heterogenous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.*"[2850]

In addition to the aforementioned respiratory symptoms, a diagnosis of asthma typically requires evidence of variable obstruction of expiratory airflow, by bronchodilator reversibility testing or bronchial hyperreactivity tests.[2850] In clinical practice patients have a variety of clinical presentations, and when patients are well, most tests show no abnormalities.[2851] Increasingly, asthma is being recognized as a disease of airway inflammation and disordered immunology, as well as aberrant physiology, with combinations of "treatable traits" in different patients.[2852] Most patients have mild or moderate disease. A small proportion (up to 10%) has severe disease that is refractory to standard inhaled medications. These patients have more severe symptoms, frequent exacerbations and need more intensive treatment regimens.[2853]

XIII.A.2 | Asthma association with allergic and non-allergic rhinitis

AR and non-allergic rhinitis have been established as important comorbidities of asthma. Increasingly, there has been a shift toward conceptualizing multimorbid chronic upper airway inflammation and asthma as a single "unified airway" pathology affecting both the upper and lower airway. (See Section VI.K Unified Airway for additional information on this topic).

The prevalence of comorbid AR and asthma varies. Recent population-based studies have shown rates between 20.3% and 93.5%.[763,2854–2858] In one study, AR was found to be an independent determinant of current asthma among adults (OR 7.72; 95% CI 6.56–9.09, $p < 0.001$).[763] Some studies have shown that patients with comorbid AR tend to have poorer asthma control, a greater number of exacerbations per year, and more visits to the emergency department.[2859–2862] Interestingly, the association of allergy with asthma weakens with more severe asthma[2863] (Table XIII.A.2).

Non-allergic rhinitis is also commonly associated with comorbid asthma.[2864,2865] Increasingly, asthma is being considered a multifactorial disease with variable endotype and phenotype presentations, particularly with regards to aberrant type 2 inflammation, which may or may not be allergic.[2866,2867] The functional relevance of this upper airway association can be summarized as follows:

(i) In line with the unified airway hypothesis, allergen and irritant challenge to the nose and upper airway elicits lower airway inflammation through shared immunological and neurogenic pathways.[2868]
(ii) Nasal obstruction results in mouth breathing, which leads to reduced filtration and humidification of inspired air, facilitating reactive lower airways.[2869]

TABLE XIII.A.2 Evidence table – asthma association with allergic and non-allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Shen et al.[2873]	2019	1	Meta-analysis of cross-sectional studies	General public, asthma patients, $n = 3182$	Asthma + AR prevalence	Asthma and AR are often comorbid diseases Asthma + AR prevalence 39%
Tohinidik et al.[2855]	2019	1	Meta-analysis of case–control and cohort studies	AR patients, $n = 274,489$	Association between AR and asthma	History of AR strongly associated with asthma, OR 3.82
Kou et al.[2874]	2018	1	Meta-analysis of cross-sectional studies	General public	Prevalence of AR in pediatric asthma patients	54.9% prevalence of AR in pediatric asthma Prevalence of AR higher in children with asthma than prevalence of asthma in children with AR
Machluf et al.[2856]	2020	2	Cross-sectional	Mild versus moderate-to-severe adolescent asthma patients, $n = 113,671$	AR association with asthma	AR associated with increased risk of developing moderate-to-severe asthma Differences between mild and moderate-to-severe asthma enhance asthma phenotype characterization with respect to comorbidities
Heck et al.[2857]	2017	2	Cross-sectional	Asthma patients in general population, $n = 79,299$	AR association with asthma	Bronchial asthma associated with AR, OR 7.02 Allergic comorbidities should be considered in management of bronchial asthma
Pols et al.[2858]	2017	2	Cross-sectional	Pediatric AR patients versus age- and gender-matched population controls, $n = 7887$	AR association with asthma symptoms	Airway symptoms significantly more frequent in children with asthma Increased risk of asthma-associated symptoms in children with AR: shortness of breath/dyspnea, OR 2.7; wheezing, OR 4.3
Carr et al.[2875]	2019	3	Prospective cohort	Childhood rhinitis (AR and NAR) patients followed from age 6 to 32, $n = 521$	Risk of asthma development in patients with childhood rhinitis	Childhood rhinitis (AR and NAR) confers significant risk of asthma development in adulthood
Togias et al.[2864]	2019	3	Prospective cohort	Pediatric asthma patients followed for 1 year, $n = 749$	Rhinitis in pediatric asthma patients	Rhinitis in 93.5% Perennial AR most common and most severe (34.2%) NAR least common and least severe (11.3%) Rhinitis almost ubiquitous in urban children with asthma; activity tracks that of lower airway disease

(Continues)

TABLE XIII.A.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tosca et al.[2876]	2019	3	Prospective cohort	Pediatric allergy patients, $n = 619$	Rhinitis association with asthma	88% of children with asthma had rhinitis Rhinitis frequently associated with asthma in children
Ji et al.[2880]	2020	4	Retrospective case series	Pediatric asthma/wheezing patients, $n =$ 333,029	AR association with asthma	5.5% of asthma/wheezing patients had AR Comorbidity of allergic diseases common
Kisiel et al.[2877]	2020	4	Cross-sectional	Primary care asthma patients, $n = 1291$	Prevalence of rhinitis in asthma patients	70.7% rhinitis prevalence in asthma patients
Pedersen et al.[2854]	2020	4	Cross-sectional	General public, $n =$ 7275	Prevalence of rhinitis and asthma	7% asthma and 4% rhinitis prevalence Higher prevalence of rhinitis in asthma patients versus without (20.3% versus. 2.9%, OR 8.39) Atopic disease burden high Asthma and rhinitis strongly associated with each other
Heffler et al.[2878]	2019	4	Prospective case series	Asthma patients, $n =$ 437	Comorbidities in asthma patients	Rhinitis in 70% High frequency of comorbidities in patients with asthma
Huang et al.[2879]	2019	4	Cross-sectional survey	General public, $n =$ 57,779	Asthma prevalence, AR association	Overall asthma prevalence 4.2% AR associated with asthma, OR 3.06
Ozoh et al.[763]	2019	4	Cross-sectional	General public, $n =$ 20,063	AR association with asthma	74.7% of those with clinical asthma have AR AR is an independent determinant of current asthma among adults
Sonia et al.[2881]	2018	4	Cross-sectional	General public, $n =$ 4470	Rhinitis association with asthma	48.8% of those with asthma have rhinitis Strong association between asthma and rhinitis
Ziyab[2882]	2017	4	Cross-sectional	Young adults (age 18–26) in the general public, $n =$ 1154	Rhinitis association with asthma	Concurrent asthma and rhinitis in 5.1% Allergic multimorbidity common

Relevant studies prior to 2017 are included in the listed meta-analyses. Abbreviations: AR, allergic rhinitis; LOE, level of evidence; NAR, non-allergic rhinitis; OR, odds ratio.

(iii) Nasal blockage resulting in mouth breathing can be associated with breathing pattern disorders and increased breathlessness in patients with asthma.[2868,2869]

Several recent molecular studies have shed light on the mechanisms underlying the phenomenon of this multimorbidity. GWAS studies have demonstrated independent risk variants, which are common between asthma, AR, and eczema.[801] Moreover, gene expression analyses suggest that type 2 mediated inflammation has a similar molecular basis across disease types.[2870] These findings underscore the proposed "one airway" model, which recognizes similar disease mechanisms occurring in both the upper airway and the lower airway.[2871]

In summary, upper airway symptoms can impact asthma disease control and patient QOL.[2872] Assessment and treatment via a multidisciplinary approach,

encompassing pulmonologists, allergists, immunologists, otolaryngologists/rhinologists, should be considered.

Asthma association with allergic and non-allergic rhinitis

Aggregate grade of evidence: B (Level 1: 3 studies, level 2: 3 studies, level 3: 3 studies, level 4: 8 studies; Table XIII.A.2)

XIII.A.3 | Allergic rhinitis and asthma – association of risk factors

Up to 30% of patients with AR develop asthma.[900] Indeed, several large epidemiological studies have demonstrated that AR is an independent risk factor for developing asthma. Specifically, persistent AR appears to portend a significantly greater risk for development of asthma compared to intermittent AR[845] (Table XIII.A.3).

The Children's Respiratory Study showed that there is a doubling of the risk of developing asthma by age 11 when AR is diagnosed by a physician during infancy.[2883] Rhinitis is also a significant risk factor for adult-onset asthma whether patients are atopic or non-atopic.[2884–2887] In contrast, in childhood, asthma is frequently associated with allergy.[2883,2888] Limited data fail to demonstrate a relationship between a diagnosis of AR and severity of comorbid asthma.[2889] Nevertheless, data on whether the severity of AR itself impacts the prevalence of comorbid asthma remains conflicting.[2890,2891]

Asthma and AR have overlapping risk factors. Aeroallergen sensitization may be the most important and has been demonstrated among adults and children across different geographic regions and populations around the world.[845,2892,2893] Indeed, most inhaled allergens are associated with both nasal and bronchial hyperresponsiveness.[2894] Occupational rhinitis is also a risk factor for occupational asthma caused by HMW agents.[124] Genetic polymorphisms common to AR and asthma, such as unique subtypes of deregulated circulating microRNAs, may also provide a mechanistic link between the two disease processes.[2895]

There is growing evidence that exposure to traffic related air pollutants, (i.e., black carbon, NO_2, NO, SO_2, CO, CO_2, and PM) may increase the risk of developing both asthma and AR. Nevertheless, additional studies with improved study designs incorporating confounder variables (e.g., allergens), and standardized definitions of traffic related air pollutants are needed.[2896–2898] (See Section VIII.B.3. Pollution for additional information on this topic.)

Similarly, a cross-sectional study of 325 non-asthmatic AR patients suggest that cigarette smoking may be an independent risk factor for the development of new asthma among patients with AR, although confirmatory studies are still needed.[2899] (see Section VIII.B.4. Tobacco Smoke for additional information on this topic.)

In summary, AR is a significant risk factor for asthma. However, there is currently limited evidence for the role of traffic related air pollutants and smoking as additional risk factors in the development of asthma among patients with AR.

Allergic rhinitis and asthma – association of risk factors

Aggregate grade of evidence: C (Level 2: 3 studies, level 3: 19 studies; Table XIII.A.3)

XIII.A.4 | Treatment of allergic rhinitis and its effect on asthma

AR and asthma are linked both epidemiologically and pathophysiologically along one common airway.[2906–2910] Indeed, there is a body of evidence to suggest that the following AR therapies may benefit both conditions: INCS,[1887,2911–2913] intranasal antihistamine,[2914] oral antihistamines,[2915,2916] LTRAs,[2917] and AIT.[2634,2918,2919] AIT has shown promising results in altering the course of the allergic inflammation seen in both AR and asthma.[2794,2845,2920] There is extensive literature in this area; therefore, this section focuses primarily on prospective randomized trials and systematic reviews to minimize inherent biases and weaknesses of retrospective studies.[2921]

Allergen avoidance

Allergen avoidance is often recommended for allergies, specifically for AR and allergic asthma.[182,297,2922] Despite being intuitive and having reasonable biological plausibility, the actual evidence for benefit in AR and asthma is limited. No benefit was identified for chemical or physical methods to reduce HDM methods in a 2008 Cochrane review examining randomized trials of subjects with asthma.[2923] Similarly, single allergen avoidance or elimination plans such as removing or washing pets, mattress coverings, removing carpeting, and use of HEPA filters have not shown strong evidence-based clinical benefit for reducing asthma and/or AR symptoms, although there are some exceptions (e.g., acaricides for HDM allergy).[152,2923,2924] Nevertheless, there is theoretical benefit of reducing allergen exposure, a paucity of data

TABLE XIII.A.3 Evidence table – allergic rhinitis risk association with asthma

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Guerra et al.[2885]	2005	2	Nested case–control	Longitudinal cohort	Asthma onset	Rhinitis is a significant risk factor for adult-onset asthma in atopic and nonatopic subjects
Arshad et al.[2893]	2001	2	Cohort	Birth cohort	Atopy and development of allergic diseases (asthma, AR, eczema) by age 4	Atopy is significantly associated with AR (OR 5.85; CI 3.42–10.00) and asthma (OR 4.56; CI 3.16–6.57)
Wright et al.[2883]	1994	2	Cohort	Birth cohort	Respiratory symptoms at age 6	Development of asthma in the child (OR 4.06; CI 2.06–7.99)
Ma et al.[2900]	2021	3	Cross-sectional	Adults with AR, asthma, AR + asthma in northern China	Risk factors for AR, asthma, and AR+asthma	Sensitization to pollen is a risk factor for both AR (OR 16.23; CI 10.15–25.96) and AR + asthma (OR 6.16; CI 1.28–29.66)
Nordeide Kuiper et al.[2898]	2021	3	Cohort	Adult patients from the RHINESSA study (Norway/Sweden)	Impact of air pollution and greenness from birth to adulthood on prevalence of rhinitis, adult asthma, and lung function	Exposure to air pollutants associated with increased risk of developing asthma attacks, rhinitis, and decreased lung function
Sio et al.[2892]	2021	3	Cross-sectional	General population (Malaysian/ Singaporean)	Impact of fungal aeroallergen exposure on risk of developing AR and asthma	Exposure to fungal aeroallergens conveyed a significant increased risk of developing AR (OR 1.66; CI 1.17–2.33) and asthma (OR 1.69; CI 1.18–2.41)
Wang et al.[2897]	2021	3	Cross-sectional	General population of young adults (China)	Impact of health and home environment on risk of developing asthma and AR	Exposure to NO_2, urbanization and traffic exhaust increased risk of developing asthma and AR
Lipiec et al.[845]	2020	3	Multicenter, cross-sectional	Children and adults in Poland with AR and asthma	Exposure to airborne allergens as risk factor for development of AR and asthma	Exposure to airborne allergens is a risk factor for development of AR and asthma Persistent AR portends a greater risk of developing comorbid asthma compared to intermittent AR across all ages
Deng et al.[2896]	2016	3	Cohort	Children with AR (China)	Impact of exposure to TRAP on prevalence of AR	Exposure to TRAP in early life (pregnancy and first year of life) may increase likelihood of developing AR in childhood

(Continues)

TABLE XIII.A.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Panganiban et al.[2895]	2016	3	Cohort	Adults with AR, asthma, AR + asthma, control	Differentially expressed microRNA in blood serum	Same 10 circulating microRNA deregulated in both asthma and AR
Ibanez et al.[2901]	2013	3	Cross-sectional	Children with AR	Associated diseases	Asthma present in 49.5% of AR patients
Jarvis et al.[1817]	2012	3	Cross-sectional	General population	Self-reported current asthma	Asthma associated with chronic rhinosinusitis
Rochat et al.[2888]	2010	3	Cohort	Birth cohort	Development of wheezing	AR is a predictor for subsequent wheezing onset
Polosa et al.[2899]	2008	3	Cross-sectional	Adult smokers with AR versus AR + asthma	Risk factors for AR + asthma	Cigarette smoking is a risk factor for the development of new asthma among AR patients (OR 2.98; CI 1.81–4.92)
Shaaban et al.[2865]	2008	3	Cohort	Population-based study	Frequency of asthma	Rhinitis (±atopy) is a powerful predictor of adult-onset asthma
Burgess et al.[2902]	2007	3	Cohort	General population	Incidence of asthma in preadolescence, adolescence, or adult life	Childhood AR increased the likelihood of new-onset asthma
Shaaban et al.[2887]	2007	3	Cohort	General population	Changes in bronchial hyperresponsiveness in non-asthmatic subjects	AR associated with increased onset bronchial hyperresponsiveness
Bodtger et al.[2903]	2006	3	Cohort	Population-based study	Rhinitis onset	Asymptomatic sensitization, but not non-allergic rhinitis, was a risk factor for later development of AR
Porsbjerg et al.[2904]	2006	3	Cohort	Random population sample	Asthma prevalence	Presence of bronchial hyperresponsiveness and concomitant atopic manifestations in childhood increases the risk of developing asthma in adulthood
Toren et al.[2886]	2002	3	Case–control	General population	Adult-onset physician-diagnosed asthma	Non-infectious rhinitis and current smoking, especially among non-atopics, are associated with increased risk for adult-onset asthma

(Continues)

TABLE XIII.A.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Plaschke et al.[2905]	2000	3	Cohort	Random sample	Risk factors and onset or remission of AR and asthma	AR, sensitization to pets, and smoking were risk factors for onset of asthma
Settipane et al.[2884]	2000	3	Cohort	University students	Asthma development	Allergic asthma depends on elevated IgE, eosinophilia, airway hyperresponsiveness, exposure to allergens, and the predominance of the Th2 pathway of immunologic reactions

Abbreviations: AR, allergic rhinitis; CI, confidence interval; IgE, immunoglobulin E; LOE, level of evidence; NO_2, nitrogen dioxide; OR, odds ratio; RHINESSA, Respiratory Health in Northern Europe, Spain and Australia study; TRAP, traffic related air pollutants.

on multimodality approaches to reduce allergen load, and minimal downside to attempting these various techniques. (See Section XI.A. Allergen Avoidance for additional information on this topic.) Allergen avoidance is mentioned here for completeness in discussing treatment modalities for AR with an effect on asthma, but given poor evidence of effect, an aggregate grade of evidence and literature summary table are deferred.

Pharmacotherapy

Oral H_1 antihistamines. Six RCTs were identified that specifically evaluated H_1 antihistamines for the treatment of asthma in the context of coexistent AR.[2925–2930] Cetirizine and loratadine are the two most highly studied second-generation antihistamines used concomitantly in AR and asthma. Elevated histamine levels after allergen challenge are associated with bronchoconstriction responses in acute asthma episodes. Cetirizine also has bronchodilatory effects which are significant both as monotherapy and in combination with albuterol.[2931] Despite biological plausibility of antihistamines as effective treatment and improvement in subjective asthma symptoms, objective measures using PFT and PEF have failed to demonstrate significant improvements.[2929,2932,2933] Antihistamines may also have a preventive effect on the development of asthma in atopic patients.[2934] In a subgroup analysis, the Early Treatment of the Atopic Child trial found a near 50% reduced risk of developing asthma among cetirizine-treated patients with grass pollen and HDM sensitivities. (See Section XI.B.1. Antihistamines for additional information on this topic.) (Table XIII.A.4.-1).

Oral corticosteroids. Oral corticosteroids are commonly used in asthma patients who are inadequately controlled with bronchodilators and inhaled corticosteroids.[2935] They are also effective for symptoms of rhinitis.[1855] Due to the side-effect profile associated with these medications, especially with increasing duration of use,[2936] oral steroids are not recommended for the routine treatment of AR. For these reasons, an aggregate grade of evidence and evidence summary table are deferred. (See Section XI.B.2.a. Oral Corticosteroids for additional information on this topic.)

Intranasal corticosteroids. In the 1980s, INCS were reported to improve asthma symptoms in patients with coexistent AR and asthma.[2040,2937] Two meta-analyses and 12 RCTs address the potential "unified airway" effect of INCS on asthma, and a single historical cohort study evaluates the impact of combination INCS and intranasal antihistamine on asthma outcomes in patients with both AR and asthma.[1886,1887,1990,2911,2913,2914,2938–2946] A 2003 Cochrane review evaluated the efficacy of INCS on asthma outcomes in patients with coexistent rhinitis, finding no significant improvement in asthma outcomes with INCS.[1886] Heterogeneity in study designs may have limited the findings of this meta-analysis and explain the discrepancy of the results compared to high-quality RCTs. Alternatively, a 2013 SRMA demonstrated improvements in asthma outcomes with the use of INCS compared to placebo in patients with asthma and AR, although the addition of INCS to inhaled corticosteroids was not associated with improved asthma outcomes.[1887] Patient education was noted to be important as patients with concomitant AR and asthma who received training on the proper use of INCS and education on the relationship of AR and asthma demonstrated significant reductions in asthma symptoms and albuterol use compared to patients receiving INCS without additional education.[2947] Finally, intranasal azelastine-fluticasone propionate spray is a known effective treatment for AR alone. Recently, a pre-post historical cohort also reported its potential utility in asthmatics with AR, demonstrating a significant reduction

TABLE XIII.A.4.-1 Evidence table – antihistamines for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Pasquali et al.[2925]	2006	2	RCT	Persistent AR and asthma, $n = 50$: Levocetirizine 5 mg Placebo	Daily rhinitis and asthma symptoms QOL by Rhinasthma questionnaire QOL by SF-36	Rhinitis and asthma symptoms reduced with levocetirizine Rhinasthma QOL score reduced with levocetirizine No differences in SF-36
Baena-Cagnani et al.[2926]	2003	2	RCT	Seasonal AR and asthma, $n = 924$: Desloratadine 5 mg Montelukast 10 mg Placebo	TASS FEV_1 β-agonist use	Desloratadine versus placebo: reduction in mean TASS, improvement in FEV_1, reduction in β-agonist use Desloratadine versus montelukast: no difference
Berger et al.[2927]	2002	2	RCT	AR and asthma, $n = 326$: Desloratadine 5 mg Placebo	TSS Asthma symptom scores β-agonist use	Desloratadine reduced rhinitis symptoms and asthma TSS Desloratadine reduced β-agonist use
Grant et al.[2928]	1995	2	RCT	AR and asthma, $n = 186$: Cetirizine 10 mg Placebo	Rhinitis and asthma symptoms Spirometry	Cetirizine improved asthma symptoms No differences in objective measures
Aubier et al.[2929]	2001	3[a]	RCT	Seasonal AR and asthma, $n = 12$: Cetirizine crossover to placebo Placebo crossover to cetirizine	BHR[b] NBI[c]	Cetirizine increased BHR Cetirizine reduced NBI versus placebo at 6 h
Aaronson[2930]	1996	3[a]	RCT	AR and perennial asthma, $n = 28$: Cetirizine 20 mg Placebo	Daily rhinitis and asthma symptoms Medication use PEFR, PC_{20}, PFTs Asthma management	Cetirizine reduced asthma and rhinitis symptoms No difference in albuterol use No difference in PFTs, PC_{20}, PEFR No difference in asthma management

Abbreviations: AR, allergic rhinitis; BHR, bronchial hyperresponsiveness; FEV_1, forced expiratory volume in 1 second; LOE, level of evidence; NBI, nasal blocking index; PC_{20} and PD_{20}, provocation "concentration" or "dose" of methacholine causing a 20% decrease in FEV_1; PFT, pulmonary function test; PEFR, peak expiratory flow rate; QOL, quality of life; RCT, randomized controlled trial; SF-36, 36-item Short Form Survey; TASS, Total Asthma Symptom Score; TSS, Total Symptom Score.
[a]LOE downgraded due to small sample size, no power analysis or power calculation, which limits interpretation of negative findings.
[b]BHR measured as methacholine PD_{20}.
[c]NBI measured using peak expiratory flow meter and calculated as (oral peak flow – nasal peak flow)/(oral peak flow).

in acute respiratory events and rescue inhaler medication usage, as well as an increase in the overall number of well-controlled asthmatics[2914] (See Section XI.B.2.b. Intranasal Corticosteroids for additional information on this topic.) (Table XIII.A.4.-2).

Leukotriene receptor antagonists. LTRAs (montelukast and zafirlukast), often in combination with topical corticosteroids, have demonstrated benefit for the treatment of both asthma and AR, consistent with efficacy in addressing inflammation in the "unified airway."[2948] ARIA 2008 guidelines supported the effectiveness of montelukast in treating patients with asthma and AR, finding improvement of both nasal and bronchial symptoms as well as reduction of β-agonist use.[152] The 2010 ARIA

TABLE XIII.A.4.-2 Evidence table – intranasal corticosteroids for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lohia et al.[1887]	2013	1	SRMA	18 RCTs, $n = 2162$: INCS versus placebo INCS spray + oral ICS versus oral ICS alone Nasal INH steroid versus placebo	Asthma symptoms Rescue medication use FEV_1, PEF, PC_{20} QOL	INCS improved FEV_1, PC_{20}, asthma symptom scores, and rescue medication use No asthma outcome changes with INCS + oral ICS versus oral ICS alone Nasal INH steroid improved PEF
Taramarcaz and Gibson[1886]	2003	1	SRMA	14 RCTs: INCS versus placebo INCS versus conventional asthma treatment INCS plus conventional versus conventional alone	Asthma symptoms β-agonist use Asthma exacerbations QOL FEV_1, PEF, PC_{20}, PD_{20} Inflammatory markers	Non-significant symptom improvement INCS versus placebo No difference in FEV_1, PEF, PC_{20}, PD_{20}
Jindal et al.[1990]	2016	2	RCT	AR and asthma, $n = 120$: FP INCS 200 μg BID MON 10 mg PO QHS	Symptom scores of rhinitis and asthma PEF	Reduction in asthma symptom severity score with FP versus MON Increase in PEF with FP versus MON
Dahl et al.[2938]	2005	2	RCT	Pollen-induced AR and asthma, $n = 262$: INFP 200 μg daily + IHFP 250 μg BID INFP + inhaled placebo Intranasal placebo + IHFP Intranasal placebo + inhaled placebo	Asthma and AR symptoms PFTs Methacholine BHR PEF	Increased PEF for IHFP + INFP versus other groups PEF increase for IHFP versus no IHFP FEV_1 higher with IHFP Increased BHR with INFP; no increase with IHFP
Nathan et al.[2939]	2005	2	RCT	Seasonal AR and persistent asthma, $n = 863$; all received FSC: INFP 200 μg and FSC daily MON 10 mg + FSC Placebo + FSC	Daily PEF Daily asthma and AR symptoms Rescue albuterol use	INFP added to FSC improved nasal symptoms No asthma outcome improvement with INFP addition to FSC
Stelmach et al.[2940]	2005	2	RCT	Perennial AR and mild-to-moderate persistent asthma, $n = 59$: Nasal Bdp 400 μg + placebo MDI Placebo nasal spray + Bdp MDI 1000 μg Bdp nasal spray 400 μg + Bdp MDI 1000 μg daily	Asthma and AR symptom scores PEF FEV_1 and BHR (PC_{20}) Proxy indicators of asthma-related morbidity (work absence, emergency visits, etc.)	Reductions of AR and asthma symptoms in all groups No change PEF or BHR Increased FEV_1 with nasal Bdp alone and for Bdp MDI alone Asthma morbidity reduced for all

(Continues)

TABLE XIII.A.4.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Thio et al.[2941]	2000	2	RCT	Two grass pollen seasons of treatment (season 1, $n = 21$; season 2, $n = 67$): FP nasal spray 200 μg Bdp nasal spray 400 μg Placebo nasal spray	Asthma scores Use of prn salbutamol Methacholine PD_{20} FEV_1	No difference in asthma scores or as-needed salbutamol for all groups PD_{20} not significantly different FEV_1 increased with FP and BDP in season 2
De Jong et al.[2914]	2020	3	Pre/post-historical cohort	Patients with AR and asthma, $n = 1188$, 1 year before and 1 year after initiation of azelastine/fluticasone propionate nasal spray	Acute respiratory events Asthma exacerbations	Pre versus post: Significant reduction acute respiratory events No difference in asthma exacerbations Significant improvement in well-controlled asthmatics Significant reduction in short acting β2-agonists
Kersten et al.[2911]	2012	3[a]	RCT	AR and mild-to-moderate exercise exacerbated asthma, $n = 32$: Fluticasone furoate nasal spray Placebo nasal spray	Exercise induced FEV_1 change AUC of FEV_1 curve ACQ score PAQLQ score FeNO	Exercise-induced decrease in FEV_1 reduced with FP No difference in FEV_1, ACQ, PAQLQ, FeNO
Baiardini et al.[2942]	2011	3[a]	RCT	Moderate/severe persistent AR with intermittent asthma, $n = 47$: MFNS nasal spray 200 μg per day Placebo nasal spray	QOL by GS Symptom scores Rhinasthma scores of RAI, LA, and UA[a] Rescue asthma medication use	GS score reduction with MFNS LA score decreased with MFNS No difference MFNS versus placebo for rescue meds
Nair et al.[2943]	2010	3[a]	RCT	Persistent AR and asthma, $n = 25$: INH FP 100 μg/day + placebo nasal spray INH FP 500 μg/day + placebo nasal spray INH FP 100 μg/day + FP INCS 200 μg/day	Methacholine PC_{20} FeNO PNIF FEV_1 Asthma and rhinitis QOL	PC_{20} improvement in all groups No PC_{20} improvement with INCS and INH steroid versus INH FP alone No change in asthma QOL FeNO and PNIF reduced only with INCS
Agondi et al.[2944]	2008	3[a]	RCT	AR and asthma, $n = 33$: Bdp nasal spray 400 μg per day Placebo nasal spray	Rhinitis and asthma symptom scores Rescue medication use BHR (histamine provocation)	Changes with Bdp versus placebo: Asthma symptoms reduced Medication use decreased BHR reduced
Pedroletti et al.[2945]	2008	3[a]	RCT	Perennial rhinitis and allergic asthma, $n = 40$: MFNS Placebo	FeNO ECP in nasal lavage PEF FEV_1	No difference in FeNO for MFNS versus placebo Nasal ECP reduced No difference in PEF or FEV_1

(Continues)

TABLE XIII.A.4.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Watson et al.[2946]	1993	3[a]	RCT	AR and controlled asthma, $n = 21$: Intranasal Bdp 100 μg twice daily, then placebo Placebo nasal spray, then intranasal Bdp 100 μg twice daily	Asthma and rhinitis symptoms PC_{20} Bdp deposition[b]	No difference in asthma symptoms with Bdp PC_{20} improved with Bdp Evening asthma symptoms reduced with Bdp
Corren et al.[2913]	1992	3[a]	RCT	Mild seasonal AR and asthma, $n = 18$: Placebo nasal spray (vehicle of Bdp formulation) Bdp nasal spray	Nasal and chest symptoms NBI BHR (PC_{20})	PC_{20} decreased over pollen season with placebo, not Bdp AM NBI decreased with placebo, improved with Bdp No difference in symptoms

Abbreviations: ACQ, Asthma Control Questionnaire; AR, allergic rhinitis; AUC, area under the curve; Bdp, beclomethasone dipropionate; BHR, bronchial hyperresponsiveness; BID, twice daily; ECP, eosinophil cationic protein; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; FSC, inhaled fluticasone propionate and salmeterol; GS, Rhinasthma global summary; ICS, inhaled corticosteroid; INCS, intranasal corticosteroid; INFP, intranasal fluticasone propionate; INH, inhaled; LA, lower airway; LOE, level of evidence; MDI, metered dose inhaler; MFNS, mometasone furoate nasal spray; MON, montelukast; NBI, nasal blocking index (based on PEF and calculated as (oral peak flow − nasal peak flow)/(oral peak flow)); PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PC_{20} and PD_{20}, provocation "concentration" or "dose" of methacholine causing a 20% decrease in FEV_1; PEF, peak expiratory flow; PFT, pulmonary function test; PNIF, peak nasal inspiratory flow; PO, per os (by mouth); QHS, each night; QOL, quality of life; RAI, respiratory allergy impact; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis; UA, upper airway.

[a]LOE downgraded due to small sample size.

[b]Radiolabeled Bdp <2% deposition in lungs, 20%–50% in nasal cavity, and 48%–78% swallowed.

update specified that LTRAs are not recommended over other first-line therapies for the respective conditions, recommending treatment of asthma and AR with a nasal and inhaled corticosteroid as first-line therapies, rather than an LTRA to treat both conditions.[1004] A more recent review in 2015 also identified some utility of LTRAs for patients with concomitant AR and asthma.[2949] However, the limited additional benefit must be weighed against added cost and an FDA boxed warning regarding serious neuropsychiatric events when comparing inhaled corticosteroids to LTRAs for single-modality treatment of asthma in patients with comorbid AR[1004] (See Section XI.B.4. Leukotriene Receptor Antagonists for additional information on this topic) (Table XIII.A.4.-3).

Pharmacotherapy treatment of AR and its effect on asthma

Aggregate grade of evidence: A

- Oral H_1 antihistamines (Level 2: 4 studies, level 3: 2 studies; Table XIII.A.4.-1)
- Intranasal corticosteroids (Level 1: 2 studies, level 2: 5 studies, level 3: 8 studies; Table XIII.A.4.-2)
- Leukotriene receptor antagonists (Level 2: 7 studies; Table XIII.A.4.-3)

Biologics

Omalizumab. Omalizumab is a monoclonal anti-IgE antibody which binds free IgE, preventing interactions with high-affinity IgE receptors and resulting in receptor downregulation on inflammatory cells.[2950] Omalizumab has demonstrated effectiveness separately for asthma as well as AR.[2076,2950–2953] There are several published studies evaluating omalizumab in AR or asthma,[2950,2954] with one RCT specifically evaluating the efficacy of omalizumab in patients with concomitant moderate-to-severe asthma and persistent AR.[2955] Omalizumab as an adjunct to SCIT has also been evaluated.[2765] Both studies show a reduction in symptoms as well as an improvement in QOL measures.[2765,2955] Additional biologics are currently in varying stages of development/emergence with further evaluation needed to determine their role for the treatment of coexistent AR and asthma. (See Sections XI.B.7. Biologics and XI.D.10. Combination Biologic Therapy and Subcutaneous Immunotherapy for additional information on this topic.) (Table XIII.A.4.-4).

TABLE XIII.A.4.-3 Evidence table – leukotriene receptor antagonists for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim et al.[2153]	2018	2	RCT	Perennial AR and mild to moderate asthma, $n = 228$: MON 10 mg MON 10 mg + levocetirizine 5 mg	Mean daytime and nighttime nasal symptom score Mean composite symptom score Overall assessment AR FEV_1, FVC, FEV_1/FVC Asthma control test Rescue medication usage	MON-levocetirizine safe and more effective than MON alone across all observed endpoints
Jindal et al.[1990]	2016	2	RCT	AR and asthma, $n = 120$: FP INCS 200 μg BID MON 10 mg PO QHS	Symptom scores of rhinitis and asthma PEF	Reduction in asthma symptom severity score with FP versus MON Increase in PEF with FP versus MON
Katial et al.[2964]	2010	2	RCT	Seasonal AR and asthma, $n = 1385$: FSC 100/50 μg BID FSC BID + FPNS 200 μg daily FSC BID + MON 10 mg daily MON 10 mg daily	PEF Rescue albuterol use Asthma and rhinitis symptoms	No additional improvements in asthma with MON-FSC FSC improved all outcome measures versus MON
Price et al.[2965]	2006	2	RCT	Asthma symptoms despite ICS, subgroup with coexistent AR, $n = 889$: MON + budesonide Double-dose budesonide	Improvement in AM PEF versus baseline	PEF had greater increase from baseline in MON-budesonide versus double-dose budesonide
Nathan et al.[2939]	2005	2	RCT	Seasonal AR and persistent asthma, $n = 863$; all received FSC: INFP 200 μg and FSC daily MON 10 mg + FSC Placebo + FSC	Daily PEF Daily asthma and AR symptoms Rescue albuterol use	INFP added to FSC improved nasal symptoms No asthma outcome improvement with INFP addition to FSC
Philip et al.[2009]	2004	2	RCT	Seasonal AR and asthma, $n = 831$: MON 10 mg daily Placebo	Rhinitis symptoms RQLQ Global evaluations of asthma β-agonist use	Global evaluation of asthma by patients and physicians improved with MON Reduction in β-agonist use with MON
Baena-Cagnani et al.[2926]	2003	2	RCT	Seasonal AR and asthma, $n = 924$: Desloratadine 5 mg MON 10 mg Placebo	TASS FEV_1 β-agonist use	Desloratadine versus placebo: Reduction in mean TASS Improvement in FEV_1 Reduction in β-agonist use Desloratadine versus MON: no differences

Abbreviations: AR, allergic rhinitis; BID, twice daily; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; FPNS, fluticasone propionate nasal spray; FSC, inhaled fluticasone propionate and salmeterol; FVC, forced vital capacity; ICS, inhaled corticosteroid; INCS, intranasal corticosteroid; INFP, intranasal fluticasone propionate; LOE, level of evidence; MON, montelukast; PEF, peak expiratory flow; PO, per os (by mouth); QHS, each night; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TASS, Total Asthma Symptom Score.

TABLE XIII.A.4.-4 Evidence table – omalizumab for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kopp et al.[2765]	2009	2	RCT	AR and seasonal asthma, $n = 140$, all patients received SCIT: SCIT + omalizumab SCIT + placebo	AR and asthma symptoms Rescue medication use PEF Patient and provider GETE Asthma symptoms by ACQ Disease-specific QOL by AQLQ and RQLQ PFTs	Omalizumab addition to SCIT: Reduced symptom severity No difference in rescue medication use Improved QOL by ACQ and AQLQ No difference in FEV_1 or mean PEF
Vignola et al.[2955]	2004	2	RCT	Moderate-to-severe persistent AR and allergic asthma, $n = 405$: Omalizumab Placebo	Asthma exacerbations AQLQ score RQLQ score Rescue medication use Symptom scores Patient and investigator GETE ICS use FEV_1, FVC, AM PEF	Omalizumab: Reduced asthma exacerbations Increased AQLQ and RQLQ Reduced asthma symptoms Increased FEV_1, FVC, PEF No difference in β-agonist use

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; AR, allergic rhinitis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; ICS, inhaled corticosteroid; LOE, level of evidence; PEF, peak expiratory flow; PFT, pulmonary function test; QOL, quality of life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SCIT, subcutaneous immunotherapy.

Biologic treatment of AR and its effect on asthma

Aggregate grade of evidence: B (Level 2: 2 studies; Table XIII.A.4.-4)

**Note: There is high level evidence with multiple RCTs and reviews for asthma individually, but only one RCT specifically evaluating omalizumab versus placebo in patients with concurrent conditions.

Allergen immunotherapy

Both SCIT and SLIT improve control of AR and comorbid asthma.[2438,2440,2663,2956,2957] Several studies indicate that AIT, often in addition to traditional antihistamine pharmacotherapies, may help halt the progression of allergic disease, including prevention of new allergic sensitivities and the development of asthma.[2426,2428,2541,2794,2795,2845,2920,2958,2959] However, several systematic reviews have concluded that the evidence for AIT possible prevention of further allergic sensitization is low, due to limited analyses of asthma exacerbations, mixed population recruitment, and a focus on mild disease only.[2645,2960,2961] Further evaluation is required to assess safety in patients with uncontrolled asthma.[2961] Of note, the 2010 ARIA statement recommended both SCIT and SLIT for the treatment of asthma in patients with AR and asthma.[1004] The 2019 GINA guidelines recommend adding HDM SLIT for adult patients with AR and FEV_1 >70% who are suboptimally controlled on high dose inhaled corticosteroids.[2962] Finally, the National Heart Lung and Blood Institute Expert Panel conditionally recommends SCIT as an adjunct treatment to standard pharmacotherapy for those 5 years and older with mild to moderate persistent asthma who show clear evidence of a relationship between symptoms and exposure to an allergen to which the individual is sensitive.[2963] (See Section XI.D. Allergen Immunotherapy for additional information on this topic.) (Table XIII.A.4.-5).

Allergen immunotherapy treatment of AR and its effect on asthma

Aggregate grade of evidence: A (Level 1: 7 studies, level 2: 3 studies, level 3: 3 studies; Table XIII.A.4.-5)

TABLE XIII.A.4.-5 Evidence table – allergen immunotherapy for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Fortescue et al.[2961]	2020	1	Systematic review	Systematic review of 66 RCTs (mild or intermittent asthma ± AR)	Asthma exacerbations and QOL Adverse effects Asthma symptoms and medication usage	Limited evidence: asthma exacerbations and QOL SLIT may be safe for well-controlled, mild-to-moderate asthma; further evaluation needed to assess safety in uncontrolled asthma
Blanco et al.[2663]	2018	1	Systematic review	Systematic review of 112 RCTs: AR ± asthma Asthma mild-to-moderate or moderate-persistent when present	Efficacy of SLIT (symptoms, medication usage) Safety of SLIT (adverse events)	SLIT reduced AR-related symptoms and medication usage SLIT reduced ICS dose and improved asthma control among AR + asthma patients Results durable within 2 years post-SLIT Few local and mild-moderate adverse events
Di Bona et al.[2645]	2017	1	Systematic review	Systematic review of 18 studies (4 RCT, 10 prospective, 2 retrospective, 2 observational): Mono- or polysensitized AR patients ± asthma, treated with AIT versus not treated with AIT	New allergic sensitization	Low evidence that AIT prevents further allergic sensitization among mono- and polysensitized patients with AR
Di Lorenzo et al.[2960]	2017	1	Systematic review	Systematic review of 8 studies (1 RCT, 7 prospective): Monosensitized children ± asthma with HDM sensitivity, treated with AIT versus not treated with AIT	New allergic sensitization	Low evidence that AIT prevents further allergic sensitization among children monosensitized to HDM
Kristiansen et al.[2426]	2017	1	Systematic review	Systematic review of 32 studies (17 RCTs, 15 controlled before-after studies): SLIT or SCIT versus no intervention, placebo, or comparator	Development of first or new allergic disease in setting of previous allergic condition ≤2 years after completion AIT (short-term) and ≥2 years after completion AIT (long-term)	Overall AIT did not significantly reduce development of first allergic disease Among those with AR, AIT significantly reduced risk of developing asthma within 2 years of treatment; long-term impact unclear

(Continues)

TABLE XIII.A.4.-5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Erekosima et al.[2956]	2014	1	Systematic review	Systematic review of 61 RCTs (26 specifically asthma and rhinitis): SCIT versus placebo SCIT versus pharmacotherapy	Asthma and RC symptoms and medication use Safety of SCIT	Asthma plus rhinitis/RC symptoms and medications reduced with SCIT[a] Most adverse reactions mild
Lin et al.[2666]	2013	1	Systematic review	Systematic review of 63 RCTs: SLIT versus placebo SLIT versus pharmacotherapy	Asthma and rhinitis/RC symptoms Combined medication use plus symptoms	Asthma and rhinitis/RC symptoms reduced with SLIT[b] Medication plus symptom scores reduced with SLIT[b]
Marogna et al.[2845]	2008	2	RCT	Rhinitis ± intermittent asthma, $n = 216$: Standard drug therapy control group Standard drug therapy plus SLIT[c]	Development of persistent asthma (not at baseline) Symptom and medication scores Daily medication use New sensitization	Persistent asthma incidence lower with SLIT versus control Methacholine-positive patients after 3 years reduced with SLIT Lower symptom and medication scores with SLIT
Novembre et al.[2920]	2004	2	RCT	RC, no asthma, $n = 97$: SLIT; maintenance 3 years Standard symptomatic treatment	Symptoms Rescue medication use Development of asthma	Rescue medication use reduced with SLIT Relative risk of asthma after 3 years greater in control group versus SLIT
Moller et al.[2794]	2002	2	RCT	RC ± asthma, $n = 191$: SCIT Control	Development of asthma (if none at trial start) BHR by PC_{20} VAS of symptoms	Asthma incidence greater in controls BHR improved with SCIT after 1 year pollen season
Sidenius et al.[2957]	2021	3	Non-interventional, prospective, multicenter, observational study	AR with ($n = 83$) or without asthma ($n = 115$), 1 year treatment SQ HDM SLIT	Adverse events AR symptoms Asthma symptoms Asthma control	SQ HDM SLIT is safe and well tolerated SQ HDM SLIT decreases AR and asthma symptoms and medication usage SQ HDM SLIT improves asthma control
Inal et al.[2958]	2007	3	Non-randomized, prospective, parallel group, open study	AR and/or mild-to-moderate asthma. HDM sensitization, $n = 147$: SCIT Medication only	Asthma and rhinitis medication use Atopy (HDM skin prick) Development of asthma	Decreased asthma medication use with SCIT Improved atopy scores with SCIT Asthma incidence nearly half with SCIT

(Continues)

TABLE XIII.A.4.-5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Grembiale et al.[2918]	2000	3[d]	RCT	AR and BHR to methacholine, HDM allergy, n = 44: SCIT (HDM allergen extract) Placebo	BHR by PD_{20} Serum IgE levels Rescue medication use Additional visits for symptoms Development of asthma	BHR increased with SCIT No HDM IgE difference Increased medication use and visits with placebo No difference in asthma incidence

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; BHR, bronchial hyperreactivity; HDM, house dust mite; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LOE, level of evidence; PC_{20} and PD_{20}, provocation "concentration" or "dose" of methacholine causing a 20% decrease in FEV_1; QOL, quality of life; RC, rhinoconjunctivitis; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VAS, visual analog scale.

[a]Strength of evidence moderate to high for asthma-focused studies and rhinitis-focused studies, respectively.

[b]Strength of evidence is moderate for both comparisons.

[c]SLIT administered as sublingual drops of standardized allergen for a build-up phase and then continued for maintenance phase.

[d]LOE downgraded due to small sample size.

XIII.B | Rhinosinusitis

XIII.B.1 | General association of allergic rhinitis with chronic rhinosinusitis

AR may be associated with CRS in several clinical settings.[7] CRS is a condition of the sinonasal cavity characterized by persistent inflammation. While the causes of inflammation vary, CRSwNP is generally associated with type 2 mediated inflammation, while CRSsNP tends to have less predominance of type 2 inflammation.[7,183] AR is predominantly driven by type 2 mediated inflammation and is thought to potentially be an inciting factor in the development of CRS, though the relationship remains unclear.[376,2966] This section will discuss the overall association between AR and CRSsNP as well as CRSwNP.

Allergic rhinitis and chronic rhinosinusitis without nasal polyposis. Since the previous iteration of ICAR-AR, there have been no new studies examining CRSsNP and AR.[376,2966] There are no controlled studies examining the role of AR in the development of CRSsNP and no studies showing that the treatment of allergic disease alters the progression of CRSsNP, or vice versa.[1,7] The Wilson et al.[2967] review continues to provide the most robust assessment of the relationship between allergy and CRSsNP, reporting four studies that supported an association between allergy and CRSsNP and five that do not. Because the correlation remains unclear, allergy testing is listed as an option in CRSsNP patients based on the theoretical benefit of identifying and treating comorbid allergic disease[7,2967] (Table XIII.B.1.-1).

Associated conditions – chronic rhinosinusitis without nasal polyps

Aggregate grade of evidence: D (Level 2: 1 study, level 3: 1 study, level 4: 8 studies, conflicting evidence; Table XIII.B.1.-1) Table adapted from Wilson et al.[2967]

Allergic rhinitis and chronic rhinosinusitis with nasal polyposis. The pathogenesis of CRSwNP is strongly associated with type 2 inflammation.[7,183] Additionally, nasal polyps have high levels of tissue eosinophils, as well as mast cells and basophils.[7,183] AR follows a similar inflammatory pathway and this suggests there may be a pathophysiologic similarities between CRSwNP and AR.[1,7,183] However, the clinical evidence for or against an association between AR and CRSwNP has been mixed.[1,7] Similar to CRSsNP, there have been no new studies specifically examining CRSwNP and AR since ICAR-Allergic Rhinitis 2018.[1] There is an expanding area of research on CCAD. (See Section XIII.B.3. Central Compartment Atopic Disease for additional information on this topic.) The evidence for a relationship between AR and CRSwNP remains conflicted. Ten studies support an association while ten do not, or have equivocal findings.[2967] Hypersensitivity to HDM, cockroach, and *Candida* have been associated with CRSwNP. Despite the overlapping pathophysiologic features between allergy and CRSwNP, conflicting evidence exists regarding an association between AR and CRSwNP. Allergy testing remains an option in CRSwNP patients based on the theoretical benefit of identifying and treating comorbid allergic

TABLE XIII.B.1.-1 Evidence table – association between allergic rhinitis and chronic rhinosinusitis without nasal polyposis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Baroody et al.[2968]	2008	2	RCT	CRSsNP with or without ragweed allergy, $n = 18$	Reactivity in ragweed season determined by symptoms and sinus inflammation	Allergic patients have increased reactivity and sinonasal inflammation in ragweed season
Wilson et al.[2967]	2014	3	Systematic review	CRSsNP with or without allergy	Association between CRSsNP and allergy	Conflicting evidence, no clear association
Tan et al.[2969]	2011	4	Prospective case–control	CRSsNP with or without allergy, $n = 63$	Rates of atopy in rhinitis versus CRSsNP	No significant difference in rates of atopy (72% in rhinitis, 79% in CRSsNP)
Pearlman et al.[2970]	2009	4	Prospective case series	CRSsNP with or without allergy, $n = 115$	CT scores	No difference in CT scores
Gelincik et al.[2971]	2008	4	Prospective case series	CRSsNP with or without allergy, $n = 66$	Prevalence of CRSsNP in allergic and non-allergic rhinitis patients	CRSsNP equally prevalence in allergic (43%) and non-allergic (50%) rhinitis patients
Kirtsreesakul and Rutta-naphol[2972]	2008	4	Retrospective case series	CRSsNP with or without allergy, $n = 198$	Sinus x-rays Nasal endoscopy	Allergic patients had a higher incidence of abnormal sinus x-rays
Robinson et al.[2973]	2006	4	Prospective case series	CRSsNP with or without allergy, $n = 193$	Lund–Mackay CT scores Symptom scores	Allergy not associated with CT findings or symptoms scores
Alho et al.[2974]	2004	4	Prospective case series	CRSsNP with or without allergy, $n = 48$	CT findings during viral URTI Incidence of *S. aureus* sensitization	Allergic patients had higher CT scores and higher incidences of *S. aureus* sensitization
Van Zele et al.[2975]	2004	4	Prospective case–control	CRSsNP with or without allergy, $n = 31$	Rates of *S. aureus* colonization	No difference in colonization rates
Berrettini et al.[2976]	1999	4	Prospective case–control	CRSsNP with or without allergy, $n = 77$	CT scan findings Nasal endoscopy Nasal swabs Rhinomanometry	Increased CT evidence of sinusitis in allergy (68%) versus non-allergic (33%) patients

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps; CT, computed tomography; LOE, level of evidence; RCT, randomized controlled trial; URTI, upper respiratory tract infection.

disease, especially since allergy may be seen in these patients[7,2967] (Table XIII.B.1.-2).

Associated conditions – chronic rhinosinusitis with nasal polyps

Aggregate grade of evidence: D (Level 3: 5 studies, level 4: 16 studies, conflicting evidence; Table XIII.B.1.-2) Table adapted from Wilson et al.[2967]

In summary, the association between AR and CRSwNP or CRSsNP remains unclear, with conflicting evidence. The available literature is limited by varying definitions of allergy versus AR as well as a failure to separate CRSwNP and CRSsNP. Studies that combined CRSwNP and CRSsNP in their evaluation of a potential CRS-AR association were excluded from the Wilson et al.[2967] review and the ICAR-Allergic Rhinitis 2018[1] and are not included here. As our understanding of CRS endotypes and inflammatory patterns evolves, it becomes more pertinent to specify the relationship of AR with specific CRS disease processes (allergic fungal rhinosinusitis [AFRS], CCAD, AERD), which are discussed in the following sections.

Despite the unclear relationship, the diagnosis and treatment of comorbid allergy is an option in rhinosinusitis patients balancing the cost and low evidence with the low

TABLE XIII.B.1.-2 Evidence table – association between allergic rhinitis and chronic rhinosinusitis with nasal polyposis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Al-Qudah[2977]	2016	3	Prospective cohort study	CRSwNP compared to CRSsNP, $n = 155$	Rates of food sensitivity	No difference between allergic and non-allergic patients
Li et al.[2978]	2016	3	Prospective cohort study	CRSwNP with or without allergy, $n = 210$	Nasal endoscopy CT scores Serum inflammatory markers	No difference between allergic and non-allergic patients
Wilson et al.[2967]	2014	3	Systematic review	CRSwNP with or without allergy	Association between CRSwNP and allergy	Conflicting evidence, no clear association
Houser and Keen[2979]	2008	3	Retrospective case series	CRSwNP with or without allergy, $n = 373$	Nasal polyposis	AR associated with the development of nasal polyposis
Kirtsreesakul[2980]	2002	3	Prospective cohort study	CRSwNP with or without allergy, $n = 68$	Response to budesonide nasal sprays (sneezing, oral and nasal peak flow, overall response to therapy)	Improved response in non-allergic patients
Gorgulu et al.[2981]	2012	4	Prospective case–control	CRSwNP compared to controls, $n = 60$	Rate of allergen sensitivity	No difference between allergic and non-allergic patients
Lill et al.[2982]	2011	4	Prospective case–control	CRSwNP compared to controls, $n = 50$	Rates of food sensitivity	Higher rate of milk sensitivity in CRSwNP
Tan et al.[2969]	2011	4	Prospective case–control	CRSwNP with or without allergy, $n = 62$	Rates and number of antigen sensitivity	No difference in rates of sensitivity
Munoz del Castillo et al.[2983]	2009	4	Prospective case–control	CRSwNP compared to controls, $n = 190$	Rates of allergy compared to control	Higher rates of allergy in CRSwNP versus control
Pearlman et al.[2970]	2009	4	Prospective case series	CRSwNP with or without allergy, $n = 40$	Prevalence of CRSwNP in allergic or non-allergic patients	No difference between allergic and non-allergic patients
Bonfils and Malinvaud[2984]	2008	4	Prospective case series	CRSwNP with or without allergy, $n = 63$	Postoperative course Recurrence	No difference between allergic and non-allergic patients
Erbek et al.[2985]	2007	4	Retrospective case series	CRSwNP with or without allergy, $n = 83$	Polyp size Symptom scores Recurrence	No difference between allergic and non-allergic patients
Bonfils et al[2986]	2006	4	Prospective case series	CRSwNP with or without allergy, $n = 180$	Endoscopy CT scores	No difference between allergic and non-allergic patients
Collins et al.[2987]	2006	4	Prospective case–control	CRSwNP compared to controls, $n = 40$	Rates of food sensitivity	Higher rates of food sensitivity in CRSwNP
Van Zele et al.[2975]	2004	4	Prospective case–control	CRSwNP compared to CRSsNP and controls, $n = 55$	Rates of *S. aureus* colonization	Higher rates of colonization in CRSwNP
Asero and Bottazzi[2988]	2001	4	Prospective case–control	CRSwNP compared to non-polyp controls, $n = 68$	Rates of *Candida* and house dust sensitivity	Higher rates of sensitivity in CRSwNP

(Continues)

TABLE XIII.B.1.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Vogels et al.[2989]	2001	4	Prospective case–control	CRSwNP with or without allergy, n = 39	Rates of asthma in allergic or non-allergic patients	Higher rates of asthma in allergic patients
Asero and Bottazzi[2990]	2000	4	Prospective case–control	CRSwNP compared to allergic controls, n = 20	Rates of *Candida* sensitivity	Higher rates of sensitivity in CRSwNP
Pang et al.[2991]	2000	4	Prospective case–control	CRSwNP compared to controls, n = 80	Rates of food sensitivity	Higher rates of food sensitivity in CRSwNP
Pumhirun et al.[2992]	1999	4	Prospective case–control	CRSwNP compared to controls, n = 40	Incidence of house dust and cockroach allergy	Higher rates of allergy in CRSwNP compared to control
Keith et al.[2993]	1994	4	Prospective case–control	CRSwNP with or without allergy, n = 64	Symptom scores Serum levels of inflammatory markers	No difference except in patients with ragweed allergy Ragweed positive patients had increased symptom scores and serum levels

Abbreviations: AR, allergic rhinitis; CT, computed tomography; CRSwNP, chronic rhinosinusitis with nasal polyps; LOE, level of evidence.

risk of allergic rhinosinusitis treatment and the theoretical benefits of reducing allergic sinonasal inflammation.[7]

XIII.B.2 | Allergic fungal rhinosinusitis

AFRS is a non-invasive, chronic, hypertrophic form of rhinosinusitis that affects immunocompetent hosts and is associated with an IgE-mediated local inflammatory response to extramucosal fungi present in the sinonasal cavities.[2994,2995] The Bent and Kuhn criteria are the most commonly cited diagnostic criteria for AFRS and include type I IgE-mediated hypersensitivity, recognizing that the diagnosis of AFRS requires a positive allergy history[2996] and that type I hypersensitivity can be used to distinguish IgE-mediated forms of rhinosinusitis, such as AFRS and CCAD, from other forms of non-IgE-mediated rhinosinusitis.[2997]

Various studies have demonstrated the importance of IgE in the pathophysiology of AFRS, with both systemic and local IgE and fungal sIgE production consistently shown to be elevated in this disease process.[2998–3000] Additionally, it has been determined that most AFRS patients have detectable fungal sIgE in their allergic mucin.[3001,3002] Wise et al.[3003] further established that there is a significant increase in localized IgE staining of the sinus epithelium and subepithelium in AFRS patients compared to controls and CRSsNP patients. The role of type I hypersensitivity in AFRS, even in the absence of positive serum sIgE to fungal allergens, has also been demonstrated[3004,3005] (Table XIII.B.2).

Although generally both CRSsNP and CRSwNP have been found to have an equivocal association with allergy,[2967] 100% of AFRS patients in a study by Marcus et al.[1225] demonstrated positive allergy testing. Allergy testing and treatment is not recommended in CRS unless there are concurrent AR symptoms and sensitivities, respectively,[6] but some data support a role for AIT in improving AFRS patient outcomes in terms of reliance on systemic or topical corticosteroids, need for revision surgery, sinonasal crusting, QOL scores, and objective endoscopy scores.[3006,3007] Still, a systematic review by Gan et al.[3008] reported a grade C in quality of evidence for AIT in AFRS, so it is considered an option in refractory AFRS cases.

The exact role of allergy and fungal hypersensitivity in the pathogenesis of AFRS has long been debated, partially due to a vague understanding of eosinophilic mucin CRS subtypes, including those classified as CRS with eosinophilic mucin but without the presence of fungi. Furthermore, eosinophilic mucin and polyps, which must be present to diagnose AFRS, can occur in the absence of allergy.[3009,3010] Pant et al.[3010] showed that elevated IgG3 levels specific to *Alternaria alternata* and *Aspergillus fumigatus* could distinguish eosinophilic mucin CRS from control groups, which suggests a possible fungal-specific non-allergic immune response in AFRS, and Clark et al.[3011] found significantly higher levels of *Staphylococcus aureus* in AFRS patients as compared to non-AFRS patients, again suggesting a different type of immune mechanism in the pathophysiology of AFRS. In addition, with improved fungal culture techniques, some

TABLE XIII.B.2 Evidence table – association between allergic rhinitis and allergic fungal rhinosinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Gan et al.[3008]	2014	2[a]	Systematic review	Adults, AFRS (Bent and Kuhn[2996] criteria), post-sinus surgery, clearly defined endpoint	Efficacy of six medical modalities for AFRS: oral steroids, INCS, oral antifungals, topical antifungals, AIT, leukotriene modulators	Recommend: systemic and standard INCS Option: nonstandard INCS, oral antifungals, AIT No recommendation: topical antifungals, leukotriene modulators
Chang and Fang[3004]	2008	3	Prospective cohort	CRSwNP patients, $n = 34$: AFRS Fungal sinusitis CRS	sIgE profile of maxillary sinus mucosa Allergic symptoms Fungal hyphae Eosinophilic mucin	All AFRS patients had allergic symptoms and positive sIgE to mites or house dust None had positive serum sIgE to Aspergillus 85.7% had tissue sIgE to Aspergillus
Wise et al.[3003]	2008	3	Prospective comparative	Sinus mucosa from: AFRS patients, $n = 11$ CRSsNP patients, $n = 8$ Controls, $n = 9$	Tissue assessed for: IgE localization by immunohistochemistry sIgE to 14 common antigens	More IgE staining in AFRS sinus epi-/subepithelium versus controls and CRSsNP AFRS sinus tissue had more sIgE versus control for 7 of 14 antigens ($p < 0.05$) and total IgE ($p = 0.004$)
Saravanan et al.[2997]	2006	3	Prospective comparative	70 consecutive patients with CRS ± polyps: M+F+ (likely AFRS, n=36) M+F− (likely EMCRS, n=12) M−F+ (likely sinus mycetoma, n=4) M−F− (CRS from other causes, n=18)	Skin test against aspergillin antigen, $n = 47$ Histopathologic monitoring for the presence of mucin Mycologic monitoring for the presence of fungus	Type 1 hypersensitivity was significantly associated with the AFRS group ($p < 0.05$)
Pant et al.[3010]	2005	3	Prospective comparative	EMCRS patients grouped based on ± fungi within mucin and systemic fungal-sIgE: AFRS, $n = 12$ AFRS-like, $n = 5$ Non-allergic fungal eosinophilic sinusitis, $n = 8$ Nonallergic, nonfungal eosinophilic sinusitis, $n = 5$ Healthy control, $n = 15$ Diseased control, $n = 41$	*Alternaria alternata* and *Aspergillus fumigatus*-specific serum IgE, IgG, IgM, and IgA levels	Fungal-specific IgG and IgA levels higher in EMCRS versus healthy controls but not versus diseased controls Fungal-specific IgG3 levels elevated in all EMCRS subgroups versus controls ($p < 0.0001$) Fungal-sIgE levels not significantly different between fungal-allergic EMCRS and diseased controls

(Continues)

TABLE XIII.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Collins et al.[3002]	2004	3	Prospective cohort	86 consecutive patients with polyps and "fungal-like" mucin	Mucin tested for fungal-sIgE and fungal culture Serum fungal-sIgE and total IgE, eosinophil count, CRP, and ECP levels	AFRS patients more likely to have fungal-sIgE in sinus mucin (17/24, 71%, $p = 0.02$) In fungal culture (+) patients, positive mucin fungal-sIgE associated with systemic fungal allergy ($p = 0.005$) Mean ECP and total IgE elevated in AFRS group
Stewart and Hunsaker[3000]	2002	3	Prospective cohort	AFRS, $n = 13$ AFRS-like, $n = 11$ Non-AFRS polypoid CRS, $n = 27$ Non-polyp controls, $n = 28$ (17 with AR, 11 non-atopic)	Fungal sIgG and sIgE using a 9-mold RAST panel	Among patients with polypoid CRS, patients with AFRS had increased sIgE levels to an average of five molds versus 0.1 mold in those without AFRS
Ponikau et al.[3012]	1999	3	Prospective cohort	210 consecutive patients with CRS	Detection of fungi in nasal lavage Value of allergy testing in AFRS diagnosis	Fungal cultures positive in 96% of CRS patients AFRS diagnosed in 93% of 101 consecutive surgical cases with CRS based on histopathologic findings and culture results Type 1 hypersensitivity not prevalent in majority of AFRS patients
Folker et al.[3007]	1998	3	Prospective case control	AFRS patients treated with sinus surgery, corticosteroids, antibiotics as needed, $n = 22$: Postoperative AIT No postoperative AIT	Objective outcomes based on EMSS Sinusitis-specific QOL scale (CSS) Reliance on systemic and topical corticosteroids	Improvement in treatment group: EMSS $p < 0.001$ CSS $p = 0.002$ Reliance on systemic ($p < 0.001$) and topical ($p = 0.043$) corticosteroids to control disease
Mabry et al.[3006]	1998	3	Prospective cohort	AFRS patients post-sinus surgery had allergy testing for 11 fungal and 12 nonfungal antigens, then AIT for 1–36 months ($n = 23$; 15 still on AIT at publication) Patients with early discontinuation of AIT	Need for systemic or topical nasal steroids Nasal crusting, accumulation of allergic mucin or debris in the sinus cavities, mucosal edema, or reformation of polyps Need for repeat surgery	No adverse events or deleterious effects of AIT Treatment group: revision surgery (two patients), methylprednisone (one patient) Control group: two patients with frequent use of oral steroids and recommendation for revision surgery, one patient with recurrent disease at 4 months post-op

(Continues)

TABLE XIII.B.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Marcus et al.[1225]	2020	4	Retrospective	252 polyp patients who underwent allergy testing: AERD, $n = 75$ AFRS, $n = 70$ CCAD, $n = 27$ CRSwNP NOS, $n = 75$ CRSwNP/CC, $n = 5$	Positive allergy history and testing	Positive allergy history and testing: AERD 82.6%, 77.3% AFRS 100%, 100% CCAD 97.6%, 92.6% CRSwNP NOS 56.1%, 88% CRSwNP/CC 84.6%, 80%
Clark et al.[3011]	2013	4	Retrospective case series	AFRS patients, $n = 19$ CRSwNP patients, $n = 21$	Bacterial cultures Fungal cultures	*S. aureus* more prevalent in the AFRS group versus non-AFRS group (63.2% versus 24.1%, $p = 0.005$)
Hutcheson et al.[2998]	2010	4	Case–control	AFRS patients, $n = 64$ CRS patients, $n = 35$	Serum total IgE IgG anti-*Alternaria*-specific antibodies IgE antifungal antibodies	Mean serum total IgE, IgG anti-*Alternaria*-specific antibodies, and IgE antifungal bands increased in AFRS versus CRS patients
Cody et al.[3013]	1994	4	Retrospective cohort	789 histologic specimens, 44 had allergic mucin: AFRS based on fungal hyphae in mucin or positive fungal culture, $n = 26$ AFRS-like mucin, $n = 18$	Culture results of 31 of the 44 AFRS patients	19 of the 31 had negative culture results
Manning et al.[2999]	1993	4	Case–control	AFRS patients with positive fungal cultures, $n = 16$ Control patients with similar clinical findings but no histologic or culture evidence of AFRS, $n = 5$	RAST to multiple fungal antigens	All AFRS patients RAST-positive to at least one fungal antigen in the family of their cultured organism No control patient was RAST-positive to either dematiaceous or Aspergillus fungal antigens

Abbreviations: AERD, aspirin exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; AIT, allergen immunotherapy; CC, central compartment; CCAD, central compartment atopic disease; CRP, C-reactive protein; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CSS, Chronic Sinusitis Survey; ECP, eosinophilic cationic protein; EMCRS, eosinophilic mucin chronic rhinosinusitis; EMSS, endoscopic mucosal staging system; F, fungal/mycelial element; Ig, immunoglobulin; INCS, intranasal corticosteroid; LOE, level of evidence; M, allergic mucin; NOS, not otherwise specified; QOL, quality of life; RAST, radioallergosorbent test; sIgE, allergen-specific immunoglobulin E.

[a]LOE downgraded due to inclusion of cohort studies primarily.

studies report the presence of fungi in nearly 100% of non-AFRS CRS patients and control subjects, further complicating the true role of fungi in AFRS.[3009,3012–3014] Despite these debates, there is evidence demonstrating the important role allergy and type 2 inflammation play in the pathophysiology, diagnosis, and treatment of AFRS.[3015]

Associated conditions – allergic fungal rhinosinusitis

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 9 studies, level 4: 5 studies; Table XIII.B.2)

XIII.B.3 | Central compartment atopic disease

CCAD is a distinct variant of CRS described as polypoid changes of central compartment (CC) structures where airflow is most prominent, including the MT, superior turbinate, and or/posterosuperior nasal septum. There is relative disease sparing of the peripheral sinus cavities, and studies suggest a strong association with allergy.[1222] In 2014 White et al.[1219] first described the association between allergy and isolated MT polypoid edema, with 16/16 patients having allergen sensitization. Hamizan et al.[1220] found that MT edema/polyposis has a high specificity and positive predictive value for the presence of inhalant allergy, with the highest grades of MT edema having the strongest association. In comparing patients with isolated MT polyposis to those with paranasal sinus polyposis, Brunner et al.[1221] found clinically distinct features as patients with isolated MT polyposis were more commonly younger, female, had lower Lund–Mackay CT scores, and had a significantly higher association with AR compared to those with diffuse polyposis ($p < 0.001$) (Table XIII.B.3).

In 2017, DelGaudio et al.[1222] introduced the term CCAD to describe this distinct variant of sinonasal disease. Further progression of CCAD results in involvement of the sinuses by lateralization or polypoid changes of the MT causing secondary obstruction of the sinuses in a medial to lateral progression. In a multi-institutional case series including 15 patients, all patients had symptoms consistent with AR and allergen sensitization was seen in the 14 patients who underwent allergy testing. Based on computational fluid dynamics, the proposed pathophysiology is a local immune response related to antigen deposition in CC structures exposed to inhaled allergens.[1222] To further characterize CCAD, Roland et al.[1226] described radiologic features that differentiate CCAD from other CRSwNP subtypes, including oblique MT orientation, septal involvement, and lower Lund–Mackay score.

While there is conflicting data regarding the association between allergy and CRS in general, there is evidence to support an association between allergy and CCAD. In a subtype analysis of patients with CRSwNP, Marcus et al.[1225] reported significantly higher allergy prevalence in patients with CCAD compared with CRSwNP not otherwise specified ($p<0.001$). In patients with radiologic features of CCAD, Hamizan et al.[1224] noted a significantly higher association with allergen sensitization compared to the non-CCAD group ($p = 0.03$). Abdullah et al.[1228] reported similar results with 100% of patients with CCAD having sensitization to HDM, compared to only 13.6% of non-CCAD patients ($p = 0.00$). Additionally, Lee et al.[1227] found higher blood eosinophil and serum IgE levels, and higher prevalence of allergen sensitization in pediatric patients with CCAD compared to non-CCAD ($p = 0.008$). While no association between CCAD and allergy sensitization was noted in CRS patients in East Asia, patients with CCAD had significantly higher peripheral eosinophils ($p = 0.001$), tissue eosinophils ($p = 0.005$), and IL-13 ($p < 0.05$) and IL-5 levels ($p < 0.05$) in MT tissue compared to the non-CCAD group, suggesting an eosinophilic/type 2 inflammatory response.[3016] Radiologic features can be predictive of CCAD, but edema/polyposis of the CC on endoscopy remains the current diagnostic standard. In a study by Lin et al.,[3016] patients with minor CC radiologic findings and essentially normal endoscopy were included in the CC-CRSsNP group, which may not meet the definition of CCAD according to DelGaudio et al.[1222] While CCAD is a distinct variant of sinonasal disease, CC disease can be found in other processes such as AERD and respiratory epithelial adenomatoid hamartoma, with studies reporting a positive association with AR.[1223,3017,3018]

Associated conditions – central compartment atopic disease

Aggregate grade of evidence: C (Level 3: 2 studies, level 4: 11 studies; Table XIII.B.3)

XIII.B.4 | Aspirin exacerbated respiratory disease

AERD is a chronic inflammatory condition that includes the tetrad of asthma, nasal polyposis, eosinophilic rhinosinusitis, and a non-IgE-mediated reaction to inhibitors of the COX-1 enzyme.[3019] Although considered an inflammatory disease that results from dysregulation of arachidonic acid metabolism leading to an overproduction of leukotrienes and not a true allergic condition, there are data that suggest an association between AERD and IgE-mediated allergy.

Historically, Samter and Beers reported the prevalence of atopy in AERD as less than 3% ($n = 182$) using the criteria of positive SPT, and either a family history of atopy or a correlation between allergen exposure and clinical symptoms.[3020] However, recent evidence supports a higher atopic rate in AERD.[3021–3024] In one cohort, 200 of 300 (66%) AERD subjects had a history of positive SPT,[3022] and in a latent class analysis of AERD sub-phenotypes, 105 of 201 (52.2%) patients had positive aeroallergen SPT responses,[3021] with the most common allergen being HDM (29.6%).[3024] In another study that evaluated personal atopic history, SPT, and elevated total and specific IgE,

TABLE XIII.B.3 Evidence table – association between allergic rhinitis and central compartment atopic disease

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lee et al.[1227]	2021	3	Cross-sectional	Pediatric CRS subtypes, $n = 82$	Allergen sensitivity Peripheral eos tIgE CT and endoscopy pattern of disease	Increased peripheral eos ($p = 0.020$), serum IgE ($p = 0.23$) in CCAD versus non-CCAD Higher prevalence of allergen sensitization in CCAD (87.1%) versus non-CCAD (62.4%) ($p = 0.008$)
Hamizan et al.[1220]	2017	3	Cross-sectional	Patients with rhinitis and negative CT scan, $n = 187$	Allergen sensitivity Endoscopic MT edema grading	MT edema/polyps associated with inhalant allergy; higher grades have stronger association PPV 85.1%, specificity 94.7%, and sensitivity 23.4% determined multifocal MT edema as a cutoff on ROC analysis
Lin et al.[3016]	2021	4	Case–control	CRS subtypes, $n = 67$: CC CRS Non-CC CRS	Symptoms SNOT-22 Peripheral eos Allergen sensitivity L–M score Inflammatory markers	CC CRS higher peripheral eos ($p = 0.001$), tissue eos ($p = 0.005$), MT IL-13 and MT/polyp IL-5 versus non-CC CRS No difference in allergen sensitization in CC and non-CC CRS
Makary et al.[3017]	2021	4	Case–control	Eosinophilic CRS subtypes, $n = 200$: AERD AFRS eCRSwNP Control	Radiologic pattern of disease and CC involvement	Preop and postop CC distance significantly higher in AERD compared to controls, AFRS, and eCRSwNP ($p < 0.0001$)
Abdullah et al.[1228]	2020	4	Case–control	CRSwNP, $n = 38$	Allergen sensitivity CT and endoscopy pattern of disease	Increased allergen sensitivity in CCAD (100%) versus non-CCAD pattern (13.6%) ($p = 0.00$) CCAD associated with higher rates of MT polypoid edema ($p = 0.009$–0.017)
Marcus et al.[1225]	2020	4	Case–control	CRSwNP subtypes, $n = 356$: AFRS AERD CCAD CRSwNP NOS	Allergy and asthma prevalence by subtype	Allergen sensitivity increased in CCAD, AERD and AFRS compared with CRSwNP NOS ($p < 0.001$) CCAD significantly higher association with allergy ($p < 0.001$) than CRSwNP NOS

(Continues)

TABLE XIII.B.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Roland et al.[1226]	2020	4	Case–control	CRSwNP subtypes, $n = 356$: AFRS AERD CCAD CRSwNP NOS	CT pattern of opacification	CCAD radiologically associated with oblique MT orientation, septal involvement, and lower L–M score
Schertzer et al.[3018]	2020	4	Case series	REAH, $n = 26$	CCAD involvement in REAH	94.7% of REAH patients had clinical AR CCAD identified in 19.2% of REAH patients
DelGaudio et al.[1223]	2019	4	Case series	AERD, $n = 72$	CC involvement in AERD	80.6% AERD patients had CC disease CC findings in AERD are associated with clinical allergy ($p < 0.0001$)
Hamizan et al.[1224]	2018	4	Case series	CRS, $n = 112$	CT disease pattern: diffuse versus central Allergen sensitivity	CCAD higher association with allergen sensitization versus non-CCAD (73.53% versus. 53.16%, $p = 0.03$) Central disease was associated with allergen sensitization ($p = 0.03$, specificity 90.82%, PPV 73.53%).
Brunner et al.[1221]	2017	4	Case series	$n = 67$ Diffuse sinonasal polyposis Isolated MT polypoid change	Demographics Presence of CRS, AR, asthma SNOT-22, NOSE L–M score Eos, tIgE	Isolated MT polypoid patients had greater association with AR versus diffuse paranasal sinus polyposis (83% versus. 34%, $p < 0.001$) Isolated MT polypoid patients: more commonly female, younger, lower L-M score, lower incidence of CRS
DelGaudio et al.[1222]	2017	4	Case series	CCAD, $n = 15$	Characteristics of CCAD	Introduced the term CCAD 100% of patients had allergy symptoms 93.3% had positive allergy testing
White et al.[1219]	2014	4	Case series	Isolated MT polyps/polypoid edema, $n = 25$	Allergen sensitivity	First described strong association between allergy and isolated MT polypoid edema/polyps 100% undergoing allergy testing positive for inhalant allergy

Abbreviations: AERD, aspirin exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; AR, allergic rhinitis; CC, central compartment; CCAD, central compartment atopic disease; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; eCRSwNP, eosinophilic chronic rhinosinusitis with nasal polyps; eos, eosinophils; IgE, immunoglobulin E; IL, interleukin; L–M, Lund–Mackay CT score; LOE, level of evidence; MT, middle turbinate; NOS, not otherwise specified; NOSE, Nasal Obstruction Symptom Evaluation; PPV, positive predictive value; REAH, respiratory epithelioid adenomatous hamartoma; ROC, receiver-operating characteristic curve; SNOT, Sinonasal Outcome Test; tIgE, total immunoglobulin E.

AERD subjects had a higher rate of atopy than controls (53.9% vs. 14%, $p < 0.001$)[3025] (Table XIII.B.4).

When compared to other forms of CRS, greater rates of physician diagnosed AR and positive SPT were found in AERD subjects when compared with CRSwNP subjects (80% vs. 66%, $p < 0.001$).[3026] Recently, a retrospective study investigated the prevalence of atopy in patients with various CRS phenotypes ($n = 380$) and found that a significantly higher percentage of atopic CRS patients had AERD (9.4% atopic vs. 1.1% non-atopic subjects).[3027]

Although the aforementioned studies demonstrate a higher rate of atopy in AERD compared to other forms of CRS, it should be noted that AERD is not driven by sIgE-mediated reactions. Even though local IgE levels within AERD nasal polyps are significantly elevated when compared with nasal tissue from other CRSwNP patients and healthy controls, this does not reflect atopic status.[3028] Similarly, serum tIgE is often elevated in AERD patients but does not discriminate atopic from non-atopic AERD populations.[3021]

The understanding that AERD is not driven by traditional atopic mechanisms has important ramifications regarding treatment. In a survey of 190 patients with AERD, 86 (45%) of respondents had concomitant AR treated with AIT.[3029] More than half did not perceive any clinical benefit, and only 8% reported significant efficacy. This contrasts with non-AERD patients with AR, in whom rates of improvement with AIT are greater than 80%.[2419] The high failure rate of AIT in AERD suggests that amelioration of any atopic component of their symptoms is overwhelmed by the non-allergic AERD mechanisms. Although it is important to note that AIT has not been properly studied as a treatment option for AERD.

In summary, despite the high rate of concomitant atopy in AERD, symptoms related to inhalant sensitization are not responsible for the majority of AERD symptoms. Therefore, allergen-directed therapies, such as standard AIT, are unlikely to be efficacious for most AERD patients. Nevertheless, clinicians should elicit atopic histories for contributory comorbid AR, as recent expert guidance suggests routine allergy testing in AERD for sensitization to inhalant allergens.[3030] However, AIT may only be highest yield for candidates with obvious seasonal variation to their symptoms and identifiable environmental triggers.

Associated conditions – aspirin exacerbated respiratory disease

Aggregate grade of evidence: C (Level 3: 3 studies, level 4: 3 studies; Table XIII.B.4)

XIII.C | Conjunctivitis

Although the association between AR and AC is well recognized, accurate insight into ocular allergy prevalence is complicated by multiple factors.[3031,3032] Most prevalence studies use variable definitions of AC and may employ several different assessment questionnaires. Additionally, most studies do not distinguish specifically between AR and AC symptoms. Rather, AC is considered a secondary manifestation of AR.[756,773] There is phenotypic diversity of both AR and AC, with very few studies adequately characterizing the phenotypes of their study samples. Further, many epidemiologic studies are based solely on subjective questionnaires rather than incorporating objective evidence of allergic sensitization (Table XIII.C).

Overall, there is a significant burden of associated AC in patients with AR. In the US, the 1988–1994 NHANES III survey ($n = 33{,}994$) found a 30% prevalence of concomitant AR and AC.[3033] Isolated ocular symptoms were reported by 6%, more frequently in patients over 50 years old – which may be attributable to dry eye and concomitant ocular conditions contributing to symptom severity. AC was associated with skin test positivity to all allergen classes except mold.

Similar AC prevalence trends are echoed globally,[3034–3039] with higher rates noted in some studies. In one report, 95% of 187 Australian patients with allergist-diagnosed AR reported ocular allergy.[3040] A Swiss survey of hay fever patients showed 85% prevalence of concomitant nasal and eye symptoms.[3041] A cross-sectional Italian study of 2150 adolescents determined that more than half of the respondents with AR also had AC.[3038] Comorbid AC also conferred an increased risk of asthma (OR 5.23) versus AR alone (OR 2.28).[3038]

The largest global data source regarding the AR–AC association derives from the ISAAC investigations, a series of worldwide studies established in 1991 with the aim of investigating the epidemiology of allergic diseases. ISAAC used a standardized questionnaire and obtained unified assessments of the time trends of the global prevalence in different regions or countries. Current rhinoconjunctivitis was defined as self-reported "current rhinitis" along with a positive answer to "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?"

ISAAC Phase 1 reported AC prevalence in 257,800 children aged 6–7 years in 91 centers (38 countries) and 463,801 children aged 13–14 years in 155 centers (56 countries). Although the ISAAC survey was not validated for the diagnosis of AC, ISAAC studies support the frequent association of AR with itchy/watery eyes; Phase 1 results revealed that ocular symptoms affect 33%–50% of children with AR.[759] ISAAC Phase 3 analyzed temporal trends in prevalence of allergic rhinoconjunctivitis over 7 years in

TABLE XIII.B.4 Evidence table – association between allergic rhinitis and aspirin exacerbated respiratory disease

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Brown et al.[3027]	2021	3	Retrospective cohort	380 CRS patients, including 28 patients with comorbid AERD	Prevalence of atopy in CRS subtypes Clinical characteristics, histopathology, serum IgE, symptom and radiographic scores Atopy defined by clinical symptoms + SPT	75.3% of CRS patients were atopic Polysensitization in 76.2% 27/28 AERD patients atopic
Stevens et al.[3026]	2017	3	Retrospective cohort	US patients with CRSwNP: AERD, $n = 171$ CRSwNP + asthma, $n = 412$ CRSwNP, $n = 459$	Clinical characteristics in AERD patients versus CRSwNP patients ± comorbid asthma Atopy defined by physician-diagnosed AR on chart review + SPT	AR: AERD (85%) versus CRSwNP (66%) SPT positivity: AERD (83%) versus CRSwNP (66%)
Bochenek et al.[3025]	1996	3	Observational cohort	Polish cohort: 120 NSAID-sensitive patients (78 AERD, 42 pyrazolone sensitive) 50 controls	Atopy defined by personal/family atopic history, skin testing, serum tIgE and sIgE	Prevalence of atopy in AERD 46.2%–66.7% depending on defining criteria Atopy more frequent in AERD versus controls
Jakiela et al.[3023]	2021	4[a]	Observational cohort	Polish cohort: AERD, $n = 22$ NSAID-tolerant asthma, $n = 22$ Controls, $n = 11$	Distinguish inflammatory sub-endotypes of lower airway inflammation in AERD SPT, spirometry, nasal lavage, bronchoscopy Cytokine and eicosanoid levels in bronchoalveolar lavage	36% of AERD patients with positive SPT SPT positivity did not differ between eosinophilic and non-eosinophilic AERD endotypes
DelGaudio et al.[1223]	2019	4	Retrospective cohort	US cohort, 72 AERD patients	Describe CC involvement and association with atopic status in AERD Atopy defined based on personal history of AR and positive SPT	80.6% of AERD subjects had CC disease 100% of CC-AERD patients had atopic history, 93.8% had positive SPT Lower rate of atopy in non-CC patients ($p<0.0001$)

(Continues)

TABLE XIII.B.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dona et al.[3024]	2018	4[b]	Observational cohort	Spanish cohort, 880 patients with NSAID hypersensitivity: 108 with comorbid AERD 511 with NSAID-induced anaphylaxis 261 with blended reactions	Clinical characteristics of NSAID hypersensitivity Rates of concomitant rhinitis, asthma, nasal polyps, atopy Atopic status assessed with SPT	Positive SPT in 54.6% of AERD patients Dust mite was most common allergen (29.6%)

Abbreviations: AERD, aspirin exacerbated respiratory disease; AR, allergic rhinitis; CC, central compartment; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; IgE, immunoglobulin E; LOE, level of evidence; NASID, non-steroidal anti-inflammatory drug; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test; tIgE, total immunoglobulin E; US, United States.

[a]LOE downgraded due to very limited study sample.

[b]LOE downgraded due to poor inclusion criteria.

the two age groups (n = 498,083). There was a global increase in rhinoconjunctivitis prevalence, with considerable heterogeneity between test centers. The average overall prevalence of allergic rhinoconjunctivitis was 14.6% for adolescents.[756]

Recently, the Global Asthma Network used ISAAC methodology to update the prevalence of pediatric atopic diseases.[773] The study surveyed 74,361 adolescents and 45,434 6–7-year-olds from 27 centers (14 countries). Overall, the prevalence of current rhinoconjunctivitis had decreased slightly from ISAAC Phase 3 among young children (−0.44%) and adolescents (−1.32%). Additionally, an analysis of 2914 patients from the Alergológica 2015 study revealed AC in one-third of participants, and AC was associated with AR in 88%.[3042] The duration and severity of AC was also associated with that of AR ($p < 0.001$).

Underreporting of ocular allergy may be attributable to symptom variability and increased attention to non-ocular allergy symptoms. Although the burden of illness (i.e., QOL impairment) associated with AC is established,[3043] AC is often underrecognized and undertreated except when severe.[3031] More than half of AR patients endorsed that red/itchy/watery eyes were moderately to extremely bothersome in the Allergies in America Survey.[3044] Another survey of allergic rhinoconjunctivitis patients (n = 2765) ranked red/itchy eyes as the second most bothersome symptom after nasal obstruction.[3045]

Ocular allergy symptoms also contribute significantly to QOL impairment associated with AR. Ocular symptoms of allergic rhinoconjunctivitis are among the most common symptoms which cause patients to seek allergy treatment.[3045] When assessing AR patients, one should evaluate ocular symptoms and consider treatment specific to AC. AIT may have a role in AC management; however, most studies investigating AIT efficacy have studied allergic rhinoconjunctivitis rather than AC alone.[3046] In a prospective study of patients with AC receiving SCIT or SLIT, both groups had similar rates of clinical improvement in terms of decreased symptoms, medications, tIgE and skin test wheal diameters after 1 year.[3047]

Associated conditions – allergic conjunctivitis

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 8 studies; Table XIII.C)

XIII.D | Atopic dermatitis

AD is a chronic/relapsing, inflammatory skin disorder characterized by recurrent eczematous lesions and pruritis that affects all ages and ethnicities.[3050] AD is the leading cause of the global burden from skin disease.[3051] AD is associated with increased risk of multiple allergic comorbidities, including food allergy, asthma, and AR.[1169,3050] AD that starts in infancy usually precedes the development of other atopic diseases, and therefore, is considered the first step of the "atopic march," or an early marker of the predisposition toward type I hypersensitivity.[3052,3053]

AD and AR are the most prevalent allergic diseases, but many epidemiological studies focus on asthma; only 15.7% and 24.5% of epidemiological studies provide data on AD and AR, respectively.[1169] Studying the epidemiology of AR and its comorbidities, in particular AD, is complicated by different disease definitions and reporting, and different testing to confirm diagnoses. In one study, for

TABLE XIII.C Evidence table – association between allergic rhinitis and allergic conjunctivitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Strachan et al.[773]	2022	2[a]	Cross-sectional survey	Adolescents (n = 74,361) and 6–7-year-olds (n = 45,434) from 27 centers in 14 countries	Prevalence of current RC using a standardized questionnaire in schoolchildren	RC prevalence slightly decreased since ISAAC Phase 3: −1.32% per 10 years (adolescent group), −0.44% per 10 years (younger children)
Kim et al.[3036]	2016	2[a]	Cross-sectional survey	General population: 14,356 students, 2010–2014	AR prevalence in children Skin test positivity Comorbid disease	34.5% comorbidity of AC in AR
Han et al.[3037]	2015	2	Prospective cohort	1020 children, 338 with AR	Questionnaire Skin prick test Endoscopy	History of AC is a risk factor for AR (OR 14.25; 95% CI 4.99–40.74)
Singh et al.[3033]	2010	2[a]	Cross-sectional survey	NHANES III participants (n = 33,994), 1988–1994	Describe the epidemiology of AC in the United States	40% of adults with AC Isolated ocular symptoms reported by 6% 30% prevalence of concomitant AR and AC
Sanchez-Hernandez et al.[3042]	2022	3	Retrospective cohort analysis	Patients referred for allergy evaluation, n = 2914	History Skin test sIgE Provocation tests	33% diagnosed with AC; AC associated with AR in 88% of cases Duration and severity of AC associated with that of AR ($p < 0.001$)
Alexandropoulos et al.[3048]	2013	3	Retrospective cohort	Adult patients referred to immunology clinic (n = 1851), 2001-2007	Questionnaire Skin prick test Serum sIgE	AR documented in 38.4% AR associated with AC (OR 6.16; 95% CI 4.71–8.06, $p < 0.001$).
Almaliotis et al.[3049]	2013	3	Retrospective cohort	Patients referred to clinic, confirmed AC diagnosis by ophthalmologist, n = 448	Questionnaire Skin prick test	70% of patients with AC also had a diagnosis of AR Symptoms of ocular allergy are common in patients with AR and asthma
Williams et al.[3040]	2013	3	Observational cohort study	AR patients in Australia, n = 187	History Ocular antihistamine challenge	95% of patients with AR were diagnosed AC based on history and therapeutic antihistamine challenge
Navarro et al.[3034]	2009	3	Cross-sectional	Patients referred for allergy evaluation (n = 4991), Alergologica 2005	Characteristics of patients with AR	55% of patients diagnosed with AR, 65% had associated AC
Gradman and Wolthers[3039]	2006	3	Retrospective survey	Danish children from a secondary pediatric outpatient clinic (n = 458), 5–15 years old with AC, asthma, AR, or eczema	Prevalence of AC in children with rhinitis, asthma, eczema	316 children with rhinitis, 42% had concomitant AC Of patients with AC, 97% also had AR

(Continues)

TABLE XIII.C (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kosrirukvongs et al.[3035]	2001	3	Observational cohort	445 patients (24.5 ± 16.3 years old), history of itching, foreign body sensation, lacrimation, red eyes	Physical examination Skin prick test	73.8% of patients with perennial AC had associated AR Most common sensitization was house dust mite
Wuthrich et al.[3041]	1998	3	Cross-sectional	Swiss patients with AR symptoms, n = 509	Clinical history	AR associated with AC in 85% of cases AC symptoms were as severe as AR symptoms in 70%

Abbreviations: AC, allergic conjunctivitis; AR, allergic rhinitis; CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; LOE, level of evidence; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; RC, rhinoconjunctivitis; sIgE, specific immunoglobulin E.
[a]LOE upgraded due to very large sample size.

example, less than half of all patients reporting AR had a physician-confirmed diagnosis of AR.[3054] Therefore, the link between AR and AD remains poorly defined due to methodologic differences and limitations of the studies that have examined this association[739,2854,3055–3065] (Table XIII.D).

The largest study to assess the association between AR and AD was based on data collected in the ISAAC study, which started in 1991 and aimed to investigate the epidemiology and etiology of asthma, rhinitis, and AD in each country using standard questionnaires, SPT, and flexural dermatitis examination.[3066] The study involved 256,410 children age 6–7 years in 90 centers from 37 countries, and 458,623 children age 13–14 years in 153 centers from 56 countries, demonstrating a prevalence of AD between 5% and 20%.[3066] Several longitudinal studies show improvement or resolution of AD with age, but children often remain atopic for the rest of their lives with a prevalence of AR among those with AD ranging from 15% to 61%.[3067–3070]

Multiple studies performed in different countries and age groups, using a variety of methodologies, conclude that there is a disease association between AR and AD. The available evidence suggests that there is a two- to four-fold increase in AR among people with AD.[739,2854,3055–3064,3071] For example, in the cross-sectional multicenter study titled "Epidemiology of Allergic Diseases in Poland" conducted in children age 6–7 and 13–14 years and adults aged 20–44 years, allergic diseases were common in children and young adults. Single disease AR occurred in 29.3% and AD in 7.2%. A single disease (asthma, AR, or AD) was observed in 27.7% of the subjects and allergic multimorbidity was noted in 9.3%. Allergic multimorbidity was more common in children (10.7%–10.9%) than in adults. There was an increasing risk of multimorbidity depending on the number of positive SPTs.[3064]

High prevalences of AR and AD were also shown in an independent Phase 3 follow-up study of unselected 8th-grade school children in Denmark participating in the Odense Adolescence Cohort Study. The participating children were reassessed after reaching 28–30 years of age. The lifetime prevalence of atopic diseases increased significantly from adolescence (31%) to adulthood (57%), particularly AR (incidence 17.5/1000 person-years). The lifetime prevalence of AD was 34.1%. Childhood predictors for adult AR were AR, asthma, asymptomatic sensitization to pollen, and AD (OR 1.7; 95% CI 1.1–2.5, $p = 0.021$). Seven percent of subjects with AD developed AR.[739]

The Canadian Healthy Infant Longitudinal Development study recruited pregnant women from the general population across four Canadian provinces and followed them until their children were 5 years old. The authors defined five distinct classes of individuals: healthy (81.8%), AD (7.6%), inhalant sensitization (3.5%), transient sensitization (4.1%), and persistent sensitization (3.2%). Children in the AD groups were at increased risk of developing AR (OR 2.36; 95% CI 2.13–2.62).[3060]

The increased risk of AR in patients with AD has been seen in multiple studies using different research strategies (i.e., prospective, population-based, cross-sectional) in different age groups and in different continents (Asia, Europe). This supports the notion that AR and AD are related diseases.[739,2854,3055–3064]

Associated conditions – atopic dermatitis

Aggregate grade of evidence: C (Level 2: 16 studies, level 3: 12 studies, level 4: 3 studies; Table XIII.D)

TABLE XIII.D Evidence table – association between allergic rhinitis and atopic dermatitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Biagini et al.[3062]	2022	2	Prospective longitudinal cohort	Children with AD/eczema in Cincinnati enrolled ≤2 years old, n = 601	SPT Symptoms upon allergen exposure	AD associated with AR (-asthma) in White (3x risk) and Black (6x risk) children
Schoos et al.[3058]	2022	2	Prospective cohort	Children with AD evaluated at age 6 and 12 years, n = 368	Comorbidities in relation to time of AD onset	Early onset (≤1 year) and more severe AD associated with aeroallergen sensitization and AR in childhood
Pedersen et al.[2854]	2020	2	Cross-sectional	Individuals of all ages, n = 2149	Prevalence, severity, and factors associated with AD	Highest prevalence of AD at 2 years (18%), AR at 25–29 years (6.0%) AD associated with AR (OR 3.68)
Gonzalez-Mendoza et al.[3055]	2019	2	Cross-sectional	Mexican students aged 15–18 years, n = 1992	Diagnosis of AD and AR by ISAAC criteria	AR prevalence 9.0% AD prevalence 5.2% AR and AD more frequent in women AR associated with AD (OR 2.98)
Mortz et al.[739]	2019	2	Observational cohort	Follow-up cohort of 8th grade children, n = 899	Questionnaire SPT, sIgE, spirometry	Lifetime prevalence of atopy increases from adolescence (31%) to adulthood (57%) Lifetime prevalence of AD 34.1% 37.7% of AD subjects develop AR
Dharma et al.[3060]	2018	2	Prospective longitudinal cohort	Birth cohort, n = 2629	SPT to common food and inhalant allergens at age 1 and 3 years	7.6% of children had AD Children in AD group at risk for developing rhinitis (OR 2.36)
Schneiner et al.[3070]	2016	2	Prospective longitudinal cohort	Infants with AD at ages 3 months and 18 months, n = 1091	Development of allergic comorbidities	18.5% developed AR 11.9% developed allergic conjunctivitis Comorbidities developed more often in infants with severe AD
Mortz et al.[3071]	2015	2	Cohort	Follow-up cohort of 8th grade children, n = 899	Prevalence of AD and comorbidities	Lifetime prevalence of AD was 34.1% Among those with AD, 60.8% reported AR
Sybilski et al.[3072]	2015	2	Cross-sectional	Polish subjects: 6–7 years, 13–14 years, 20–44 years (n = 18,617)	Questionnaire	AD in 3.91% AR occurred in 26.17% of AD patients
Bozek and Jarzab[3073]	2013	2	Cross-sectional	Adult participants, mean age 66–67 years, n = 7124	Questionnaire Physical exam SPT tIgE, sIgE	AD/eczema in 1.6% Seasonal AR in 12.6% Perennial AR in 17.1%
Lowe et al.[3074]	2007	2	Birth cohort	Infants with family history of atopy, n = 620	SPT at 6, 12, 24 months Interview at 6, 7 years	Children with atopic AD by age 2 have greater risk of AR (OR 2.91)

(Continues)

TABLE XIII.D (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Karaman et al.[3075]	2006	2	Cross-sectional	Students in 3rd, 4th, 5th grades in Turkey ($n = 1217$)	Physical exam SPT	AR prevalence 17%, physician-diagnosed AD prevalence 4.9%, physician-diagnosed HDM sensitization most frequent
Kuyucu et al.[896]	2006	2	Cross-sectional	Children aged 9–11 years, $n = 2774$	Questionnaire SPT	Prevalence of ever AR 36.3% Prevalence of current AR 30.6% SPT positive in 20.4% AD associated with current AR
Yemaneberhan et al.[3076]	2004	2	Cross-sectional	All-age sample from urban and rural populations, $n = 12,876$	Questionnaire SPT	Lifetime cumulative prevalence of AD symptoms 1.2% AD symptoms strongly associated with AR symptoms (OR 61.94)
Min et al.[3077]	2001	2	Cross-sectional	Otolaryngology patients in Korea, $n = 71,120$	Questionnaire Rhinologic exam SPT sIgE	Prevalence of perennial AR 3.93% AD associated with perennial AR in 20.9%
Leung and Ho[3078]	1994	2	Cross-sectional	School age children in Hong Kong, Malaysia, China ($n = 2208$)	Assess prevalence of asthma & allergic disease	Prevalence of hay fever 2.1%–15.7% Prevalence of eczema 7.2-20.1%
Huang et al.[3057]	2020	3	Population database	Database registry in Taiwan, $n = 26,525,074$	Diagnosis of AD and AR	Crude prevalence of AD 4.7% Increased risk of AD (RR 2.25) and AR (RR 1.23) if there is a family member with AD
Wang and Chiang[3059]	2020	3	Prospective observational cohort	Infants with AD (transient or persistent) Controls ($n = 109$)	Development of allergic comorbidities	42% with persistent AD 4.2% new diagnosis of AD in control group Transient AD did not increase risk for AR or asthma Early-onset persistent AD increased risk for AR and inhalant allergen sensitization (OR 2.83)
Huang et al.[3061]	2018	3	Cross-sectional	Residents in a rural area of Beijing, $n = 1084$	Questionnaire SPT	Prevalence of self-reported AR 46.80%, AD 3.69% SPT confirmed AR 16.78% Comorbid AD and AR 16.77%
Batlles Garrido et al.[3079]	2010	3	Cross-sectional	Children aged 10–11 years, $n = 1143$	Questionnaire Physical exam SPT	Prevalence of AD 11.4% Severe AD is a risk factor for AR (OR 7.7)

(Continues)

TABLE XIII.D (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Peroni et al.[3080]	2008	3	Cross-sectional	Preschool children aged 3–5 years, n = 1402	ISAAC questionnaire SPT	AR symptoms in 32.2% of AD patients Risk factors for AD: allergen sensitization, rhinitis, family history of atopy
Kidon et al.[3081]	2005	3	Cohort	Newly diagnosed AR patients, mean age 7.9 years, n = 175	Questionnaire SPT	48% had AD SPT positive for HDM in 85%; most significant factor associated with HMD sensitization was AD (OR 31.8)
Kusel et al.[3082]	2005	3	Prospective birth cohort	Longitudinal cohort, n = 263	Evaluation at 6 months, 2 years, 5 years Physical exam SPT	Persistent AD associated with AR (OR 2.8)
Peroni et al.[3083]	2003	3	Cross-sectional	Preschool children aged 3–5 years, n = 1402	ISAAC questionnaire SPT	Prevalence of AR in 12 months 16.8% AD significantly associated with AR (22.9%) versus non-AR (13.9%), $p < 0.001$
Rhodes et al.[3068]	2002	3	Longitudinal cohort	Infants from atopic families in the UK followed for 22 years, n = 100	Development of atopic comorbidities	AD prevalence peaked at 1 year of age (20%), then declined to 5% Prevalence of AR increased over time to 15%
Gustaffson et al.[3069]	2000	3	Longitudinal cohort	Children with AD followed for 8 years, n = 94	SPT Serum tIgE, sIgE	AD improved in 91.3% 45% developed AR AD severity was a risk factor for developing AR
Ozdemir et al.[3084]	2000	3	Cross-sectional	College students in Turkey, n = 1603	Physical exam SPT	Eczema in 5.4% of females, 6.3% of males AR in 11.1% of females, 8.9% of males
Garcia-Gonzalez et al.[3085]	1998	3	Cross-sectional	Secondary school children in Spain, mean age 17.9 years, n = 365	SPT Serum tIgE, sIgE	AR in 19.9% AD in 0.8%
Moreno-Lopez et al.[3065]	2021	4	Cross-sectional	Adolescents aged 13–14 years Parents of children aged 6–7 years (n = 261)	Questionnaire	Prevalence of AR (11.49%), asthma (8.81%), AD (6.13%) AR associated with female sex, asthma, AD, higher maternal education

(Continues)

TABLE XIII.D (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bekic et al.[3056]	2020	4	Case series	Primary care patients, $n = 2056$	Physician diagnosis of AD and allergic comorbidities	AD identified in 10.53% AR + AD identified in 41%
Jeong et al.[3063]	2020	4	Retrospective cross-sectional	AR patients, primarily Korean adults, $n = 1615$	Patient and history characteristics SPT	Rhinitis may be mono- or poly-sensitized, or non-sensitized Eczema most common in polysensitized rhinitis patients (12.3%)

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; HDM, house dust mite; ISAAC, International Study of Asthma and Allergies in Childhood; LOE, level of evidence; OR, odds ratio; RR, relative risk; sIgE, allergen-specific immunoglobulin E; SPT, skin prick test; tIgE, total immunoglobulin E; UK, United Kingdom.

XIII.E | Food allergy

XIII.E.1 | Pollen food allergy syndrome

Immune responses to foods may produce a spectrum of symptoms and disorders including pollen food allergy syndrome (PFAS; also known as oral allergy syndrome [OAS]).[3086,3087] PFAS is an IgE-mediated allergy which localizes to the oral mucosa, leading to transient itching, perioral hives, angioedema, and rarely systemic symptoms. Patients with pollen allergies may have allergic reactions confined to the oral cavity after consuming specific fruits, vegetables, nuts, or spices. PFAS symptoms manifest as a result of cross-reactivity of IgE specific for an offending pollen with highly homologous proteins found in a variety of fruits, vegetables, and nuts. The most common example of this cross-reactivity in Western populations is birch pollen and apples, which is due to the high degree of sequence homology between Bet v 1 (major allergen of birch pollen) and Mal d 1 (major allergen of apple), leading to IgE-mediated cross-reactivity.[3088] Table XIII.E.1.-1 lists common pollen allergens with plant-derived foods that may demonstrate cross-reactivity.[3089] A 2018 review by Carlson et al.[3090] reported PFAS prevalence ranged from 4.7% to over 20% among children and 13%–58% among adults, with prevalence varying widely by geographic region. A study conducted in 1360 Italian children with pollen-related AR noted that a longer duration of AR symptoms was related to developing PFAS, suggesting that individuals living in areas with more pollen seasons have a higher rate of PFAS, possibly reflecting the higher range of prevalence in adults.[3091,3092] Table XIII.E.1.-2 summarizes the evidence link between PFAS and AR.

The diagnosis of PFAS is typically established by a detailed history and physical exam that explores a given patient's underlying allergy to pollen and raw foods with shared homologous proteins. As per the Joint Task Force Practice Parameters, sIgE testing to pollens is recommended in patients with a suggestive clinical history.[223] The estimated rates of systemic and anaphylactic reactions from a pollen-food allergy are 10% and 2%–10%,[3093,3094] respectively, and such a history must be thoroughly elicited. The gold standard for establishing a diagnosis of PFAS is a double-blind food challenge, but this can still be confounded by biases inherent to the appearance, texture, and taste of foods.[3095] It is important to note that skin testing using commercially available fruit or vegetable extracts may not be useful as the allergens are heat labile.[3096] Oral food challenge, SPT, and food sIgE levels have also been used to diagnose PFAS or food allergy.[3090,3097–3099] Another technique that has also shown promise in accurate diagnosis of PFAS and food allergy is CRD utilizing pure and potentially cross-reactive allergenic components in certain foods.[3100] This has been demonstrated in refining diagnosis of true peanut allergy, where the component Ara h 2 has been identified as a better predictor of clinical allergy.[3101]

The standard recommendation for the treatment of PFAS has been to identify and eliminate offending foods from the diet. There is no consensus on whether patients should be provided auto-injectable epinephrine.[3094] Some

TABLE XIII.E.1.-1 Pollen-food allergy cross-reactivity[3106]

Pollen	Food
Birch	Fruits: apple, apricot, cherry, peach, pear, plum, kiwi Vegetables: carrot, celery, parsley Legumes: peanut, soybean Nuts: almond, hazelnut
Timothy and orchard grass	Fruits: peach, watermelon, orange, tomato Vegetables: white potato
Ragweed	Fruits: cantaloupe, honeydew, watermelon, banana Vegetables: cucumber, white potato, zucchini
Mugwort	Vegetables: bell pepper, broccoli, cabbage, cauliflower, chard, garlic, onion, parsley Spices: aniseed, caraway, coriander, fennel, black pepper

TABLE XIII.E.1.-2 Evidence table – association between allergic rhinitis and pollen-food allergy syndrome

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
de Jong et al.[3097]	2021	3	Cohort	Patients with birch pollen allergy, n = 15	Allergic response to pear challenge	Selected patients with birch pollen related pear allergy can consume small doses of Cepuna pear following challenges
Dondi et al.[3091]	2013	3	Cohort	Children with pollen-induced AR	AR severity Presence of comorbidities	23.9% of children with AR also had PFAS Longer duration of AR associated with development of PFAS
Skamstrup Hansen et al.[3095]	2001	3	Cohort	Patients with birch pollen allergy, n = 46	IgE reactivity to apple	It is possible to perform double-blind placebo-controlled food challenges with apple in birch pollen-allergic individuals
Cudowska et al.[3107]	2021	4	Cross-sectional	Pediatric patients with pollen and food allergies, n = 43	Prevalence of AR Association of food allergy with AR	65% of children with food allergies had AR, of which PFAS is most common
Lee et al.[3098]	2019	4	Cross-sectional	Korean adults with suspected food allergy, including many PFAS, n = 812	Clinical features and culprit food allergens	77.8% food allergy patients had comorbid allergic diseases (AR was most common at 53.4% of all patients) One-third of food allergy patients had accompanying PFAS 94.8% of PFAS patients had accompanying AR
Thong et al.[3108]	2018	4	Retrospective series	Adults referred to an allergy clinic for food allergy, n = 77	Pattern of food allergy, symptomatic manifestations, and reactions	AR was the second most common (6%) atopic condition among individuals with shellfish/crustacean oral allergy
Ortolani et al.[3093]	1993	4	Limited meta-analysis	Adults with allergy to vegetable allergens	Clinical features of vegetable and fresh fruit allergy	Allergy to fresh fruits and vegetables is IgE-mediated Clinical associations with AR due to cross-reactive pollens and foods allergens are frequent
Ebner et al.[3088]	1991	4	Case series	Adults with birch-pollen allergy, n = 83	Comparing epitopes of birch pollen and apples	Antigens in birch pollen and apples share allergenic epitopes leading to IgE cross-reactivity

(Continues)

TABLE XIII.E.1.-2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Diaz-Cabrera et al.[3109]	2021	5	Narrative review	Patients with atopy	Developing collection of comorbid conditions	Optimal care of atopy requires recognition and treatment of all atopic comorbidities, which may include AR and PFAS
Matsumoto et al.[3110]	2021	5	Cross-sectional survey	First year university students, $n = 2688$	Prevalence of PFAS and factors associated with it	2.7% PFAS prevalence, significantly associated with AR (OR 3.8; 95% CI 2.7–5.5)
Ota et al.[3111]	2020	5	Cross-sectional survey	Children, aged 7–15 years, $n = 3365$	Prevalence of seasonal AR and PFAS	Prevalence: seasonal AR 38.1%, PFAS 15.6% AR and PFAS highly correlated ($R = 0.848$; OR 2.751; 95% CI 2.259–3.351)
Carlson et al.[3090]	2019	5	Narrative review	Patients with PFAS	Symptoms, risks, treatments	Prevalence and implicated foods in PFAS depend on the location Systemic or anaphylactic reactions are possible Various diagnostic methods exist
Katelaris[3087]	2010	5	Narrative review	Adults with PFAS	Diagnosis and management of PFAS	PFAS prevalence influenced by the rising prevalence of AR In vitro screening of food allergic patients with large panels of allergens will help in accurate diagnosis and management

Abbreviations: AR, allergic rhinitis; CI, confidence interval; IgE, immunoglobulin E; LOE, level of evidence; OR, odds ratio; PFAS, pollen-food allergy syndrome.

pollen-associated foods may lose their cross-reactivity potential once the often-labile proteins are denatured by heat. In one study, food challenges were performed with apple, carrot, or celery in patients with AD and birch pollen allergy, who reported oral allergy symptoms and dermatologic symptoms upon ingestion of the raw foods.[3102] Cooked versions of the offending foods did not cause oral allergy symptoms.

Several studies have evaluated the effect of targeted AIT for pollen allergy at reducing PFAS symptoms with mixed results. There has been some published evidence of pollen-specific AIT resulting in increased tolerance to the PFAS-associated offending foods.[3102–3105] However, one RCT failed to demonstrate any improved tolerance to apple in birch allergic patients treated with birch specific AIT compared to placebo.[3095] One study evaluating the persistence of tolerance for apple after birch AIT demonstrated that AIT resulted in increased apple tolerance for some patients up to 30 months; however, there was no difference between the AIT and control groups.[3104] Currently, AIT is not recommended for the sole purpose of treating PFAS, although patients receiving AIT should be counseled on the potential benefit of improved food tolerance (Table XIII.E.1.-3).

Associated conditions – pollen food allergy syndrome

Aggregate grade of evidence: C (Level 3: 3 studies, level 4: 5 studies, level 5: 5 studies; Table XIII.E.1.-2) for link between AR and PFAS, including cross-reactivity; C (Level 2: 2 studies, level 3: 2 studies; Table XIII.E.1.-3) for AIT in treatment of PFAS

TABLE XIII.E.1.-3 Evidence table – allergen immunotherapy as a treatment for pollen-food allergy syndrome

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mauro et al[3105]	2011	2	RCT	Patients with seasonal rhinitis and Bet v 1 birch allergen: AIT, $n = 40$ Food challenge, $n = 15$	Apple challenge and IgE to Bet v 1 and Mal d 1 allergen after AIT (1 year)	Different doses of birch extract needed to improve the associated apple allergy Finer diagnostic work-up required to select patients with birch-apple syndrome who are candidates to respond to birch pollen AIT
Bolhaar et al.[3102]	2004	2	RCT	Birch pollen and apple allergic patients, $n = 25$	Effect of birch-pollen AIT on apple allergy	Birch pollen AIT decreases reactivity to foods containing Bet v 1-homologous allergens
Inuo et al.[3103]	2015	3	Cohort	Children with Japanese cedar pollen allergy induced AR, $n = 23$	Response to pollen SCIT	Japanese cedar pollen SCIT efficacious in relieving and preventing PFAS symptoms in AR
Asero[3104]	1998	3	Cohort	Birch pollen-sensitive with apple induced PFAS, $n = 49$	Response to pollen-specific AIT	Pollen-specific AIT with birch pollen extracts effectively reduces clinical apple sensitivity and skin reactivity in most cases

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; LOE, level of evidence; PFAS, pollen-food allergy syndrome; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy.

XIII.E.2 | Anaphylactic food allergy

Like AR, food allergy may be driven by an IgE-mediated response and as a result may sometimes lead to anaphylactic reactions.[3112] There is an abundance of consistent evidence, largely in the form of large sample cross-sectional and retrospective analyses, that the occurrence of food allergy is independently associated with AR[766,855,857,3107,3110,3111,3113–3122] (Table XIII.E.2). In an analysis of over 8000 families, Alm et al.[857] found a strong, independent association between the development of food allergy and AR (OR 10.21; 95% CI 4.22–24.73). A separate analysis of more than 300,000 children by Hill et al.[3119] found that a diagnosis of food allergy was highly associated with later development of AR (OR 2.72; 95% CI 2.45–3.03).

Peanut allergy is one of the most common and well-studied food allergies, and its prevalence has been linked to AR in the existing literature.[3119,3123–3125] Similarly, AR is a relatively more common atopic condition among people with allergies to shellfish,[3108,3119,3126,3127] and specifically shrimp.[3108,3126,3128] Identifying infants at high risk of peanut allergy and introducing peanuts to them early can significantly decrease the frequency of developing peanut allergy[3129,3130]; however, it is currently unclear whether such measures can have a protective effect on developing AR in the future.[3131] There is reported low- to very low-certainty evidence that early fish introduction to the diet before age 6–12 months can be associated with reduced AR before age 14.[902]

Long-term management of food allergies mainly includes identification and avoidance of each food item and provision of counseling regarding food-related systemic or anaphylactic reactions; in some circumstances, oral immunotherapy may be an option. Epinephrine auto-injectors with associated instructions for use should be provided to patients who are at risk for anaphylactic reactions.[3132,3133] Finally, there are ongoing studies investigating several possible type 2 targeted biologics in treatment of food allergy.

It is suggested that AIT is perhaps the only possible disease-modifying treatment for allergic diseases by inducing long-term tolerance against specific allergens.[3134] AIT prompts the inhibition of early and late-phase allergic responses and induction of immunological tolerance of AR and food allergy via diverse mechanisms on T cells (e.g., Th1/2, Treg), regulatory B cells, innate lymphoid cells, dendritic cells, mast cells, eosinophils, and basophils.[3134] When studied separately, AIT treatment has

TABLE XIII.E.2 Evidence table – association between allergic rhinitis and food allergy

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Ierodiakonou et al.[902]	2016	1	SRMA	Infants at risk of allergic or autoimmune disease, $n = 1915$ across five trials	Food allergy, wheeze, eczema, AR, allergic sensitization, autoimmune disease	Low- to very low-certainty evidence that fish introduction before age 6–12 months was associated with reduced AR at age ≤4 years (OR 0.59; 95% CI 0.40–0.87) or at age 5–14 years (OR 0.68; 95% CI 0.47–0.98)
Blumchen et al.[3124]	2020	2	Prospective cohort	Adults or parents of patients with peanut allergy, $n = 1846$	Prevalence of allergic comorbidities	Patients with peanut allergy have AR (50%), asthma (42%), other food allergies (79%)
Wang et al.[3116]	2020	2	Cross-sectional survey	Nationally representative sample of US children, $n = 38,408$	Prevalence of shellfish food allergy, associated factors	History of AR independently associated with shellfish allergy (OR 2.0; 95% CI 1.4–2.9)
Alm et al.[857]	2011	2	Prospective cohort	Approximately 25% of all children born in western Sweden in 2003, $n = 4496$	Prevalence of AR at age 4.5 years, factors associated with AR	Prevalence of AR was 5.5% Positive food allergy test independently associated with AR (OR 10.21; 95% CI 4.22–24.73)
Diez et al.[3128]	2021	3	Cross-sectional	Patients with AR sensitized to HDM, $n = 443$	Prevalence and clinical relevance of shrimp IgE sensitization in AR patients sensitized to HDM	Of HDM AR patients, 19% had shrimp sensitization, 27% had shrimp allergy
Lyons et al.[3122]	2021	3	Cross-sectional survey	7–10-year-olds ($n = 670$) and 20–54-year-olds ($n = 844$) who self-reported adverse food reactions	Prevalence of true IgE-related food allergy, associated factors	Positive IgE detected in 25% AR independently associated with this in adults (OR 4.44; 95% CI 2.52–8.26) and children (OR 3.13; 95% CI 1.87–5.33)
Sultesz et al.[855]	2020	3	Cross-sectional	6–12-year-old children, $n = 3836$	Prevalence of AR, associated factors	29.3% prevalence of AR Food allergies highly associated (OR 2.594; 95% CI 1.995–3.378)
Bedolla-Pulido et al.[3118]	2019	3	Cross-sectional survey	Adolescents aged 15–18 years, $n = 1992$	Prevalence of food hypersensitivity and probable food allergy, associated factors	10.6% prevalence of food hypersensitivity; AR independently associated (OR 2.60; 95% CI 1.75–3.87) 7.8% prevalence of probable food allergy; AR independently associated (OR 2.46; 95% CI 1.56–3.88)

(Continues)

TABLE XIII.E.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Scott et al.[3125]	2019	3	Retrospective cohort	Patients with peanut allergy versus controls, $n = 50,483$	Incidence and prevalence of peanut allergy, atopic comorbidities, anaphylaxis	Peanut allergy patient with had 8% prevalence of AR versus 3% AR in controls RR of experiencing AR along with peanut allergy 2.6 (95% CI 2.4–3.0)
Taylor-Black and Wang[3127]	2012	3	Retrospective cohort	Children attending a pediatric clinic, $n = 313$	Prevalence and characteristics of food allergy in an urban pediatric population	Patients with shellfish allergy had significantly higher rates of AR (59% versus 44% in patients without shellfish allergy)
Tong et al.[3113]	2022	4	Cross-sectional survey	Heterogenous group of children in China, $n = 10,757$	Factors predicting AR	Presence of food allergy independently associated with AR in children (OR 1.899; 95% CI 1.597–2.258)
Bilaver et al.[3115]	2021	4	Cross-sectional	Children aged 0–19 years from a Medicaid claims database, $n = 23,825,160$	Prevalence of food allergies, associated factors	Prevalence of food allergies 0.6% AR independently associated with food allergy (OR 4.06; 95% CI 4.01–4.11)
Blaiss et al.[3123]	2021	4[a]	Retrospective cohort	US pediatric patients with ($n = 4329$) or without ($n = 43,290$) peanut allergy	Cost of care of peanut allergy among privately insured and Medicaid-insured	Children with peanut allergy had higher AR prevalence than peanut allergy-free children (66% versus 21%)
Huang et al.[3120]	2021	4	Retrospective study	Chronic rhinitis patients presenting in/out of pollen season ($n = 5174$, 1772 with AR)	Developed a nomogram predicting which patients would have IgE sensitization test-verified AR	Food allergy independently associated with AR in pollen season (OR 1.803; 95% CI 1.430–2.676) and out of pollen season cohort (OR 1.849; 95% CI 1.380–2.767)
Ruffner et al.[3117]	2020	4	Retrospective case series	Children with food protein-induced enterocolitis syndrome (FPIES; a non-IgE-mediated food allergy; $n = 214$)	Prevalence of atopic comorbidities in patients with FPIES	AR associated with FPIES (OR 1.9; 95% CI 1.4–2.6) When it was a requirement that FPIES be diagnosed before AR the association went away, indicating FPIES does not lead to AR Potential confounders
Tong et al.[766]	2020	4	Cross-sectional survey	Children aged 6–12 years, $n = 5550$	Prevalence of AR and risk factors for it	AR prevalence 28.6% Food allergy was independently associated with AR (OR 1.590; 95% CI 1.302–1.942)

(Continues)

TABLE XIII.E.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Walter and Kalicinsky[3121]	2020	4	Retrospective case series	Patients with adult-onset IgE-mediated food allergies, $n = 14$	Factors associated with adult-onset IgE-mediated food allergies	Most common concomitant allergic disease was AR
Hill et al.[3119]	2016	4	Retrospective case series	All children with eczema, asthma, or AR treated at a hospital ($n = 29,662$ in closed birth cohort; $n = 333,200$ in cross-sectional cohort)	Factors associated with AR	Food allergies, most commonly to peanut, were associated with AR development (OR 2.72; 95% CI 2.45–3.03) Multiple food allergies associated with greater risk of AR (OR 7.05 with four foods)
Celakovska and Bukac[3114]	2014	4	Retrospective case series	Patients with atopic dermatitis, $n = 65$	Prevalence of other allergic syndromes, associations among them	Among atopic dermatitis patients, those that also had food allergies were more likely to also have AR
Bedolla-Barajas et al.[3126]	2015	5	Cross-sectional	Adults in four metropolitan areas of Mexico, $n = 1126$	Allergic reactions to various nuts and seafood, association with allergic disease history	AR had probable association with shrimp (OR 2.15) and crustacean (OR 2.27) allergy

Abbreviations: AR, allergic rhinitis; CI, confidence interval; FPIES, food protein-induced enterocolitis syndrome; HDM, house dust mite; IgE, immunoglobulin E; LOE, level of evidence; OR, odds ratio; RR, relative risk; SRMA, systematic review and meta-analysis; US, United States.
[a]LOE downgraded due to peripheral focus of study.

been shown to lead to several years of symptomatic remission in AR[1671,2676] or sustained responsiveness for various food allergies.[3135,3136]

Associated conditions – anaphylactic food allergy

Aggregate grade of evidence: C (Level 1: 1 study, level 2: 3 studies, level 3: 6 studies, level 4: 9 studies, level 5: 1 study; Table XIII.E.2)

XIII.F | Adenoid hypertrophy

Children with AH and AR may exhibit similar symptoms including nasal obstruction and rhinorrhea. Adenoids commonly enlarge through the preschool years but typically involute with puberty.[3137,3138]

Literature evaluating the relationship between AH and allergic sensitization draws from two populations. The first is allergic children assessed for AH. Several studies assessing allergic children found an association with AH. In one study, the prevalence of AH in 1322 allergic children (12.4%) was higher than in 100 age-matched non-allergic controls (3%), $p < 0.0001$.[2830] Similarly, Dogru et al.[3139] found a relatively high rate (21.2%) of AH amongst 566 children with AR. Modrynksi and Zawisza[3140] reported that seasonal adenoid enlargement in birch pollen allergic children was more frequent than in controls but the increased adenoid size resolved after pollen season. However, this study was small ($n = 67$) and did not comment on blinding (Table XIII.F).

Three cohort studies have assessed the relationship of mold sensitivity and AH with mixed results. Atan Sahin et al.[3141] compared 242 children living in an arid environment to 142 children living on the coast and found no correlation between mold and pollen sensitization with AH. However, HDM-sensitive children in the coastal group had an increased prevalence of AH ($p = 0.01$). Huang and Giovanni[2831] compared 315 children who had AH with AR to age-matched controls with AR alone and found a higher prevalence of mold sensitivity in AH with AR versus AR alone ($p = 0.013$ to $p < 0.0001$). Dogru et al.[3139] also reported an increased sensitization to *Alternaria* in the AH with AR group compared to AR alone ($p = 0.032$).

The second population studied is children suspected of AH who are assessed for allergic sensitization; these studies also have mixed results. Cassano et al.[3138] reported

TABLE XIII.F Evidence table – association between allergic rhinitis and adenoid hypertrophy

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
DeCorso et al.[3158]	2021	2[a]	Systematic review	Allergy Adenotonsillar disease	Clinical evidence Biomarkers	Qualitative link between allergy and AH/ATH
Karabulut et al.[3146]	2019	4	Consecutive cohort	Children referred from pediatric allergy to otolaryngology	Nasal endoscopy SPT	AH and allergen positivity have a negative association
Dogru et al.[3139]	2017	4	Retrospective, cross-sectional, non-randomized	AR AR + AH	Symptoms Allergen sensitivities Comorbidities	AR+AH had more severe symptoms than AR alone
Atan Sahin et al.[3141]	2016	4	Case–control	Children from humid locations Children from arid locations	AH SPT IgE Vitamin D	High humidity group had higher AH, IgE levels, and association between AH and SPT for dust mite
Eren et al.[3145]	2015	4	Consecutive cohort	Children referred from pediatric allergy to otolaryngology	Endoscopic adenoid size SPT	AH negatively correlated with (+) allergy testing
Evcimik et al.[2830]	2015	4	Retrospective, cross-sectional, non-randomized	AR Non-allergic rhinitis	AH Cigarette exposure Gender Age Family history of allergies Asthma SPT	AH increased in AR group Cigarette smoke exposure associated with AH
Pagella et al.[3159]	2015	4	Retrospective case series	Referral to otolaryngology clinic for nasal symptoms, children aged 1–7 years and 8–14 years	Allergy testing, n = 169 Endoscopic adenoid size Clinical symptoms	AH and AR not associated at age 1–7 years AH and AR associated at age 8-14 years
Ameli et al.[3143]	2013	4	Consecutive cohort	Children with persistent upper airway obstruction	Endoscopic adenoid size SPT	Adenoid volume and % not associated with allergy
Karaca et al.[3142]	2012	4	Case series	Children with upper airway obstruction, n = 82	Radiographic AH Clinical tonsillar hypertrophy Allergen sensitivity	Negative correlation between SPT and tonsil hypertrophy No correlation between SPT and AH
Sadeghi-Shabestari et al.[3144]	2011	4	Retrospective cohort	ATH No ATH	SPT for food, inhalant, and latex	ATH and positive SPT 70.3% No ATH and positive SPT 10%
Mordrzynski and Zawisza[3140]	2007	4	Prospective, unblinded, controlled	Tree-sensitive Mugwort-sensitive Non-atopic Tree sensitive "treated"	Acoustic rhinometry Endoscopic adenoid size	Increased adenoid size in birch-allergic children during pollen season Decreased after pollen season and prevented by allergy pharmacotherapy

(Continues)

TABLE XIII.F (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Cassano et al.[3138]	2003	4	Cohort	Children with nasal obstruction	Endoscopic adenoid size AR diagnosed by SPT and RAST in 22 patients (20.9%)	% with "allergy" decreased with increasing adenoid size Statistical significance not reported
Huang and Giannoni[2831]	2001	4	Case–control	AR + AH AR	SPT Otitis media Sinusitis LTRI Second-hand smoke Sleep disordered breathing	Higher prevalence of mold SPT and LRTI (in some age groups) in AR + AH

Abbreviations: AH, adenoid hypertrophy; AR, allergic rhinitis; ATH, adenotonsillar hypertrophy; IgE, immunoglobulin E; LOE, level of evidence; LRTI, lower respiratory tract infection; RAST, radioallergosorbent test; SPT, skin prick test.
[a]LOE downgraded due to low quality of included studies.

that inhalant allergen sensitization decreased as AH size increased. Karaca et al.[3142] compared allergy sensitization to radiographic adenoid size in 82 children and found no association. Ameli et al.[3143] assessed 205 children with nasal endoscopy and SPT and found a negative association between SPT positivity and adenoid volume ($p < 0.0001$). Conversely, Sadeghi-Shabestari et al.[3144] compared SPT results and tIgE levels amongst 117 children with adenotonsillar hypertrophy (ATH) and 100 controls. Over 70% of the ATH group had a positive SPT versus 10% of the control group ($p = 0.04$), but this study is limited by the inclusion of SPT for foods (highest positive allergen subgroup) and latex.

In two additional studies, children referred from allergy practices were assessed for both AH with nasal endoscopy and SPT sensitivity. Both studies excluded children on allergy medication and observed a significant negative correlation between AH and SPT positivity ($r = -0.208$, $p = 0.009$)[3145] and ($p = 0.04$).[3146] The variability in study population recruitment and age range may explain the mixed findings.

Several studies have found immunologic evidence of allergic physiology in adenoid tissue. Ni et al.[3147] found a higher Th17/Treg ratio in adenoid tissue from children with AR versus non-allergic controls. Masieri et al.[3148] reported Th1 gene expression in non-allergic adenoid tissue, Th1 and Th2 gene expression in adenoid tissue of children with AH and AR, and downregulation of Th1 and Th2 gene expression in adenoid tissue during SLIT. Zhu et al.[3149] found increased tissue eosinophilia and markers of Th2 inflammation in the adenoid tissue of children with AH with AR, compared to AH alone. Local allergy may also play a role. One cohort of 102 children with ATH showing 53.9% sero-atopy and 68.6% with sIgE detected in their adenotonsillar tissue. sIgE positive adenoid tissue was found in 36.2% of the sero-negative children.[3150] Independently, Shin et al.[3151,3152] detected HDM and *Alternaria* local sIgE in adenoid tissue. Therefore, studies of allergic markers in adenoid tissue are present more often in atopic children, and there is some evidence of local allergic sensitization in children testing negative for sero-atopy.

The effect of INCS on reducing nasal obstruction in the setting of AH has been demonstrated in systematic reviews and is independent of allergy.[3153,3154] Whether INCS reduce adenoid size is unclear.[3155] One retrospective study ($n = 47$) reported improvement in rhinitis symptoms in similar percentages of AR (86%) and non-allergic rhinitis (76%) after adenoidectomy.[3156] At least one study suggests that AR is a risk factor for refractory nasal symptoms after adenoidectomy.[3157]

In summary, AH occurs in allergic children more often than non-allergic controls.[2830,3139,3140] A recent systematic review concluded that clinical and biomarker evidence favored an association between allergy and AH.[3158] However, in children referred to otolaryngology for nasal obstruction, the association between allergic sensitivity and AH is inconsistent.[3138,3142,3143,3145,3146] One possible explanation for this discrepancy is that symptomatic AH peaks earlier in childhood than AR. This is supported in the literature by Pagella et al,[3159] who reviewed records of children referred to otolaryngology for nasal symptoms ($n = 795$) and found no association between AR and AH in children aged 1–7 years ($p = 0.34$), but noted an association for children aged 8–14 years ($p = 0.0043$).

Associated conditions – adenoid hypertrophy

Aggregate grade of evidence: C (Level 2: 1 study, level 4: 12 studies; Table XIII.F)

XIII.G | Otologic conditions

XIII.G.1 | Eustachian tube dysfunction

The Eustachian tube (ET) is a bony and cartilaginous canal that connects the middle ear to the nasopharynx and functions to equalize pressure between the middle ear and the environment, protect the middle ear from harmful sounds and nasopharyngeal pathogens, and provide mucociliary clearance of middle ear secretions.[3160,3161] Obstructive ETD refers primarily to ventilatory dysfunction and is considered to have multifactorial etiologies including inflammation around the ET orifice (e.g., upper respiratory tract infection, rhinosinusitis, and reflux), pressure dysregulation (e.g., air travel, scuba diving), and obstructive lesions (e.g., nasopharyngeal tumor, AH). Evidence suggests a causal role of AR in the etiology of ETD due to allergic secretions, nasal mucosa edema, and hypersecretion of nasal cavity seromucous glands, all resulting in obstruction of the ET lumen.[3162–3164]

Data supporting a causal role of AR in the development of ETD comes from experimental studies using intranasal and transtympanic allergen challenges. Multiple studies have demonstrated transient ETD following allergen challenges in adult and pediatric subjects with[3165–3168] and without AR,[3163] as well as in animal models,[3169–3171] although ET responses have not been found to correlate with IgE levels[3164] (Table XIII.G.1).

In addition to experimental evidence suggesting a link between AR and ETD, observational data also supports this association. For example, ET obstruction is observed during natural exposure to allergens during pollen season, even without subjects being intranasally or transtympanically challenged.[3172,3173] Furthermore, in a representative adult cohort from the NHANES data, odds of reporting allergies was 1.71 times higher in subjects with ETD compared to those without ETD.[3174] Similarly, a pediatric population study found that significantly more children with AR had abnormal tympanograms compared to those without AR.[3175] Histologically, increased levels of allergic cytokines such as IL-4, IL-5, and eosinophils have been found at both ends of the ET,[3161] suggesting that an allergic response could be activated at the ET in sensitized patients.

However, despite both experimental and observational data supporting an association between allergy and ETD, studies have failed to consistently demonstrate improvement in ETD and its associated symptoms with allergy treatment. Gluth et al.[3176] found no significant normalization of abnormal tympanometric signs and no improvement in ETD symptoms between patients treated with INCS and those in placebo groups, and a clinical consensus statement found no role for systemic decongestants, antihistamines, nasal topical decongestants, or INCS in the diagnosis or treatment of patients with ETD.[3177] On the other hand, Pollock et al.[3178] found that ETD could be prevented in sensitized rats when pre-treated with IL-4 receptor decoys, and Derebery et al.[3179] reported improvement in the ETD symptom of ear fullness in allergic patients treated with AIT in a retrospective case series (although the presence of reported food allergy in this group may confound the results).

Overall, there is experimental and observational evidence to support a causal role of allergy in the development of ETD. However, the exact pathophysiologic mechanism behind this association is unclear since not all patients with ETD have AR, and traditional allergy treatment has not consistently shown benefit in reducing symptoms of ETD.

Associated conditions – Eustachian tube dysfunction

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 12 studies, level 4: 3 studies; Table XIII.G.1)

XIII.G.2 | Otitis media

OME is a common pediatric condition characterized by pressure changes and inflammation in the middle ear resulting in serous or mucoid fluid buildup behind the tympanic membrane.[3181] A relationship between middle ear effusion (MEE) and allergy and has long been a subject of epidemiologic study. The reported prevalence of allergy amongst patients with OME has varied widely, from essentially no difference compared to controls,[3182,3183] to varying degrees of difference,[2827,3184–3190] to a near universal association.[3191–3196] However, cross-sectional studies and one recent SRMA have reported that AR and atopy are independent risk factors for OME.[3197–3199] The inconsistencies of findings in these observational studies likely represent differences between highly selected populations and OME diagnostic criteria, variability of allergy testing methods, and sensitivities and the challenges of accounting for cofounders, such as age[2828] or OME phenotype[3200] (Table XIII.G.2).

Proposed pathogenic mechanisms of the development of OME center around Eustachian tube dysfunction;[3201] and theories regarding causal mechanisms that directly link allergy and otitis media without concurrent Eustachian tube dysfunction are controversial. (See Section XIII.G.1. Eustachian Tube Dysfunction for additional information

TABLE XIII.G.1 Evidence table – association between allergic rhinitis and Eustachian tube dysfunction

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Gluth et al.[3176]	2011	2	RDBPCT	91 subjects, aged 6–96 years: TAA-AQ nasal spray, $n = 45$ Control aqueous solution nasal spray, $n = 46$	Resolution of abnormal tympanometry Change in severity and frequency of ETD symptom scores	No difference in normalization of tympanometry between the two groups per patient (19% versus 32%; $p = 0.18$) or per ear (22% versus 35%; $p = 0.15$) No difference in symptom score between the two groups ($p = 0.27$)
Ebert et al.[3170]	2002	3[a]	Randomized observational	Rats randomly assigned to receive: Intranasal histamine infusion, $n = 24$ PBS, $n = 16$	Passive opening and closing pressures of the ET Active clearance of positive and negative pressure MCTT	Intranasal histamine elevated passive and active opening and closing ET pressures ($p < 0.001$) versus controls MCTTs were 2.4 times longer in histamine group versus control
Pollock et al.[3178]	2002	3[a]	Randomized observational	Treatment groups: sIL-4R/OVA sensitized rats injected with sIL-4R 1 h before OVA challenge, $n = 7$ Control groups: OVA or saline sensitization and/or challenge but no sIL-4R treatment, $n = 7$	Ventilatory and clearance functions of the ET Histologic inflammatory changes in the ET mucosa	sIL-4R-pretreated rats showed no significant changes in ventilatory or clearance functions of the ET or inflammatory changes in ET mucosa sIL-4R was effective in treating ETD and subsequent OME during the late-phase allergic response
Downs et al.[3169]	2001	3[a]	Randomized observational	Rats randomly assigned to receive: Transtympanic histamine, $n = 13$ Intranasal histamine, $n = 3$ Transtympanic PBS, $n = 3$	Passive opening and closing pressures of the ET (transtympanic and intranasal histamine groups) MCTT (transtympanic histamine and PBS groups)	Increase in passive opening and closing pressures with transtympanic histamine versus intranasal histamine Increase in MCTT after transtympanic histamine compared with transtympanic PBS control
Hardy et al.[3171]	2001	3[a]	Randomized observational	Rats randomly assigned to receive: SC injection of OVA followed by transtympanic injection of OVA, $n = 7$ No SC injection of OVA followed by OVA in PBS, $n = 5$ No SC injection of OVA followed by PBS only, $n = 5$	Passive opening and closing pressures of the ET Active clearance of positive and negative pressure MCTT	Sensitized rats had significant increases in passive and active opening pressures, decreased ability to actively clear middle ear pressure, and impaired MCTT

(Continues)

TABLE XIII.G.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Knight et al.[3173]	1992	3	Cohort	Seasonal AR patients ($n = 198$ subjects, 396 ears)	Middle ear pressure on tympanometry ETD symptoms during pollen season	Symptoms or tympanogram evidence of ETD in 24% of subjects Increased to 48% in pollen season
Doyle et al.[3163]	1990	3	Cohort	Intranasal challenge of increasing doses of histamine, methacholine, bradykinin, PGD2, and PGE2 in: Adult male subjects with AR, $n = 10$ Adult male controls, $n = 10$	Rhinomanometry for nasal patency Sonotubometry for ET function Tympanometry for middle ear pressure Spirometry for pulmonary function Subjective scoring for symptoms	Intranasal challenge with PGD2, histamine, and bradykinin provoked tubal dysfunction, although no changes in middle ear pressure were found No significant differences between AR and control groups
Osur et al.[3172]	1989	3	Cohort	Children with ragweed sensitivity, $n = 15$	9-step tympanometric ET function test	60% of cases developed ET obstruction following natural pollen exposure
Skoner et al.[3164]	1989	3	Cohort	Intranasal challenge of increasing doses of ragweed and histamine in subjects with ragweed AR before, during, and after ragweed season; $n = 8$	Rhinomanometry for nasal patency Sonotubometry for ET function	Mean ET obstruction dose for histamine decreased during and up to 6 weeks after ragweed season versus preseason and 3–5 months postseason doses ET hyperresponsiveness to ragweed limited to the ragweed season Responses did not correlate with serum IgE
Skoner et al.[3167]	1987	3[b]	Double-blind crossover	Adults with AR, $n = 5$ Adults without AR, $n = 5$	9-step tympanometric ET function test	All AR subjects had ET obstruction after histamine provocation (56% at 0.1 mg, 100% at 0.5 mg) Two non-AR subjects developed ET obstruction following a much higher dose (20% at 5 mg) Remainder did not develop ET obstruction (up to 10 mg)
Skoner et al.[3166]	1986	3	Cohort	Adults with AR sensitive to house dust mite, normal ET function ($n = 23$ subjects, 40 ears)	9-step tympanometric ET function test	55% of ears developed ET obstruction after provocation
O'Connor et al.[3168]	1984	3	Cohort	Children with AR, $n = 37$	Middle ear pressure Nasal airway resistance after pollen challenge	69% of children demonstrated negative middle ear pressure after allergen challenge

(Continues)

TABLE XIII.G.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Friedman et al.[3165]	1983	3[b]	Double-blind crossover	Adult patients with AR sensitive to ragweed, grass pollen, or both; $n = 8$	9-step tympanometric ET function test	All subjects experienced bilateral ET obstruction following pollen provocation
Juszczak et al.[3174]	2019	4	Cross sectional	Participants with Type A tympanograms, no ETD, $n = 1049$ Participants with Type B or C tympanograms, with ETD, $n = 204$	Participants with reported hay fever/AR	Presence of ETD correlated with presence of hay fever/AR (OR 1.71, $p = 0.039$)
Lazo-Sáenz et al.[3175]	2005	4	Case control	Subjects with AR: adults ($n = 40$), children ($n = 40$) Subjects without AR: adults ($n = 33$), children ($n = 17$)	Type B or C tympanogram Palmu criteria[3180] for children younger than 11 months	Adults with AR demonstrated a significant difference in tympanogram peak admittance versus controls 15.5% of children with AR and 0% of controls had abnormal tympanograms ($p = 0.03$)
Derebery et al.[3179]	1997	4	Retrospective case series	Patients with ETD and positive allergy testing (100% reactivity to inhalants and 92.3% positivity to one or more foods) who had undergone allergy treatment with immunotherapy and diet ($n = 151$)	Ratings of fullness, allergy symptoms, and well-being as "improved," "no change," or "worse"	Majority improved on all three symptoms – fullness 70.9%, allergy symptoms 82.8%, and well-being 80.2%

Abbreviations: AR, allergic rhinitis; ET, Eustachian tube; ETD, Eustachian tube dysfunction; IgE, immunoglobulin E; IL, interleukin; LOE, level of evidence; MCTT, mucociliary clearance time of the tubotympanum; OME, otitis media with effusion; OR, odds ratio; OVA, ovalbumin; PBS, phosphate buffered saline; PG, prostaglandin; RDBPCT, randomized double-blind placebo-controlled trial; SC, subcutaneous; TAA-AQ, triamcinolone acetonide aqueous.

[a]LOE downgraded due to animal study.

[b]LOE downgraded due to small sample size.

on this topic.) Some have proposed that the middle ear itself can be a site of targeted allergic reaction.[3202] Several cohort studies suggest that the middle ear is capable of developing a local IgE-mediated inflammatory reaction irrespective of a systemic inflammatory reaction.[3203–3206] Additionally, type 2 inflammatory patterns, such as eosinophil growth, mucus production, and mast cell presence, have been found in effusions of atopic patients when compared to non-atopic patients.[3207–3209] Furthermore, the chemoattractant cytokine RANTES, ECP, IL-4, IL-5, and MBP were found to be higher in effusions of atopic children than non-atopic children.[3208,3210–3213] Arguably the strongest evidence to date directly establishing the middle ear as an allergic target and linking it with the upper airway is the presence of similar cytokine expression patterns from biopsies of middle ear and nasopharyngeal specimens in atopic patients with OME.[3213]

Despite evidence suggesting that the middle ear is a site of allergic inflammation in patients with OME, high quality evidence has failed to demonstrate significant improvement or resolution of effusions after traditional allergy treatments. Placebo-controlled RCTs have shown that INCS do not improve OME outcomes.[3214,3215] Two Cochrane reviews have demonstrated the statistical

TABLE XIII.G.2 Evidence table – association between allergic rhinitis and otitis media

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Cheng et al.[3198]	2017	1	SRMA	Comparison of AR between: OME patients, n = 630 Controls, n = 380 Comparison of allergy between: OME patients, n = 1233 Controls, n = 4504	Prevalence of AR Prevalence of allergy	OME patients are more likely to have AR (OR 3.06; 95% CI 2.01–4.66) and allergy (OR 3.94; 95% CI 1.60–9.72) than controls
Griffin and Flynn[3216]	2011	1	SRMA	Children with OME, n = 1300	Resolution of OME after oral or nasal decongestant and/or antihistamine compared to placebo	No benefit of antihistamines or decongestants in resolution of fluid, hearing problems, or need to refer to a specialist
Simpson et al.[3217]	2011	1	SRMA	Children with OME, n = 945	Differences in hearing level Degree of CHL after oral/intranasal steroids ± other treatments, compared to placebo or no treatment	Oral steroids impart short-term but not long-term resolution of OME No short- or long-term benefit from INCS
Norhafizah et al.[3196]	2020	2	Cross-sectional	Children with OME, n = 130	Prevalence of AR at baseline Prevalence of AR for patients with persistent OME after 3 months	Prevalence of AR in OME children was 52.3% and 80.3% for those with persistent OME
Byeon[3199]	2019	2	Cross-sectional	Children, n = 472	Prevalence of AR Prevalence of OME	Children with AR were at greater risk of OME (OR 2.04; 95% CI 1.30–3.18) versus children without AR
Roditi et al.[2828]	2016	2	Cross-sectional	1,491,045,375 pediatric visits	Age Prevalence of OME Prevalence of AR	AR increases odds of OME in children over 6 years (OR 2.65; 95% CI 1.02–6.85), but not under 6 years
Ertugay et al.[3219]	2013	2	RCT	Children with OME, n = 120	Resolution of effusion after 1 month of montelukast or placebo	Montelukast is no more effective than placebo in eliminating effusion
Gultekin et al.[3188]	2010	2	Cross-sectional	Primary school-aged children, n = 1740	Prevalence of OME Prevalence of OME risk factors	8.7% prevalence of OME History of allergy was significant OME risk factor
Schoem et al.[3218]	2010	2	RCT	Children with OME, n = 38	Clearance of effusion at 1 month after montelukast or placebo	Montelukast is no more effective than placebo in eliminating effusion

(Continues)

TABLE XIII.G.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Williamson et al.[3215]	2009	2	RCT	Children with bilateral OME, n = 217	Proportion of pts with resolution of effusion at 1, 3, and 9 months after INCS compared to placebo	INCS were no more effective than placebo for OME resolution
Lindholdt & Kortholm[3214]	1982	2	RCT	70 children (4–14 years old) with MEE	Tympanometry Hearing improvement after 1 month of intranasal beclomethasone spray versus placebo	Beclomethasone nasal spray is no more effective than placebo for MEE resolution
Songu et al.[3190]	2020	3	Cohort	Children undergoing surgery for adenoid hypertrophy, n = 539	Prevalence of OME Prevalence of risk factors for OME	Prevalence of atopy or AR was greater in OME pts (34%) than those without OME (25%)
Sharifian et al.[3189]	2019	4	Case- control	Children with OME, n = 37 Controls, n = 52	AR prevalence Serum tIgE Eosinophil count Nasal scraping cytology	AR prevalence higher in OME (24.3%) than controls (5.8%) No difference in serum tIgE and eosinophil count
Torretta et al.[3200]	2018	4	Case–control	Children with RAOM, 3–10 years old, n = 153	Prevalence of OME after RAOM Prevalence of allergy (by skin or in vitro test) Prevalence of atopy (by serum IgE)	Prevalence of allergy and atopy were higher in children with OME after RAOM than without OME
Kwon et al.[2827]	2013	4	Case–control	Children with OME, n = 370 Controls, n = 100	History of allergy	Incidence of AR higher in OME (33.8%) versus controls (16%)
Kreiner-Moller et al.[3197]	2012	4	Cohort	6-year-old children, n = 262	Prevalence of OME Prevalence of AR	39% of cohort with OME OR of 3.36 for AR and OME
Hurst[3195]	2008	4	Cohort	OME patients treated with AIT, n = 89 OME patients not given AIT, n = 21	Resolution of effusion at 2–8-year follow-up	100% of OME with positive allergy tests 85% of AIT-treated patients cured
Yeo et al.[3183]	2007	4	Case–control	Children with OME, n = 123 Controls, n = 141	History of AR Skin prick tests	AR in 28% of OME group versus 24% of control
Chantzi et al.[3187]	2006	4	Case–control	Children with OME, n = 88 Controls, n = 80	Allergy history Allergy tests	IgE sensitization is independent risk factor for OME
Nguyen et al.[3213]	2004	4	Cohort	Patients with OME undergoing tympanostomy tube and adenoidectomy, n = 45	Skin prick test Cellular and cytokine profiles of effusions and nasopharyngeal tissue	Effusions of atopic pts had higher levels of eosinophils and IL-4 mRNA cells than non-atopics Nasopharyngeal biopsies had similar profiles to effusions in atopics

(Continues)

TABLE XIII.G.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jang and Kim[3212]	2003	4	Cohort	OME patients: With allergy, $n = 25$ Without allergy, $n = 20$	Allergy tests Effusion levels of RANTES and ECP	Levels of RANTES and ECP were higher in effusions of OME pts with allergy than without
Jang and Kim[3211]	2002	4	Case- control	OME patients: With allergy, $n = 20$ Without allergy, $n = 15$	Allergy tests Effusion cytokine concentrations	Higher levels of IL-4, IL-6, and TNF-α in effusions of allergy positive group than allergy negative group
Sobol et al.[3208]	2002	4	Case series	26 OME patients	Skin prick tests Effusion immunocy-tochemistry	Higher levels of eosinophils and T lymphocytes in effusions of atopics than non-atopics
Alles et al.[3194]	2001	4	Cohort	Children (3–8 years old) with OME	Prevalence of AR Skin prick tests	57% with positive skin prick test, almost all with rhinitis
Hurst and Venge[3207]	2000	4	Cohort	Patients with OME, $n = 97$	In vitro allergy tests Effusion levels of ECP, MPO, tryptase Serum tIgE	Atopic patients had higher levels of ECP, MPO and tryptase in effusions versus non-atopic No difference in serum tIgE
Wright et al.[3210]	2000	4	Case–control	Children with OME, $n = 7$ Controls, $n = 7$	In vitro allergy testing CD3, MBP, IL-5 expression in middle ear mucosa	OME patients all tested positive to at least three allergens Middle ear biopsies of OME patients had higher expression of T cells, eosinophils, and IL-5 mRNA versus controls
Hurst et al.[3206]	1999	4	Cohort	Children with OME, $n = 18$	Effusion IgE levels Serum sIgE levels	No relation between serum and effusion sIgE levels
Caffarelli et al.[3182]	1998	4	Case- control	Patients with OME, 4-14 years old, $n = 172$ Controls, $n = 200$	Skin prick tests	Equal rates of sensitization between OME group and controls
Hurst[3193]	1996	4	Cohort	Patients with OME, $n = 73$ Controls, $n = 16$	Allergy tests Effusion ECP	Positive allergies in 97% of COME
Corey et al.[3186]	1994	4	Case- control	Children with OME, $n = 89$ Controls, $n = 59$	RAST	61% positive RAST in OME group versus 41% in controls
Tomonaga et al.[3185]	1988	4	Cohort	Children with OME, $n = 259$ Nasal allergies, $n = 605$ Controls, $n = 104$	Allergy testing	50% of OME patients had nasal allergy versus 17% controls

(Continues)

TABLE XIII.G.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bernstein et al.[3205]	1985	4	Cohort	Patients with OME and allergy, $n = 35$ Patients with OME, non-allergic, $n = 65$	tIgE and sIgE in effusion tIgE and sIgE in serum	23% of allergic OME patients had evidence of local IgE
Bernstein et al.[3204]	1983	4	Cohort	Children with OME and history of myringotomy tubes, $n = 77$	Allergy evaluation Serum tIgE Nasal IgE MEE IgE	Higher levels of IgE in MEE of allergic children than non-allergic children
Borge[3184]	1983	4	Case- control	Patients with SOM, $n = 89$ Controls, $n = 67$	Allergy history Allergy testing	41% of SOM patients had perennial rhinitis versus 11% of controls
Bernstein et al.[3203]	1981	4	Cohort	Patients with OME and allergy, $n = 20$ Patients with OME, non-allergic, $n = 21$	Serum tIgE Serum sIgE MEE tIgE MEE sIgE	15% of allergic OME cases had evidence of local IgE
McMahan et al.[3191]	1981	4	Case series	Patients with COME, $n = 119$	RAST	93% of COME patients tested positive to inhalants

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; CD, cluster of differentiation; CHL, conductive hearing loss; CI, confidence interval; COME, chronic otitis media with effusion; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IL, interleukin; INCS, intranasal corticosteroid; LOE, level of evidence; MBP, major basic protein; MEE, middle ear effusion; MPO, myeloperoxidase; OME, otitis media with effusion; OR, odds ratio; RANTES, regulated upon activation, normal T cell expressed and secreted; RAOM, recurrent acute otitis media; RAST, radioallergosorbent test; sIgE, specific immunoglobulin E; SOM, serous otitis media; SRMA, systematic review and meta-analysis; tIgE, total immunoglobulin E; TNF, tumor necrosis factor.

ineffectiveness of antihistamines, decongestants, antihistamine/decongestant combinations, and INCS in resolution of OME.[3216,3217] In two RCTs of children with OME, LTRAs provided no benefit over placebo in resolution of effusions.[3218,3219] Finally, though one prospective cohort demonstrated a significant improvement in OME after targeted SCIT compared to a group of controls self-selected to avoid AIT, some aspects of the study design are flawed, including significant selection bias and inclusion of a generally older population than that most affected by OME.[3195]

In summary, observational studies provide low grade evidence of an association between allergy and OME. Nevertheless, moderate grade evidence from histologic studies suggest that the middle ear could be a primary site of allergy. Additionally, a high level of evidence suggests that traditional allergy treatment is not effective in resolving OME.

Associated conditions – otitis media

Aggregate grade of evidence: C (Level 1: 3 studies, level 2: 8 studies, level 3: 1 study, level 4: 24 studies; Table XIII.G.2)

XIII.G.3 | Meniere's and inner ear disease

Meniere's disease is a chronic condition that occurs almost exclusively in adults and is characterized by aural fullness, tinnitus, fluctuating sensorineural hearing loss (SNHL), and episodic vertigo. While the underlying pathophysiologic mechanism of Meniere's disease remains uncertain, it is associated with a dysregulation of inner ear fluid volume resulting in endolymphatic hydrops.[3220] Theories linking allergy to Meniere's disease have centered on the role of the endolymphatic sac in the development of hydrops and clinical symptoms through its release of allergic mediators or its susceptibility to circulating immune complexes and dormant viral antigens.[3221] A causal relationship between allergy and Meniere's disease is supported by limited studies, though there have been a number of observations of association between Meniere's disease and allergic conditions. Patient-reported and physician-reported data suggest that Meniere's disease patients have higher rates of concurrent AR than expected in the general population[3222] and have increased odds of allergies versus controls.[3223] Similar patient-reported data suggests higher rates of allergy and migraine in Meniere's disease patients.[3224] Overall, these studies generally provide low grade evidence (Table XIII.G.3).

TABLE XIII.G.3 Evidence table – association between allergic rhinitis and Meniere's/inner ear disease

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tyrell et al.[3223]	2014	2	Cross-sectional	MD patients, $n = 1376$ Controls, $n = 501{,}306$	OR of allergy OR of rhinitis	MD patients have increased odds of rhinitis but not allergy
Derebery[3232]	2000	3	Cohort	MD patients treated with AIT + diet, $n = 113$ MD controls, $n = 24$	Self-reported MD symptoms	Allergy treatment reduced tinnitus and vertigo
Ma et al.[3227]	2021	4	Case–control	Sudden SNHL patients, $n = 127$ Acute low frequency SNHL patients, $n = 115$	Serum tIgE Serum sIgE ECoG SP/AP ratio	Patients with acute low frequency SNHL have higher serum tIgE and sIgE High IgE levels correlate with increased SP/AP amplitudes
Roomiani et al.[3226]	2021	4	Case–control	MD patients, $n = 39$ Controls, $n = 41$	Serum tIgE Serum immunoreactivity to inhalant allergens	MD patients have higher serum tIgE Association between MD and reactivity to inhalant allergens
Singh et al.[3234]	2011	4	Cohort	Patients with AR, $n = 30$ Controls, $n = 20$	Audiometry OAE ABR	AR subjects had evidence of inner ear dysfunction
Sen et al.[3224]	2005	4	Case–control	MD patients, $n = 180$ Controls, $n = 100$	Prevalence of self-reported migraines Prevalence of self-reported allergy	MD patients have higher prevalence of migraine and allergy than controls Prevalence of allergy higher in MD patients with migraines than without
Keles et al.[3225]	2004	4	Case–control	MD patients, $n = 46$ Healthy controls, $n = 46$	Serum lymphocyte populations Serum cytokine levels sIgE levels tIgE levels	MD patients more likely to have positive allergy test 41% of MD patients had elevated tIgE
Derebery and Berliner[3222]	2000	4	Case–control	MD patients, $n = 734$ Controls, $n = 172$	Allergy symptoms History questionnaire	MD patients have more AR and food sensitivity
Gibbs et al.[3230]	1999	4	Case series	Patients with MD and inhalant allergy, $n = 7$	Change in ECoG after allergen challenge	57% of subjects had >15% change in SP/AP ratio after challenge
Derebery and Valenzuela[3231]	1992	4	Cohort	MD patients with suspected allergy, $n = 93$	Allergy skin test In vitro allergy tests Serum IgE Provocative food testing AIT response	82% had normal serum IgE AIT improved vertigo in 62%
Viscomi and Bojrab[3229]	1992	4	Case series	Patients with MD and AR, $n = 5$	Rate of having >15% change in SP/AP ratio on ECoG after allergen challenge Rate of provocation of MD symptoms after allergen challenge	6/27 intracutaneous food challenges with induction of aural symptoms and >15% change in SP/AP ratio
Hsu et al.[3228]	1990	4	Case–control	MD patients, $n = 42$ Controls, $n = 18$	Serum tIgE	No difference in serum tIgE between groups

Abbreviations: ABR, auditory brainstem response; AIT, allergen immunotherapy; AR, allergic rhinitis; ECoG, electrocochleography; IgE, immunoglobulin E; LOE, level of evidence; MD, Meniere's disease; OAE, otoacoustic emissions; OR, odds ratio; sIgE, specific IgE; SNHL, sensorineural hearing loss; SP/AP, summation potential/action potential ratio; tIgE, total immunoglobulin E.

Objective evidence of heightened immunopathologic profiles and reactivity in Meniere's disease patients has been mixed. Higher rates of serum IgE levels were observed in Meniere's disease patients versus controls,[3225,3226] as well as in patients with acute low frequency SNHL compared to those with sudden SNHL.[3227] However, in another small study, there was no difference in serum tIgE levels between Meniere's disease and controls.[3228] In two small studies, electrocochleographic summation potential/action potential [SP/AP] ratios increased in response to allergen challenge in Meniere's disease patients,[3229,3230] suggesting that allergy may worsen endolymphatic hydrops. Likewise, serum IgE levels were found to correlate with elevated SP/AP ratios in patients with low frequency SNHL.[3227] Overall, studies on IgE levels and electrocochleography are of low-grade evidence with significant shortcomings in design.

Lastly, there have been two studies on the treatment of allergies in Meniere's disease patients, both of low-grade evidence, suggesting that AIT results in improvement of Meniere's disease symptoms in patients with concurrent allergies (although potentially confounded by inclusion of non-IgE-mediated food allergy).[3231,3232] However, a double-blind RCT, expected to conclude in April 2022, is being conducted to investigate the efficacy of a leukotriene inhibitor in reducing vertigo and hearing loss in Meniere's disease patients.[3233] In conclusion, though observational studies have found associations between Meniere's disease and allergy, no data to date supports reflexive allergy testing and treatment in Meniere's disease patients without a concurrent history of allergies.

Associated conditions – Meniere's and inner ear disease

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 1 study, level 4: 10 studies; Table XIII.G.3)

XIII.H | Cough

Cough clears the lower airways of irritants. Vagal afferent nerves regulate involuntary cough, yet there is cortical control of the overall visceral cough reflex.[3235] AR has been associated with cough. Allergens may stimulate the nasal mucosa, resulting in the rhinobronchial reflex and bronchospasm.[3236] Inflammation in the upper airways with eosinophil activation and cytokine release may also lead to inflammation of the lower airways and cough. There is a complex interplay between cells and inflammatory cytokines, and the upper and lower airways can be considered a single functional unit.[3236] The exact pathways and mechanisms of this unified airway model continue to unfold.

Patients with AR and concomitant cough may have asthma and/or a nonspecific bronchial hyper-reactivity, and generalized inflammation of the upper and lower airways can be present.[1004] Patients with cough and AR may cough due to their underlying asthma. However, many patients with AR and cough do not have the diagnostic airflow obstruction or bronchodilator-associated FEV_1 reversibility that is necessary to meet asthma diagnostic criteria.[1004] Krzych-Falta et al.[3237] performed nasal allergen challenges in AR patients and noted extra-nasal symptoms, including cough and breathlessness, especially in those with perennial AR. Additionally, Chakir et al[3238] showed increased lymphocytes, eosinophil recruitment, and IL-5 expression in the bronchial mucosa after exposure with natural pollen in patients with AR without current or prior asthma. The same group noted deposition of type I and III collagens and fibronectin by bronchial myofibroblasts in patients with AR in a previous study, suggesting structural remodeling of the lower airways in patients with AR which was similar to asthma, albeit less severe.[3239] In an animal model, HDM-sensitized guinea pigs had a significantly enhanced cough response compared to non-sensitized animals.[3240] These studies demonstrate that AR, independent of asthma, may result in bronchial inflammation, lower airway remodeling, and ultimately cough (Table XIII.H).

Several publications in 2016 reported results of relatively large studies evaluating the characteristics of respiratory diseases in the Asia Pacific region. In a 1000-person cross-sectional observational study, it was noted that patients with asthma and/or COPD present to physicians with a primary complaint of cough, whereas AR patients typically present with watery rhinorrhea and/or sneezing.[1188,3241] In addition, combined respiratory disease may be seen; this occurred in 33.5%, with the most common combination being AR and asthma.[1188,3241] A multi-country observational study of 5250 subjects reported that 47% of patients with AR reported cough; however, only 11% of these patients reported cough as the main reason for seeking medical care.[3242] Interestingly, for patients with asthma, 61% reported cough, and for 33% cough was the primary reason for seeing medical care. In a prospective study of 2713 patients with AR, He et al.[3243] found the prevalence of comorbidities, including cough, to gradually increase with increasing AR severity and frequency.

Publications from 2020 to 2021 provide additional evidence to support the association between cough and AR. In two RCTs that enrolled patients with either refractory or unexplained cough, concomitant AR was present in 15%

TABLE XIII.H Evidence table – association between allergic rhinitis and cough

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hua et al.[2397]	2022	2	RCT	Participants with AR: Posterior nasal neurectomy and pharyngeal neurectomy, $n = 25$ Posterior nasal neurectomy alone, $n = 27$	Cough severity on visual analog scale	Postoperative cough severity significantly lower in both groups Postoperative cough severity significantly lower with nasal+pharyngeal neurectomy versus nasal neurectomy alone
Dicpinigiatis et al.[3244]	2021	2	Secondary analysis of RCTs	Patients ≥18 years with refractory/unexplained cough in COUGH-1 and COUGH-2 RCTs of the P2 × 3 receptor antagonist gefapixant, $n = 2044$	Concurrent AR	AR was present in 20% of COUGH-1 and 15% in COUGH-2 participants
Lin et al.[2096]	2017	2	RCT	Patients with chronic cough, AR, elevated sIgE to HDM (aged 18–75 years): Nasal saline irrigations, $n = 23$ Fluticasone nasal spray, $n = 22$	Cough Symptom Score Leicester Cough Questionnaire Capsaicin cough threshold	All endpoints improved significantly in the nasal saline arm, but did not improve with fluticasone nasal spray
Deot et al.[3250]	2019	3[a]	SR	RCTs evaluating effect on INCS on secondary symptoms of AR, including cough	Cough severity	Two studies identified: one showed improvement on daytime cough, one showed no difference in cough
He et al.[3243]	2016	3	Prospective, non-randomized	Serum sIgE from patients with AR symptoms from 2011 to 2014, $n = 2713$	Questionnaire Allergen profile Clinical features of AR	*D. pteronyssinus* most common allergen Occurrence of co-morbidities, including cough, increased with AR severity
Passali et al.[3236]	2011	3	Cohort	Patients from otolaryngology and pulmonary centers, $n = 159$	Analysis of rhino-bronchial syndrome signs and symptoms	Increased frequency of the rhino-bronchial-syndrome in allergic disease (37.9% versus 20.9%) Cough in 96%
Chen et al.[3248]	2021	4	Case series	Consecutive chronic cough patients, 18–75 years old, $n = 328$: CVA Non-CVA	FeNO MMEF	AR more common in CVA group FeNO higher with concomitant AR FeNO more accurate in differentiating CVA from non-CVA when AR present
Nakajima et al.[3247]	2021	4	Case series	Consecutive patients with cough >3 weeks and CVA or CPA, $n = 99$	FeNO Cough duration after initial evaluation	FeNO higher and cough duration longer in those with AR versus non-AR

(Continues)

TABLE XIII.H (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim et al.[3245]	2020	4	Case series	AR patients presenting to allergy clinic: 1990s cohort, $n = 2722$ 2010s cohort, $n = 4980$	Self-reported cough on questionnaire	Proportion of patients with cough increased from 1990s (22%) to 2010s (27.9%)
Liu et al.[3249]	2019	4	Case series	Consecutive patients with AR and chronic cough, $n = 316$	FeNO $FEF_{25–75}$	FeNO can differentiate chronic cough patients with CVA or NAEB from patients with UACS or GERC Lower $FEF_{25–75}$ can then be used to identify CVA patients
Tang et al.[3246]	2018	4	Case series	Consecutive newly diagnosed CVA patients, $n = 99$	FeNO levels dichotomized as high (≥25 ppb) and normal (<25 ppb)	More patients with concurrent AR in the high FeNO group Higher odds of having elevated FeNO with concurrent AR (OR 5.03; 95% CI 1.88–13.49)
Cho et al.[3242]	2016	4	Case series	Adults with primary diagnosis of asthma, AR, COPD, or rhinosinusitis, $n = 5250$	Respiratory disease and demographics questionnaire completed by participants and physicians	Cough symptoms in COPD (73%), asthma (61%), rhinosinusitis (59%), AR (47%) Cough was the primary reason for medical visits with COPD (43%), asthma (33%), rhinosinusitis (13%), AR (11%)
Ghoshal et al[1188]	2016	4	Case series	Adults with primary diagnosis of asthma, AR, COPD, or rhinosinusitis, $n = 1000$	Respiratory disease questionnaire Direct and indirect costs of treatment	Asthma was the most frequent primary diagnosis 33.5% patients were diagnosed with combined respiratory diseases Most frequent combinations were asthma/AR and rhinosinusitis/AR
Lin et al.[3241]	2016	4	Case series	Adults with primary diagnosis of asthma, AR, COPD, or rhinosinusitis, $n = 1001$	Respiratory disease questionnaire completed by participants and physicians	AR was the most frequent primary diagnosis (31.2%) 25% presented with a combination of respiratory diseases Asthma/AR was the most frequent combination (14.1%) Cough was the primary reason for medical visits for patients with asthma and COPD; nasal symptoms were the primary reasons for AR and rhinosinusitis
Krzych-Falta et al.[3237]	2015	4	Case–control	Patients with allergy to common environmental allergens, $n = 30$ Controls, $n = 30$	Assess safety of nasal allergen challenge, and the use of certain parameters applied in assessing the condition of the respiratory system	Extra-nasal symptoms observed early in reaction, namely cough and breathlessness, and more common in those with perennial AR

(Continues)

TABLE XIII.H (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chakir et al.[3238]	2000	4	Case series	Participants with recurrent seasonal pollen-induced rhinitis, no past or current history of asthma, aged 21–35 years, $n = 12$	Bronchial biopsy immunohistochemistry Cytokine expression, inflammatory cell numbers and activation during and out of pollen season	Natural pollen exposure associated with increased lymphocytes, eosinophil recruitment, IL-5 expression in bronchial mucosa
Chakir et al.[3239]	1996	4	Case–control	Non-asthmatic subjects with seasonal AR, $n = 8$ Allergic asthmatics, $n = 6$ Controls, $n = 5$	Bronchial biopsy immunohistochemistry	Content of type I and III collagens increased in rhinitic subjects Suggests the presence of an active structural remodeling in the lower airways of AR patients
Buday et al.[3240]	2016	5	Bench research	30 guinea pigs: HDM group (sensitized by HDM aerosol, then challenged, sensitization confirmed via skin test) OVA group Control group	Symptoms of AR induced by intranasal application of 15 μl 0.5 % HDM Cough challenge with citric acid performed Airway resistance measured in vivo by Pennock's method	HDM and OVA-sensitized groups showed a significantly enhanced nasal reactivity and cough response versus controls Airway resistance data did not show significant differences

Abbreviations: AR, allergic rhinitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPA, cough predominant asthma; CVA, cough variant asthma; $FEF_{25–75}$, forced expiratory flow at 25% to 75% of pulmonary volume; FeNO, fractional exhaled nitric oxide; GERC, gastroesophageal reflux-related cough; HDM, house dust mite; IL, interleukin; INCS, intranasal corticosteroid; LOE, level of evidence; MMEF, maximum mid-expiratory flow; NAEB, non-asthmatic eosinophilic bronchitis; OR, odds ratio; OVA, ovalbumin; RCT, randomized controlled trial; sIgE, specific immunoglobulin E; UACS, upper airway cough syndrome.

[a]Downgraded due to low number of included studies, inconsistent results.

and 20% of patients.[3244] Kim et al.[3245] found that more patients presenting with AR for allergy testing reported cough in the 2010s (27.9%) compared to the 1990s (22%). Increasing evidence associates AR with cough or, more commonly, cough as a comorbidity of AR.[3238–3240] Therefore, diagnostic and treatment modalities for cough in patients with AR have an increasingly important role.

Recent studies have proposed FeNO as a tool to differentiate causes of cough in patients with AR. Elevated FeNO is associated with airway eosinophilia in asthma patients. Elevated FeNO may raise suspicion for AR in patients with cough variant asthma or cough predominant asthma.[3246,3247] When AR and chronic cough are both present, FeNO may be able to differentiate between chronic cough due to cough variant asthma or non-asthmatic eosinophilic bronchitis from other forms of chronic cough.[3248,3249]

It is not clear if treatment of AR with INCS improves the associated cough,[3245,3250] but an RCT by Kim et al.[3245] suggests that nasal saline irrigations decrease cough associated with AR. Posterior nasal neurectomy with or without pharyngeal neurectomy in patients with AR may decrease cough.[2397]

Associated conditions – cough

Aggregate grade of evidence: C (Level 2: 3 studies, level 3: 3 studies, level 4: 11 studies, level 5: 1 study; Table XIII.H)

XIII.I | Laryngeal disease

AR and inhalant allergy have been associated with laryngeal disease; however, understanding of their precise role in laryngeal disease is limited. This section evaluates studies that examine the relationship between inhalant

allergy and laryngeal disease, including allergic laryngitis. Allergic laryngitis is characterized by allergen-induced laryngeal inflammation and can present with dysphonia, coughing, throat clearing, and globus.[3251] Some studies have evaluated laryngeal symptoms in individuals with AR while others have evaluated the direct effects of allergen exposure on the larynx (Table XIII.I).

Establishing a causal relationship between AR and laryngeal disease has proven difficult, although associations have been reported. Lee et al.[3252] found an association between the diagnosis of chronic laryngitis and AR in a Korean nationwide cohort. Subsequently, Wang et al.[3253] identified a strong association between AR and developing laryngeal pathology in a Taiwanese nationwide cohort. Several studies have reported higher Voice Handicap Index (VHI) scores in AR patients versus controls.[3254–3257] Ohlsson et al.[3258] reported that vocal symptoms in those with AR worsen during the allergy season and may be associated with a decrease in speech fundamental frequency. Velickovic et al.[3259] found that overall AR is common and occurs in 44.2% of professional voice users presenting with dysphonia. Singers with self-perceived voice issues were 15% more likely to have AR than those without vocal complaints.[3260] The likelihood of AR increased as the number of vocal symptoms increased.[3260]

The adverse effects of AR on voice-related QOL have also been reported,[3254,3256,3261] and Turley et al.[3261] supported this association by showing that patients who reported poor rhinitis-related QOL also had poor voice-related QOL and increased severity of chronic laryngeal symptoms. Furthermore, increased allergen load was associated with greater severity of vocal symptoms.[3257] Overall, there is a higher than anticipated incidence of AR in patients with vocal dysfunction and vice versa.[3257,3260–3262]

Findings of laryngeal inflammation have largely been attributed to laryngopharyngeal reflux (LPR), but recent studies have questioned its role as the primary source of laryngeal dysfunction.[3256,3263] Allergic laryngitis associated with AR can be difficult to distinguish from other laryngeal inflammatory disorders, including LPR, due to limitations of current diagnostic methods including poor specificity and inter-rater reliability. Patients with clinically significant LPR may be more likely to report AR symptoms.[3264] However, the opposite may be true in professional voice users presenting with dysphonia.[3259] Randhawa et al.[3263] studied patients presenting with voice concerns and reported one-third were diagnosed with LPR, whereas two-thirds of patients were diagnosed with allergies. Laryngeal findings in LPR and allergic laryngitis and LPR may be similar; laryngeal edema, laryngeal erythema, and excessive thick mucus are often seen.[3265,3266] Eren et al.[3266] demonstrated no significant difference in laryngeal appearance between allergy-positive and LPR-positive subjects. However, thick endolaryngeal mucus may predict allergy.[3267]

Several studies have evaluated the direct effect of allergens on the larynx. Belafsky et al.[3268] and Mouadeb et al.[3269] examined *Dermatophagoides farinae* exposure to the laryngeal mucosa of guinea pigs and found an increase in eosinophilia compared to saline exposure, providing some support for allergens contributing to laryngeal disease. Two studies from the same voice laboratory evaluated direct laryngeal stimulation by nebulized *Dermatophagoides pteronyssinus* in allergic patients to assess laryngeal symptoms, appearance, and function.[3251,3270] In the first study, Reidy et al.[3251] did not identify a significant difference between antigen- and placebo-challenged subjects on any of the evaluated measures, such as VHI, Sinus Symptoms Questionnaire, laryngoscopy, and acoustic/aerodynamic testing. In a follow-up, Dworkin et al.[3270] used increased allergen concentration for the challenge and noted an increase in endolaryngeal mucus, throat clearing, and coughing. Roth et al.[3271] performed a similar study but isolated the larynx by utilizing a nose clip to ensure oral inhalation and eliminated patients with reactive airways based on methacholine challenge, thus demonstrating a causal relationship between allergen stimulation and impaired vocal function. Suzuki et al.[3272] also utilized a nose clip and found more laryngeal symptoms when patients were exposed to cypress pollen compared to placebo. However, there were no corresponding objective changes in acoustic analysis or flexible laryngoscopy.[3272] These studies suggest that in subjects with inhalant allergy there can be laryngeal dysfunction due to direct allergen stimulation of the larynx as well as possible symptoms secondary to the nasal congestion, inflammation, and drainage of AR.

There is increasing evidence suggesting a relationship between AR, inhalant allergy, and laryngeal disease. Although laryngeal findings specific to allergic laryngitis are not consistently demonstrated, thick endolaryngeal mucus should raise suspicion for underlying allergy. AR should be considered in the differential diagnosis of patients with vocal complaints. Additional studies are needed on the effect of AR treatment on associated laryngeal disease.[3251]

Associated conditions – laryngeal disease

Aggregate grade of evidence: C (Level 2: 7 studies, level 3: 4 studies, level 4: 10 studies, level 5: 2 studies; Table XIII.I)

TABLE XIII.I Evidence table – association between allergic rhinitis and laryngeal disease

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lee et al.[3252]	2019	2	Cross-sectional	Korea National Health and Nutrition Examination Survey; patients with nasal endoscopy and laryngoscopy data	Chronic laryngitis Allergic laryngitis determined by serum IgE	Chronic laryngitis associated with rhinitis Allergic laryngitis had highest risk of concurrent rhinitis All allergic laryngitis patients sensitive to *D. farinae*
Roth et al.[3271]	2013	2	RCT	General public	Effect of allergen on laryngeal findings	Impaired vocal function related to allergen exposure is independent of asthma or nasal exposure
Randhawa et al.[3257]	2010	2	Cross sectional	Rhinology clinic patients, no pre-reported voice-related symptoms	Association between allergy and vocal dysfunction	Degree of allergen load correlates with the severity of vocal symptoms on VHI
Dworkin et al.[3270]	2009	2	RCT	HDM-sensitive adults: *D. pteronyssinus* challenge Placebo	Effect of allergen on laryngeal findings	Laryngeal abnormalities secondary to lower respiratory stimulation
Simberg et al.[3262]	2009	2	Cross sectional	Allergy patients undergoing AIT Non-allergic controls	Symptom prevalence	Allergic patients had more severe vocal symptoms Patients on AIT >2 years had fewer vocal symptoms
Krouse et al.[3256]	2008	2	Prospective observational	HDM skin test: Positive Negative	Effect of allergen on laryngeal findings	More perceived vocal handicap in allergic individuals even in absence of physical/functional abnormalities Findings present in subjects without LPR/GERD VHI changes seen in HDM-sensitive patients
Reidy et al.[3251]	2003	2	RCT	*D. pteronyssinus* challenge Placebo challenge	Effect of allergen on laryngeal findings	No significant differences between allergen and placebo exposed subjects
Wang et al.[3253]	2021	3	Nationwide cohort	AR patients, all ages Patients without AR matched by gender, age, urbanized level, and income	Occurrence of a laryngeal pathology ICD code (vocal cord polyps, edema of larynx, chronic laryngitis, other vocal cord diseases)	Individuals with AR had a 2.43 times higher risk of laryngeal pathology versus those without AR
Alharethy et al.[3264]	2018	3	Cohort	Patients presenting to otolaryngology clinic with LPR symptoms	SFAR in patients with positive and negative 24-h oropharyngeal pH monitoring	LPR patients based on pH testing had higher SFAR scores Higher Ryan score associated with higher SFAR score

(Continues)

TABLE XIII.I (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Velickovic et al.[3259]	2017	3	Cohort	Professional voice users with dysphonia presenting to an otolaryngology department	Prevalence of AR based on ARIA guidelines Prevalence of LPR based on RSI >13	AR present in 44.2% AR was less common in patients with LPR
Suzuki et al.[3272]	2016	3	Placebo-controlled trial	Subjects with AR to cypress pollen, $n = 25$	Subjective report of laryngeal symptoms during pollen/placebo exposure Laryngeal symptom questionnaire Acoustic analysis Flexible laryngoscopy	More laryngeal symptoms were reported with pollen exposure, especially when nose plugged No significant findings in acoustic analysis or laryngoscopy
Brook et al.[3273]	2016	4	Retrospective case series	Patients undergoing in vitro allergy testing, 2006–2010	Symptom prevalence	Yield of in vitro allergy testing for laryngeal symptoms comparable to other common allergy testing indications
Ohlsson et al.[3258]	2016	4	Case–control	Patients with AR from birch pollen, $n = 30$ Controls without AR, matched for gender and age, $n = 30$	4-question allergy questionnaire Swedish questionnaire about voice symptoms Acoustic analysis of voice recordings	AR patients had more voice symptoms during allergy and non-allergy season, voice symptoms decreased during non-allergy season Speech fundamental frequency was lower during both seasons in AR patients suggesting vocal fold edema
Brook et al.[3274]	2015	4	Retrospective case–control	Atopic patients Non-atopic patients	Endoscopic findings in AR	Findings within the nasopharynx, rather than larynx, are predictive of atopic status
Eren et al.[3266]	2014	4	Case series	Patients referred from allergy clinic with SPT testing	Laryngeal findings in AR and LPR	Thick endolaryngeal mucus predicts allergy No association between allergic sensitization and LPR No difference in laryngeal appearance between allergy and LPR patients
Koc et al.[3255]	2014	4	Case–control	Patients with AR by SPT Healthy controls without AR selected from dental clinic	Laryngeal findings in AR	AR patients had higher incidence of dysphonia and mean VHI
Turley et al.[3261]	2011	4	Case–control	Patients with rhinitis symptoms with (+) and (−) allergy tests Patients without rhinitis recruited from orthopedic clinic	Prevalence of dysphonia	Patients with AR or NAR had higher prevalence of dysphonia versus controls Patients with worse rhinitis symptoms had worse voice-related QOL and more severe chronic laryngeal symptoms

(Continues)

TABLE XIII.I (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Randhawa et al.[3263]	2010	4	Case series	Patients diagnosed with primary voice disorder or globus sensation	Prevalence of AR and LPR	Three times as many patients had allergies versus LPR, not statistically significant
Millqvist et al.[3254]	2008	4	Case–control	Patients with AR to birch pollen Healthy controls	Prevalence of vocal dysfunction	Statistically significant differences in VHI between allergic patients and controls
Hamdan et al.[3260]	2006	4	Retrospective case–control	Singers with no vocal symptoms Singers with vocal symptoms	Symptom prevalence	Incidence of AR in singers is high Occult allergies may affect professional voice
Jackson-Menaldi et al.[3267]	1999	4	Prospective observational	Subjects referred to voice center with a voice problem	Association between AR and LPR and laryngeal findings	No causative relationship between allergy and vocal symptoms
Belafsky et al.[3268]	2016	5	Bench research	Guinea pigs exposed to saline (allergen control) + filtered air (pollution control) HDMA (*Dermatophygoides farinae*) + filtered air Saline + combustion particulates HDMA + combustion particulates	Mean eosinophilic profile in the glottic, subglottic, tracheal epithelium, and submucosa	Iron soot and HDMA resulted in eosinophilia in glottic, subglottic, and tracheal epithelium and submucosa
Mouadeb et al.[3269]	2009	5	Bench research	Guinea pigs exposed to intranasal HDMA for 9 consecutive weeks	Histopathologic findings	Twice as much eosinophilia in supraglottis in animals exposed to HDMA versus saline

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; GERD, gastroesophageal reflux disease; HDM, house dust mite; HDMA, house dust mite allergen; ICD, International Classification of Diseases; IgE, immunoglobulin E; LOE, level of evidence; LPR, laryngopharyngeal reflux; NAR, non-allergic rhinitis; RCT, randomized controlled trial; RSI, Reflux Symptom Index; SFAR, Score for Allergic Rhinitis; SPT, skin prick test; VHI, Voice Handicap Index.

XIII.J | Eosinophilic esophagitis

EoE is a chronic inflammatory condition of the esophagus defined symptomatically by esophageal dysfunction and histologically by eosinophil-predominant inflammation. EoE is widely considered a type 2 inflammatory disease, and patients with EoE often have other comorbid atopic conditions such as AD, asthma, food allergies, and AR.[3275]

Several studies have examined the prevalence of clinician-diagnosed AR and aeroallergen sensitization in patients with EoE. Among both pediatric and adult patients with EoE, 50%–75% have consistently been found to have AR.[3276–3292] There is also evidence for a higher prevalence of AR among EoE patients compared with the general population.[3275,3293,3294] Although most studies were case series, the consistency of findings strongly suggests that a majority of patients with EoE have comorbid AR and that the presence of AR in EoE patients may be higher compared with the general population (Table XIII.J).

While the above associations have been well documented, the pathophysiology underpinning the specific relationship between IgE sensitization and EoE remains unclear. Hill et al.[3053] demonstrated that the presence of AR was associated with subsequent EoE diagnosis, suggesting that sensitization to aeroallergens early in life may predispose to EoE development. Additionally, several case series noted an increase in EoE diagnosis, symptoms, and/or esophageal eosinophilia during pollen season, typically with peaks during spring and summer.[3295–3302] AIT

TABLE XIII.J Evidence table – association between allergic rhinitis and eosinophilic esophagitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Allergic rhinitis prevalence in EoE						
Benninger et al.[3277]	2017	3	Population-based database	Pediatric and adult EoE patients	Demographic and clinical characteristics	45% had AR
Gonzalez-Cervera et al.[3293]	2017	3	Systematic review	Pediatric and adult EoE patients	Demographic and clinical characteristics	AR significantly more common among EoE patients versus controls (OR 5.09)
Furuta et al.[3276]	2007	3	Systematic review	Pediatric and adult EoE patients	Demographic and clinical characteristics	50%–80% had AR and sensitization to aeroallergens
Ancellin et al.[3279]	2020	4	Case series	Pediatric EoE patients, $n = 49$	Demographic and clinical characteristics	78% were atopic; 64% sensitized to aeroallergens
Azzano et al.[3278]	2020	4	Case series	Pediatric EoE patients, $n = 108$	Demographic and clinical characteristics	63% sensitized to aeroallergens; 51% had AR
Imamura et Al.[3294]	2020	4	Retrospective case–control	Pediatric and adult EoE patients ($n = 66$); controls ($n = 186$)	Demographic and clinical characteristics	Prevalence of AR was higher in EoE patients than controls (29% versus 11%)
Leigh and Spergel[3275]	2019	4	Retrospective cohort	Pediatric and adult EoE patients, $n = 950$	Demographic and clinical characteristics	70% had AR; prevalence of AR higher in EoE patients than in general hospital population (70% versus 3.5%)
Alves Marcelino et al.[3281]	2017	4	Case series	Pediatric EoE patients, $n = 25$	Demographic and clinical characteristics	92% sensitized to aeroallergens
Mohammad et al.[3280]	2017	4	Case series	Pediatric and adult EoE patients, $n = 449$	Demographic and clinical characteristics	62% had AR
Olson et al.[3282]	2016	4	Case series	Adult EoE patients, $n = 257$	Demographic and clinical characteristics	79% had AR
Castro Jimenez et al.[3285]	2014	4	Case series	Pediatric and adult EoE patients, $n = 43$	Demographic and clinical characteristics	84% were atopic; 74% sensitized to aeroallergens
Chadha et al.[3284]	2014	4	Case series	Pediatric EoE patients, $n = 311$	Demographic and clinical characteristics	86% were atopic; 67% had AR
Vernon et al.[3283]	2014	4	Case series	Pediatric and adult EoE patients, $n = 100$	Demographic and clinical characteristics	65% had AR
Spergel et al.[3286]	2009	4	Case series	Pediatric EoE patients, $n = 562$	Demographic and clinical characteristics	68% were atopic; 43% had AR
Roy-Ghanta et al.[3287]	2008	4	Case series	Adult EoE patients, $n = 23$	Demographic and clinical characteristics	78% had AR; 86% sensitized to aeroallergens

(Continues)

TABLE XIII.J (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Assa'ad et al.[3288]	2007	4	Case series	Pediatric EoE patients, $n = 89$	Demographic and clinical characteristics	79% sensitized to environmental allergens
Plaza-Martin et al.[3289]	2007	4	Case series	Pediatric EoE patients, $n = 14$	Demographic and clinical characteristics	93% had AR and sensitization to aeroallergens
Sugnanam et al.[3290]	2007	4	Case series	Pediatric EoE patients, $n = 45$	Demographic and clinical characteristics	93% had AR
Remedios et al.[3291]	2006	4	Case series	Adult EoE patients, $n = 26$	Demographic and clinical characteristics	77% were atopic; 54% had AR
Guajardo et al.[3292]	2002	4	Case series	Pediatric and adult EoE patients, $n = 39$	Demographic and clinical characteristics	64% had AR
Role of aeroallergens in EoE pathogenesis						
Armentia et al.[3295]	2019	3	Prospective case–control	Adult EoE patients, $n = 129$ Controls, $n = 100$	Pollen allergens in esophageal biopsies	Callose from pollen was found in 65.6% of esophageal biopsies from EoE patients, not controls
Armentia et al.[3303]	2018	3	Prospective longitudinal case–control	Pediatric and adult EoE patients, $n = 129$ Controls, $n = 152$	Clinical improvement after IT	EoE patients sensitized to pollens treated with AIT had greater EoE symptom improvement
Lucendo et al.[3306]	2015	3	Systematic review	Pediatric and adult EoE patients	Season of EoE diagnosis or exacerbation	No significant seasonal variation in EoE diagnosis or exacerbations
Iglesia et al.[3304]	2021	4	Case report	Pediatric patients with EoE and multiple environmental allergies treated with AIT	Clinicohistologic remission	EoE remission observed after treatment with multiallergen SCIT as monotherapy
Reed et al.[3296]	2019	4	Retrospective cohort	Pediatric and adult patients with seasonal exacerbations of EoE, $n = 13$ Patients without exacerbations, $n = 769$	Demographic and clinical characteristics	Most patients with a documented EoE exacerbation had AR; summer and fall flares were most common
Hill et al.[3053]	2018	4	Retrospective case–control	Pediatric EoE patients, $n = 139$ Controls, $n = 22,272$	Rate of EoE diagnosis in patients with AR	AR diagnosis associated with an increased rate of subsequent EoE diagnosis
Fahey et al.[3297]	2017	4	Case series	Pediatric EoE patients, $n = 38$	Season of EoE diagnosis	Correlation between onset of EoE symptoms and peak grass pollen levels

(Continues)

TABLE XIII.J (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Elias et al.[3307]	2015	4	Case series	Adult EoE patients, $n = 372$	Season of EoE diagnosis	Increased presentation of EoE in winter months
Ram et al.[3298]	2015	4	Case series	Pediatric patients with seasonal exacerbations of EoE, $n = 32$	Seasonal biopsy findings	Seasonal variation was observed in esophageal eosinophil counts, most biopsy-confirmed flares occurred during spring and summer
Frederickson et al.[3308]	2014	4	Retrospective cohort	Pediatric and adult EoE patients	Season of EoE diagnosis	Incidence of EoE consistent across all seasons
Ramirez & Jacobs[3305]	2013	4	Case report	Pediatric EoE patient with dust mite allergy treated with AIT	Eosinophils on esophageal biopsies	Resolution of esophageal eosinophilia observed after dust mite AIT
Moawad et al.[3299]	2010	4	Case series	Adult EoE patients, $n = 127$	Season of EoE diagnosis and correlation with pollen counts	Highest percentage (33%) diagnosed in spring and lowest (16%) in winter, significant correlation with grass pollen counts
Almansa et al.[3300]	2009	4	Case series	Adult EoE patients, $n = 41$	Season of EoE diagnosis	68% diagnosed in spring/summer versus 32% in fall/winter
Wang et al.[3301]	2007	4	Case series	Pediatric EoE patients, $n = 234$	Season of EoE diagnosis and biopsy findings by season	Significantly fewer patients diagnosed with EoE in winter versus spring, summer, and fall; least intense esophageal eosinophilia in winter
Fogg et al.[3302]	2003	4	Case report	Pediatric EoE patient	Seasonal biopsy findings	Increased esophageal eosinophilia during pollen seasons

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; EoE, eosinophilic esophagitis; LOE, level of evidence; OR, odds ratio; SCIT, subcutaneous immunotherapy.

has also demonstrated efficacy in the treatment of EoE in one case-control study and two case reports.[3303–3305] Of note, several case reports described the development of EoE in patients undergoing SLIT and resolution with cessation, raising the possibility that repeated esophageal stimuli with offending allergens might elicit esophageal eosinophilia.[2653] However other studies, including a systematic review by Lucendo et al.,[3306] demonstrated no seasonal variation in EoE diagnosis or exacerbations, suggesting a limited role for aeroallergens as a relevant trigger for initiating or aggravating EoE.[3306–3308] Therefore, there is limited observational data suggesting a potential association between aeroallergens and EoE pathogenesis, with some conflicting data.

Associated conditions – eosinophilic esophagitis

Aggregate grade of evidence: C (Level 3: 6 studies, level 4: 29 studies; Table XIII.J)

XIII.K | Sleep disturbance and obstructive sleep apnea

AR negatively impacts sleep and is a risk factor for OSA.[1122] Various symptoms of AR may contribute to sleep dysfunction. However, nasal obstruction, which is

present in up to 90% of AR patients, seems to have the greatest impact and is a major independent contributor to poor sleep quality and SDB.[268,1108,1116,1127,1133,3309–3315] This may be due to increased nasal obstruction during the night with a peak in the early morning.[3316] The mechanisms underlying the association between AR and sleep disturbance include inflammatory cytokines causing fatigue, direct impact of AR symptoms, combination of recumbency and diurnal variation in turbinate size and pathophysiologic changes, and as sequelae of autonomic dysfunction in AR.[1104,3317,3318] Histamine plays a role in the regulation of the sleep-wake cycle and arousal, and cysteinyl leukotrienes are involved in sleep disruption.[3319,3320] Excessive histamine results in insomnia and inadequate amounts cause hypersomnolence.[3319,3321] Cytokines released in AR patients, such as IL-1β and IL-4, are thought to reduce sleep onset latency and increase the time to onset of rapid eye movement (REM) sleep.[1113,3322,3323] Patients with OSA also have increased mediators which activate Th2 cells, such as TNF, IL-1, and IL-6, further exacerbating symptoms of AR and potentiating the severity of OSA.[3324] Further, nasal airflow stimulates respiration and improves upper airway dilatory muscle tone via the nasal-ventilatory reflex and also stimulates the genioglossus muscle, resulting in tongue protrusion and improved airway patency via the trigemino-hypoglossal reflex.[3325–3330] Therefore, nasal obstruction may reduce the stimulation of these mechanoreceptors resulting in collapsibility of the downstream pharyngeal segment of the upper airway, thereby leading to OSA[3331] (Table XIII.K).

Sleep is critical for mood, cognitive function, immune function, and endocrine functions.[1104] OSA is associated with hypertension, coronary artery disease, cerebrovascular disease, arrhythmias, insulin resistance, congestive heart failure, pulmonary hypertension, and behavioral problems in children.[3332–3337] Further, in children, SDB may negatively impact brain development, impair psychomotor, and cognitive performance, and contribute to hyperactivity.[3338–3340] REM sleep is associated with memory, cognition, dreams, and restorative sleep.[1119,1147] As the nasal cycle is prolonged, worsening nasal obstruction, people with AR have impaired REM sleep.[1119,1147,3341–3343] However, as the diagnosis of SDB typically relies upon the measurement of all-night AHI and RDI via polysomnography, many patients with AR and SDB have normal indices by this method. By considering respiratory effort-related arousals, as well as AHI and RDI measured specifically in REM sleep (REM-AHI, REM-RDI), sleep disorders in AR patients will be detected more often.[1121]

CPAP treatment for OSA may present a non-allergic trigger to AR patients with OSA and worsen nasal symptoms.[3344] Further, persistent nasal symptoms are a common reason for early CPAP non-compliance.[3344–3346] However, correction of nasal obstruction can improve CPAP compliance/tolerance,[3347–3349] though there is typically no direct impact on OSA severity.[3350]

It is important to assess AR patients for sleep disorders due to their negative impact on health. Numerous instruments are available to assess the impact of AR on sleep. These include the Stanford Sleepiness Score, Jenkins Questionnaire, Epworth Sleepiness Score, Pittsburgh Sleep Quality Index, University of Pennsylvania Functional Outcomes of Sleep, Sleep Scale from the Medical Outcome Study, Sleep Disorders Questionnaire, The Pediatric Sleep Questionnaire, and The Pediatric Daytime Sleepiness Scale.

Treatment of nasal congestion in AR patients improves sleep quality, daytime somnolence, and QOL.[3351] Numerous medical therapies have been investigated regarding the link between AR treatment and sleep quality. INCS and isolated nasal surgery have also been shown to improve sleep quality in AR patients, particularly those with moderate-to-severe pre-treatment obstruction.[1106,1107,2295,3352,3353] INCS may improve sleep in patients with AR due to improvement in nasal obstruction, but also due to reduction in local inflammatory cytokines.[3319,3320] A recent RCT and case series found significant improvements in sleep parameters following AR treatment with HDM SLIT.[1095,3354] First generation H_1 antihistamines cross the blood–brain barrier and cause sedation which may exacerbate daytime somnolence in patients with AR and SDB. Therefore, newer-generation H_1 antihistamines are favored, such as fexofenadine and loratadine, which are lipophobic and do not cross the blood–brain barrier.[1771,3355,3356] Although leukotriene antagonists have not demonstrated benefit when added to INCS in the treatment of AR, one RCT found that montelukast was more effective than cetirizine in improving sleep quality in children according to patient diaries.[2186,3357] Nasal decongestants may result in stimulatory effects causing insomnia.[3318] Nasal decongestant sprays do not significantly improve AHI.[3358] A crossover RCT comparing xylometazoline to placebo in patients with OSA and nasal congestion found that xylometazoline did not improve sleep quality and resulted in a transient improvement in AHI at the time of peak effectiveness only.[3358] As these sprays carry the potential for rhinitis medicamentosa, insomnia, and palpitations, they are not recommended for the treatment of AR in OSA patients.

Sleep disorders should be considered in any patient diagnosed with AR due to their significant association and the negative impact that SDB has on QOL. Changes in sleep parameters should also be considered when evaluating the impact of treatment of AR. (See Section IX.A.2. Allergic

TABLE XIII.K Evidence table – association between allergic rhinitis and sleep disturbance

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Liu et al.[1120]	2020	2[a]	SRMA (to August 2019)	Patients with AR, n = 19,444,043	Association of AR with sleep duration and impairment	No difference in sleep duration, AR versus controls AR: higher sleep quality, sleep disturbance, sleep latency scores; more frequent sleep medication use; lower sleep efficiency AR associated with nocturnal dysfunction (e.g., insomnia), daytime dysfunction (e.g., somnolence) Quality of evidence low to very low
Jacobi et al.[3354]	2019	2	RCT, double blind, placebo-controlled	Moderate-severe HDM AR treated with SLIT, n = 656	RQLQ	SLIT resulted in improvement in sleep quality versus placebo
Chen et al.[3357]	2006	2	RCT, placebo-controlled	Children with AR, aged 2–6 years, n = 60: Montelukast Cetirizine Placebo	Pediatric RQLQ TNSS Serum IgE Serum ECP Blood and nasal smear eosinophil count Nasal airway resistance	Montelukast superior to cetirizine for night sleep quality
Liu et al.[1104]	2020	3[b]	Cross-sectional	Children with snoring from adenotonsillar hypertrophy, aged 3–14 years, n = 660	PSG Sleep questionnaire	Prevalence of AR in SDB (25.8%), OSA (19.4%) Regardless of OSA status, AR children had more daytime hypersomnolence, behavioral symptoms, and shorter sleep time Children with AR without OSA spent shorter time in REM Children with AR had shorter sleep time
Na et al.[3359]	2020	3	Cohort	Adults with OSA and AR undergoing 3 months of CPAP treatment, n = 13	SFAR NOSE SNOT-25	SFAR intensity, NOSE scores, mean SNOT-25 scores significantly improved with CPAP
Skirko et al.[3344]	2020	3	Prospective cohort	OSA patients using CPAP, n = 102	NOSE VAS	NOSE and VAS scores improved in all groups after 3 months of CPAP Significantly less improvement in AR group versus control
Chuang et al.[3360]	2019	3	Controlled cohort	AR patients, age/sex-matched controls, n = 412,074	OSA	Incidence of OSA significantly higher in AR patients versus controls AR was significant risk factor for OSA

(Continues)

TABLE XIII.K (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wongvilairat et al.[3361]	2022	4[h]	Cohort	AR patients, $n = 120$	STOP-BANG VAS	No relationship between severity of AR and OSA Duration of AR symptoms related to risk of OSA
Kim et al.[2295]	2021	4[c]	Prospective cohort	Patients with OSA undergoing septoplasty and IT reduction, $n = 35$	NOSE PSG VAS ESS Acoustic rhinometry	Significant reduction in mean AHI and RDI post-operatively AR patients and those with moderate-to-severe obstruction achieved the better results than non-AR
Lee et al.[1144]	2021	4	Cross-sectional survey	Adolescents participating in national health survey, aged 12–18 years, $n = 1936$	Questionnaire Examination Serum sIgE	Higher prevalence of AR in inappropriate sleep duration group Endoscopic findings of AR associated with inappropriate sleep duration in males
Berson et al.[1121]	2020[d]	4[e]	Retrospective case–control	Patients with AR or SDB, $n = 100$	STOP-BANG ESS PSG	HDM AR patients more likely to have REM-RDI and REM-AHI in moderate-severe range versus controls AR patients more likely to have REM-AHI in moderate-severe range versus controls
Bosnic-Anticevich et al.[1065]	2020	4	Cross-sectional survey	Children with AR, aged 2–15 years, $n = 1541$	Parent-reported data on sleep quality	AR patients had significantly less duration of sleep and poorer sleep quality versus controls
Giraldo-Cadavid et al.[1145]	2020	4[f]	Prospective cohort	Children with AR and OSA at high altitude, 4–15 years, $n = 99$	ESPRINT-15 PSQ PSG	Significant association between severity of AR and severity of OSA Weak positive correlation between AR severity and OSA severity
Pace et al.[1122]	2020	4[g]	Prospective controlled cohort	60 participants: NARES AR Control	Home sleep study VAS STOP-BANG ESS	OSA present in: NARES 60%, AR 35%, control 10% No significant difference in OSA between NARES versus AR, or AR versus control No difference in OSA severity across groups
Berson et al.[1119]	2018	4[e]	Retrospective case–control	Patients with AR or SDB, $n = 100$	STOP-BANG ESS PSG SNOT-22	AR patients had significantly longer time to REM and lower percentage of REM Patients with moderate-severe REM-RDI range were 5.1 times more likely to have AR AR patients had a 3.92 times greater chance of having REM-RDI in moderate-severe range, independent of BMI

(Continues)

TABLE XIII.K (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Novakova et al.[1095]	2017	4	Prospective case series	Patients with AR undergoing SLIT to HDM and grass pollen, $n = 191$	RQLQ	Significant improvement in sleep quality after 3 years of SLIT in both groups (greater in HDM group)

Abbreviations: AHI, apnea-hypopnea index; AR, allergic rhinitis; CPAP, continuous positive airway pressure; ECP, eosinophil cationic protein; ESS, Epworth Sleepiness Scale; ESPRINT-15, validated health-related quality of life questionnaire for adults with AR; HDM, house dust mite; IgE, immunoglobulin E; IT, inferior turbinate; LOE, level of evidence; NARES, non-allergic rhinitis with eosinophilia syndrome; NOSE, Nasal Obstruction Symptom Evaluation; OSA, obstructive sleep apnea; PSG, polysomnography; PSQ, Pediatric Sleep Questionnaire; RCT, randomized controlled trial; RDI, respiratory disturbance index; REM, rapid eye movement; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SDB, sleep disordered breathing; SFAR, Score for Allergic Rhinitis; sIgE, allergen-specific immunoglobulin E; SLIT, sublingual immunotherapy; SNOT, Sinonasal Outcome Test; SRMA, systematic review and meta-analysis; STOP-BANG, Snoring, Tiredness, Observed breathing cessation, Pressure, BMI, Age, Neck circumference, Gender Questionnaire; TNSS, Total Nasal Symptoms Score; VAS, visual analog scale.

[a]LOE downgraded; not an SRMA of RCTs.

[b]LOE downgraded due to significant difference in group sizes.

[c]LOE downgraded due to small number of AR patients ($n = 8$) and only one female patient included.

[d]Same patient group as 2018 study

[e]Diagnosis of AR based on skin prick or serum testing.

[f]LOE downgraded as diagnosis of AR based on symptoms only.

[g]LOE downgraded as OSA diagnosed on home sleep study and AHI values only.

[h]LOE downgraded as OSA diagnosed on questionnaires, not PSG (probability of OSA calculated).

Rhinitis Disease Burden – Sleep Disturbance for additional information on this topic)

Associated conditions – sleep disturbance and obstructive sleep apnea

Aggregate grade of evidence: B (Level 2: studies, level 3: 4 studies, level 4: 9 studies; Table XIII.K)

XIV | SPECIAL SECTION ON COVID-19

XIV.A | COVID-19 effect on patient presentation for allergic rhinitis evaluation

The WHO declared COVID-19 a pandemic on March 11, 2020.[3362] With mounting evidence of rapid spread, high morbidity and mortality, and a push to maintain the healthcare system infrastructure, routine ambulatory care for conditions like AR was often reduced.[3363] As the pandemic endured, expert group consensus generally applied different recommendation strategies depending on case rates. When case rates were high, it was reasonable to suspend care temporarily, particularly if providers and healthcare facilities were redeployed.[1213,3364] However, as case rates fell, it was necessary to find ways to evaluate patients for AR.[3365,3366] Telemedicine, using phone or video where available, was rapidly implemented and provided significant access to specialty care while limiting exposure for patients and providers.[1213,3363,3364,3367,3368] However, implementation of telemedicine practices may exacerbate gaps in access for populations already at risk for health disparities.[3369]

Another evident issue became the similarities in presentation between AR and COVID-19, and it was important to identify ways to differentiate the diseases.[3363,3364] AR was not a risk factor for severe COVID-19 infection.[3370–3377] The consensus from a survey distributed to members of the ARIA/EAACI study group was that AR presented with runny nose, sneezing, stuffy nose, nasal pruritus, ocular pruritis, and redness compared to COVID-19 which presented with more smell and taste dysfunction, dyspnea, and cough.[3378] Patients scored validated questionnaires like the SNOT-22 and mini-RQLQ differently.[3379,3380] SNOT-22 scores were higher in patients with COVID-19 infection (with more frequent cough, dizziness, loss of smell/taste, psychiatric, and sleep dysfunction) compared to patients with AR (with more frequent nose blowing and sneezing).[3379] In patients with allergic rhinoconjunctivitis with COVID-19 infection, mini-RQLQ scores were lower in COVID-19 infection compared to their allergies.[3380] They specifically reported less sneezing, runny nose, itchy eyes, sore eyes, and watery eyes and generally noted a difference in their symptoms with COVID-19 infection compared to typical allergies.

Changes in exposure associated with widespread lockdowns affected the clinical presentation of patients with AR. Visits for AR increased during the COVID pandemic, with patients reporting ongoing nasal symptoms as an impetus for seeking care.[3381,3382] However, in general, AR symptoms and medication use decreased.[3383–3386] The decrease in AR symptoms was attributed to reduced

outdoor exposures, use of face masks, and decreased pollution as a result of COVID-19 lockdowns.[3363,3387] However, changes in symptom presentation depended on sensitization pattern – patients with cypress pollen allergy reported decreased symptoms but those with dust mite allergy noted increased symptoms.[3385,3388] The COVID pandemic also led to increased exposure to indoor respiratory irritants such as tobacco, cooking smoke, and cleaning products.[3389] And although use of face masks were reliably associated with fewer nasal symptoms compared to no mask, the effect on ocular symptoms was mixed.[3390,3391] Finally, patients who discontinued their therapies for AR due to pandemic concerns expectedly reported loss of symptom control.[3392]

Comorbid mental health diagnoses including depression and anxiety are commonly reported in patients with AR and positively correlated with symptom scores.[3393] This correlation persisted during the pandemic with atopic patients reporting higher symptoms of post-traumatic stress disorder, higher depression risk scores, and higher hyperarousable subscale scores[3384] than non-atopic patients.[3394]

XIV.B | Changes in allergic rhinitis diagnostic techniques related to COVID-19

Although the initial clinical evaluation of patients often could be done through telemedicine, many diagnostic techniques for AR require a face-to-face encounter with potentially aerosol generating procedures (e.g., performing spirometry on an asthmatic patient prior to allergy skin testing). Because SARS-CoV-2 viral loads are highest in the upper airway, these procedures are particularly high risk.[3366,3395] In many cases, if in-person encounters were not appropriate, diagnostic testing was deferred. In vitro serum sIgE was an alternative option to evaluate for allergen sensitization, although phlebotomy still required healthcare contact.[1213] Additionally, there was often national, regional, and/or institutional guidance for in person visits and procedures.[1210,1213,3366,3395–3399] Policies to contain and reduce spread of COVID-19 are still evolving. At the time of this writing, available publications often stemmed from early pandemic practices and expert opinion. Adjustments to the recommendation with changing COVID-19 community transmission levels are ongoing but typically involved phased de-escalation of these recommendations.[3365]

For in-person encounters, general considerations included measures to screen for COVID-19 infection, enhance social distancing, and reduce transmission. Early in the COVID-19 pandemic, screening prior to healthcare facility encounters included survey screening of symptoms suggestive of COVID-19 for patients and staff[3364,3365,3400] and, in some countries, body temperature screening and epidemiologic tracking via smartphone.[3398,3400] Social distancing of at least 6 feet was recommended when possible.[3364,3398,3401] This was important in clinical spaces and the waiting room. Visitor limitations (with one adult allowed for children and none for adult patients when possible) were enacted.[3402,3403] Clinical care modifications included asking patients to fill out health information prior to visits, using telemedicine to obtain history to minimize in person time, and adjusting clinic schedule templates to allow for social distancing and room ventilation.[3365] Finally, measures to reduce transmission included hand hygiene, appropriate personal protective equipment (generally including a mask), removing reading material to minimize indirect transmission, and enhanced cleaning of facilities.[3364,3368,3395,3400,3401]

For aerosol-generating procedures, additional action was recommended. There have not been clinical studies of COVID-19 transmission with any allergy or otolaryngologic procedures. As stated earlier in ICAR-Allergic Rhinitis 2023, nasal endoscopy is an option when evaluating the AR patient, used primarily to evaluate potential intranasal signs associated with allergy or to rule out alternate causes presenting symptoms. Studies of nasal endoscopy has provided conflicting reports on aerosol generation.[3404,3405] Initial studies by two research groups using cadaveric heads did not demonstrate aerosol generation during cold instrumentation[3406,3407] although further studies in live patients undergoing nasal endoscopy detected increased airborne particles.[3408,3409] Another study did not detect a significant change in particle concentration from pre-scope to scope, but there was a trend for increased particle concentrations in patients who required sinonasal debridement.[3410] There is also concern that nasal endoscopy can induce behaviors including sneezing, breathing, speaking, and possibly coughing that are aerosol generating.[3406,3408,3411] However, some modifications including nasal endoscopy using modified surgical or N95 masks could prevent aerosol generation,[3406,3408,3409] as well as repositioning at the back of the patient[3412] or using a tower with camera, screen, and light source.[3366] Local anesthetics and decongestants could be applied with actuated pump sprays or soaked pledgets rather than atomized forms to avoid aerosol generation.[3397,3406,3411] Immediate decontamination of equipment, especially the endoscope, was also recommended.[3395] Expert groups generally recommended against certain procedures including nasal provocation, nasal cytology, anterior rhinomanometry, and PNIF.[3397,3413,3414] If supplies were not constrained, rapid and accurate pre-procedural screening for SARS-CoV-2 was also recommended.[3365] For personal protective equipment, the WHO recommended an N95 face mask, full eye protection, and full body protective clothing.[3364,3397,3413] Techniques to improve donning

and doffing included one-step glove and gown removal, double-gloving, spoken instructions during doffing, and glove disinfection.[3413]

Aerosol clearance depends on ventilation and air exchange.[3413] The Centers for Disease Control (CDC) recommended at least 12 air changes per hour and controlled direction of airflow although the WHO recommends double this. After the patient leaves the room and 5 air exchanges occur, less than 1% of airborne contaminants will remain. With at least 12 air changes per hour, this would occur in 30 min. The COVID-19 pandemic led to changes in access to in-person healthcare and potentially aerosol-generating procedures. In making the diagnosis of AR, there were strategies employed to help contain and reduce spread of COVID-19.[3415,3416]

XIV.C | Changes in allergic rhinitis management related to COVID-19

Much of the standard management of AR was recommended by expert groups to be continued during the COVID-19 pandemic. There was specific motivation to control AR symptoms given concern that sneezing increased viral spreading and poorly controlled upper airway symptoms serve as a trigger for asthma exacerbations.[1210,3366,3387,3414,3417] In Beijing, providers made public efforts to develop pollen monitoring networks, television, and online lectures, and suggested over-the-counter drug recommendations for all patients with AR.[3398] In addition, AR is not a contraindication to receiving the COVID-19 vaccine. Patients with AR were able to tolerate COVID-19 vaccination without severe reactions.[3418–3420]

As always, the first step in management of AR remains allergen avoidance. The pandemic demonstrated that allergen avoidance could significantly improve symptoms. Practices like face masks and handwashing appear to be mutually beneficial for management of AR and COVID-19.[3387] Standard therapies for AR, including INCS, oral and topical antihistamines, montelukast, and AIT, were not identified as increasing susceptibility or severity of COVID-19 infection.[3363,3364,3370,3414,3421] Systemic corticosteroids may be a concern although this is not a standard therapy for AR.[3422] Patients on INCS were found to have a lower risk for COVID-19 related hospitalization, admission to the intensive care unit, and in-hospital mortality compared to patients who were not on INCS.[3423] Montelukast has also been associated with a reduction in COVID-infection in a small retrospective cohort study of elderly asthmatics.[3424]

AIT has been shown to improve symptom control with a decrease in respiratory infections and antibiotic use.[3425] Prior studies with viral infections including influenza, cytomegalovirus (CMV), and HIV have not shown changes in the efficacy or safety of AIT.[3392] When COVID-19 cases were high, initiating AIT was generally not recommended. However, consideration for continuing AIT includes lengthening the injection interval which minimizes healthcare visits.[1210,1213,3402,3414] Consensus from one expert panel recommended lengthening the interval to every 2 weeks during the build-up phase and every 6 weeks during maintenance. Therapy should be stopped if COVID-19 infection is suspected or diagnosed, until resolution.[3364] There was evidence that patients were more likely to be nonadherent and discontinue AIT during the pandemic leading to higher symptom scores, decreased QOL, and higher medication use than before the pandemic.[3367,3426–3429] Consideration for switching patients to or starting patients on SLIT, both tablet and aqueous forms, may be a preferred therapy since maintenance does not require in-person administration.[1210,3368,3414] In case of COVID-associated quarantine, an adequate supply of SLIT should be maintained at home.[3366,3392] Finally, home SCIT in selected patients was cost effective under pandemic considerations alone.[3363,3430] Of note, this is not currently approved and is not the standard of care.[1213]

Finally, anti-IgE therapy has been approved for severe cases of Japanese cedar pollinosis.[3414] There is no evidence of altered susceptibility or severity of COVID-19 infection with anti-IgE therapy. In fact, clinical studies have shown that pre-seasonal treatment with anti-IgE therapy decreases seasonal exacerbations of asthma related to viral infections.[3431–3433] IgE has been found to suppress the ability of dendritic cells to produce type I interferons and theorized to increase the susceptibility for respiratory viral infections.[3434–3436] However, as there is limited evidence, physician judgment is recommended.

XV | SUMMARY OF KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

Through the ICAR-Allergic Rhinitis 2023 update process, we have seen an increased number of scientific publications in many areas. We are also encouraged to see additional high-quality studies, including many SRMAs, addressing numerous individual AR topics. As highlighted in previous ICAR documents, one of the most important aspects of this process is to identify knowledge gaps and key areas where future research may further advance our knowledge in AR. The sections that follow emphasize several important areas where additional research may further expand and solidify our understanding of AR.

Epidemiology and risk factors. Studies have been undertaken to understand the prevalence of AR around the world. These are limited by differing methodology and reporting. Since ICAR-Allergic Rhinitis 2018, the Aggregate Grades of Evidence remain largely unchanged. However, there has been significant work evaluating the hygiene hypothesis, SES, and in utero influences on AR development. Challenges of these studies are the retrospective nature of most work evaluating risk factors. Randomization is difficult in such studies, and the confounding effects of other risk factors are difficult to assess. Several gaps in knowledge exist and may be helpful to address. The following are areas where we suggest additional study:

- Improved understanding of the incidence of AR based on geographic location
- Evaluation of climate change effects on incidence and severity of AR
- Improved understanding of the relationship between genetics and environmental factors in the development of AR
- High quality longitudinal studies evaluating risk factors for development of AR

Evaluation and diagnosis. Diagnosis of AR begins with history and physical exam. Classic symptoms of AR (e.g., nasal/ocular pruritis, rhinorrhea, nasal congestion) are well documented. Since the early months of the COVID-19 pandemic, awareness of hyposmia and its association with nasal pathology has been heightened, but research on the association between hyposmia and AR remains limited. Studies have suggested that AR can affect smell during pollen season,[1606] but the cause of hyposmia in AR is unclear.[3437,3438] The effect of AR on olfaction will be important to understand in more detail in the future.

Beyond history and physical exam, skin testing or in vitro sIgE are used for further evaluation. Since ICAR-Allergic Rhinitis 2018, several new sections have been added, evaluating the use of additional diagnostic techniques for AR. In addition to BAT, mast cell activation testing is a new option for in vitro allergy testing.[3439,3440] The use of this test for AR specific evaluation is currently limited, reported techniques are time consuming, and human mast cells are heterogeneous. Additional understanding of mast cell activation testing and its application in AR is needed.

The following are areas in which AR evaluation and diagnosis may be improved in the future:

- Increased understanding of hyposmia as a symptom of AR or a marker if its severity
- Further evaluation and validation of nasal sIgE testing for AR diagnosis
- Further work evaluating the use of novel AR testing techniques, such as BAT and mast cell activation testing, provocation testing, and objective measures of nasal air flow
- Improvement of low-cost diagnostic tools

Pediatrics. The pediatrics section has been added for the ICAR-Allergic Rhinitis 2023 update. This section summarizes the existing literature on pediatric allergy diagnosis and treatment. We have identified areas in which more work is needed:

- Improved treatment options for young children
- Improved interpretation of skin testing results in young children
- Optimizing treatment strategies for children who are polysensitized
- Further work developing AIT delivery routes appropriate and safe for children

Management. There are several well documented strategies for AR management with high levels of evidence and effectiveness. Avoidance strategies are cost-effective, but high-level data is lacking. However, many pharmacotherapy and AIT options have been shown to be effective, and several of these treatment strategies are strongly recommended. Since ICAR-Allergic Rhinitis 2018, additional studies have been completed; however, all avoidance strategies other than reduction of occupational exposures remain as an "option" due to relatively low-quality evidence in assessment of clinical benefit. Pharmacotherapy and AIT treatment option aggregate grades of evidence remain largely stable since ICAR-Allergic Rhinitis 2018, although there are a few notable recommendation updates including strong recommendations against oral steroids and oral decongestants for routine use in the treatment of AR. Areas of future work in AR management include:

- Continued investigation of combination therapy options, including topical therapies
- Studies of comparative effectiveness and cost-effectiveness for AR treatments
- Further work directly comparing SCIT to SLIT in large-scale RCTs
- Standardization of rush and cluster SCIT protocols for aeroallergen immunotherapy

Associated conditions. The evidence supporting the relationship between AR and other conditions is often conflicting. Since ICAR-Allergic Rhinitis 2018, the relationship of asthma to AR has been extensively studied with an increase in the Aggregate Grades of Evidence. In addition, several new sections in ICAR-Allergic Rhini-

tis 2023 highlight the potential relationship of allergy to various subtypes/endotypes of CRS, however the evidence remains conflicting. More research is needed in the following domains:

- Improved understanding of treatment effects of AR on specific comorbid CRSwNP subtypes/endotypes
- Continued work to determine the relationship of AR to ear disease
- Investigation of treatment effect of AR on cough

COVID-19. One of the notable effects of the identification of the novel coronavirus disease in 2019 was a rapid expansion in research efforts, scientific publications, and dissemination of knowledge related to the transmission, health consequences, and risk to patients and healthcare workers. The work on AR and COVID-19 continues to evolve. The following are topics of interest regarding COVID-19 and AR:

- Improved understanding of the aerosolization risk during nasal endoscopy
- Improved understanding of the risks of AR treatment, including AIT, during COVID infection
- A deeper understanding of the long-term effects of COVID on allergic diseases and their development

XVI | CONCLUSION

In this document, we summarized the available literature for AR and created recommendations based on the highest levels of evidence. Through this, we have identified several areas with robust literature and a strong evidence base. There have been many advances in the field since the publication of ICAR-Allergic Rhinitis 2018, but notable knowledge gaps remain. There are several areas of AR research which will be limited based on inherent conditions of study design. For example, it is not feasible to blind or randomize for some AR treatments, and epidemiological studies to evaluate risk factors may be inherently limited by their retrospective nature and confounding variables. Therefore, for each major content area, we have suggested practical and feasible areas of study that we believe could advance our knowledge of AR in a productive manner.

AUTHOR CONFLICT OF INTEREST DISCLOSURE

See table at the end document.

FUNDING

None.

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How to cite this article: Wise SK, Damask C, Roland LT, et al. International consensus statement on allergy and rhinology: Allergic rhinitis – 2023. *Int Forum Allergy Rhinol*. 2023;13:293–859. https://doi.org/10.1002/alr.23090

ICAR-Allergic Rhinitis 2023 Author Disclosure of Financial Relationships and Potential COI

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			NeurENT	Consultant/advisory board
			OptiNose	Consultant/advisory board
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			Glaxo Smith Kline	Advisory board, contracted clinical research, speaker
			Lyra Therapeutics	Contracted clinical research
			OptiNose	Advisory board, contracted clinical research, speaker
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			Sanofi-Regeneron	Advisory board, research funding
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			Aclex	Consultant
			Aerin	Speaker
			AstraZeneca	Consultant
			ENTvantage Diagnostics	Stock
			Glaxo Smith Kline	Consultant
			Lyra	Consultant
			Medtronic ENT	Consultant
			Sanofi	Consultant, research funding
			Stryker ENT	Consultant
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			Bristol Myers Squib	Advisory board
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			Glaxo Smith Kline	Advisory board, research funding
			Novartis	Advisory board, research funding
			Regeneron	Advisory board
			Sanofi	Advisory board
			SciBase	Advisory board, research funding
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			GlycoMira	Consultant
			NIH R44 SBIR	Research funding (co-investigator)
			Medtronic	Consultant
			OptiNose	Consultant, research site PI
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			Hypera	Speaker
			Organon	Speaker
			Sanofi	Speaker, consultant
			UCB	Speaker
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			AstraZeneca	PI, advisor, speaker
			Biocryst	PI, advisor, speaker
			Biomarin	PI, advisor
			Blueprint Medicine	PI, advisor
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			ONO	PI, advisor
			OptiNose	Speaker
			Pharming	PI, advisor, speaker
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			Medtronic	Honoraria, consultant, equipment loan for research
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			Seqirus	Honoraria
			Viatris	Honoraria
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			Novartis	Consultant
			Regeneron	Consultant
			Sanofi	Consultant
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			First Resources Ltd	Consultant
			Genting Plantation	Consultant
			National Medical Research Council	Research funding
			National Research Foundation Singapore	Research funding
			Olam International	Research funding
			Sime Darby Technology Centre	Consultant
			Singapore Food Story Grants	Research funding
			Singapore Immunology Network	Research funding
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			Biohaven	Research funding
			Glaxo Smith Kline	Advisory board, research funding, speaker' sbureau
			Lyra	Research funding
			Merck	Research funding
			Novartis	Research funding
			Optinose	Advisory board, research funding, speaker's bureau
			Regeneron	Research funding, speaker's bureau
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			MedLearning Group	Honorarium for CME lectures
			National Peanut Board	Scientific/medical advisory council
			Novartis	Advisory board
			Nutricia	Advisory board
			Prota	Advisory board
			RMEI Medical Education	Honorarium for CME lectures
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			AstraZeneca	Research grant support
			Bayer	Research grant support
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			F. Hoffmann-La Roche	Research grant support
			Genentech	Research grant support
			Glaxo Smith Kline	Research grant support
			Janssen Pharmaceutica	Research grant support
			M&P Pharma	Research grant support
			Novartis	Research grant support, speaker, honoraria
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			UCB Pharma	Research grant support
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			Sanofi/Regeneron	Clinical research, honoraria
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			Bayer	Grant
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			Circassia	Grant
			DBV Technologies	Speaker, advisory board, safety board
			Grunenthal	Speaker, advisory board, safety board
			Glaxo Smith Kline	Speaker, advisory board, safety board, grant
			Lilly	Grant
			Mylan/Viatris	Speaker, advisory board, safety board
			Menarini	Speaker, advisory board, safety board
			MSD	Speaker, advisory board, safety board
			Novartis	Speaker, advisory board, safety board, grant
			Pfizer	Speaker, advisory board, safety board, grant
			Purina	Grant
			Sanofi	Speaker, advisory board, safety board, grant
			Siegfried	Speaker, advisory board, safety board
			UCB	Speaker, advisory board, safety board, grant

(Continues)

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48	Adrienne Laury, MD	XXX		
49	Matt Lechner, MD, PhD	XXX		
50	Stella E. Lee, MD		AstraZeneca	Consultant, research funding
			Genentech/Novartis	Consultant, research funding
			Glaxo Smith Kline	Consultant, research funding
			OptiNose	Research funding
			Sanofi Genzyme Regeneron	Consultant, research funding
51	Victoria S. Lee, MD	XXX		
52	Patricia Loftus, MD	XXX		
53	Sonya Marcus, MD	XXX		
54	Haidy Marzouk, MD, MBA	XXX		
55	Jose Mattos, MD, MPH		Glaxo Smith Kline	Consultant
			Sanofi/Regeneron	Consultant, research funding
56	Edward McCoul, MD, MPH		OptiNose	Consultant
			Stryker ENT	Consultant
57	Erik Melen, MD, PhD		ALK	Consultant
			AstraZeneca	Consultant
			Novartis	Consultant
			Sanofi	Consultant
58	James W. Mims, MD		Regeneron	Research funding
			TEVA	Stock
59	Joaquim Mullol, MD, PhD		AstraZeneca	Speakers bureau
			Glaxo Smith Kline	Speakers bureau
			Noucor/Uriach Group	Consultant, research funding, speakers bureau
			Sanofi-Regeneron	Consultant, speakers bureau
			Viatris/Meda Pharma	Research funding, speakers bureau
60	Jayakar Nayak, MD, PhD		Hydravascular LLC	Advisory board
			SpirAir	Consultant
61	John Oppenheimer, MD		Abbvie	Adjudication, DSMB
			Aimunne	Consultant
			Amgen	Consultant
			Annals of Allergy, Asthma and Immunology	Executive editor
			Aquestive	Consultant
			AstraZeneca	Adjudication, DSMB
			Glaxo Smith Kline	Adjudication, DSMB, consultant
			Sanofi	Adjudication, DSMB
			Up to Date	Reviewer
62	Richard R. Orlandi, MD	XXX		
63	Katie Phillips, MD		Sound Health	Stock
64	Michael Platt, MD		GI Reviewers, LLC	Research consultant
			Legal firms	Expert legal reviews
65	Murugappan Ramanathan, Jr, MD	XXX		
66	Mallory Raymond, MD	XXX		
67	Chae-Seo Rhee, MD, PhD	XXX		

(Continues)

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68	Sietze Reitsma, MD, PhD		ALK	Research grant
			Allergy Therapeutics	Research grant
			Chordate	Research grant
			EU	Research grant
			Glaxo Smith Kline	Consultant, research grant
			Mylan	Research grant
			Novartis	Consultant, research grant
			Sanofi	Consultant, research grant
			Zon-MW	Research grant
69	Matthew Ryan, MD		OptiNose	Advisory board
			Sanofi/Regeneron	Advisory board
70	Joaquin Sastre, MD, PhD		ALK	Speaker
			FaesFarma	Speaker
			Glaxo Smith Kline	Speaker
			Mundipharma	Speaker
			Novartis	Speaker, consultant
			Sanofi	Speaker, consultant, research grant
			ThermoFisher	Speaker
71	Rodney J. Schlosser, MD	XXX		
72	Theodore A. Schuman, MD	XXX		
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76	Michael B. Soyka, MD		Glaxo Smith Kline	Consultant, research funding
			Novartis	Consultant, research funding
			Sanofi	Consultant, research funding
			Syndermix	Research funding
77	Masayoshi Takashima, MD		Acclarent	Consultant
			Aerin Medical	Consultant
			LivaNova	Consultant
			Lyra Therapeutics	Consultant
			Medtronic ENT	Consultant
78	Monica Tang, MD	XXX		
79	Pongsakorn Tantilipikorn, MD, PhD		Abbott	Research funding
			ALK	Research funding
			AstraZeneca	Research funding
			Meda	Research funding
			Mylan	Research funding
			Sanofi	Advisory board
			Viatris	Research funding
80	Malcolm B. Taw, MD	XXX		
81	Jody Tversky, MD	XXX		
82	Matthew A. Tyler, MD	XXX		
83	Maria C. Veling, MD	XXX		

(Continues)

	AUTHOR	NOTHING TO DISCLOSE	COMPANY	NATURE OF RELATIONSHIP
84	Dana Wallace, MD		Bryn	Advisory board
			OptiNose	Advisory board
			Sanofi	Speaker
85	De Yun Wang, MD, PhD	XXX		
86	Andrew White, MD		ALK	Advisory board
			Amgen	Speaker's bureau
			Astra Zeneca	Advisory board, research funding, speaker's bureau
			Blueprint	Speaker's bureau
			Genentech	Advisory board
			Glaxo Smith Kline	Advisory board, speaker's bureau
			OptiNose	Advisory board, speaker's bureau
			Regeneron/Sanofi	Advisory board, speaker's bureau
87	Luo Zhang, MD, PhD	XXX		

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4	Carlo Cavaliere, MD, PhD		AstraZeneca	Consultant
			Glaxo Smith Kline	Consultant
			LoFarma	Consultant
			Novartis	Consultant
			Sanofi	Consultant
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			Chiesi	Travel support to meetings
			GSK	Advisory board, clinical trials, research grant, travel support to meetings, speaker fee
			Novartis	Travel support to meetings, clinical trials,
			Sanofi	Advisory board, clinical trials
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33	Nadja Struss, MD	XXX		
34	Kevin Tie, MD	XXX		
35	Esmond F. Tsai, BS	XXX		
36	Sina Torabi, MD	XXX		
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HNS=Head and Neck Surgery

*No financial conflicts at the time of ICAR authorship. Transitioned to employment with Novartis prior to document submission/publication.