International consensus statement on allergy and rhinology

International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis – 2023 Update

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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.

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 with instructions to adhere to 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,[4] and an evidence-based recommendation was made considering benefit, harm, and cost for each topic, where appropriate.

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 3-5 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 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 4 consecutive weeks. Persistent AR is defined as symptoms for more than 4 days per week for at least one 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 5-50% 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 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 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]**

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

Risk factor or exposure	Year	# 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*	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	

AR=allergic rhinitis; SES=socioeconomic status
*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	# 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*	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	-----	

AR=allergic rhinitis
*Studies included in systematic reviews were not separately listed in tables

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, le vel 4: 2 studies)
Benefit: Exposure to pets at birth and in the first year of life has potential benefits of decreasing risk of A R.

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.

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.]**

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

Burden of AR	Year	# 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	

AR=allergic rhinitis; QOL=quality of life

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 judgment: 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. 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 allergen immunotherapy (AIT).
Benefits-harm assessment: The benefits of treating patients with AR may outweigh any associated risks.
Value judgment: 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.**

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

Diagnostic modality	Year	# 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	
	2023	19	B	-----	

Correlation between skin and *in vitro* testing	2018	19	B	-----	Studies differ regarding the concordance of various allergy testing methods.
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	
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	

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=fraction of exhaled nitric oxide; nNO=nasal nitric oxide

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, contact and 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.

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 – 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 misdiagnoses 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 pharmacological therapy, initiation of AIT, as well as avoidance measures. See **TABLE II.C.** in full ICAR document.
Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results.
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 whealing 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). 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 (IgE) – 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 specific IgE production and predict treatment outcomes with AIT.
Value judgments: The evidence does not support a 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., 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. 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 in local availability.
Benefits-harm assessment: Balance of benefit and harm.
Value judgments: Molecular diagnosis may be a useful tool for diagnosis of AR in some scenarios, especially in polysensitized patients.
Policy level: Option.
Intervention: Molecular diagnosis 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 atopic and non-atopic 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 $7000-10000 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.

Benefit: Possible benefit in differentiation of atopic and non-atopic rhinitis through non-invasive testing. Possible benefit in monitoring treatment response.
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.

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.]**

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	# 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	

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

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: Mild 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 & 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 antigen 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 with evidence-based recommendations below. **[TABLE I.C.7.b.]**

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

Medication	Year	# 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 steroids, 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	
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	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.
	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	No 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	

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

*Studies included in systematic reviews were not separately listed in tables

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 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 known undesirable local adverse effects such as epistaxis with some 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 STEROIDS: 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 ANTAGONIST (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) – 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: Ipratropium bromide 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 recommendation 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 two years or 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 more 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 LTRA and oral antihistamine were superior in symptom reduction and QOL improvement compared to placebo, and to 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 co-morbid 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 (2 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 (IPB) –
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 benefits 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.

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 on-going 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 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.]**

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

AIT method	Year	# 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*	Strong recommendation for SLIT in patients unable to obtain adequate relief from pharmacotherapy. *Specific recommendations for various SLIT preparations in full ICAR document.
	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	

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

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 vs aqueous SLIT vs 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 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 2009-2015.
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 IMMUBNOTHERAPY – 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 cost benefits 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 with 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. Physical exam findings include posterior pharyngeal cobblestoning, clear 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 development of asthma in pediatric patients with AR.

I.C.9. Associated conditions

There is evidence for the association of several comorbid conditions with AR, which are listed below.

Several additional conditions have been added since ICAR-Allergic Rhinitis 2018. **[TABLE I.C.9.]**

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

Condition	Year	# 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 data, but early evidence generally supports 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 improved food tolerance.
	2018	12	B	
Anaphylactic food allergy	2023	20	C	Evidence for AIT treatment for food allergies; see full section for details specifics of AIT modality.
	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	

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*	B	Sleep disturbance is associated with AR. Treatment of AR can improve sleep quality.
	2018	20	B	

AR=allergic rhinitis; AIT=allergen immunotherapy; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; AFRS=allergic fungal rhinosinusitis; CCAD=central compartment atopic disease; AERD=aspirin exacerbated respiratory disease; PFAS=pollen food allergy syndrome; OSA=obstructive sleep apnea
*Studies included in systematic reviews were not separately listed in tables

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

COVID-19 (coronavirus disease 2019) 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. Of note, anti-IgE therapy has also 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.

ALLERGIC RHINITIS SUMMARY RECOMMENDATIONS

	STRONGLY RECOMMENDED	RECOMMENDED	OPTION	NOT RECOMMENDED	INSUFFICIENT EVIDENCE
Evaluation and Diagnosis		**History and physical exam** (low level evidence) **Skin prick testing** – standardized allergen extracts improve consistency **Serum sIgE** **Nasal provocation testing** – for LAR, occupational rhinitis **Validated surveys**	**Nasal endoscopy** **Intradermal testing** – stand-alone or confirmatory following SPT **Blended skin testing techniques** – semi-quantitative **Serum tIgE** – for assessment of overall atopic status **Nasal sIgE** – may be used to evaluate for LAR **Basophil activation testing** **Nasal provocation testing** **Nasal cytology** **Rhinomanometry** **Acoustic rhinometry** **Peak nasal inspiratory flow** – with PROMs	**Radiologic studies** **Nasal histology** **Fraction of exhaled NO (FeNO)** **Nasal NO**	
Avoidance		**Occupational rhinitis** – avoidance or decreased exposure	**House dust mite, cockroach, pets, rodents, pollen** – allergen avoidance or environmental controls		
Pharmacotherapy	**Oral H1 antihistamines – newer generation** **Intranasal antihistamines** **Intranasal corticosteroid sprays (INCS)** **Nasal saline** **INCS + intranasal antihistamine** – second line	**Intranasal cromolyn (disodium cromoglycate)** – second line, preventative	**Oral corticosteroids** – short course for acute exacerbation **Intranasal decongestant** – short course **Leukotriene receptor antagonist (LTRA)** – when other options contraindicated **Intranasal anticholinergic (ipratropium bromide)** – for rhinorrhea **Biologics** – based on published evidence; not FDA approved **Probiotics** – as adjunct treatment **Oral H1 antihistamine (2G) + PSE** – short course **Oral H1 antihistamine (2G) + INCS** **Oral H1 antihistamine (2G) + LTRA** – when other options contraindicated **INCS + LTRA** – when comorbid asthma present **INCS + intranasal decongestant** – short course **INCS + intranasal anticholinergic** – for rhinorrhea	**Oral corticosteroids** – routine use **Intranasal corticosteroids, non-traditional application** **Injectable corticosteroids** **Oral decongestant** – routine use **Intranasal decongestant** – routine use **LTRA** – as first line monotherapy **Oral antihistamine (2G) + LTRA** – as first line therapy **INCS + LTRA** – when comorbid asthma present	**Oral H2 antihistamine** – data does not adequately address benefit in AR
Non-traditional			**Acupuncture**		**Other complementary modalities** **Honey** **Herbal therapies**
Surgical		**Inferior turbinate surgery** – for refractory nasal obstruction	**Septoplasty/septorhinoplasty** – for patients with obstructive septal deviation **Vidian neurectomy or posterior nasal neurectomy**– for patients with bothersome rhinorrhea **Cryoablation and radiofrequency of the posterior nasal nerves** – for patients with bothersome rhinorrhea		
Immunotherapy	**Subcutaneous immunotherapy (SCIT)** **Sublingual immunotherapy (SLIT) – general** **SLIT tablets** – grass pollen, short ragweed, house dust mite **Aqueous SLIT for tree pollen**	**High dose aqueous SLIT** **Aqueous SLIT for Alternaria** **SLIT tablet dual therapy**	**SCIT over SLIT** **Aeroallergen rush SCIT** **Aeroallergen cluster SCIT** **Aqueous SLIT for animal allergy** **Intralymphatic immunotherapy** **Oral mucosal immunotherapy**	**Epicutaneous immunotherapy** **Oral immunotherapy** **Inhaled immunotherapy**	**Local nasal immunotherapy**

INCS=intranasal corticosteroid; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; sIgE=allergen specific immunoglobulin E; LAR=local allergic rhinitis; SPT=skin prick test; tIgE=total immunoglobulin E; PROM=patient reported outcome measure; LTRA=leukotriene receptor antagonist; PSE=pseudoephedrine; NO=nitric oxide; 2G=second generation; AR=allergic rhinitis

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.

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

AR=allergic rhinitis; sIgE=allergen specific immunoglobulin E; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; CRSwNP=chronic rhinosinusitis with nasal polyps; COVID=coronavirus disease 2019

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.

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II. Table of contents and navigating through the document

II.A. Detailed table of contents

II.B. List of abbreviations used

4PR	four-phase rhinomanometry
AAO-HNSF	American Academy of Otolaryngology-Head and Neck Surgery Foundation
AAP	American Academy of Pediatrics
AC	allergic conjunctivitis
ACC	allergen challenge chamber

1	ACEI	angiotensin converting enzyme inhibitors
2	AD	atopic dermatitis
3	AERD	aspirin-exacerbated respiratory disease
4	AFRS	allergic fungal rhinosinusitis
5	AH	adenoid hypertrophy
6	AHI	apnea-hypopnea index
7	AIDS	acquired immunodeficiency syndrome
8	AIT	allergen-specific immunotherapy
9	ANA	antinuclear antibody
10	ANCA	anti-neutrophil cytoplasmic antibody
11	AP	activator protein
12	AR	allergic rhinitis
13	ARIA	Allergic Rhinitis and its Impact on Asthma
14	ARS	acute rhinosinusitis
15	ASHMI	Anti-Asthma Simplified Herbal Medicine Intervention
16	ATH	adenotonsillar hypertrophy
17	AU	allergy units
18	BAT	basophil activation test
19	BAU	biologic allergy units
20	CBER	Center for Biologics Evaluation and Research
21	CC	central compartment
22	CCAD	central compartment atopic disease
23	CCL5	C-C chemokine ligand-5
24	CD	cluster of differentiation
25	CDC	Centers for Disease Control
26	cAMP	cyclic adenosine monophosphate
27	cGMP	cyclic guanosine monophosphate
28	CGRP	calcitonin gene-related protein
29	CI	confidence interval
30	CMV	cytomegalovirus
31	COPD	chronic obstructive pulmonary disease
32	COVID	coronavirus disease
33	COX	cyclooxygenase
34	CPAP	continuous positive airway pressure
35	CPT	conjunctival provocation test
36	CRD	component-resolved diagnostics
37	CRS	chronic rhinosinusitis
38	CRSsNP	chronic rhinosinusitis without nasal polyps
39	CRSwNP	chronic rhinosinusitis with nasal polyps
40	CS	combined score
41	CSF	cerebrospinal fluid
42	CT	computed tomography
43	DAMP	damage-associated molecular pattern
44	dsDNA	double stranded DNA
45	DSCG	disodium cromoglycate
46	EAACI	European Academy of Allergy and Clinical Immunology
47	EBRR	evidence-based review with recommendations
48	ECP	eosinophil cationic protein

1	EGPA	eosinophilic granulomatosis with polyangiitis
2	EGR	early growth response
3	ECHRS	European Community Respiratory Health Survey
4	EEC	environmental exposure chamber
5	ELISA	enzyme-linked immunosorbent assay
6	eNOS	endothelial nitric oxide synthase
7	ENS	empty nose syndrome
8	EoE	eosinophilic esophagitis
9	ET	Eustachian tube
10	ETD	Eustachian tube dysfunction
11	FDA	Food and Drug Administration
12	FeNO	fractional exhaled nitric oxide
13	FEV_1	forced expiratory volume in 1 second
14	FITC	fluorescein isothiocyanate
15	FOXP3	forkhead-box P3
16	GA^2LEN	Global Allergy and Asthma European Network
17	GATA	GATA binding protein
18	GINA	Global Initiative for Asthma
19	GITRL	glucocorticoid-induced TNF receptor ligand
20	GM-CSF	granulocyte-macrophage colony stimulating factor
21	GPA	granulomatosis with polyangiitis
22	GWAS	genome-wide association studies
23	HDM	house dust mite
24	HEPA	high-efficiency particulate air [filtration]
25	HIV	human immunodeficiency virus
26	HMGB-1	high mobility group box-1
27	HMW	high molecular weight
28	HSP	heat shock protein
29	ICAM	intracellular adhesion molecule
30	ICAR	International Consensus Statement on Allergy and Rhinology
31	ICD	International Classification of Disease
32	IDT	intradermal dilutional testing
33	IFN	interferon
34	Ig	immunoglobulin
35	IgE	immunoglobulin E
36	IL	interleukin
37	ILC	innate lymphoid cell
38	ILIT	intralymphatic immunotherapy
39	IMAP	inferior meatus augmentation procedure
40	INCS	intranasal corticosteroid
41	INDC	intranasal decongestant
42	iNOS	inducible nitric oxide synthase
43	IPB	ipratropium bromide
44	IPM	integrated pest management
45	ISAAC	International Studies of Asthma and Allergies in Childhood
46	IT	inferior turbinate
47	ITAM	immunoreceptor tyrosine-based activation motif
48	KNHANES	South Korean National Health and Nutrition Examination Survey

1	LAR	local allergic rhinitis
2	LMW	low molecular weight
3	LOE	level of evidence
4	LPR	laryngopharyngeal reflux
5	LSR	lipolysis-stimulated lipoprotein receptor
6	LTRA	leukotriene receptor antagonist
7	MBP	major basic protein
8	MCP	monocyte chemoattractant protein
9	MD	molecular diagnostics
10	MEE	middle ear effusion
11	MMP	matrix metalloproteinase
12	MQT	modified quantitative testing
13	mRQLQ	mini-Rhinoconjunctivitis Quality of Life Questionnaire
14	MT	middle turbinate
15	NARES	non-allergic rhinitis with eosinophilia syndrome
16	NC	nasal cytology
17	NF	nuclear factor
18	NFAT	nuclear factor of activated T cells
19	NGF	neural growth factor
20	NH	nasal histology
21	NHANES	National Health and Nutrition Examination Survey
22	NK	natural killer
23	nNO	nasal nitric oxide
24	nNOS	neuronal nitric oxide synthase
25	NO	nitric oxide
26	NOS	nitric oxide synthase
27	NOSE	Nasal Obstruction Symptom Evaluation
28	NPT	nasal provocation test
29	NPV	negative predictive value
30	NSAID	non-steroidal anti-inflammatory drug
31	OAS	oral allergy syndrome
32	OME	otitis media with effusion
33	OMIT	oral mucosal immunotherapy
34	OR	odds ratio
35	OSA	obstructive sleep apnea
36	PAMD@	precision allergy molecular diagnostic applications
37	PAMP	pathogen-associated molecular pattern
38	PDE	phosphodiesterase
39	PEF	peak expiratory flow
40	PFAS	pollen food allergy syndrome
41	PFT	pulmonary function test
42	PG	prostaglandin
43	PM	particulate matter
44	PNEF	peak nasal expiratory flow
45	PNIF	peak nasal inspiratory flow
46	PNN	posterior nasal nerve
47	PO	per os (by mouth)
48	Ppb	parts per billion

1	PPV	positive predictive value
2	PROM	patient reported outcome measure
3	PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
4	PSG	polysomnogram
5	QALY	quality adjusted life year
6	QID	four times daily
7	QOL	quality of life
8	RANTES	regulated upon activation, normal T cell expressed and presumably secreted
9	RAP	Respiratory Allergy Prediction
10	RAPP	RhinAsthma Patient Perspectives
11	RARS	recurrent acute rhinosinusitis
12	RAST	radio allegro-sorbent test
13	RCT	randomized controlled trial
14	RDI	respiratory disturbance index
15	REM	rapid eye movement
16	RMS	rescue medication score
17	RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
18	RR	relative risk
19	RSDI	Rhinosinusitis Disability Index
20	RTSS	Rhinitis Total Symptom Score
21	SARS-CoV-2	virus that causes COVID-19
22	SCIT	subcutaneous immunotherapy
23	SDB	sleep disordered breathing
24	SES	socioeconomic status
25	sIgE	allergen-specific immunoglobulin E
26	sIgG	allergen-specific immunoglobulin G
27	SLIT	sublingual immunotherapy
28	SMA	smooth muscle actin
29	SMD	standardized mean difference
30	SNHL	sensorineural hearing loss
31	SNOT	SinoNasal Outcome Test
32	SNP	single nucleotide polymorphism
33	SPT	skin prick test
34	SRMA	systematic review and meta-analysis
35	STAT	signal transducer and activator of transcription
36	TARC	thymus and activation-regulated chemokine
37	TGF	transforming growth factor
38	TCM	Traditional Chinese Medicine
39	Th	T helper
40	tIgE	total immunoglobulin E
41	TJ	tight junction
42	TL1A	tumor necrosis factor-like cytokine 1A
43	TLR	toll-like receptor
44	TNF	tumor necrosis factor
45	TNSS	Total Nasal Symptom Score
46	TOSS	Total Ocular Symptom Score
47	TPRV	transient receptor potential vanilloid
48	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.

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

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

*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 available evidence for allergic rhinitis (AR), including major content areas of epidemiology, risk factors, diagnosis, management, and associated conditions of 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, an additional 5803 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 provides 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.[1,3-6]

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 reviewed by all authors. 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.[7] 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.

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IV. Methods

IV.A. Topic development

The methods of ICAR-Allergic Rhinitis 2023 largely follow previous ICAR documents,[1-3] with utmost reliance on published evidence and minimal influence of expert opinion and other biases. The 2011 EBRR method described by Rudmik and Smith[4] 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 assigned 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 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 specific instructions to perform a systematic review of the literature for each topic area using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) standardized guidelines.[5] 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 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.[5]

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 to 5, **TABLE IV.A.-1**).[6] 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.[7] At the completion of the systematic review and research quality evaluation for each EBR or EBRR topic, an aggregate grade of evidence (A to D) was produced for the topic based on the guidelines from the American Academy of Pediatrics (AAP) Steering Committee on Quality Improvement and Management.[8] **[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.[8] **[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 with a high evidence level, while others would assign a lower level of evidence 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 (SKW) 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 3-5 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.

TABLE IV.A.-1 Levels of evidence[6]

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*	Non-randomized controlled cohort/follow-up study**
4	Case-series or case control studies, or poor-quality prognostic cohort study**	Case-series, case-control studies, or historically controlled studies**
5	n/a	Mechanism-based reasoning

*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.
**As always, a systematic review is generally better than an individual study.

TABLE IV.A.-2 Aggregate grade of evidence[8]

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

RCT=randomized controlled trial

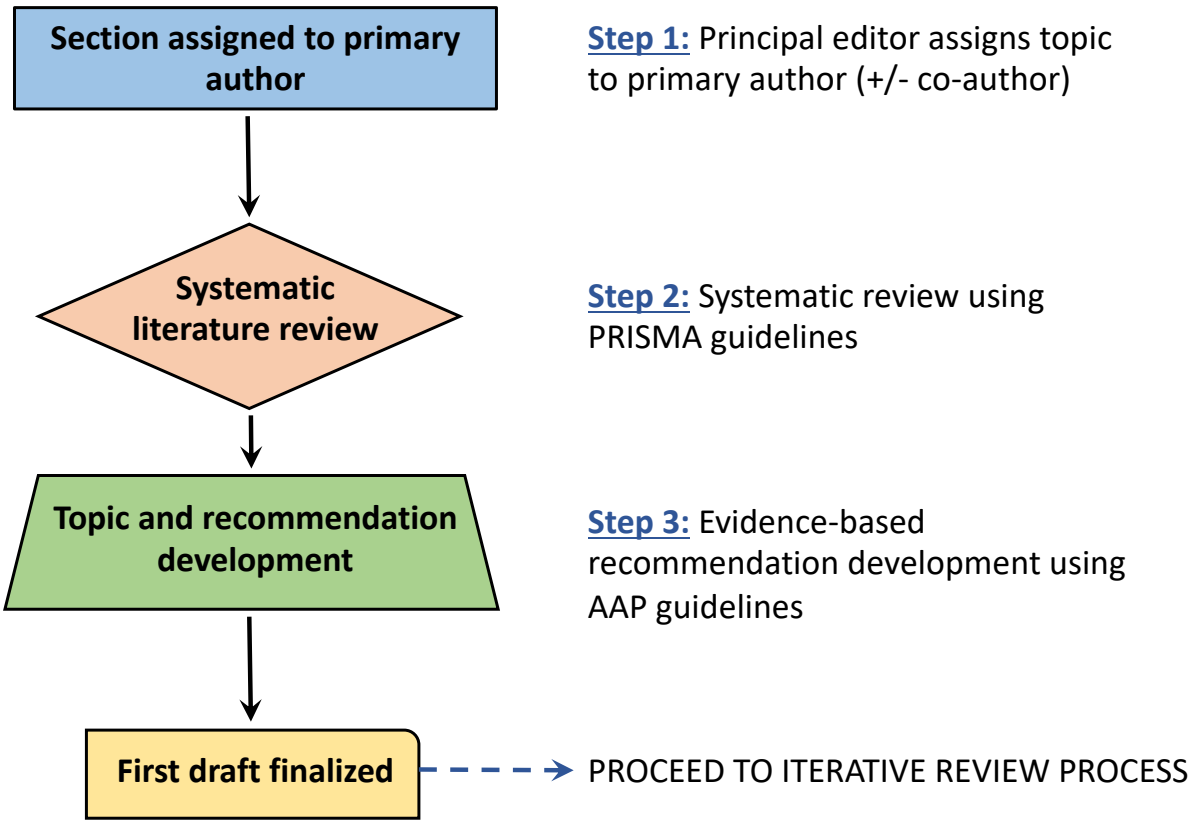
TABLE IV.A.-3 American Academy of Pediatrics defined strategy for recommendation development[8]

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit

<table>
<tr><td>A. Well-designed RCT’s</td><td>Strong recommendation</td><td rowspan="3">Option</td><td rowspan="2">Strong recommendation against</td></tr>
<tr><td>B. RCT’s with minor limitations; overwhelmingly consistent evidence from observational studies</td><td rowspan="2">Recommendation</td></tr>
<tr><td>C. Observational studies (case-control and cohort design)</td><td rowspan="2">Recommendation against</td></tr>
<tr><td>D. Expert opinion, case reports, reasoning from first principles</td><td>Option</td><td>No recommendation</td></tr>
</table>

RCT=randomized controlled trial

FIGURE IV.A. Topic development (Stage 1)



PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AAP=American Academy of Pediatrics

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

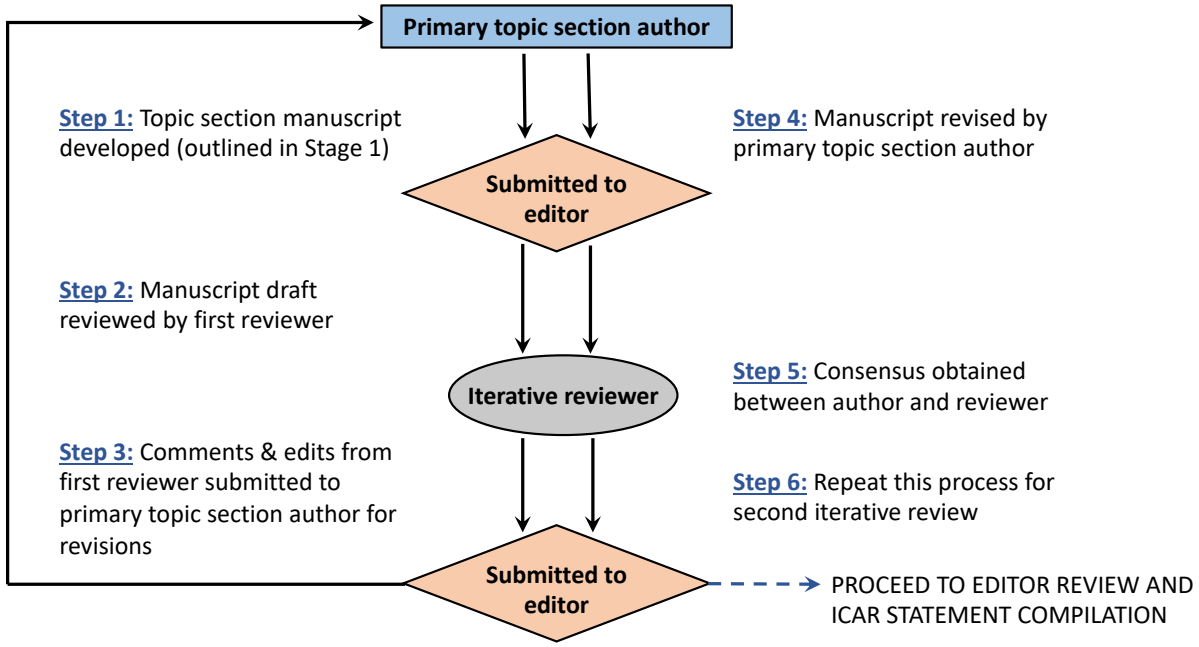
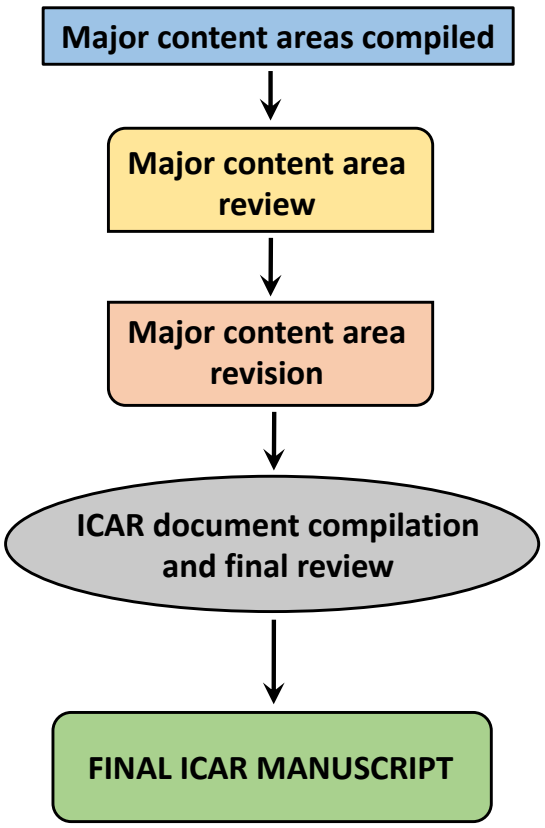


Figure IV.C. ICAR-Allergic Rhinitis 2023 statement development (Stage 3)



Step 1: ICAR major content areas containing topic sections of similar subject matter are compiled

Step 2: Each major content area reviewed by 3-5 associate editors for validity and consistency

Step 3: Consideration of revisions to major content area to ensure consistency throughout ICAR document

Step 4: All authors review final ICAR document draft

ICAR=International Consensus Statement on Allergy and Rhinology

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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.[1] Symptomatically, it is characterized by anterior or posterior rhinorrhea, nasal congestion/blockage, nasal pruritis, and sneezing.[2] AR is widely prevalent and can result in significant physical sequelae and recurrent or persistent morbidities.[1] Additionally, it is strongly associated with asthma, supporting the unified airway theory which postulates that upper and lower airway inflammation share common pathophysiologic mechanisms.[3] *(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.[4] 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.[5] The late-stage reaction often occurs during the 4- to 8-hour 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.[1] *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.[1] Mold exposure may occur indoors or outdoors depending on the specific environmental situation.

Of note, the classification of seasonal vs 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.[6-9]

Because of the priming effect on the nasal mucosa introduced by low levels of pollen exposure,[10-15] and minimal but persistent nasal inflammation in patients with "symptom-free rhinitis",[8,16,17] 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.[18] *(See Section VII.D. 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.[19] *Intermittent AR* is characterized by symptoms for less than 4 days per week or less than 4 consecutive weeks. *Persistent AR* is characterized by symptoms occurring more than 4 days per week for at least 4 consecutive weeks.[20] 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.[21-24]

The ARIA guidelines have likewise proposed another stratification of severity (mild and moderate-severe) with respect to these disabilities.[7] 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 the 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.[25,26] Currently used taxonomy is largely organ-based and does not fully take into account the mechanisms leading to symptoms.[27] For example, the 2016 Melbourne epidemic thunderstorm asthma event saw a dramatic increase in asthma-related hospitalizations and ten deaths over a 30-hour period.[28] Interestingly, most patients hospitalized with severe asthma attack did not have a diagnosis of asthma. They did have a diagnosis of AR[29] and allergen-specific immunotherapy (AIT) appeared to offer protection.[30] 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).[31]

Although patients with AR and allergic asthma are by definition sensitized, many individuals with allergic sensitization do not have symptoms of allergic disease,[32] and in a proportion of patients with AR and allergic asthma, sensitization is not related to the presence or severity of symptoms.[27] Furthermore, the reliability of skin testing depends greatly on allergen extracts and methods used.[33] 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.[31] *(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.[34-37] However, the problem of false-positive test results remains.[37] 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%.[38,39] 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.[40-44] Recent novel analyses of CRD data demonstrated that the pattern of interaction between allergen component-specific IgEs predicts asthma[45] and that networks of interactions between sIgE to multiple components are predictors of asthma severity across the lifespan.[46] 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,[45] severity assessment,[46] prediction of future risk,[41] and ultimately, the prediction of response to treatment.[47]

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.[48-50] 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.[51] NSAIDs inhibit cyclooxygenase (COX)-1, leading to decreased prostaglandin (PG) E2 and increased leukotriene production due to an imbalance towards 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.[48,52-54]

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.[55]

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.[56-58]

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.[59,60] 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-generated cyclic guanosine monophosphate (cGMP), causing vasodilation of the corpus cavernosum and pulmonary vasculature as well as changes in the lower urinary tract. Nitric oxide/cyclic nucleotide mediated vasodilation occurs in the nasal mucosa causing nasal mucosal engorgement and edema.[61-65] **[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.[66] Bradykinin B1 and B2 receptors have been demonstrated in nasal mucosa,[67] and bradykinin application to nasal mucosa has resulted in increased sneezing.[63,68] In addition to cough, rhinorrhea and nasal obstruction have been associated with ACEI.[66]

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.[69,70] In contrast to oral agents, intranasal administration bypasses portal filtration.

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.[71] 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.[72] 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.[73-76] In the repeat user, vasoconstriction, direct trauma compounded by anesthetic effects, and/or injury secondary to contaminants may result in tissue necrosis.[77-80] Similarly, prescription narcotics,[81] antidepressants,[67] anticholinergics, and psychostimulants can be abused by intranasal administration.[67,81] Tissue necrosis has also been associated with intranasal opioid and acetaminophen abuse.[82-84] Possible mechanisms of injury include hyperosmotic conditions, vasculitic-like inflammation, or direct injury secondary to talc.[84,85]

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.

TABLE V.B.1. Drug-induced rhinitis medication list[48,50,62]

Local inflammatory type			-NSAIDs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, naproxen, piroxicam, sulindac) -Aspirin -Ketolorac (if administered via nasolacrimal duct)

Neurogenic type	**Alpha and β-adrenergic receptor modulators**	Alpha 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
		Beta-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

V.B.2. Rhinitis medicamentosa

Rhinitis medicamentosa is a drug-induced rhinitis resulting from prolonged topical intranasal decongestant (INDC) use.[20,86] 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.[86] Patients present with nasal congestion, often lack rhinorrhea or sneezing, and may note reduced efficacy, or tachyphylaxis, with further use of INDCs.[76,87,88] 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. Stimulation of these receptors results in vasoconstriction with resultant decongestion due to decreased blood flow and increased sinusoid emptying.[86,89] 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.[86,90]

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.[75,76,86,89-91] 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.[92-94] Benzalkonium chloride, an antimicrobial preservative used in many nasal sprays, has been implicated in the mechanism of rhinitis medicamentosa. Studies have demonstrated that benzalkonium chloride is toxic to nasal epithelium and induces mucosal edema, propagating rhinitis medicamentosa, although the data are inconclusive.[95-99] Neither duration, nor cumulative dose of INDC needed to initiate rhinitis medicamentosa is known. Rebound congestion has developed after three to ten days of medication use,[76,93] but may not occur until after 30 days.[100,101] Other studies have demonstrated a lack of rebound congestion after eight weeks of continuous use.[100-103] Furthermore, doubling the dose of intranasal imidazoline did not increase the extent of rebound edema.[100] Although inconclusive, studies suggest that INDC use should be discontinued after three days to avoid rebound congestion.[87,104,105]

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.[87,89,106-111] Intranasal corticosteroids (INCS) are the most common treatment for rhinitis medicamentosa. Many initiate INCSs while weaning INDCs.[90,94,109-112] 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 reduction have been considered.[111]

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.

TABLE V.B.2. Intranasal decongestants associated with rhinitis medicamentosa[20,86]

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

OTC=over the counter

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.[113,114] While many social activities or hobbies can result in overlapping symptoms, stimuli that are encountered outside the workplace are not considered occupationally related.[115]

The pathophysiological mechanisms of occupational rhinitis are the same as other forms of chronic rhinitis although symptoms may be intimately tied to work exposure.[113,115,116] Occupational rhinitis may be classified as allergic, resulting from an immunological exposure to a sensitizing high molecular weight protein (HMW > 5kD) or non-allergic, mediated by non-immunological low molecular weight chemical irritant (LMW < 5kD).[117,118] 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.[113,116]

Cross sectional studies of various workers show a wide range of occupational rhinitis prevalence rates (3-87%),[113,115,119] although rates are higher for HMW agents compared to lower for LMW agents.[115]

Occupations and commonly implicated agents are reported in **Table V.B.3**.[120-125] 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.[126,127]

Occupational rhinitis tends to be three times more prevalent than occupational asthma,[119] but the two disorders are often associated (up to 92% of cases).[115] In most cases, work-related nasal symptoms develop 5-6 months before the onset of bronchial symptoms.[113,128] 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.[116,129,130]

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.[113] 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.[116,131,132] Sensitization to a suspected HMW agent by SPT may be preferred over serum sIgE assessment as skin testing has been reported to be more sensitive and specific in various reports.[133-136] 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.[33,115,136-138] 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.[38,113,136,139,140] **[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.[141] 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.[115,116]

The primary treatment of allergic occupational rhinitis is avoidance or reduction of culprit exposures.[115] 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.[142] In allergic occupational rhinitis due to HMW sensitizers, AIT may be considered when validated extracts are available.[143] However, AIT may have limitations in those individuals with continued high workplace exposure; therefore, simultaneous mitigation and avoidance strategies are essential.

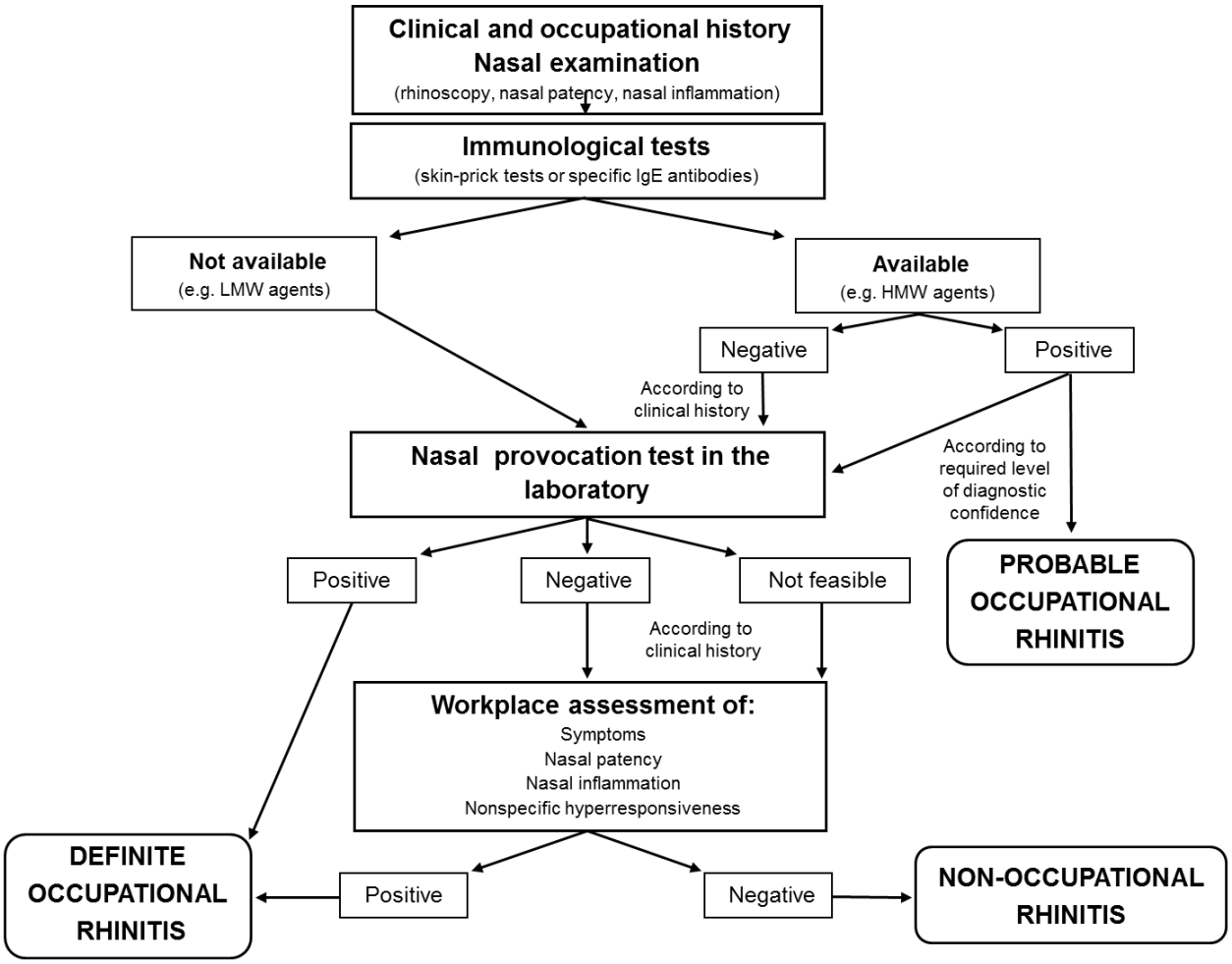
Occupational rhinitis has both medical and socioeconomic implications,[144] and may be the cause of leaving work.[145] Since occupational rhinitis is acknowledged as a risk factor for the development of occupational asthma, the prevention and early identification of occupational rhinitis of exposed workers may provide an excellent opportunity to prevent the development of occupational asthma.[146] *(See Section XI.A.6. Allergen Avoidance – Occupational for additional information on this topic.)*

TABLE V.B.3. High risk occupations and causal agents for occupational rhinitis[120-125]

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 & detergent industries
Non-allergic agents (low molecular weight)	
Persulphates	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

FIGURE V.B.3. Diagnostic algorithm for occupational rhinitis



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 dysfunction, epistaxis and is often associated with lower airway symptoms and conjunctival irritation.[115] 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 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.[124,147,148] Larger chemical particles greater than 10 microns 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.[113]

In general, inquiring about exposures to vapors, fumes, smoke, and dust can be helpful to determine if a patient has an element of chemical rhinitis. These responses are often non-IgE mediated by a reflex response which is often termed neurogenic inflammation.[149] 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.[150,151]

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.[124,152-154] 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.[155,156]

V.B.5. Smoke induced rhinitis

Tobacco smoke exposure is associated with chronic rhinitis and CRS.[157-159] 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.[160,161] 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.[162-165]

Symptoms of rhinitis are provoked by exposure to the chemicals in smoke and can correlate with serum cotinine levels in patients using tobacco.[164] Furthermore, smoking in combination with occupational irritants are additive risk factors for nasal symptoms and may be independent of allergic sensitization.[165] Although smoke-induced rhinitis does not require allergen sensitization, there has been at least one report of potential allergenic compounds in smoke.[166] 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.[167] This may be due in part to the fact that tobacco smoke exposure results in decreased mucociliary clearance.[168]

One of the mechanisms to explain nasal irritation resulting from smoke exposure may be related to capsaicin-sensitive neurons in the nasal mucosa.[169] This neurogenic type of nasal inflammation is mediated by neuropeptides such as substance P, neurokinin A, and calcitonin gene-related peptide. These mediators are released by sensory nerve fibers in the nose and result in vasodilation, edema, and inflammation.[170]

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.[168] 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 minutes) leads to increased nasal resistance as measured by posterior rhinometry (although there were no significant increases in histamine levels noted).[171] However, *prolonged* exposure to moderate levels of smoke (15 ppm for 2 hours) induced a congestive response lasting for an hour or longer in both individuals with and without a history of smoke-induced rhinitis.[168] 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.[20,172]

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.[173] *(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.[20] The incidence of acute viral rhinosinusitis is expected to be as high as 98%.[174,175] Common organisms are rhinovirus, adenovirus, influenza virus, and parainfluenza virus.[109] 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.[176] Prolonged symptoms of more than two weeks duration suggest a non-infectious etiology or post-viral rhinosinusitis.

The relationship between viral infection and AR has been studied. The upregulation of Intracellular Adhesion Molecule (ICAM)-1, which is the major human receptor of rhinovirus, was shown in patients with underlying allergic disease.[177-179] The increased expression of ICAM-1 was demonstrated in both upper and lower allergic airway diseases compared with healthy controls.[180-182] 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*.[174,175] This occurs in 0.5-2.0% of all viral infections.[173,174] Clinical presentation distinguishing viral from bacterial rhinitis/rhinosinusitis is often impossible.[183-186] 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.[187-189]

The possibility of bacterial infection increases if there is deterioration in symptoms after day 5.[176] Predicting criteria for bacterial infection has been suggested using clinical characteristics, the pattern of symptoms and laboratory reports.[173,190,191] However, the maximum sensitivity and specificity only reach 69% and 81%, respectively, among various criteria.[189,192] 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.[176]

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.[193-195] Symptoms include rhinorrhea, sneezing, hyposmia, and nasal itching.[196] In a multicenter study of 599 previously asymptomatic women, prevalence of rhinitis of pregnancy was 22%.[197] A history of AR and smoking increase risk for its development.[193-195]

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.[195,196,198] Electron microscopy demonstrates glandular hyperactivity, increased phagocytotic activity, and increased amounts of acid mucopolysaccharides in the ground substance.[199] Studies using validated patient reported outcome measures (e.g., Nasal Obstruction Symptom Evaluation [NOSE] scale, Rhinitis Quality of Life Questionnaire [RQLQ])[198,200] confirm the subjective component of pregnancy-induced rhinitis.[195,196,198]

The precise pathophysiology of pregnancy-induced rhinitis remains unknown.[196,201,202] Estrogen, progesterone, and placental growth hormonal have all been implicated.[193-195,198] 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.[203] Additionally, serum levels of placental growth hormone were significantly higher in patients with pregnancy-induced rhinitis throughout their pregnancy.[204]

Pregnancy-induced rhinitis has been implicated in potential risks for the mother and fetus.[193,194,202] Mouth breathing from pregnancy-induced rhinitis bypasses the benefits of nasal breathing, including preparation of inspired air for the lungs and nitric oxide release from the maxillary sinuses, which reduces pulmonary vascular resistance and contributes to increased pulmonary oxygenation.[194,202] Additionally, maternal sleep disruption, when severe, can be associated with snoring and obstructive sleep apnea (OSA) and may contribute to increased risks for pre-eclampsia, maternal hypertension.[205] Intrauterine growth retardation and decreased Apgar scores are also possible.[193,205]

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.[172,201,202] 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.[172,201,202] INCS are generally considered safe for use during pregnancy; however, triamcinolone is associated with congenital respiratory defects.[172] 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.[206] 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.[172,207-209] 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.[207]

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.[207,208,210] These patients may also have prolonged mucociliary clearance time.[211] 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.[212]

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.[172,213-216] 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.[213] There is also no associated disturbance of smell or taste.[217] 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.[215]

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.[214,216] 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.[216] 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.[218] A direct effect on goblet cell secretion may be triggered when capsaicin is ingested.[217] A well-known culprit of gustatory rhinitis is chili peppers, which contain capsaicin.[217] A variety of other foods are associated with gustatory rhinitis including horseradish, wasabi, black pepper, hot mustard and vinegar.[215,216]

Treatment of gustatory rhinitis is avoidance of the inciting food. Topical anticholinergic medications such as ipratropium bromide are used when avoidance is impractical.[214,216,217] Use of topical capsaicin and resection of the posterior nasal nerve have been proposed as a last resort for intractable gustatory rhinitis.[217,219]

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), emphysema.[220] Up to 75% of aspirin-exacerbated respiratory disease (AERD) patients suffer exacerbations of respiratory symptoms when they consume alcohol.[221-223] 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.[223] Such symptoms can arise regardless of the type of alcohol ingested.[220,222] 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.[223]

In AERD patients, the severity of aspirin-induced respiratory symptoms is positively correlated with the severity of alcohol-induced reactions.[223] Exacerbations of respiratory symptoms in response to alcohol has been shown to be decreased after aspirin-desensitization in patients with AERD.[221] Patients with AERD have elevated baseline cysteinyl leukotriene levels, which are proposed to mediate the upper and lower airway reactions to aspirin.[221,222] Cardet et al[222] propose that cysteinyl leukotrienes also 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.[224]

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.[225] 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 nonallergic rhinitis that was first described by Jacobs and colleagues in 1981.[226]

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.[227] 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.[225,228] In addition, nasal biopsies from these patients commonly show increased numbers of mast cells with prominent degranulation.[229,230]

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.[231,232] Specifically, NARES is characterized by elevated nasal fluid levels of tryptase (which is also seen in perennial AR) and eosinophilic cationic protein.[233] 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.[234,235]

A correlation between the concentration of RANTES with nasal symptoms and eosinophil counts in perennial AR patients has been shown.[236] 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.[236] Several studies from European cohorts have found a lack of nasal mucosal IgE in

NARES patients.[237,238] 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.[239] Elevated cysteine protease inhibitor cystatin SN was also observed with greater loss of sense of smell.[240] Neuropeptide mediated eosinophil chemotaxis, including substance P, calcitonin gene-related peptide and cholecystokinin octapeptide, has also been described as a contributing factor to the symptomatology in NARES patients.[241]

NARES may occur in isolation, but it can be associated with (and may be a precursor for) AERD.[225] NARES has also been identified as a risk factor for the induction or exacerbation of obstructive sleep apnea[242] and has been associated with increased tendency for lower airway hyperresponsiveness.[243]

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.[244,245] 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.[246] 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.[142,247-249]

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.[56] 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 7-9.6% in the adult population in the United States (US) and Europe.[23,49] Vasomotor rhinitis is the most common cause of non-allergic rhinitis, and is found in 71% of cases.[250-252] Non-allergic rhinopathy occurs with a female-to-male ratio of 2:1 to 3:1[56] and is typically seen after the age of 20.[253] It is defined by the absence of an IgE-mediated immune response.[142] 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.[254]

Local allergic rhinitis (LAR) is a distinct rhinitis that presents with features in between AR and non-allergic rhinopathy.[255] 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.[255,256] The prevalence of LAR among non-allergic rhinopathy has been reported to be 26.5%.[257] *(See Section VI.A.3. Local IgE Production for additional information on this topic.)* Additional forms of nonallergic 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.[56] 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.[258,259]

Medical management of non-allergic rhinopathy includes topical nasal sprays that have variable responses which have been used alone or in combination: INCS,[246,260] topical azelastine,[261] and

ipratropium bromide (IPB).[262] In addition adjunctive treatments include nasal saline sprays or lavage, especially with tenacious post nasal drip.[254]

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.[219,263] These include botulinum toxin injection 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 rate of complication of dry eyes than vidian neurectomy.[264] Recent studies show that office based cryotherapy can achieve improvement in rhinorrhea and congestion for up to 1 year.[265,266]

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.[267,268] This, in turn, can result in symptoms of rhinorrhea, nasal congestion, postnasal drip, dry nose, intranasal crusting, and decreased olfaction in the elderly population.[269,270]

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).[271] 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.[271-274] 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 vasodilate and the mucus glands to become overactive, resulting in hypersecretion and excessive drainage.[275] Vasomotor rhinitis is the most common type of nonallergic rhinopathy/rhinitis, and the highest prevalence of non-allergic rhinopathy is seen in the elderly,[250,270,276,277] 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,[278-280] loss of nasal cartilage elasticity and tip support,[268,270,280] mucus stasis secondary to a less effective mucociliary clearance system, [270,279,281] and age-related central nervous system changes that affect the physiologic nasal cycle,[278,282] 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.[283] This, in turn, results in intranasal volume increase due to nasal mucosal atrophy.[269] Schrodter et al[284] 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.[270]

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,[268] with the prevalence estimated to be around 5-10%.[280,285] 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,[286,287] whereas age-related rhinitis is more similar to vasomotor or nonallergic 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,[280,288] and AIT.[289] For age-related/nonallergic rhinitis rhinorrhea, saline lavage and topical anticholinergics may be therapeutic.[267] 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.[290,291] 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.[292] Both primary and secondary atrophic rhinitis are significantly different in their clinical presentation and underlying pathophysiology compared to AR.[172]

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.[293-297] It is also more commonly found in young to middle-aged adults, with a predominance of females.[293] 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.[293] 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.[296,298]

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).[299] 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.[294] 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 critical step for correct diagnosing secondary atrophic rhinitis.[290]

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[300] 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.[300] Endoscopic findings usually include nasal crusting and enlarged lateral sidewalls.[294]

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.[301] The most common bacteria found in affected individuals is *Klebsiella ozaenae*,[293,294,302,303] albeit many other bacteria such as *Staphylococcus aureus* or *Pseudomonas aeruginosa* have also been isolated from nasal cultures.[293,296] 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).[299] Interestingly, there have also been case reports which suggest primary atrophic rhinitis may have a genetic inheritance pattern.[304]

V.B.13. Empty nose syndrome

Empty nose syndrome (ENS) is a rare and complex acquired upper airway disease. 'ENS' was coined nearly 3 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.[294,305-309] 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").[294,310,311]

ENS is linked to several inferior turbinate (IT) reduction approaches, such as total turbinectomy, IT trimming, and radiofrequency ablation.[311,312] Presentation can be immediate or delayed, secondary to over-aggressive IT reduction or suboptimal post-surgical healing and scarring, respectively.[306,313,314] While ENS is mostly associated with inferior turbinoplasty (ENS-IT), ENS from MT tissue loss (ENS-MT) has been reported.[307]

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.[315-320] 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.[321] Additionally, objective shifts in nasal airflow support a novel 'aberrant airflow' hypothesis.[322-324] 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.[313] 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 $\geq$ 11 indicates ENS.[310] 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.[325] A positive blinded cotton test both confirms the ENS diagnosis and informs candidacy for possible treatment interventions.[325]

ENS has historically been a challenging disease to effectively treat due to debilitating nasal symptoms and, in a minority of patients, concerning psychiatric overtones.[326-330] 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.[331,332]

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.[333] 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.[334-339] Importantly, a procedure originally reported by Houser,[308] 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.[340] IMAP has yielded statistically significant short[341] and long[342] 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,[343] 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[326,327] 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.[344,345]

Granulomatosis with polyangiitis (GPA). This 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.[346] It is a chronic, relapsing, and idiopathic disease characterized by necrotizing and granulomatous inflammation affecting predominantly small to medium sized blood vessels.[347] 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.[348] Recurrent serous otitis, mastoiditis causing hearing loss, and lower respiratory tract symptoms (e.g., cough, breathlessness, stridor, wheeze) occur in 80-90% of patients.[344,349] Additionally, renal (75% of patients), ocular (50% of patients), and systemic manifestations (e.g., fever, arthritis, weight loss) are also possible.[350]

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).[351,352]

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.[353]

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.[354] 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.[355] Diagnosis should be suspected in patients with asthma, increased peripheral-blood eosinophil count (>10%) and pulmonary infiltrates.[355] CRSwNP is present in approximately 50% of patients. Nasal crusting, purulent or bloody discharge can be present, but is less common than in GPA.[356] 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).[345,357]

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.[358] 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%).[345,347,359] 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).[360] Diagnosis is usually made by a lung (transbronchial), skin, minor salivary gland, or lymph node biopsy.[358]

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.[361] Biological therapy with anti-TNF agents has improved the therapeutic options in refractory organ-threatening sarcoidosis.[361]

Systemic lupus erythematosus. This is an autoimmune disease that predominantly affects women (10:1) with an incidence of 5.6 per 100,000 people.[362] Oral, nasal (nasal skin or vestibule), and pharyngeal mucosal lesions are seen in 9-18% of cases.[347,362] Diagnosis requires a detailed medical history, physical examination, and laboratory tests (ANA [antinuclear antibody] or anti-dsDNA [double stranded DNA]).[344,363]

Therapy with corticosteroids, immunomodulators (e.g., prasterone, vitamin D, hydroxychloroquine), or immunosuppressants (e.g., azathioprine, cyclophosphamide, mycophenolate) are 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.[364] Anifrolumab, an IFN-type 1 monoclonal antibody, has substantial evidence in effectively and safely treating moderate to severe active lupus.[365]

V.B.15. Rhinosinusitis

The symptoms of AR may overlap with those of rhinosinusitis.[366,367] 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.[173,366] AR and rhinosinusitis have several overlapping symptoms, namely rhinorrhea and nasal congestion, which can make it challenging to differentiate these conditions.[366,368,369] 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.[173,174,191,366,370] In ARS, nasal discharge is often unilateral and purulent.[173,191] Associated facial pressure and pain is described as moderate to severe.[191] Viral ARS is typically present for less than 10 days, whereas a longer duration of

illness suggests bacterial ARS.[173,191] Progressive worsening over a short period of time (i.e. 5 days) is also suggestive of bacterial ARS.[173,191] RARS is defined as at least 4 episodes of ARS per year.[173,191,370,371] 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.[173,174,191,366,370] 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.[173,174,191,370]

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.[368,369] 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.[173,191,366] AR symptoms are variable in duration and tend to have daily and/or local environmental fluctuations.[173,191,366] As a result, AR symptoms have been classified by duration (intermittent vs. persistent) and severity. AR symptoms, in general, present for at least 1 hour on most days; however, patients may have symptom-free intervals.[368,369] AR symptoms are also exacerbated by exposure to allergens in a time-dependent fashion.[368] The early reaction occurs immediately after exposure, lasting approximately 30 minutes (sneezing, nasal/ocular itching, rhinorrhea), while the late reaction occurs up to 6 hours after exposure (nasal obstruction and congestion).[368] 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.[368,369] The development of acute, unilateral, moderate to severe symptoms, and nasal purulence may be consistent with ARS or RARS.[173,191,366] 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.[173,191,366] 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.[173,366,367] *(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.[372] Septal deviations often have an asymmetry in airflow, with one side being more obstructed than the other.[373-375] Nasal valve collapse is often associated with obstruction on inspiration or during exercise.[372,373,376] 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.[377] The majority of these structural conditions should be evident on a physical examination including nasal endoscopy.

Sinonasal neoplasms often present with nasal obstruction.[378] The differential for sinonasal masses is extensive, including papillomas, hemangiomas, encephaloceles, osseous lesions, congenital masses, carcinomas, melanomas, and lymphomas.[372,375,378-380] 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.[378] When sinonasal neoplasms cause unilateral nasal obstruction, they can also be associated with unilateral rhinorrhea, which is more likely to be thick or mucopurulent.[378] Rarely, neoplasms can erode through the skull base and cause CSF rhinorrhea, discussed below.[381,382] The onset of symptoms in sinonasal neoplasms usually spans weeks to months with a progressive worsening of symptoms.[378] Associated symptoms including epistaxis, hypoesthesia, visual changes, epiphora, trismus, or dental changes should raise the clinical suspicion for a nasal mass versus AR.[378,383,384] 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.[378]

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.[385] Unlike AR, CSF rhinorrhea is most commonly unilateral and often reproducible with positional maneuvers.[385] 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.[279,386] Retained foreign bodies or rhinolithiasis can also cause nasal obstruction and rhinorrhea, though these are usually associated with unilateral symptoms and purulent nasal drainage.[279,387,388] Disorders which affect mucociliary clearance, including primary ciliary dyskinesia or cystic fibrosis can also lead to nasal obstruction and rhinorrhea.[389,390] 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.[373,389]

There is increasing evidence suggesting an association between reflux disease and sinonasal symptoms.[391] Reflux disease (gastroesophageal, laryngopharyngeal) has been associated with nasal congestion and postnasal drip.[392,393] 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.[391,393] Reflux symptoms may warrant treatment but whether this improves sinonasal symptoms or not is unclear.[391]

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.

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
Neoplastic	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	Unilateral rhinorrhea
	Retained foreign bodies	Positional rhinorrhea
	Rhinolithiasis	Purulent nasal drainage
	Primary ciliary dyskinesia	Systemic organ dysfunction
	Cystic fibrosis	Retrosternal burning
	Gastroesophageal reflux disease	Globus
	Laryngopharyngeal reflux disease	Dysphagia

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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.[1] 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.[1] 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.[2] FcεRIII is expressed by B cells and regulates IgE production and facilitates antigen processing and presentation.[3] 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.[4] 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.[3,5] This process is known as the early allergic response and is associated with vasodilation, edema, and bronchoconstriction.[3,5]

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.[6] Through conformational changes and tyrosine phosphorylation, Syk is activated.[7] 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.[8,9]

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.[10,11] Following stimulation of the FcεRI receptor, human mast cells have been demonstrated to upregulate 260 genes and downregulate 84 genes for up to 2 hours.[12] The upregulated genes include gene sets encoding cell surface molecules, cytokines/chemokines, signaling molecules, transcription factors, proteases, and other enzymes.[4] The downregulated genes include gene sets involved in signal transduction, apoptosis, cell proliferation, and genes encoding receptors.[13]

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)-kB, and early growth response (EGR)-2 function in FcεR1 upregulated gene expression.[14] Ultimately, this complex process of de novo gene transcription, and upregulation/down regulation of genes results in the production and release of cytokines and chemokines.[15] This includes IL-3, IL-4, IL-5, IL-13, C-C chemokine ligand-5 (CCL5), and granulocyte-macrophage colony stimulating factor (GM-CSF).[16-18] The effect of these cytokines and chemokines is the recruitment of inflammatory cells including eosinophils, basophils, neutrophils, macrophages, and T cells.[16-18] This is referred to as the late allergic response characterized by airway inflammation, hyperresponsiveness, airway remodeling, and mucus hypersecretion.[5]

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 interferon IFN-γ as its canonical cytokine.[19] 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, -5 and -13.[19,20] These ILs represent integral mediators responsible for driving IgE- and eosinophil-associated inflammation that often characterizes atopic disease.[19] 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 aero-allergens during allergic inflammation.[21-23]

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).[24,25] These mediators possess pro-inflammatory properties and have been shown to assist in initiating and maintaining a Th2 immune response.[26,27] 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.[28-31] 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 family is the most well-known.[32]

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.[20] Once exposed to antigen/allergen in the appropriate costimulatory environment, Th0 cells become activated and differentiate into allergen-specific Th2 cells. Th2 differentiation requires co-stimulation via the interaction of CD28 on T cells with CD80 and CD86 on antigen presenting cells and the presence of IL-4.[33,34] IL-4 binds STAT-6 on Th0 cells which activates the master switch GATA-3 (GATA-binding protein 3).[28] 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.[20,32] Class switching occurs via up-regulation 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 allergen-specific IgE (sIgE).[33] The end result is the creation of a pool of memory Th2 and B cells.[32] 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.[32] During IgE-mediated reactions, 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.[35,36] 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.[37,38] The classic example of systemic reactivity in AR is the cutaneous reaction elicited during traditional skin testing.[39] 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.[40-43] 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 nasal provocation test NPT and/or detection of nasal sIgE and/or positive basophil activation test (BAT) demonstrate a localized allergic response.[41,43-48]

Local IgE production has been demonstrated in patients with AR[49-52] and LAR.[53-62] In LAR, sIgE in nasal secretions has been confirmed after natural exposure,[54,55] after controlled exposure to aeroallergens by NPT,[55,57-59,63] and also during periods of non-exposure to aeroallergens.[54,55] 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.[64]

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.[42,53-65]

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.[61] As a result, serum IL-5 levels increase and IL-5 is

transported into the pulmonary circulation, causing increased exhaled nitric oxide and bronchial hyperreactivity.[60,62] Finally, in a study by Campo et al,[66] following NPT with nOle e 1 (the most significant allergen of *Olea europea*), 83% of LAR *Olea 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.[49,67] 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.[67] 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.[68]

Studies report LAR prevalence is approximately 26% in Mediterranean countries (Portugal, Spain, Italy and Greece)[69] and 7-10% in Asian countries (China and Korea).[70-72] LAR may affect approximately 47% of children previously classified as non-allergic rhinitis.[42,63,65,73,74] Exposure to environmental factors such as temperature, humidity and pollution are associated with higher incidence of LAR.[65,75] There is a low rate of conversion (~3%) to systemic detection of allergen sensitivity, development of asthma, and worsening clinical progression is rarely seen.[47,75-78]

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

AR is thought of as mainly an IgE-driven response.[79] 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.[80]

The pathophysiological mechanisms of inflammatory airway diseases are associated with large biological networks involving the environment and the host.[81] 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.[82,83] This may also occur with irritants like chlorine[84] and air pollution.[85] Epithelial barrier dysfunction has been shown to contribute to the development of inflammatory diseases including AR.[86] However, additional research is needed to determine the extent to which primary (genetic) versus secondary (inflammatory) mechanisms drive barrier dysfunction.[87] *(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 pattern recognition receptors called toll-like receptors (TLRs).[81,88,89] 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.[90-92] 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.[93]

Allergen challenge in AR subjects induces increased numbers of peripheral blood ILC2s[94,95] and results in and influx of ILC2 in the nasal mucosa.[96] Pre-treatment with INCS attenuates allergen-induced increases in ILC2s in the nasal mucosa of AR patients.[97] ILC2s also contribute to epithelial barrier leakiness through IL-13.[98] Treatment with anti-IL13 has shown significant reduction of AR symptoms,[99] 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.[100] 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.[81]

VI.C. Cellular inflammatory infiltrates

Various types of inflammation are involved at different AR stages, including sensitization, exacerbations, remodelling and remission. Different mediators orchestrate a type 2 immune response.[101] Most commonly a type 2 inflammatory environment is observed with Th2 cells, M2 macrophages, eosinophils and type 2 ILCs playing important roles.[102] 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.[103,104] As it is virtually impossible to define one inflammatory pattern, endotyping in AR seems highly important to drive personalized medicine.[105]

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.[106] In the induction of a type 2 response, IL-25 acts on Th2 cells and ILC2s while TSLP mainly activates dendritic cells.[101]

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[107] and loaded with sIgE contributing to atopy, while elimination of dendritic cells suppresses AR.[108] Dendritic cells are crucial in the initiation of a Th2 response, while basophils will merely amplify it.[109] Myeloic dendritic cells may activate ILC2s and plasmacytoid dendritic cells play important roles in AR through IL-2 and IL-6 pathway alterations.[110]

Innate and effector mechanisms affect allergic disease.[111] A skew towards Th2 with GATA-3 overexpression are hallmark findings in AR mucosa.[112,113] Tissue γ/δ-T cells and CD4+ memory T cells are increased.[114] 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.[101,115-118]

Distinct phenotypes of regulatory T cells (Treg) subsets include $CD4^{+}CD25^{+}$ Forkhead-box P3 (FOXP3)+ Tregs and type 1 Tregs.[119-121] 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.[122-124] 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.[125,126] Increased levels of CD4+T cells were identified in AR patients' blood with reduced CXCR3 expression.[127]

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 more in remodeling. ILC2s closely interact with epithelial cells and others leading to a

type 2 favoring cytokine environment.[128] 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.[129] However, B cells and plasma cells also produce IgE locally which is becoming a hallmark finding of AR.[130] In AR, numbers of circulating memory B cells were found to be increased.[131]

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.[132]

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.[133,134] Basophils accumulate within one hour after allergen provocation in the lamina propria.[135]

Adhesion molecules are upregulated and chemoattractants facilitate the influx of inflammatory cells during the late phase.[136] This allows for further accumulation of cells promoting remodelling with upregulation of matrix metalloproteinases and angiogenic factors.[137]

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.[138-140] 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.[141] TSLP is a critical upstream cytokine for ILC2s, mast cells, dendritic cells, T cells, and basophils.[142-144] 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.[145] Nasal epithelial cells are also a source for IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α, and through these signals, play a role in the migration and activation of eosinophils, basophils, and Th2 cells.[146]

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.[110,145,147] 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.[102] Both TL1A and GITRL are responsible for ILC2 proliferation and the release of type 2 cytokines from these cells.[148] IL-2, IL-7, and IL-9 are regulatory factors necessary for the development, maintenance, and survival of ILC2s.[148] IL-2 activates ILC2s and induces them to secrete IL-9, which is also critical for maintaining the activity and survival of ICL2s.[90,149,150]

Airway mast cells are a source of type 2 cytokines, proinflammatory cytokines, chemokines and TSLP.[138,151-153] 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.[154] 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.[139] 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 up-regulate eosinophil chemoattractants including eotaxin, macrophage/monocyte chemotactic protein 4, RANTES (regulated upon activation, normal T cell expressed and presumably secreted) , and cysteinyl leukotrienes.[155-157] 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.[158,159]

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-IL-17f.[160] Currently, it is understood that IL-17a and IL-17f play

roles in allergic-type inflammation.[160] 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.[126] A recent systematic review by Hofmann et al[126] 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 Th-17 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.[161] 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.[162] 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.[163] Inflammatory mediators (e.g. bradykinin, histamine, acetylcholine, capsaicin) are capable of activating sensory neurons in the trigeminal nerve, largely through transient receptor potential (TRP) ion channels.[164-167] 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[166,168] Studies investigating treatment with intranasal capsaicin, the prototypic ligand for TRPV1, have demonstrated significant improvement in nasal congestion, sinus pressure, pain and headache within five minutes after administration in patients with non-allergic and mixed rhinitis but not clearly in AR.[169] 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.[164,165]

Depolarization of these nociceptive channels on sensory nerves leads to the release of neuropeptides including substance P, calcitonin gene-related peptide (CGRP), and neurokinin-A.[165] 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.[163,167,168] 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.[168,170,171] Substance P and CGRP also activate mast cells to release more inflammatory mediators, such as histamine, that further propagate the hypersensitivity reaction.[166] 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.[163,165,168] Understanding these biologic pathways has led to investigation of novel therapies including bradykinin antagonists and TRP receptor calcium ion channel blockers.[168]

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.[167,168] Sympathetic nerves respond to neurokinin Y leading to vasoconstriction and nasal decongestion.[168] 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.[172]

The neuropeptides previously discussed are significantly increased in nasal lavage of AR patients compared to controls.[170,173] 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.[170] 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.[173-176] Unfortunately, clinical trials investigating neuropeptide and TRP antagonists in seasonal AR have been unsuccessful this far.[177-179]

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.[180-182] 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.[117] 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.[183] Overlying the sinonasal epithelium is a mucus blanket, which consists of water, mucin glycoproteins and antimicrobial peptides such as lactoferrin, lysozyme and defensins.[184] 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.[32,185] 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.[186] This inflammatory response translates into mucosal edema, increased mucosal secretions and hyper-responsiveness 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.[187] 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.[188] 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.[189]

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.[190] Mucin production, regulated by the mucin genes MUC5AC and MUC5B in particular, is upregulated by

allergens.[191] 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.[192] 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.[86] Impairment of ZO proteins are observed in AR patients and dysfunction of ZOs allows allergens to pass into the subepithelium.[193] This may also be mediated by various factors such as histone deacetylase activity[194] and deficiency of the MUC1 gene.[195] Some allergens, such as Der p 1 in HDM, have protease activity and can directly compromise the epithelial barrier.[25] 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.[196] 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), and leading to viscous secretions and impairment of mucocilliary clearance.[197] Microbial derived short chain fatty acids also impact the epithelial barrier. Sodium butyrate leads to blocking of histone deacetylase, restoring defective TJs.[198] Synthetic histone deacetylase inhibitors show strong antiallergic effects in a HDM-sensitized mouse model.[194]

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.[86,115] Disruption of

different parts of the TJs in AR have 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 labelled small molecule (fluorescein isothiocyanate [FITC])-dextran assays. Pollen peptidases and Der p 1 were shown to actively disrupt the epithelial barrier specifically at the level of TJs.[199,200] 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.

AR derived nasal secretions and histamine are strong disruptors of the epithelial barrier function.[201] 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.[202] 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.[203] TSLP seems to play an important role in AR; interestingly it increases TJ proteins thus preserving the epithelial barrier.[204] Finally, epithelial to mesenchymal transition has been shown to occur in type 2 CRS affecting the barrier function of the epithelium.[205] Similar findings are expected to occur in AR.[206]

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.[206] The cause and consequence of a defective epithelial barrier in AR remains open for additional research.

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

Reference	Mediator	Affected protein	Function	Type of dysregulation
Steelant et al[201]	IL-4	Occludin	TJ protein	Downregulation
Steelant et al[201]	IL-4	ZO-1	Adaptor protein	Downregulation
Steelant et al[201]	IL-13	Occludin	TJ protein	Downregulation
Steelant et al[201]	IL-13	ZO-1	Adaptor protein	Downregulation
Wang et al[198] Steelant et al[194] Wawrzyniak et al[207]	HDAC	Occludin Claudin-4, -7 ZO-1	TJ protein	Increased in AR Decrease in TJ
Ohwada et al[202]	HMGB-1	Angulin1/LSR	TJ protein	Downregulation

Steelant et al[201]	Nasal secretions from AR patients	unknown	unknown	TER decrease
Henriquez et al[200]	HDM	Claudin-1 JAM-A	TJ protein	Downregulation
Runswick et al[199]	Pollen	Occludin ZO-1 Claudin-1	TJ protein	Disruption
Steelant et al[201]	Histamine	unknown	unknown	TER decrease
Fukuoka et al[203]	Particulate matter 2.5	ZO-1	TJ protein	Downregulation
Nur Husna et al[208]	Second-hand smoke	Claudin-7 Occludin	TJ protein	Downregulation
Kamekura et al[204]	TSLP	Claudin-1,4,7 Occludin	TJ protein	Upregulation

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

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-alpha hydroxylase. VD3 is obtained from two distinct sources, diet and ultraviolet-mediated synthesis in the epidermal layer of the skin.[209] 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.[210] VDRs are present in several organ systems including bone, skin, intestines, kidneys, brain, eyes, heart, pancreas and immune cells.[211] 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.[209] 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.[212] 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.[213-215]

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.[216,217] 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).[218] 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.[219] 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.[220] 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.[221,222] However, a recent systematic review concluded that there is insufficient evidence to support VD3 supplementation for AR prevention.[220] 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 nitric oxide (NO) production in human airways, and AR is characterized by increased release of NO.[223-228] NO plays several important roles in the maintenance of physiological homeostasis and regulation of airway inflammation[229,230] through the

expression of three isoforms: neuronal NO synthase (nNOS), endothelial NO synthase (eNOS), and inducible NO synthase (iNOS).[231]

NO is a key molecular player in the primary host defense and its cytotoxic effects are essential to prevent pathogen infection.[232-235] However, the bacteriostatic or bactericidal effects of NO may be species-specific.[236] Recent studies demonstrated that bactericidal activities could elicit bitter taste receptor-activated downstream responses, enhancing the production of NO.[237-239] NO has also shown antiviral effects against DNA and RNA viruses, including SARS-CoV-2, by partially inhibiting virus replication.[240-242] Moreover, NO is an important modulator of epithelial ciliary beating-important for the clearance of pathogens-through activation of the sGC-GMPc-PKG pathway.[243-246] Based on these findings, NO plays a protective role against a variety of microbial infections[232,247-251] and has been considered an important mediator in pathophysiological events underlying inflammatory airway responses.[252,253]

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.[254,255] The function of T cell mediated immunity can be regulated by endogenous NO at various concentrations.[256-258] NO secreted by activated dendritic cells plays a complicated role in restricting T cell activity, by inducing dendritic cell stimulatory capacity on T cells.[259-264] 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[265-269] 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,[270-272] whereas type 2 cell proliferation can be induced by higher NO concentrations.[256,273-276] 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.[270,271] 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.[277] NO increases IL-8 expression in airway epithelial cells, which may be important to initiate an inflammatory response in the airway epithelium.[278,279] In addition, the IL-33–ST2 axis is believed to control Th2 and Th17 immune responses in allergic airway diseases,[280] and the balance between oxidative stress and antioxidant responses plays a key role in controlling IL-33 release in airway epithelium.[281]

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 – Nitric Oxide for additional information on this topic.)*

VI.J. Microbiome

Humans are colonized by an estimated 100 trillion microorganisms.[282] 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.[283-286] 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.[287-292] However, differing methodologies, sample sizes, and culture techniques used in each study made it difficult to interpret results and draw conclusions.[293] 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[294] 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[295] in a smaller

patient series and by Hua et al[296] 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.[294] In a mouse model studying the effect of intranasal sodium butyrate in AR, Wang et al[198] 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.[297] In a study comparing the nasal microbiome of patients with AR, CRS, and a control group, Gan et al[298] 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[299] 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[298] 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[294] were not always consistent with those found in reports with children.[300] 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.[301] 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.[302] 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.G. 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.[303] Inflammation in either the upper or lower airway influences the other, giving rise to the concept of united airway disease.[303,304] As the development of biological treatments options progresses, understanding the unified airway system has been recently underscored.[305,306]

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.[307] Indeed, evidence has uncovered the association between AR and asthma, as well as between CRS and asthma.[307-309] 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.[303] Interestingly, both AR and asthma have similar hyperreactivity, further solidifying the concept a unified response between the upper and lower airways.[310-312]

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.[79,93,313-315] In general, the type 2 profile in AR and asthma is related to a good response to corticosteroids.[316] However, systemic corticosteroids carry serious adverse effects and side effects which generally outweigh the benefits especially in the upper airways.[317,318] 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.[305] 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.[319,320]

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.[321-325] *(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.[326] Most convincingly, AR may result in nasal blockage and the preference for oral breathing, which is associated with asthma.[327] 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.[328] 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-labelled allergen deposited in the upper airway it is not detected in the lower airway.[329] Instead, stimulation of pharyngolaryngeal receptors has been suggested as the more likely cause of a postnasal drip-related cough.[328] 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.[328]

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.[330-332] 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.[333] 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.[332] 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[333] and can be inhibited by local corticosteroids in rhinitis patients.[334] 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.[305,335] 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.

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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 all recognized and adopted a more standardized definition and methodology for diagnosing AR in a given population.[1-3] 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%.[4,5]

As noted in ICAR-Allergic Rhinitis 2018,[6] 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 2008-2012 (35.02% according to questionnaire responses and ARIA guidelines; 14.89% when "diagnosed with AR by a medical doctor").[7] 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 2008-2012 (current AR, 35.02%; AR based on allergy tests: 17.56%).[7-9] Identification of AR according to ICD codes from databases generally yielded lower estimates for AR (German AOK Saxony database study, 6.2%).[10] 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 study, an expansion of the Tromsø Study (current AR, 26.0%; ever AR, 28.9%).[11-13]

Additionally, age ranges of given study samples may also capture subjects at different stages of the putative atopic march.[14] KNHANES identified a falling AR prevalence from 21.1% in 20- to 29-year-olds, to 5.4% in over 60-year-olds.[15] 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.[16,17] 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.[18] 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;[19] another study comprising randomly selected ECRHS subjects has estimated that prevalence for AR has changed from 19.7% in 1990-94, to 23.1% in 1999-2001, to 24.7% in 2010-2012, with an overall change of 5.1%.[20] In contrast, in Brazil the prevalence of ever having hay fever in adults decreased from 52.0% in 2011 to 43.3% in 2018.[5]

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 5-50%.

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.[21] 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%.[22] Kulig et al,[23] 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.[24]

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.[25-28] The average prevalence of AR across all centers included was 8.5% for 6-7-year-olds and 14.6% in 13-14-year-olds.[25] In the 6-7-year age group, a lower current symptom prevalence was observed in the Indian subcontinent (4.2%) and 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% to 35.4% in children over 10 years of age), and Ecuador (48% in 3-5-year-olds).[29-34] 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.[35,36]

The regional variations in reported AR prevalence highlight some limitations in questionnaire-based, "open" studies of AR prevalence.[37] Many of these studies might be over- or underestimating prevalence of AR because of disparities in responder education and researcher definitions of AR.[38] Also, one must consider differences accounted for by measuring point prevalence and lifetime prevalence of AR. Pols et al[39] 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[40] in the Isle of Wright 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[41] 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.[42] 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 et al,[43] 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,[44] 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.[45,46] 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.[47]

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.[48] Climate change has been estimated to be associated with increased seasonal pollen exposures, and as a result, sensitizations are anticipated to be more than double in the next few decades, particularly in colder climates that previously were spared from higher rates of seasonal AR.[49] 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.[50,51]

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.[52-55] Li et al[53] 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.[52]

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.[43,53] 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.[56] Latitude may also be 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.[48]

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.[51,57]

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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.[1] Studies on twins have shown that genetic factors account for up to 70-80% of interindividual variability in susceptibility to development of AR.[2,3] 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.

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,[4-8] as well as with asthma,[5,9] eczema,[6,10] and other allergy-related co-morbidities.[4,9,11] LRRC32 is known to regulate T cell proliferation, cytokine secretion and TGF-β activation.[12] 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 ($p<5x10^{-8}$; *TLR*-locus top hit).[5] Strong overlap between top loci for sensitization and self-reported allergies also are found in two of the larger GWASs.[5,13] 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.[14] In a follow-up study, additional novel loci for comorbid allergic disease were identified by applying a gene-based test of association.[15] 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.[16]

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*.[7,8] 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.[8]

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 well-replicated genes, as summarized previously.[17-19] 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.[17-23] However, many of the candidate gene study findings have not been well-replicated across studies and populations.[24,25] This could be due to lack of power from small sample sizes, inconsistent phenotype definition, or lack of true disease association.

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,[26] air pollution exposure,[27] and length of pregnancy.[28] 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[29-31] and IgE-related outcomes.[32,33] Recently, methylation signatures in nasal epithelial brushes were shown to be strongly associated with AR (and also asthma).[34] Also, epigenetic studies have highlighted shared molecular mechanisms underlying asthma, eczema and AR pathophysiology.[35]

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.

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**)

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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[36]	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[6]	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[5]	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[4]	2014	Meta-analysis of four cohorts/data sets	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
Bunyavanich et al[37]	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[8]	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	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:	Known loci: 1) *HLA-DQB1, HLA-DQA1* 2) *IL1RL1* 3) *TLR1, TLR10* 4) *CAMK4, WDR36* 5) *LRRC32, C11orf30* Novel loci: 1) *CAPSL, IL7R*	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	3

					in total): 1) rs7717955 2) rs63406760 3) rs28361986 4) rs2070902 5) rs1504215	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	2) *CDK2AP1, C12orf65* 3) *CXCR5, DDX6* 4) *AL590714.1, FCER1G* 5) *BACH2, GJA10*	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	
Johansson et al[7]	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 × 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[38]	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[16]	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

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

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[39]) concur with the conclusion that there is no established association of early mite exposure and the development of AR.[40-42] 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.[43] Likewise, other studies implement dust mite reduction interventions without pre and post dust mite allergen measurements and/or combine environmental changes with dietary changes.[44-46] **[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.[47-51] Exposure levels that are less than 2mg dust mite allergen/gram of house dust may be a "safe" level for atopic children for primary allergic disease prevention.[52,53] The risk of allergic disease in childhood may also depend upon mono- vs polysensitization at age 1 or 2.[54]

Aggregate grade of evidence: C (Level 3: 7 studies; **TABLE VIII.B.1.a.**)

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*
Schoos et al[55]	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[56]	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[42]	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[40]	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[57]	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 vs nonatopic CRC -In univariate analysis there was protective factor for current CRC (OR 0.81; 95% CI 0.68-0.98)
Marks et al[41]	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)
Kuling et al[58]	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)

LOE=level of evidence; COPSAC=Copenhagen Prospective Study on Asthma in Childhood; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval; PAULA=Perinatal Asthma and Environment Long-term Allergy; PIAMA=Prevention and Incidence of Asthma and Mite Allergy; MAAS = Manchester Asthma and Allergy Study; CRC=chronic rhinitis conjunctivitis; RR=relative risk
*ORs are unadjusted and reported with 95% CI

VIII.B.1.b. Pollen

Since ICAR-Allergic Rhinitis 2018,[39] 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.[59,60] While very few 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.[61,62] [62] In fact, following initial pollen sensitization in children, there is a progressive increase in both the level and number of pollen sensitizations.[63] 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.[61,64,65] 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.[66] **[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.[67] 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.[68] 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 component resolved diagnosis in early childhood may prove to be the best tool for predicting pollen-induced AR in adolescence and adulthood.

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

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions*
Erbas et al[59]	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[a] during infancy (0-3 months)	Risk factor for hay fever (OR 1.14; 95% CI 1.001-1.29)
Kihlstrom et al[60]	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)

LOE=level of evidence; MACS=Melbourne Atopy Cohort Study; RCT=randomized controlled trial; OR=odds ratio; CI=confidence interval

*ORs are adjusted and reported with 95% CI

[a]Defined as birth "inside" or "outside" the pollen season and by measuring daily 24-hour average pollen concentrations for grass and others (which include trees, weeds,and herbs).

VIII.B.1.c. Animal dander

Since the ICAR-Allergic Rhinitis 2018,[39] high quality studies have found that early life exposure to animal dander may be protective from the development of AR,[69-71] while two lower quality studies concluded that it was a risk factor.[72,73] A 2020 systematic review and pooled analysis of 5 cohort studies found a protective effect for early life exposure to cats and dogs.[69] Two additional prospective birth cohorts found a similar protective effect.[70,71] Animal exposure during the first two years of life offers the best possibility for protection.[54,70,71,74] 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; child's microbiome).[75] 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.[76] At this time, it is not possible to make evidence-based recommendations regarding early life animal exposure. **[TABLE VIII.B.1.c.]**

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.

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions*
Early exposure to animal dander as a protective factor for AR (Level 3 studies listed. Level 4 studies referenced.[77-82])						
Gao et al[69]	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[70]	2020	3	Prospective birth cohort	3782 children (5 years old)	Exposure at home to cats or dog or visit to building housing farm	-Dogs: protective factor for AR (OR 0.72; 95% CI 0.53-0.97) -Exposure to cats and farm animals non-significant

					animals during first year of life	
Al-Tamprouri et al[71]	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 (aORs 0.82; 95% CI 0.47-1.45, p=0.503)
Lodge et al[54]	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[74]	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[83]	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[84] §	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)
Nafstad et al[85] §	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.[72,73,82,86-94])						
Early exposure to animal dander is not associated with AR (Level 3 studies listed. Level 4 studies referenced.[86,88,90,95-101])						
Schoos et al[55]	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	-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

					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)	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[56]	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[102]	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[103]	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[83]	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[76]	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)
Chen et al[104] §	2008	3	Prospective birth cohorts	2355 children (6 years old) from GINI (intervention & 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[105]	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[57] §	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[58]	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)

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

§ Part of GAO meta-analysis

*All ORs are adjusted unless differently specified and are reported with 95% CI

VIII.B.1.d. Fungal allergens

Further supporting the ICAR-Allergic Rhinitis 2018[39] 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.[106-108] 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.[109,110] 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.[109] 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.]**

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

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*
Early exposure to fungal allergens as a risk factor for AR						
Behbod et al[107]	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[106]	2011	3	Meta-analysis of 6 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[108]	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[111]	2016	4	Cross-sectional	2598 children (3-6 years old) attending kindergarten	Prenatal (whole pregnancy) or postnatal (from birth	Risk factors for rhinitis-like current symptoms: prenatal

					to current) exposure to indoor mold/dampness	(OR 1.5; 95% CI 1.2-1.9); postnatal (OR 2.1; 95% CI 1.6-2.8)
Lin et al[112]	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[100]	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)
Kim et al[99]	2012	4	Cross-sectional	4554 schoolchildren (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[88]	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[89]	2007	4	Cross-sectional	3360 schoolchildren (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[113]	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[114]	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[115]	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[111]	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[93]	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[116]	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 $\geq$0.2 m^2 or a combined area of visible mold and water damage on	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)

					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)	

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

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,[69,109,117,118] 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,[39] 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.[119-124] Older publications (not part of ICAR-Allergic Rhinitis 2018) have looked at the effect of fish and tree nuts in the maternal diet[125-127] and early introduction of specific or diverse foods into the infant's diet.[128-131] **[TABLE VIII.B.2.]**

A maternal diet that avoids or strictly limits highly allergenic foods, e.g., cow's milk, egg, peanut, and fish has not been shown to reduce the risk of AR.[126,132-134] However, a maternal diet high in oily fish or tree nuts has been reported to reduce the risk of AR.[125,135]

Early sensitization to food has been linked to the development of AR in childhood.[58,136,137] A meta-analysis of high-risk infants found that food sensitization at age less than 24 months increased the risk of AR during childhood.[136] 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.[121] 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.[137-141]

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.[132] In an open label RCT, there was no association of avoiding or consuming peanuts from 4-11 months on the risk of developing AR at age 5 years.[120]

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.[119] Three additional prospective birth cohort studies support this conclusion.[123,130,131] 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.[130] However, there are conflicting conclusions regarding the timing of introduction of complementary foods and risk for AR.[142,143]

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.[144] Food diversity has been reported to increase,[124] decrease,[128] decrease if there are concurrent skin symptoms,[124] or have no effect[129] 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.[145-148] Furthermore, it is recommended that complementary foods be 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.[145] Guidelines have not made recommendation on the early introduction into the infant's diet of any specific foods to prevent the development of AR.

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

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[120]	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[136]	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[119]	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 [I2=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 & Heller[132]	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[133]	1989	2	RCT	163 infants (18 months old) of high-risk mothers -79 mothers with egg and	Maternal diet very low in egg and milk during last 3 months of pregnancy	No association with the development of AR at 18 months

				milk restricted diet -83 daily ingestion of one egg and 11 oz milk		
Falth-Magnusson & Kjellmanl[134]	1987	2	RCT	212 infants (18 months 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
Ekelund et al[143]	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[121]	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[123]	2019	3	Prospective birth cohort	2245 children (6 years old)	Effect of early introduction of fish into infant's diet	Earlier vs. 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[124]	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[128]	2014	3	Prospective birth cohort	442 high risk children (6 years old)	Effect on 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)
Roduit et al[129]	2014	3	Prospective birth cohort	848 children (6 years old)	Effect on 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[126]	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[130]	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) -Note: study also included in Ierodiakonou et al[119] systematic review -Introduction of egg <11 months associated with reduced risk of AR (OR 0.72; 95% CI 0.55-0.94)
Maslova et al[125]	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	-Maternal tree nut ingestion associated with reduced risk for self-reported AR at age

					peanuts/pistachios/week from mid-pregnancy to delivery	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[131]	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 6-8.5 months associated with a dose dependent reduced risk of AR at age 5 (6 months: HR 0.34; 95% CI 0.22-0.54) (6-8.6 months: HR 0.28; 95% CI 0.57-0.70)
Zutavern et al[142]	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[135]	2007	3	Longitudinal birth cohort	1253 children (5 years old)	Maternal intake of oily fish ≥ 1x/week vs. 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)

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

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".[149] 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 microns (PM_{10}) and PM <2.5 microns ($PM_{2.5}$). The effect of air pollution on human morbidity is well-known, though the relationship with AR is complex.[39,150,151] 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.[152,153]

At the time of ICAR-Allergic Rhinitis 2018,[39] the strongest evidence in the literature suggested minimal or no significant associations between air pollutants and AR development.[154-159] Kim et al[160] found that the incidence of AR was not significantly associated with exposure to air pollutants, while Codispoti et al[161]

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.[162]

In more recent years, the interest in understanding a potential relationship between air pollution and AR has further increased. Li et al[163] reported a positive association between air pollution and AR while Burte et al[164] 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[165] 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.[166] A meta-analysis by Zou et al[167] 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 a SRMA by Lin et al[168] who reported that $PM_{2.5}$ exposure may be correlated with childhood AR. Hao et al[169] 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.[170-172] In a controlled allergen challenge facility study by Ellis et al,[173] 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 6 European countries.[174] 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.[175]

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.

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

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[163]*	2022	3	SRMA, cross-sectional & 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[168]**	2021	3	SRMA, cross-sectional & 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[166]	2020	3	Prospective cohort	Exposure to oxidant air pollutants: -High exposure -Low exposure	Diagnosis AR, birth through adolescence	Oxidant air pollutants, specifically O_3 and NO_2, associated with an 8% increased risk of AR
Zou et al[167]***	2018	3	Meta-analysis, cross-sectional & 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[165]	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[161]	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[162]	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[160]	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[169]	2021	4	Case-control	Exposure to PM_{10} and NO_2 in	Diagnosis or parent-	Early exposure to PM_{10} and NO_2 among

				males with or without family stress: -High exposure -Low exposure	reported symptoms of AR at age 2-4 years	young boys with family stress may increase risk of AR
Singh et al[156]	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
Chiang et al[155]	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[159]	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[157]	2015	4	Cross-sectional	Traffic-related air pollution exposure within 200m 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, 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[158]	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[154]	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; PM=particulate matter; AR=allergic rhinitis; DEP=diesel exhaust particles

*The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Kim et al,[160] Chung et al,[176] Deng et al,[111] Liu et al,[177] Wang et al.[178]
**The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Chung et al,[176] Deng et al,[111] Liu et al,[177] Kim et al.[179]
***The following individual studies from ICAR 2018 are included in this meta-analysis: Chung et al,[176] Deng et al,[111] Liu et al,[177] Wang et al,[178] Kim et al.[179]

VIII.B.4. Tobacco smoke

Most prospective cohort studies and systematic reviews presented in ICAR-Allergic Rhinitis 2018[39] have found no correlation between active or passive tobacco smoke and AR.[180-183] One study suggested that tobacco smoke may have a protective effect against the development of AR.[184] 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.[185] 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.[186] Conversely, nicotine has been shown to suppress type 2 responses to allergens, effectively acting as an immunosuppressant.[187]

Since the last ICAR-Allergic Rhinitis 2018,[39] two large meta-analyses have investigated the impact of tobacco smoke on AR.[188,189] Skaaby et al[188] 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[189] 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,[190] including 5 European birth cohort studies and 10,080 participants followed from

pregnancy to 14 to 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[191] 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[192] 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 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.[193] Future research should focus on understanding the effects of these new products on a mechanistic level.

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.

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

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

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions

Zhou et al[189]	2021	2	SR, case-control & 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[190]	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[188]	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[191]	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[193]	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[192]	2018	4	Cross-sectional	Patients with AR	Asthma risk	-Cluster including smoking, among other factors, is associated with asthma risk

LOE=level of evidence; SR=systematic review; AR=allergic rhinitis; SNP=single nucleotide polymorphism; sIgE=allergen specific IgE

*Studies included in systematic reviews and meta-analyses are not listed separately in the evidence table

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.[194] 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).[195] *(See Section VIII.G.3. Hygiene Hypothesis for additional information on this topic.)* As an example, Wee et al[196] 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.[197-200] 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).[199]

Chen et al[201] 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[202] 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[203] 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,[204] 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.[205] Similarly, Lewis et al[206] 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[207] 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[65] 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[208] 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.

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

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[196]	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[208]	2016	2	Cross-sectional	Children & 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[209]	2016	2	Cross-sectional	Children (n=75,643), South Korea	Prevalence of AR	Greater affluence and education increased risk of AR
Li et al[202]	2011	2	Cross-sectional	Children (n=23,791), China	Prevalence of AR	Parental education, income predicts increased AR prevalence
Braback et al[210]	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[204]	2004	2	Cross-sectional	Children (n=4947)	Prevalence of AR symptoms	Education associated with AR
Chen et al[201]	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
Grabenhenrich et al[65]	2016	3	Prospective cohort	Children (n=941), Germany	Prevalence of AR	Parental income and education had no association with AR development
Penaranda et al[211]	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
Hammer-Helmich et al[203]	2014	3	Cross-sectional	Children (n=9,720), 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[199]	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[207]	2005	3	Prospective cohort	Children (n=4089 families), Sweden	Prevalence of AR at 4 years	Higher SES decreases risk of AR
Lewis et al[206]	2001	3	Cross-sectional	Adults (n=458), North America	Prevalence of allergen sensitivities	Sensitivity is associated with lower income and education level
Bergmann et al[212]	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 & Britton[213]	1998	3	Prospective cohort	Children (n=6000), British Isles	Prevalence of AR symptoms	Social advantage independently predicts risk of AR
Goh et al[214]	1996	3	Cross-sectional	Children (n=6238), Singapore	Prevalence of AR	Higher SES associated with better housing and higher household income
Talay et al[205]	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

LOE=level of evidence; AR=allergic rhinitis; IgE=immunoglobulin E; SES=socioeconomic status; US=United States

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 advise exclusive breastfeeding for 4-6 months.[215,216] 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.[39] 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.[217,218] 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.[219] 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.[220] The only statistically significant association was found by Codispoti et al,[221] noting that longer duration of breastfeeding was associated with a lower risk of AR in 3-year-old African Americans (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.[220] **[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 (odds ratio [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.[222] 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.[215] A recent cohort study of children with AR compared to

non-AR 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).[223] 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).[224]

These inconsistencies in studies, which are mainly observational surveys, can possibly be influenced by demographic, socioeconomic, educational, ethnic, cultural, psychological status, and study design.[223,225,226] 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.[227] Furthermore, differences in methodological factors such 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.

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.

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

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hoang et al[219]	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[220]	2019	2	Systematic Review	1 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[143]	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[223]	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[224]	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[215]	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 a[222]l	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized controlled trial; PACT = Prevention of Allergy among Children in Trondheim; ARCO= Allergic Rhinitis Cohort; IoW=Isle of Wight; FAIR=Food Allergy and Intolerance Research; CCHH= China, Children, Homes, Health
*The systematic reviews in this table are appropriately inclusive of previously published studies on this topic.

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 recommendation of guidelines for AR in relation to childhood pet exposure remains conflicting.[39,228,229] 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.[39]

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.[69] 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).[77] **[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.[70] Additional studies support the finding that exposure to pets during childhood reduces the risk of AR.[230,231] 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.[69,232]

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.[73] 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.[233] 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.[69,234-236]

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.

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 A R.
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 p rovided based on current evidence.

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

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dharmage et al[236]	2012	2	Systematic review	19 studies: 9 longitudinal, 8 cross-sectional, 2 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[69]	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[70]	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 & Wu[73]	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[233]	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

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

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.[237] 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.[238] 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.[239,240]

A SRMA was conducted to determine the effect of the number of siblings on AR development; this analysis assessed 53 studies with 300,062 participants.[241] 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 years and 13-14 years also saw an inverse association between the number of siblings and AR but only in affluent countries.[242] **[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.[243-253] In a recent meta-analysis by Campbell et al,[243] 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.[244] While an isolated exposure to bacterial endotoxin was claimed to have a similar protective effect, the results thus far have been inconclusive.[254,255]

Increased diversity in the gut and skin microbiome has been associated with a protective effect on atopy.[239,256-261] 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.[239,262,263] Notwithstanding this, a meta-analysis of 29 trials did not find supplementation of probiotics to pregnant mothers or infants beneficial in preventing atopy.[264] 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.[259] 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.[265-267] Interestingly, in a meta-analysis of 21 studies assessing the association between *H. pylori* infection and allergic diseases, 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.[267]

Lower biodiversity on the skin and in the home living environment is associated with an increased risk of atopy.[260] Ruokolainen et al[268] 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.)*

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.**)

TABLE VIII.C.3. Literature summary – Protective factors against development of allergic rhinitis: hygiene hypothesis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Campbell et al[243]	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[264]	2015	1	SRMA	29 RCTs in infants	Association of AR with probiotic supplementation to pregnant mothers, breast-feeding women, or infants	No effect on allergies
Lionetti et al[267]	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 & Botezan[241]	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 vs. no siblings	-Higher number of siblings was associated with less atopy -Effect was not explained by hygiene factors
House et al[244]	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[268]	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
Fujimura et al[258]	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[259]	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[257]	2015	3	Nested case-control	319 children followed from	Association of sensitization and wheezing at 1 year	Suggests that reduced colonization of *Faecalibacterium*,

				birth until 5 years of age	with fecal microbiota at age 3 months and 1 year	*Lachnospira*, *Veillonella* and *Rothia* during the first 3 months of life may increase the risk of atopic asthma
Strachan et al[242]	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 vs. 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[269]	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[265]	2012	3	Prospective cohort	545 Dutch children	Association between *H. pylori* and AR	No association between *H. pylori* and AR
Bisgaard et al[239]	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[270]	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[255]	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
von Hertzen et al[271]	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[266]	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[256]	2014	4	Case-control	47 infants (20 with IgE-associated eczema and 27 healthy	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

				controls) followed until 7 years of age		
Sjogren et al[262]	2009	4	Prospective cohort	47 Swedish infants followed up to five 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 & Martinez[254]	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[263]	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

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

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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.[1-6] 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.[7] As this has become more accepted, use of general health related QOL metrics such as Short Form 12 and 36 (SF-12/36) has decreased.[8,9] A measure of QOL used in CRS, the SNOT-22, has now been studied in AR.[10] 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.[11] 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.[2] There are numerous individual RCTs evaluating the effect of INCS,[12] oral antihistamines,[13-16] and AIT.[17-20] 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,[21] 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 D_4-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.[22]

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.[23-26] In one study, parents overestimate their children's QOL.[27] 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®.[28] 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.[23,29] In children and adolescents with persistent AR, those with nasal obstruction secondary to septal deviation or turbinate hypertrophy have the worst QOL.[26] 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.[15,16] 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.[1] This latter finding, however, was based on a single study.[30] 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.[17,18,20] 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.[31]

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 ris ks of treatment.
Value judgment: 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.

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[1]	2021	1	SRMA	51 full text manuscripts screened, 5 studies with data extracted (n=2,055), 1947-2021	TNSS, TOSS, RQLQ, RCAT	Intranasal antihistamine-INCS provides short-term but not long-term QOL improvement
Li et al[3]	2021	1	SR	1,341 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
Zhang et al[2]	2021	1	SRMA	2,671 full text manuscripts screened, 22 studies with data extracted (n=4,673), 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
Calderon et al[4]	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[5]	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[6]	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 & Kumar[32]	2021	2	Cross-sectional	AR, n=40	RQLQ	AR negatively impacts QOL
Passali et al[11]	2021	2	Cross-sectional	AR, n=1063	Sniffin' Sticks olfactory test	Olfactory dysfunction in 44% of AR patients
Bosnic-Anticevich et al[24]	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[17]	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[27]	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[25]	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[30]	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[33]	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[34]	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[35]	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[36]	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[37]	2016	2	Cross-sectional	AR, n=200	SF-12, TSS	Extra-nasal symptoms in AR correlate with physical and mental health QOL domains
Song et al[38]	2015	2	Cross-sectional	Adolescents (n=6,407):	VAS	-AR in 15.8-19.4%

				-Likely AR from stratified sample, n=515 -Cluster sample, n=814		-AR impacts QOL, sleep, emotions, and memory
Bousquet et al[13]	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[39]	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[40]	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[22]	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[41]	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[42]	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[12]	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[18]	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

Holmberg et al[14]	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[43]	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[44]	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[45]	2008	2	RCT, crossover	AR (n=5,237): -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[46]	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[47]	2007	2	Cross-sectional	AR, n=123	RQLQ	-QOL significantly affected by AR -Greater than 2 sensitivities, eosinophil count, and nasal flow related to QOL -Eye symptoms correlate most strongly to QOL
Canonica et al[15]	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[20]	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[19]	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[16]	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
Radcliffe et al[48]	2003	2	DBRCT	Seasonal AR (n=183):	RQLQ, problem-free days	Enzyme potentiated desensitization does not

				-Enzyme potentiated desensitization, n=90 -Placebo, n=93		improve QOL or symptom scores compared to placebo
Gerth van Wijk et al[49]	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[50]	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 -Co-morbid asthma caused more physical limitations than AR alone
Juniper et al[7]	1991	2	DBRCT	AR (n=145): -RQLQ questionnaire development (n=85) -Validation (n=60): beclomethasone 200µg qDay (n=30); beclomethasone 400µg 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[23]	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[10]	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[51]	2019	3	Cohort	AR undergoing SCIT, n=120	RQLQ, ARIA	-SCIT treatment increases QOL -Reduction in asthma symptoms with SCIT
Gillman et al[52]	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 nonallergic patients -After septoplasty and IT reduction allergy related QOL improves
Baiardini et al[53]	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
Novakova et al[54]	2017	3	Cohort	AR treated with SLIT, n=191	RQLQ	SLIT significantly improved QOL

Schwanke et al[55]	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[26]	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[56]	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[57]	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[58]	2013	3	Cohort	AR, n=990	VAS, RQLQ, TSS	VAS can detect QOL variations with high sensitivity
Ciprandi et al[59]	2010	3	Cohort	AR undergoing SLIT, n=167	RQLQ	-QOL significantly affected by AR -SLIT improves QOL and symptoms
Cadario et at[60]	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[61]	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[31]	2001	3	Cohort	Seasonal AR, n=33	SF-36, SAT-P	QOL significantly affected by AR during peak season

LOE=level of evidence; SRMA=systematic review and meta-analysis; TNSS=Total Nasal Symptom Score; TOSS=Total Ocular Symptom Score; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RCAT=Rhinitis Control Assessment Test; INCS=intranasal corticosteroid; QOL=quality of life; SR=systematic review; VAS=visual analog scale; PNIF=peak nasal inspiratory flow; AR=allergic rhinitis; PROMs=patient reported outcome measures; SF-12/36=Short Form (12 or 36 questions); HDM=house dust mite; SCIT=subcutaneous immunotherapy; ISAAC=International Study of Asthma and Allergies in Childhood questionnaire; CARATKids=Control of Allergic Rhinitis and Asthma Test for Children; ARIA=Allergic Rhinitis and its Impact on Asthma; CT=controlled trial; AIT=allergen immunotherapy; ESPRINT-15=Cuestionario ESPañol de Calidad de Vida en RINiTis; HRQOL-health-related quality of life; T4SS = Total 4 Symptom Score; EQ-5D = EuroQoL QOL Questionnaire; DBRCT=double blind randomized controlled trial; RCT=randomized controlled trial; PNSS=Physician-assessed Nasal Symptom Score; ARCT=Allergic Rhinitis Control Test; BIP-Q=Brief Illness Perception Questionnaire; WPAIAS=Work Productivity and Activity Allergy Specific questionnaire; SNOT-22; Sinonasal Outcome Test 22-item; NOSE = Nasal Obstruction Severity Evaluation; TSS=Total Symptom Score; WPAI = Work Productivity and Activity questionnaire; DM =

diabetes mellitus; ESS=Epworth Sleepiness Scale; MOS-12 Sleep=Medical Outcomes Study 12-Item Sleep Scale; PANAS-X=Positive and Negative Affect Schedule-Expanded Form; 15D=Generic 15 Dimension Instrument for measuring health related quality of life; SPT=skin prick test; SLIT=sublingual immunotherapy; qDay=daily; PRN=as needed; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; GRC=Global Rating of Change scale; EOB=Ease-of-Breathing scale; IT=inferior turbinate; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; AdolRQLQ=Adolescent Rhinoconjunctivitis Quality of Life Questionnaire; PSQI=Pittsburgh Sleep Quality Index; RQOL=Rhinitis Quality of Life; SAT-P=Satisfaction Profile;

IX.A.2. Sleep disturbance

AR affects 20-30% of adults and children with OSA and sleep disordered breathing (SDB).[62,63] 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.[64-68] 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.[63,69] Furthermore, AR has been suggested to be a risk factor for deterioration of OSA QOL after adenotonsillectomy.[70] Additionally, AR may increase the risk of nocturnal enuresis in children.[71]

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)[72] and AR patients have worse PSG parameters and sleep disturbance when their symptoms are present or during their peak allergen season.[73] The data on PSG parameters in adults is mixed. Most studies that perform PSG found that AR worsens PSG parameters;[62,72-81] however two studies found either no difference or a modest change.[82,83]

AR patients have improvements of sleep quality, daytime sleepiness, sinonasal symptoms, and QOL after treatment with INCS[64-66,84] or a combination of INCS and montelukast.[64] Additionally, AR has been associated with worse sleep fragmentation[77,85] and snoring.[75,86] In addition to reducing sleep disturbance, treatment of AR has been suggested to also improve CPAP compliance.[87] *(See Section XIII.K. Associated Conditions – Sleep Disturbance for additional information on this topic.)*

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 judgment: 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.

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[88]	2021	2	SRMA	28 AR articles, n=8515 AR patients	RQLQ, ESS, PSQI	Treatment of AR improves subjective sleep quality
Liu et al[79]	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[64]	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 & Posey[68]	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[89]	2018	3	Prospective cohort	AR, n=670	Sleep quality, MOSSS	AR symptoms negatively impact sleep quality
Parikh et al[87]	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[74]	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[90]	2012	3	Prospective cohort	AR, n=2275	TSS, RQLQ, PSQI	AR disease severity has strong relationship with sleep disturbance
Gurevich et al[65]	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 improve sleep quality
Hughes et al[66]	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[67]	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[80]	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
Pace et al[81]	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[91]	2019	4	Survey study	AR, n=511	Sleep questionnaire	AR negatively impacts sleep metrics and daily functioning
Berson et al[78]	2018	4	Case-control	-AR, n=67 -Non-allergic rhinitis, n=33	ESS, PSG	AR worsens sleep quality
Roxbury et al[92]	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)
Leger et al[93]	2017	4	Prospective, cross-sectional	Adults with AR, n=907	ESS, insomnia severity, sleep questionnaire	AR induced by HDM (especially severe & persistent) negatively impacts sleep
Zhang et al[62]	2017	4	Cross-sectional	OSA, n=240, 27% with AR	PSG	AR does not influence severity of OSA
Bozkurt et al[83]	2016	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[94]	2015	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
Lavigne et al[76]	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[95]	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[82]	2011	4	Case-control	-Persistent AR, n=98 -Control, n=30	PSG	PSG parameters showed modest changes in persistent AR patients
Rimmer et al[85]	2009	4	Case-control	-Persistent AR, n=10 -Control, n=10	Actigraphy	AR has increased sleep fragmentation and reduced sleep quality
Udaka et al[96]	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[97]	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
Canova et al[98]	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[99]	2004	4	Uncontrolled open-label study	AR, n=651	NRQLQ, PSQI	Treatment with triamcinolone improves nocturnal rhinitis QOL and sleep quality
Stuck et al[100]	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[72]	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[86]	2000	4	Survey study	Subjects from TESOAD with sleep problems/snoring, n=437	Questionnaire	AR risk factor for snoring
Young et al[75]	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[101]	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[73]	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[77]	1981	4	Case-control	-AR, n=14 -Control, n=7	PSG	AR patients had 10-fold increase in micro-arousals vs controls

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

Study of Obstructive Airway Disease; SDB=sleep disordered breathing; ECRHS=European Community Respiratory Health Survey; OR=odds ratio

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[102]	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 et al[71]	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[103]	2021	4	Survey study	Adolescents, n=1936, 23.7% with AR	Sleep questionnaire	AR associated with inappropriate sleep duration
Liu et al[63]	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
Giraldo-Cadavid et al[104]	2019	4	Cross-sectional	AR children at high altitude, n=99	PSG	AR in children at high altitude associated with more severe OSA
Bilgilisoy Filiz et al[69]	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[105]	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 sleep-disordered breathing
Leger et al[93]	2017	4	Cross-sectional	Children with AR, n=843	ESS, insomnia severity, sleep questionnaire	AR induced by HDM (particularly severe & persistent) negatively impacts sleep
Di Francesco & Alvarez[106]	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[107]	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 & Han[70]	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[108]	2015	4	Cross-sectional	Non-white Latino and African	Clinical evaluation and follow-up	Poor AR and asthma control related to high frequency of sleep

				American urban children, n=195		problems and poor sleep hygiene
Poachanukoon et al[109]	2015	4	Case-control	-AR, n=65 -Control, n=104	Questionnaire	Higher incidence of sleep disturbance in AR
Kwon et al[110]	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[111]	2010	4	Cross-sectional	Children undergoing T&A for OSA, n=578	PSG	39% of OSA children have AR pre-operatively
Li et al[112]	2010	4	Survey study	Children, n=6349	Questionnaire	Habitual snoring associated with AR (OR 2.9; 95% CI 2.0-4.2)
Vichyanond et al[113]	2010	4	Case series	Children with rhinitis, n=302	History	Upper airway obstruction associated with non-allergic rhinitis
Barone et al[114]	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[115]	2009	4	Cross-sectional	Turkish children, n=1030	Questionnaire	AR associated with habitual snoring (OR 3.7; 95% CI 1-13)
Liukkonen et al[116]	2008	4	Cross-sectional	Children in Helsinki, n=2100	Questionnaire	AR more common in snorers
Kalra et al[117]	2006	4	Cross-sectional	Children in CCAAPS, n=681	Questionnaire	29% of patients with HS have positive SPT, significant association
Goldbart et al[118]	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[119]	2005	4	Cross-sectional	School children, n=3047	Questionnaire	AR associated with witnessed apnea
Sogut et al[120]	2005	4	Cross-sectional	Turkish children, n=1198	Questionnaire	AR associated with habitual snoring (OR 4.23; 95% CI 2.14-8.35)
Chng et al[121]	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[122]	2004	4	Cross-sectional	Children with AR undergoing SPT, n=202	History	17% of AR patients reported HS
Mansfield et al[123]	2004	4	Case series	Children with AR, n=14	PSG, RQLQ	Treating AR decreases AHI
Anuntaseree et al[124]	2001	4	Cross-sectional	Randomly selected children, n=1142	PSG, questionnaire	Prevalence habitual snoring 8.5%, OSA 0.69%. OR 5.27 in children with AR

McColley et al[125]	1997	4	Case series	Children with HS, n=39	PSG	Positive skin test associated with OSA

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

IX.B. Societal burden

AR has a high prevalence globally and imposes negative effects on QOL and therefore a burden to individuals and society. Due to its chronicity and prevalence, AR poses a significant socioeconomic burden.[126,127] 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.[128-131]

In the US, AR is the fifth most burdensome chronic condition when considering total cost.[132] Direct costs of AR in the US exceed $4.5 billion per year.[133-137] Likewise, AR represents a large direct economic burden in several other countries.[130,138,139] Medication expense makes up most of the direct cost, but additional costs include office visits, testing, and procedures.[140] These costs are even higher when considering patients with related illnesses such as asthma, allergic conjunctivitis, and CRS.[128,141,142] Despite many treatments being available over the counter, US medication costs for only AR are estimated to exceed $1 billion (US),[134] and patients with AR are also more likely to utilize clinic visits, further driving direct costs.[133,143]

AR leads to increased direct costs in countries around the world.[128] 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.[134] In a 2020 Danish study comparing 350 AR patients to controls, those with AR spent an additional €208 per year in direct costs.[138] In a 2016 study of 8,001 Swedish residents, direct costs attributable to AR were €210 per individual per year.[144] A 2017 French study demonstrated median direct costs of €159 for AR without asthma and €375 for AR with asthma.[145] Studies from Turkey showed

increased costs of $79 to $139 (US) for AR patients.[146] Studies from South Korea and India also demonstrate significant direct costs.[147-149]

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.[150] However, indirect costs account for a larger proportion of the burden of AR than the direct costs.[137] In the US, AR has been shown to contribute to greater than $5 billion (US) in lost productivity yearly.[151] 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.[152] As such, presenteeism accounts for the majority of reduced productivity related to AR.[153-155]

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.[156] In the UK, impaired productivity and/or missed work occurred as a result of AR in 52% of patients.[143] In India, 37% percent of surveyed patients with AR endorsed presenteeism and AR was responsible for $460 (US) loss per patient annually.[149] in Sweden, indirect costs were calculated to be €751 per patient annually.[144] In the Netherlands, indirect costs were estimated to be €3681 per patient annually, and presenteeism accounted for the majority of lost productivity.[138] In a Spanish study, presenteeism made up 95% of the loss in productivity and was estimated €1772 per year.[153]

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.[157]

AR is also the most prevalent chronic disorder among children, as such it has a significant impact on education.[158,159] On any given day in the US, approximately 10,000 children are absent from school because of AR.[160] 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.[79,159,161] 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.[159]

Additionally, AR has been associated with negative impact on mental health with functional decline as well as major depression, further reducing overall QOL.[35,162,163] This relationship has been shown in studies from Europe, the US, and Asia.[163]

AR represents a significant personal and socioeconomic burden that will likely worsen as the prevalence continues to increase.[164,165] 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.[160]

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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.[1-5] 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.[1-6] Other comorbid conditions in the past medical history, such as asthma, OSA, family history of atopic disorders, and medications currently taken should be gathered.[1-6] 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.[7]

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).[1-6] Snoring or sleep-disordered breathing, aural congestion or pruritis, and wheezing are other frequent symptoms.[3-6] 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.[6,8,9]

Patients with suspected AR will commonly present with multiple complaints, frequently with two or more symptoms.[6,7,9] Perennial AR patients have a tendency to report more congestive symptoms (sinus pressure, nasal blockage/congestion, and snoring) than seasonal AR patients.[8] Also, perennial AR patients more frequently complain of sore throat, cough, sneezing, rhinorrhea, and postnasal drip.[6] 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.[8 6,10]

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.[1-4,9,10] **[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.[11] The reliability and predictive value of the patient history for AR exceeds that of the physical exam alone.[11] 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.[9,10,12]

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.

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[7]	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[10]	2011	4	Cohort	Adults with AR	Physician interview and structured questionnaire	Many patients diagnosed on history alone without confirmatory testing
Raza et al[11]	2011	4	Cross-sectional	Adults with AR	-History -Physical examination -SPT	Physical examination alone yields unreliable and inconsistent results in diagnosing AR
Shatz[6]	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[8]	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[9]	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[12]	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[5]	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[2]	2015	5*	Guideline		Recommendations on diagnosis and treatment of AR	Clinical diagnosis of AR made with a history and physical examination
Wallace et al[3]	2008	5	Guideline		Recommendations on the diagnosis and treatment of rhinitis	Thorough allergic history remains the best diagnostic tool available
Small et al[1]	2007	5	Guideline		Recommendations on diagnosis and treatment of rhinitis	History of allergic symptoms is essential in the diagnosis of AR
Bousquet et al[4]	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

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

X.A.2. Physical examination

Whenever possible, it is important to include physical examination as part of the evaluation of suspected AR patients.[1-4,9,12] Telemedicine may complicate this part of the evaluation, but a limited visual examination may be obtained.[12] An assessment of head and neck organ systems should be completed with the use of any necessary personal protective equipment.[1-3,12] 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.[4]

An unremarkable physical examination is common for AR patients, particularly those with intermittent exposure.[8] 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).[1,3] 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.[1-3] Eye examination may reveal conjunctival erythema and/or chemosis.[1,3]

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, and negative predictive values of the patient history higher than those of the physical examination.[11] 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.[12] **[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 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.[11]

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.

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[11]	2011	4	Cross-sectional	Adults with AR	-History	Physical examination alone yields unreliable and

					-Physical examination -SPT	inconsistent results in diagnosing AR
Ng et al[8]	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[12]	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[5]	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[2]	2015	5*	Guidelines		Recommendations on diagnosis and treatment of AR	Clinical diagnosis of AR made with history and physical examination
Wallace et al[3]	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[1]	2007	5	Guidelines		Recommendations on diagnosis and treatment of rhinitis	Physical examination findings aid in supporting the diagnosis of AR
Bousquet et al[4]	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

LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; sIgE=allergen-specific immunoglobulin E; COVID-19=coronavirus disease 2019

*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

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[13] 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[14] and Eren et al[15] 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[16] 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.[17] The possible explanation could be related to the smaller sample analyzed in the previous study.

Polypoid change of the MT has also been also correlated with the diagnosis of AR as shown by White et al,[18] who described 16 patients with polypoid changes/polyps of the MT, all of which had positive allergy testing. Hamizan et al[19] reported that multifocal, diffuse, and polypoid edema – the highest grades of MT edema – had the strongest association with allergy, with positive predictive values of 85.15%, 91.7%, and 88.9%, respectively. Brunner et al[20] 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[21] in 2017, is a phenotype of nasal inflammatory disease which presents with isolated polypoid changes 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.[22] *(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.

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 MT or IT edema, contact and 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.

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[16]	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[13]	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[19]	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[22]	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[20]	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[21]	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[18]	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[15]	2013	4	Case series	Adults with rhinitis	-Nasal endoscopy -AR diagnosis	Nasal endoscopic findings do not provide reliable diagnosis of AR
Ameli et al[17]	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[14]	1999	4	Case series	Adults and children with perennial AR	-Nasal endoscopy -Nasal symptoms	No significant correlation between individual symptoms and endoscopic findings

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

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.[23-27] 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.[28,29]

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.[30-32] These factors preclude the routine utilization of radiographic studies for the diagnosis of AR.

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.

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[26]	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[27]	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[29]	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[25]	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[23]	2018	4	Cross-sectional	CRS patients without sinus surgery	-CT scan -Allergy testing	Central radiologic disease patterns associated with inhalant allergy
Sharhan et al[33]	2018	4	Cross-sectional	Patients with septal deviation	-CT scan -Allergy testing	IT size is not associated with AR
DelGaudio et al[21]	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[28]	2015	4	Cross-sectional	Patients with nasal symptoms and suspected AR	-Allergy testing -CT scan	Patients with AR showed smaller overall maxillary sinus volumes

LOE=level of evidence; CRS=chronic rhinosinusitis; CCAD=central compartment atopic disease; CRSwNP=chronic rhinosinusitis with nasal polyposis; CT=computed cosmography; IT=inferior turbinate; AR=allergic rhinitis

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 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.[34] Prick testing devices 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.[35,36] 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.[35-37] 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 minutes.[38,39]

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.[40] After approximately 20 minutes, 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.[41,42] Therefore, whenever possible, standardized allergens should be used.[43] 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.[44]

Given the limited depth of penetration, SPT is safe with very rare reports of anaphylaxis and no reported fatalities.[45] 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%.[43,45,46] It is felt to be more sensitive than serum sIgE testing with the added benefits of lower cost and immediate results.[45,47,48] 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.[2]

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.[49] 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 be used routinely in one's clinical practice to improve the reliability, comparability, and interpretation of testing.[50] 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.[50]

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.

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 pharmacological 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[51]	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[52]	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[48]	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[2]	2015	4*	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[45]	2008	4*	Practice parameter	N/A	N/A	-Sensitivity of SPT ranges from 85-87%, specificity ranges between 79-86% -Many studies have verified the sensitivity and specificity of SPT Aggregate evidence grade B
Gungor et al[53]	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
Krouse et al[54]	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[55]	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[56]	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 $\geq$3 mm had a sensitivity of 100% and specificity of 74.1%; improved with increasing size of wheal
Pumhirun et al[57]	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[50]	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[58]	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; SPT=skin prick test; AR=allergic rhinitis; N/A=not applicable; s=antigen-specific; IgE=immunoglobulin E; NPT=nasal provocation test; SET=skin endpoint titration; RAST=radio allegro-sorbent test; PPV=positive predictive value; NPT=negative predictive value
*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, 0.02-0.05mL 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 minutes 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.[45] 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.[59] 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.[60] Intradermal dilutional testing (IDT) is roughly equivalent to SPT in the diagnosis of inhalant allergy,[53] and IDT endpoint correlates with SPT wheal size.[61] 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.[62]

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., 0.10mg/mL).[45] 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.[45,62]

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.[63] 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 60-79%, while specificity is in the range of 68-69%.[52,53] In comparison, a meta-analysis of SPT trials had pooled estimates of 88.4% sensitivity and 77.1% specificity for SPT,[64] 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.[45] Negative intradermal testing may be helpful in ruling out IgE mediated disease.[62] 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.[65] 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[55] 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[54] 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[66] 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.[52] 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[67] 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 5 different allergens. If SPT with the multi-test II device was negative, only 17% of 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.[68]

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.

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.

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 & Reisacher[65]	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[69]	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[67]	2005	3	Cohort	97 subjects: -SPT followed by IDST if SPT(-) -If SPT(-) and IDST(+) positive, nasal challenge performed for 5 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[70]	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 vs SPT -SPT wheal size and IDT endpoint correlated for several allergens -IDT may be more sensitive than SPT
Wood et al[52]	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[63]	1993	3	Cohort	-497 patients with suspected allergy	IDST, RAST, clinical history	-Ideal cutoff for positive IDST is wheal diameter 0.7 times the size of histamine control

				-Standardized grass pollen, tree pollen, cat, HDM tested		-IDST has 83% predictive value vs RAST and 77% predictive value vs history
Niemeijer et al[71]	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 & McDaniel[72]	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
Erel et al[73]	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 & Ryan[61]	2007	4	Cohort	-134 volunteers -Simultaneous SPT and IDT for 5 common allergens	SPT wheal size vs IDT endpoint	IDT endpoint correlates with SPT wheal size
Peltier & Ryan[74]	2006	4	Cohort	86 volunteers tested simultaneously for mold allergens with SPT and IDT	SPT wheal size vs 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[75]	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[76]	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[53]	2004	4	Case series	62 patients with ragweed allergy	Nasal provocation, rhinomanometry	Sensitivity and specificity of IDT comparable to SPT
Krouse et al[55]	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[54]	2004	4	Prospective case-control	44 patients with AR: --Group I: SPT(+) -Group II: SPT(-), IDST(+)	Nasal allergen provocation for *Alternaria* compared to skin tests	IDST after SPT increased the sensitivity from 42% to 58%

				-Group III: SPT(-), IDST(-)		
Nelson et al[66]	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
Escudero et al[59]	1993	4	Prospective case-control	-66 patients, 31 with *Alternaria* allergy -SPT, IDST, challenge tests, sIgE	Comparison of test methods vs clinical history and nasal/bronchial challenge	-SPT, IDST, and challenge more sensitive than serum sIgE -All testing methods had similar specificity
Brown et al[77]	1979	4	Case series	311 subjects with and without allergy complaints	SPT vs IDST (if prick negative), paper radioimmunosorbent test, or RAST	No relationship between sIgE and SPT(-)/IDST(+) results
Reddy et al[78]	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 ID 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

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

X.B.3. Blended skin testing techniques

The combined use of SPT and intradermal testing for a specific antigen is referred to as "blended" allergy testing.[61,74,79] One example, originally described by Krouse and Krouse[80] as a method to establish an "end-point" for a specific antigen, was described as "modified quantitative testing" (MQT) and serves as an example of a blended technique. MQT involves an algorithm where a SPT is used initially to apply an antigen. Depending upon the SPT result, an intradermal test may or may not be applied.[61,74,79,80] With these results, the algorithm is used to determine an endpoint for each antigen tested.[61,74,79,80] The endpoint is considered to be a safe starting point for AIT.[80] Other protocols may combine the use of SPT and intradermal testing but not for the purposes of establishing an endpoint.[73,81] Instead, an intradermal test may be used following a negative SPT to determine allergen sensitization.[73,81]

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.[80] However, literature is lacking on 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.[61,74,79] 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.[82 5]

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.

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[73]	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[81]	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[79]	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[82]	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 & Ryan[61]	2007	4	Cohort	134 adults with AR	-IDT with 5 antigens -MQT protocol with 5 antigens	MQT is a safe alternative to IDT for

						determining starting doses for AIT
Krouse, et al.[4]	2006	4	Case series	9 adults with AR	-MQT -sIgE and sIgG4 for 3 antigens -SNOT-20, AOS, RSDI	MQT-based AIT results in immune system changes and QOL improvements
Peltier et al.[3]	2006	4	Cohort	86 adults with AR	-IDT with 6 mold antigens -MQT with 6 mold antigens	MQT is a safe alternative to IDT for determining starting doses for AIT for fungal allergens

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

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,[83,84] with the duration of suppression dependent on the tissue concentration and half-life of the medication.[85] Orally ingested antihistamines typically suppress skin test responses for 2-7 days after stopping the medication.[86,87] Topical antihistamines may also suppress skin wheal and flare responses.[88] Furthermore, H_2 receptor antagonists like ranitidine can reduce skin whealing responses,[89,90] and a combined suppressive effect of H_1 and H_2 antihistamines on skin whealing has been demonstrated.[91] Antidepressants with antihistaminic properties (such as doxepin) impair the wheal and flare,[92] but newer antidepressant classes such as selective serotonin reuptake inhibitors do not alter allergy skin test reactivity.[93] **[TABLES X.B.4.a.-1** and **X.B.4.a.-1]**

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;[94] whereas skin test response returned to normal within 8 weeks of discontinuation of omalizumab in another study.[49]

Hill and Krouse[95] and Simons et al[96] found no effect of montelukast on intradermal skin tests, and Cuhadaroglu et al[97] 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,[98,99] but some less rigorous retrospective studies contradict these findings.[100,101] Topical steroid treatment does suppress the wheal and flare reaction in treated skin areas, according to several studies.[102-105] 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.[106,107] Calcineurin inhibitors demonstrate conflicting findings. Tacrolimus has been shown to inhibit SPT whealing,[105] whereas pimecrolimus does not appear to affect skin whealing responses.[108] 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[109] 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) 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.

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

H_1 antihistamines	Should be discontinued 3-7 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)

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 & Wolthers[105]	2008	2	Randomized crossover, cohort	12 children with atopic eczema treated with topical mometasone or tacrolimus x2 weeks	SPT for 10 allergens	-Topical mometasone & tacrolimus reduced wheal diameter -Topical mometasone reduced histamine-induced wheal
Kupczyk et al[90]	2007	2	DBRCT, crossover	21 atopic subjects treated with ranitidine, loratadine, or placebo x5 days	Wheal, flare, pruritis following SPT with histamine and allergen	-Ranitidine: reduced wheal (41%), flare (16%), allergen-induced wheal (23%) & flare (22%) -Loratadine: reduced wheal (51%), flare (33%), allergen-induced wheal (40%) & flare (44%) -Ranitidine and loratadine both reduced pruritis score
Spergel et al[108]	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 & Krouse[95]	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[109]	2003	2	RCT	15 subjects received single-blind dose of placebo, fexofenadine, 23 other herbals	Histamine 1mg/mL wheal at baseline and 4 hours after	-Fexofenadine significantly reduced SPT wheal size vs placebo

					dose of herbal preparation	-None of the 23 herbal preparations showed significant effect on wheal size vs placebo
Noga et al[94]	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 vs placebo
Pearlman et al[88]	2003	2	RCT	78 patients with seasonal AR: single dose vs 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 hours after cessation
Simons et al[96]	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 & Simons[110]	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 hours
Miller & Nelson[89]	1989	2	DBRCT	23 healthy subjects treated with ranitidine or placebo x7 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[104]	1989	2	DBRCT, placebo-controlled	10 patients with AR treated with clobetasol cream or placebo BID x2-4 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[92]	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 & Pipkorn[103]	1987	2	DBRCT	17 patients with AR treated with topical clobetasol x1 week	-Histamine SPT -Allergen SPT	Topical clobetosol significantly suppresses allergen induced wheal and flare response
Slott and Zweiman[99]	1974	2	DBRCT, crossover	15 atopic patients treated with methylprednisolone	Intradermal wheal size for histamine, allergen, and compound 48/80	No effect of 7 days methylprednisolone on intradermal wheal size

Cook et al[86]	1973	2	DBRCT	18 adults with skin test positive AR treated with chlorpheniramine, tripelennamine, promethazine, hydroxyzine, or diphenhydramine x3 days	Intradermal wheal size suppression	-All antihistamines suppressed wheal size to varying degrees -Hydroxyzine suppressed responses for 4 days after cessation vs 2 days for diphenhydramine
Isik et al[93]	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[49]	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[102]	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[97]	2001	3	Cohort	Zafirlukast 20mg BID for at least 5 days: -9 patients with AR/asthma -8 controls	SPT to histamine and allergens	Zafirlukast did not suppress histamine or allergen induced wheal and flare response
Des Roches et al[98]	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
Almind et al[87]	1988	3	Cohort	23 healthy individuals treated with dexchlorpheniramine, astemizole, cyproheptadine, loratidine, or terfenadine x2 days	-Effect on histamine SPT wheal -Duration of SPT wheal suppression	-All antihistamines suppressed SPT wheal response to histamine -Duration of suppression exceeded 72 hours for all agents tested
Long et al[83]	1985	3	Cohort	-18 subjects, 10 had positive SPT to grass or ragweed allergens -6 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
Phillips et al[84]	1983	3	Cohort	10 atopic subjects received injection of ketotifen, clemastine,	Inhibition of allergen and histamine induced wheals	Ketotifen, clemastine, and chlorpheniramine but not sodium cromoglycate

				chlorpheniramine or sodium cromoglycate		significantly inhibit skin whealing responses
Harvey & Schocket[91]	1980	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 vs either alone
Geng et al[101]	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[106]	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[107]	2009	4	Uncontrolled cohort	42 drug abusers taking alprazolam TID	Histamine (10mg/mL) SPT and allergen skin tests	-All subjects taking alprazolam had negative histamine SPTs -Incomplete data reported.
Olson et al[100]	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

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

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.[45] 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.[111] 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.

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;[112-115] in others it is less clear.[116,117] Moreover, it seems from these studies that other comorbidities, especially

asthma, give rise to elevated tIgE.[114,115] 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[118-120] or versus controls.[121,122] Some studies investigated the correlation between serum sIgE and tIgE[123,124] showing a good overall fit. In hospital-based studies, the influence of asthma is seen as well[125] but again not accounted for in most reports.

Taken together, an elevated tIgE is indicative of an atopic condition,[126] 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 a 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.[127] 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.[50] However, these specific cases are exceptions to the rule that serum tIgE is not needed for the diagnosis and evaluation of AR.

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).

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[115]	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[116]	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[114]	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[113]	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[122]	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[121]	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 (IgE 814.36 IU/ml), and in controls: 4.43 (tIgE 96.62 IU/ml), p<0.001 -No difference between age groups
Li et al[120]	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[117]	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[124]	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[123]	2013	3	Retrospective cohort	295 patients, mean age 33.9 (6-80) years, with at least 2 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 U/ml, 20-100 U/ml and >100 U/ml	-23.7% had tIgE <20 U/ml -38.3% had tIgE between 20-100 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[126]	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[119]	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
Kalpaklioglu & Kavut[118]	2009	3	Retrospective case-control	323 consecutive and unselected patients	tIgE levels between AR and NAR	-tIgE: AR 261 (359), NAR 126 (172), p<0.01

				from tertiary clinic, mean age 31.8 years, 205 with AR, asthma equally present in both groups		-Differences in complaints and seasonality between AR and NAR
Satwani et al[125]	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 & Shima[112]	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

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

X.C.2. Serum allergen specific IgE

Determining the presence of sIgE that verifies allergen sensitization is the cornerstone of diagnostic testing in suspected allergic conditions. The assessment of sIgE can be done by skin tests, serological immunoassays and/or cellular immunoassays.[50]

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.[128] The ability to perform serum sIgE immunoassays with recombinant or highly purified allergens has increased the sensitivity, specificity, and diagnostic accuracy of these tests.[44] Additionally, development of miniature computer-driven autoanalyzers and nanotechnology-based devices, enhanced signal detection instrumentation, and new solid phase chip and particle materials have improved the diagnostic accuracy and consistency of in vitro tests.[129,130] 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.[130]

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.[50] 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.[131] 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.[50,130] 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 to 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, mite) will detect up to 95% of patients who would have been identified on a larger battery.[132,133] If the test is negative, absence of allergy is probable.[129]

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.[134] In addition, serum sIgE seems to correlate with the severity of AR symptoms.[135-139] 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.[135,140]

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.[50]

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.[141] Undergoing SPT is also limited by the presence of certain medical conditions.[141] 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.[140] Unless molecular allergy diagnostic approach with allergenic components is used (precision allergy medicine diagnosis or PAMD@),[130] serum sIgE to regular allergens cannot accurately predict the risk of severe allergic reaction. If PAMD@ is not used, cross-reacting allergens and poly-sensitizations can confound in vitro testing, leading to false positive results.[142]

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 6 laboratories, only 2 demonstrated precision and accuracy in their results.[143] Further studies have demonstrated poor agreement on results from testing the same sera by different commercially available assay systems.[143-145] 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 ranging between 67-96% and specificity of between 80-100%.[48,52,57,145,146] Further, serum sIgE correlates well with NPT and SPT for AR diagnosis.[48,57,78,145,147] While there is good evidence to show that serum sIgE is often equivalent to SPT, it is generally accepted that SPT is more sensitive.[2,52,148] 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.[50] 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.]**

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.

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[149]	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[150]	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[151]	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[152]	2005	3	Prospective cohort	118 patients with AR and/or bronchial asthma	Compare skin test reactivity with serum sIgE	-For 4 indoor allergens, skin test more sensitive than RAST -Skin test and RAST scores had weak to moderate correlation
Wood et al[52]	1999	3	Prospective cohort	-Patients with cat allergy determined by history	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

				-Cat exposure model		-Sensitivity and specificity of RAST were 69% and 100%, respectively
Tschopp et al[48]	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 & Murray[147]	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%
Ownby & Bailey[146]	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[148]	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[153]	2019	4	Retrospecti ve cohort	793 patients referred for respiratory allergy	SPT and sIgE by IFMA procedure for 5 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 & Lee[154]	2017	4	Retrospecti ve 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[2]	2015	4*	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[45]	2008	4*	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
Pumhirun et al[57]	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[78]	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[50]	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; sIgE=allergen-specific immunoglobulin E; OR=odds ratio; AUSROC= areas under the summary receiver operating curve; SPT=skin prick test; PPV=positive predictive value; NPV=negative predictive value; AR=allergic rhinitis; RAST=radio allergo-sorbent test; ID=intradermal; MAST=multiple allegro-sorbent test; NPT=nasal provocation test; IgE=immunoglobulin E
*LOE upgraded due to established methodology, several rounds of review, long history of EBM guideline development

X.C.3. Nasal allergen specific IgE

AR is frequently diagnosed by history alone in clinical practice.[155] 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.[156-161]

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.[162-165] Collection of mucosal tissue can be achieved with either tissue biopsy or with a cytology brush.[159,166] There is no consensus on which technique is superior, and most appear to yield similar results in identifying nasal sIgE.[167,168] Cut-off values for nasal sIgE levels 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.[164,169,170] **[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.[163,165,171-178] 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.[179] *(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.[180-183]

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.[184] 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.[185] 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.

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.[179] In this population, early studies suggest that AIT can decrease symptoms and medication usage and improve QOL.[186] 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.

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.

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[184]	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[182]	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[181]	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[187]	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[169]	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[164]	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[180]	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[183]	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[172]	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[188]	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
Bozek et al[189]	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[190]	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[171]	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[173]	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[191]	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[192]	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[176]	2009	2	Cross-sectional	Collection via nasal lavage: -LAR, n=30 -Control, n=30	Nasal sIgE, sIgE, tryptase, ECP	-30% with nasal sIgE -LAR have local production of sIgE, mast cell/eosinophil activation
Rondon et al[175]	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[177]	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[174]	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
KleinJan et al[161]	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[158]	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[160]	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[157]	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 & Brostoff[165]	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[193]	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 vs serum sIgE
Hamizan et al[167]	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[170]	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[163]	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[194]	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[166]	2016	4	Case series	Collection via mucosal biopsy: AR, n=11	Nasal and serum sIgE	Detection of sIgE in inferior turbinate mucosa and serum
Zicari et al[178]	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[168]	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[159]	2003	4	Case-control	Collection via mucosal biopsy: -AR, n=6	Nasal IgE heavy chain	Somatic hypermutation, clonal expansion, and class switching occurs within the

				-Control, n=1		nasal mucosa of AR patients
Sensi et al[195]	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[156]	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

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

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.[196-202] 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.[50,196,198] A 2016 SRMA indicates that SPT is an accurate test that when utilized along with a detailed clinical history, helps confirm the diagnosis AR.[51]

The performance and reliability of serum sIgE testing depends on choice of reagents, age of equipment, and patient demographics.[69] Sensitivity and specificity are affected by the cutoff value of a positive test.[203] 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.[204]

Several studies have compared serum sIgE to SPT.[52,150,153,154,203,205,206] 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.[130] 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.[51] 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.

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.**)

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[51]	2016	1	Systematic review	AR	SPT accuracy	Various factors determine SPT accuracy
Westwood et al[131]	2016	1	Systematic review	AR	Microarray results	Utility and cost of microarray testing needs further validation

Gendo et al[207]	2004	1	Systematic review	AR	Utility of allergy testing	History and pre-test probability determine allergy testing utility
Knight et al[150]	2018	2	Cross-sectional	AR	Concordance between SPT and sIgE	Overall concordance between SPT and sIgE was >70%
Tversky et al[196]	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[208]	2014	2	Cross-sectional	AR and asthma	Concordance of SPT and serology	SPT and serology are discordant
Jung et al[204]	2010	2	Cross-sectional	HDM allergies	ImmunoCAP versus SPT	Sensitivity and specificity depend on demographics of patients
Pastorello et al[205]	1995	2	Cross-sectional	AR	ImmunoCAP vs SPT	Specific IgE accuracy depend on cutoff values
Haxel et al[206]	2016	3	Retrospective cohort	AR	Nasal challenge v SPT v RAST	Nasal challenge should be performed to confirm eligibility to HDM AIT
Sharma et al[69]	2008	3	Cohort	Mouse allergies	RAST vs SPT vs ID	Sensitivity and specificity differ among various tests
McCann et al[202]	2002	3	Cohort	AR	SPT measurements	SPT results are not reproducible across centers
Wood et al[52]	1999	3	Cohort	Cat allergies	RAST vs SPT vs ID	Sensitivity and specificity differ among various tests
Bignardi et al[153]	2019	4	Case series	AR	SPT and sIgE	SPT and sIgE are fairly concordant; different sensitivity and specificity depending on the allergen
Nam & Lee[154]	2017	4	Case series	AR	SPT and sIgE	Higher sensitivity and specificity of sIgE than SPT
Tantilipikorn et al[81]	2015	4	Case series	AR	ID versus in vitro	ID testing has higher sensitivity and lower specificity than sIgE for DM
Choi et al[203]	2005	4	Case series	HDM allergies	RAST versus SPT	sIgE cutoff level determine sensitivity and specificity
Nelson et al[66]	1996	4	Case series	AR to grass	ID vs challenge	ID positive may not be relevant if SPT negative
Ansotegui et al[50]	2020	5	World Allergy Organization position paper	N/A	N/A	SPT is considered the first-line approach
Steering Committee[130]	2020	5	World Allergy Organization consensus paper	N/A	N/A	PAMD@ can be important in polysensitized patients

LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; sIgE=allergen-specific immunoglobulin E; RCT-randomized controlled trial; HDM=house dust mite; RAST=radio allegro-sorbent test; AIT=allergen immunotherapy; ID=intradermal; PAMD@=precision allergy molecular diagnostic applications

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.[209]

In HDM sensitive children, BAT has excellent sensitivity (82-100%) and specificity (96-100%).[210] Similar findings were reached in 31 grass pollen sensitive adults: sensitivity 87-100% and specificity 100%.[211] In a combined study in 47 children with HDM and/or grass pollen 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.[212] BAT is also able to distinguish between AR based on HDM allergy and irrelevant HDM-sensitization.[213] For birch allergy, BAT sensitivity was shown to increase after the pollen season compared to placebo.[214] Results of BAT are valid in both in-season and pre-season measurements.[215] 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.[216]
[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.[217] 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.[218] 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.[219] SLIT for Parietaria showed reduced basophil activation in 16 patients after 12 months of treatment.[220]

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.[221] In another study with 50 grass pollen sensitized patients, SCIT gave a clear reduction in BAT outcomes 3-5 years after treatment.[222] 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.[223]

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.[224] Feng et al[225] 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.[226] 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.[227]

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.[220] Ma and Qiao[228] 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., contra-indication 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.

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. 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 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.

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[214]	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 vs 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[227]	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 vs controls; effect larger in SCIT -BAT outcomes not correlated to other markers
Özdemir et al[221]	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[219]	2012	2	RCT, phase 1	30 AR subjects with HDM and Timothy grass allergy treated	Clinical outcomes and laboratory markers, including BAT	-BAT based on CD203c positivity

				with dual SLIT (n=20) or placebo (n=10)		-HDM SLIT decreased basophil activation in treatment group at 24 months vs baseline -BAT can be useful to monitor changes from SLIT
Van Overtvelt et al[218]	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 & Qiao[228]	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
Qiao & Chen[216]	2021	3	Prospective cohort	Children with AR or asthma (n=30) and healthy controls (n=15), o 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[223]	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[225]	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 -0.15µg/ml allergen concentration: basophil activation decreased in the SCIT group from week 16 to 104

						-15µg/ml allergen concentration: no changes in SCIT or control group -Basophil sensitivity can be used as marker for SCIT efficacy
Zidarn et al[213]	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%, 3.33ng/mL in symptomatic patients, 33.3ng/mL in asymptomatic group -BAT can help clinicians to distinguish between HDM-AR patients and asymptomatic subjects
Caruso et al[220]	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 vs control -Symptom reduction only related to reduced basophil activation based on CD203c
Kim et al[224]	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[212]	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[226]	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 vs 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[222]	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 0.1µg/ml grass pollen, baseline vs end of study nonsignificant -At 1.0µg/ml grass pollen: baseline 56.2% (2.6-92.6), end of study 12.1% (0.9-88.6), p=0.004 -At 10µg/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
Özdemir et al[211]	2011	3	Prospective cohort	31 adult patients with seasonal AR for grass pollen without asthma and 9 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[210]	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 vs atopic controls: at 8% activated basophils as cut-off with 16µg/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[215]	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 preseason and in-season to diagnose seasonal AR
Nagao et al[217]	2008	4*	Prospective cohort	9 pts 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 4 patients -Does not confirm BAT is useful for monitoring all patients

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; BAT=basophil activation test; CD=cluster of differentiation; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; HDM=house dust mite; SPT=skin prick test; AIT=allergen immunotherapy; AD=atopic dermatitis; AUC=area under the curve; PPV=positive predictive value; NPV=negative predictive value
*LOE downgraded due to very small number of patients

X.C.6. Component resolved diagnostic testing

The implementation of molecular allergy diagnostic approach, or PAMD@, is increasingly entering into routine clinical care.[130] 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.[130,229-232] Changes in AIT prescriptions as a result of MD have demonstrated cost-effectiveness.[233] 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.[234] 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.[235,236] 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.[237,238] 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.[130,229] 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* and *D. farinae* sensitize the majority of mite-allergic patients, with double sensitization to groups 1 and 2 being common.[239] Recently, Der p 23 has been described also as a frequent allergen and associated with increased asthma risk.[130,240] Other good markers of sensitization are Lep d 2 for *Lepidoglyphus destructor* (storage mite, with limited cross-reactivity with other HDMs)[241] and Blo t 5 for *Blomia tropicalis* (non-Pyroglyphidae mite).[242] 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.[243,244] 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.[245]

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.[246-249] The pattern of sensitization should be kept in mind since the content of dog allergens in AIT extracts is very heterogeneous.[250] 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.[251-253] 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.[254]

Alt a 1 is a major allergen that is recognized in approximately 80–100% of *Alternaria*-allergic patients.[255] There are twenty-three *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.[229,256]

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.[236,257] 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.[258]

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

TABLE X.C.6.-1. **MAMMALIAN ALLERGENS** (www.allergen.org)

	Specific component	Percent sensitization	Cross-reactivity
DOG	Can f 1-lipocalin*	50-90%	Fel d 7
	Can f 2-lipocalin*	20-33%	
	Can f 3-serum albumin*	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*	23-61%	Fel d 4 and Equ c 1
	Can f 7-epididymal secretory protein E1	17%	
CAT	Fel d 1-secretoglobin*	90%; monosensitization 30%	
	Fel d 2-serum albumin*	14-54%	70-80% with other serum albumins
	Fel d 3-cystatin	10%38%	
	Fel d 4-lipocalin*	63%; monosensitization 6%	Can f 6 and Equ c 1
	Fel d 5W-IgA	38%	
	Fel d 6W-IgM	?	
	Fel d 7-lipocalin*	38%	Can f 1
	Fel d 8-latherin-like protein	19%	
DOMESTIC HORSE	Equ c 1-lipocalin*	76-100%	Can f 6 and Fel d 4
	Equ c 2-lipocalin	50%	
	Equ c 3-serum albumin*	36%	70-80% with other serum albumins
	Equ c 4-latherin	77%	
	Equ c 6-lysozime	?	

*allergens currently available for molecular diagnosis

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TABLE X.C.6.-2. POLLEN ALLERGENS

POLLEN	Specific components	Percent sensitization[130]	Cross-reactivity components
Ragweed	Amb a 1 (Peptate Lyase)*	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)*	95%	Art v 3 (LTPs)
	Art v 3 (LTP)*	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)*	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)*	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)*	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)*	70%	Phl p 12 (profilin)
			Phl p 5 & Phl p 2 & Phl p 6
	Phl p 5 (ribonuclease)*	50-95%	
	Phl p 6 (?)*	44-75%	
	Ph l p 7 (polcalcin)*	10%	
	Ph l p 11 (Ole-1 like)	32-43%	
	Ph l p 12 (profilin)*	15%	
	Ph l p 13 (polygalacturonase)	50%	
Bermuda grass	Cyn d 1 (expansin)*	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)*	95%	Bet v 1 (PR10)
	Bet v 2 (profillin)*	22%	Bet v 2 (profilins)
	Bet v 3 (polcalcin)*	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)*	90%	Ole e 2 (profilins)
	Ole e 2 (profilin)	50%	Ole e3 (polcalcins)
	Ole e 3 (polcalcin)	?	
	Ole e 4 (?)	80%	

	Ole e 5 (superoxide dismutase) Ole e 6 (?) Ole e 7 (LTP)* Ole e 8 (polcalcin) Ole e 9 (glucanase)* Ole e 10 (X8 domain protein) Ole 11 (pectin methylesterase) Ole e 12 (isoflavone reductase)	35% 15% 47% ? 68% 90% ? 4-33%	
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)* 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)* Pla a 2 (polygalacturonases)* Pla a 3 (LTP)*	87% 83% 45%	Pla a 3 (LTP)

LTP= lipid transfer protein
*allergens currently available for molecular diagnosis

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[259]	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[260]	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[261]	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[262]	2013	2	Observational study	175 patients with a diagnosis of spring pollinosis	-SPT -In vitro study of the application of a specific recombinant	Choice of immunotherapy was changed in more than 50% of patients

					IgE protocol (nOle e 1, rPhl p 1-5b, rPhl p 12, rPhl p 7, and rPru p 3)	
Nolte et al[263]	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[236]	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[264]	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
Rodriguez-Dominguez et al[245]	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[265]	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	2019	4	Retrospective	Patients with	-Post hoc analysis of	-Der p 1, Der p 2, and Der p

al[266]			case series	HDM allergy treated with AIT in a double-blind placebo-controlled clinical study	serum IgE and IgG reactivity against a comprehensive panel of HDM allergens -Respiratory symptoms during controlled HDM exposure in the Vienna Challenge Chamber	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[267]	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
Saltabayeva et al[234]	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 & Sastre[248]	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[268]	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[269]	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
Tripodi et al[270]	2012	4	Case series	200 children with grass pollen AR, asthma, or both ascertained through validated questionnaires	-SPT -sIgE assays with 9 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[271]	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[249]	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

LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; AIT=allergen-specific immunotherapy; sIgE=allergen-specific immunoglobulin E; Ig=immunoglobulin; CRD=component resolved diagnostics; SLIT=sublingual immunotherapy; EAACI=European Academy of Allergy and Clinical Immunology; HDM=house dust mite; VAS=visual analog scale

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.[272]

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 atopic dermatitis.[273] Also, the impact of exposure with pollen allergen fragments[274] and the aggravating effect of diesel exhaust particles on AR symptoms has been shown.[275] 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,[276] as well as severity phenotypes of allergic asthma and rhinoconjunctivitis.[277,278]

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.[279-287] Also, repeatability of outcome measures in the ACC has been systematically investigated and verified for TNSS,[288] peak nasal inspiratory flow (PNIF),[289] conjunctivitis symptoms,[290,291] and inflammatory nasal biomarkers.[292] 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.[293] With the given level of technical and clinical validation, ACC have been used in clinical drug development to study pharmacological properties of new drugs during phase 2 trials, such as optimal dose,[294-296] onset of action,[297-303] and duration of action.[304-306] 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,[307-311] or with immediate therapeutic activity, such as antihistamines.[312-318] Novel anti-inflammatory compounds,[319-323] drug-free nasal fluids,[324,325] and probiotics[326,327] have also been tested by this method. Additionally, the efficacy of AIT[328-339] and air cleaners[340,341] has been tested, as well as the influence of allergic nasal symptoms on the absorption of nasally applied drugs.[342] 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,[279,284] birch,[280] HDM,[285,343,344] Japanese cypress,[345] and ragweed.[346] 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.[347-349] 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 population (all-comers versus 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.[350] Hybrid approaches combining ACC and field study might provide proper robustness to determine drug efficacy.[272,351]

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.[352-354]

NPT aims to reproduce the upper airway response to nasal allergen exposure.[355,356] 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.[355] Positive NPT can be assessed by symptom scales, rhinometry, PNIF, nasal lavage inflammatory markers, and nasal nitric oxide (nNO).[356] NPT contraindications include acute rhinosinusitis, recent AR exacerbation, history of anaphylactic reactions, severe general diseases (cardiopulmonary diseases with reduced lung capacity), and pregnancy.[357] 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,[357] 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.[209,358-360]

The characteristics and safety of NPT were investigated in 518 children and 5830 adults by Eguiluz-Gracia et al,[361] 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.[362] Regarding HDM, Wanjun et al[363] 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[364] evaluated the EAACI NPT protocol, concluding that standardized NPT could help diagnose AR caused by HDM. Finally, Xiao et al[365] 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)".[366] 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.[367]

For LAR, the SPT and serum sIgE are negative and diagnosis requires the measurement of local IgE in nasal secretions or a positive NPT.[368] 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;[369] however, in 28 children with non-allergic rhinitis, NPT was positive in only 25% of subjects.[370] 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.[371]

CPT is generally performed by instilling 20-30µL of an allergen solution into the inferolateral quadrant of the conjunctiva, using a control diluent in the contralateral eye.[352] A positive CPT response results in a reaction 5-20 minutes 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.[372] CPT sensitivity and specificity in HDM-allergic patients were reported as 90% and 100%, respectively.[373] A systematic review contributed to the EAACI guidelines for the practice of CPT with grade B evidence for identifying the allergen trigger.[374] 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.[375]

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 provocation 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.

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[362]	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[376]	2021	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[364]	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[361]	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: 3 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[377]	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[378]	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
Jang & Kim[379]	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[380]	2013	3	Cohort	11 patients with mold allergy -11 controls	Results of NPT by optical rhinometry	No significant difference between allergic and control subjects

LOE=level of evidence; RCT=randomized controlled trial; NPT=nasal provocation test; EEC=environmental exposure chamber; TNSS=Total Nasal Symptom Score; PNIF=peak nasal inspiratory flow; RT-PCR=reverse transcriptase polymerase chain reaction; VAS=visual analog scale; EAACI=European Academy of Allergology and Clinical Immunology; HDM=house dust mite; MCA=minimal cross-sectional area; TNV=total nasal volume; AR=allergic rhinitis; SPT=skin prick test; NPT-R=rapid nasal provocation test

X.E. Nasal cytology and histology

Nasal cytology (NC) is a diagnostic procedure that evaluates cell types present in the nasal mucosa.[381] NC starts with sampling the surface cells of the nasal mucosa; typically with a Rhino-probe (Arlington Scientific, Springville, UT, USA).[382] [2] 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 1000x optical microscope.[381] 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.[383] 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.[384-387] Elevated nasal eosinophil counts had an OR of 1.14 (95% CI 1.10-1.18) of identifying AR.[385] NC in poly-allergic patients showed a

more intense inflammatory infiltrate than in mono-allergic patients,[386] and demonstrated seasonal changes of inflammatory cells, probably due to changes in allergen exposure.[388]

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%); positive predictive value (PPV) of 56% (95% CI 50-62%), and negative predictive value (NPV) of 100% (95% CI 96-100%) with a non-allergic rhinitis prevalence of 39%.[389] 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.[390,391]

Nasal histology (NH) was the only technique to study nasal tissues and cells for many decades. Biopsy-based investigations in the 1990's allowed researchers to define the role of the different inflammatory cells in AR.[392] 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).[393,394] 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.[395] 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.[396] **TABLE X.E.-**2 shows studies on AR as evaluated by NH.

Aggregate grade of evidence – nasal cytology: 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.

Aggregate grade of evidence – nasal histology: 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.

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[397]	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[389]	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[398]	2019	3	Prospective cohort	48 NAR patients with negative SPT	Diagnostic performance of NC (vs NPT with 3 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[385]	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[386]	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[399]	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[387]	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)

LOE=level of evidence; NARES=non-allergic rhinitis with eosinophilia syndrome; NC=nasal cytology; NAR=non-allergic rhinitis; PPV=positive predictive value; NPV=negative predictive value; SPT=skin prick test; NPT=nasal provocation test; LAR=local allergic rhinitis; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval; NARMA=non-allergic rhinitis with mast cells; NARESMA=non-allergic rhinitis with eosinophils and mast cells; ARIA=Allergic Rhinitis and its Impact on Asthma

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[400]	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[401]	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[402]	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 vs placebo
Asai et al[403]	2008	2	RCT	19 patients, ragweed pollen AR: -AIT, n=12 -Placebo, n=7	Allergen-induced CD4+-, CD4+ CD25+-, IL-10-, TGF-β-positive 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 vs placebo group and vs baseline
Rak et al[404]	2005	2	RCT	41 patients with birch pollen AR: AIT vs 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[405]	2002	2	RCT, single-blind	30 patients with grass pollen AR:	Anti-CD4, CD8, anti-eosinophil peroxidase, anti-	Eosinophil peroxidase-positive staining cells significantly increased in the placebo-treated

				-Omalizumab, n=19 -Placebo, n=11	human neutrophil lipocalin, IgE and FcεRI in nasal biopsies	group but not in the actively treated group
Pullerits et al[406]	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 vs controls -Pollen season increased IL-16 and CD4+ cells in placebo group, but not beclomethasone group
Wilson et al[407]	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[408]	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 compared vs baseline -Out of season, Foxp3+CD25+ and Foxp3+CD4+cells greater in AIT group vs controls
Till et al[409]	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

LOE=level of evidence, CRS=chronic rhinosinusitis; AR=allergic rhinitis; DBRCT=double-blind randomized controlled trial; SAR=seasonal allergic rhinitis; RCT=randomized controlled trial; AIT=allergen immunotherapy; CD=cluster of differentiation; IL=interleukin; TGF=transforming growth factor; IgE=immunoglobulin E

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, 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.[410,411] Rhinomanometry can be used in adults and children, and normative/reference values exist for both.[412-419] However, reference values vary widely as rhinomanometry results depend on factors such as ethnicity, height, sex, smoking status, adenoid tissue and age.[414,420]

Rhinomanometry has certain disadvantages. It is expensive, time consuming and requires trained personnel.[421] 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 Pa or 150 Pa). This is no longer recommended as this represents a portion of the curve where the pressure/volume flux relationship is non-linear and a pressure of 150 Pa is often not achieved in normal relaxed breathing cycles.[410,422] 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.[410,411] Logarithmic measures taken during 4PR correlate significantly with subjective scores of nasal obstruction.[423] 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 process.[424] Further, acoustic rhinometry may overestimate the cross-sectional area of the posterior nasal cavity due to leakage into patent sinuses.[425]

***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 20L/min has been defined and a lack of improvement of 20L/min or 20% after decongestion may indicate a structural

cause of obstruction.[426-428] A SRMA reported mean PNIF values in normal adults of 128.4L/min and 97.5L/min for obstructed adults.[429] 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.[430,431] It would appear that PNEF correlates best with symptoms of nasal obstruction.[432] PNIF/PNEF measures should be supported by subjective measures to improve diagnostic accuracy.[433]

In summary, many papers have reported a lack of correlation between objective measures of nasal patency and subjective perceptions of nasal obstruction.[434] 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.[423,434-437] It has also been shown that patient symptoms do not necessarily correlate with the degree of measured obstruction.[423,435,438] 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.[439-445] Therefore, nasal cavity volume, airflow and resistance may only be a few of many factors contributing to the sensation of nasal obstruction.[424] [424] 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 allergen challenges, in patient selection for surgery, and in the research setting.[446]

Aggregate grade of evidence – rhinomanometry: 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.

Aggregate grade of evidence – acoustic rhinometry: C (Level 2: 1 study, level 3: 5 studies, level 4: 3 studies, level 5: 2 studies; **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.

Aggregate grade of evidence – peak nasal inspiratory flow: B (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study, level 5: 1 study; **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 patient reported outcome measures (PROMs) to improve utility.

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[424]	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[447]	2008[#]	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[448]	2021	2*	Systematic review	Patients with sinonasal disorders, including AR	PROMs (VAS, NOSE) and RM	-Weak to moderate correlation between RM and PROMs -1 paper reported a strong correlation between VAS and AAR in AR patients -Routine AAR not recommended
Vogt et al[449]	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 & Athavale[450]	2020	3	Prospective prevalence cohort	AR, n=32	AAR, spirometry, histamine challenge test	94% of moderate-severe AR had significantly elevated resistance vs 56% of mild AR patients
Pantin et al[451]	2019	3	Prospective validating cohort	AR and asthma, AR without asthma, n=24	NAC, cytokines, ARM at 3cm, 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[436]	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)	-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
Wong & Eccles[452]	2014	3**	In vitro, non-randomised 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[434]	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[453]	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 vs controls (lower nasal flow in AR) -Mild negative correlation between nNO and mean nasal flow
Hou et al[454]	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[455]	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 5cm had highest sensitivity and specificity
Passali et al[435]	2000	4***	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[456]	2021	5****	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

Rimmer et al[412]	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[457]	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[292]	2017	5*****	Prospective case-control study	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[458]	2017	5******	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[459]	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

LOE=level of evidence; N/A=not applicable; GRADE=Grading of Recommendations Assessment, Development and Evaluation; RM=rhinomanometry; PNIF; peak nasal inspiratory flow; ARM=acoustic rhinometry; VAS=visual analog scale; AR=allergic rhinitis; PROM=patient reported outcome measure; NOSE-Nasal Obstruction Symptom

Evaluation; AAR=anterior active rhinomanometry; Reff=effective resistance; VR=vertex resistance; L=logarithmic value; NAC=nasal allergen challenge; FEV_1=forced expiratory volume in 1 second; TNSS=Total Nasal Symptom Score; NSS=nasal symptom score; CFD=computational fluid dynamics; CT=computed tomography; mCSA=mean cross-sectional area; 4PR=four phase rhinomanometry; NSD=nasal septal deviation; nNO=nasal nitric oxide; ECP=eosinophil cationic protein; NPT=nasal provocation test; MCCT=mucociliary clearance time; POCT=point of care test; FeNO=fractional exhaled nitric oxide

*LOE downgraded due to failure to include relevant studies and for misclassifying one included study

**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

***LOE downgraded as not all patients in the AR group were diagnosed with SPT or RAST

****LOE downgraded as only included 3 studies

*****LOE downgraded due to the limited number of patients

******LOE downgraded as retrospective and not blinded

#paper not included in systematic review.[448]

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[448]	2021	2*	Systematic review	Patients with sinonasal disorders, including AR	Correlation between ARM and PROMs	-Majority (9) studies showed no correlation with PROMs -Four studies showed variable strength of significant correlation -In AR patients a weak-moderate correlation with PROMs was found
Eguiluz-Gracia et al[460]	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[451]	2019	3	Prospective validating cohort	AR with asthma AR without asthma, n=24	NAC, cytokines, ARM at 3cm, RM (posterior and passive anterior RM), FEV_1, TNSS, NSS	-ARM closely associated with symptom scores -ARM had excellent reproducibility
Aksoy et al[437]	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[436]	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 = 0.37cm^2
Isaac et al[461]	2015	3**	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
Wandalsen et al[455]	2016	4	Case-controlled 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 5cm had the highest sensitivity and specificity
Wandalsen et al[462]	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 2.2-5.4cm
Passali et al[435]	2000	4***	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[457]	2018	5	Position paper	Patients with nasal obstruction (including AR)	Evaluation of nasal obstruction	ARM better than RM for NPT
Ozturk et al[463]	2004	5****	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 -Study was excluded in the AR group in the systematic review[448]

LOE=level of evidence; AR=allergic rhinitis; ARM=acoustic rhinometry; PROM=patient reported outcome measure; NAC=nasal allergen challenge; NOSS=Lebel nasal ocular symptom score; PPV=positive predictive value; NPV=negative predictive value; RM=rhinomanometry; FEV_1=forced expiratory volume in 1 second; TNSS=Total Nasal Symptom Score; NSS=nasal symptom score; CCCRC=Connecticut Chemosensory Clinical Research Center; CFD=computational fluid dynamics; CT=computed tomography; NOSE=Nasal Obstruction Symptom Evaluation; VAS=visual analog scale; mCSA=mean cross-sectional area; NPT=nasal provocation test; AAR=anterior active rhinomanometry; MCCT=mucociliary clearance time

*LOE downgraded due to failure to include relevant studies and for misclassifying one included study.

**Study used unvalidated subjective scoring systems, was not blinded and only 22% of population had AR

***LOE downgraded as no data provided for correlation analysis

****LOE downgraded due to uneven groups

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[429]	2021	2*	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 128.4L/min, and for obstructed population 97.5L/min
Ta et al[448]	2021	2**	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[433]	2021	3***	Cross-sectional, blinded	Rhinitis and control, n=256	PNIF, SNOT-22, VAS	-PNIF cut-off of ≤95L/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[464]	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[465]	2018	3	Non controlled, non-randomized clinical trial	AR undergoing AIT, n=19	TNSS, PNIF	Modest correlation between TNSS and PNIF
Boelke et al[289]	2017##	3****	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[428]	2020	4*****	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 27.93L/min and of PNIF 19.74L/min
Valero et al[457]	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

LOE=level of evidence; AR=allergic rhinitis; PROM=patient reported outcome measure; VAS=visual analog scale; NOSE=Nasal Obstruction Symptom Evaluation; PNIF=peak nasal inspiratory flow; SRMA=systematic review and meta-analysis; SNOT-22=Sinonasal Outcome Test (22 item); PPV=positive predictive value; NPV=negative predictive value; QOL=quality of life; KINDL-R=generic assessment of health related quality of life for children and adolescents; AIT=allergen immunotherapy; TNSS=Total Nasal Symptom Score; PNEF=peak nasal expiratory flow; NMCCT=nasal mucociliary clearance time; MCID=minimal clinically important difference
*LOE downgraded due to heterogeneity of included studies
**LOE downgraded due to failure to include relevant studies and for misclassifying one included study
***LOE downgrade due to vague inclusion criteria
****LOE downgraded as study involved grass pollen exposure, yet participants were atopic to grass and/or birch pollen and/or HDM
*****LOE downgraded due to lack of blinding and significant gender asymmetry
Paper excluded from both systematic reviews[429,448]

X.G. Exhaled nitric oxide

NO is a volatile gas which functions as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator in the airway.[466] NO is formed in the upper and lower respiratory tract with high concentrations found in the nasal cavity and paranasal sinuses,[467-469] 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 modify NO levels.[470] Height and body surface area may also modify NO in pediatric population.[470-473]

Fractional exhaled nitric oxide (FeNO). FeNO is a measurement of NO in orally exhaled breath. The American Thoracic Society published recommendations for FeNO measurement.[474] 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.[475] FeNO is primarily utilized in the diagnosis and monitoring of therapeutic response and compliance in asthma,[476-479] 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.[480-483] This finding was also seen in a

large population study from the Netherlands which showed independent association of elevated FeNO in patients with positive skin testing, eczema, or AR.[475] **[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.[473] Pediatric patients also show decreased FeNO after appropriate medical therapy.[484-486]

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.[487] Additionally, there is no agreed upon cut off to indicate an abnormal result for the diagnosis of AR versus asthma.[474]

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.[488] nNO is reduced in several rhinologic diseases, including primary ciliary dyskinesia and cystic fibrosis, but is elevated in AR.[484,488-490]

Three small case-control studies have shown significant increase in nNO when comparing non-atopic healthy adults with atopic adults without asthma.[489,491,492] Additionally, two systematic reviews (total n=953 and n=4093, respectively) showed significant increase in nNO in healthy controls versus patients with AR.[493,494] However, these results conflict with other small case control studies showing no difference.[495-497] There is a reported nNO increase during pollen season in AR patients,[492] and reduction after appropriate medical treatment of atopy.[470] **[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.[498] Even small differences in testing application dramatically changes captured NO, making comparisons across research groups and establishment of normative values challenging.[488] There is currently no agreed upon cut off point for the diagnosis of AR.

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 atopic and non-atopic 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 $7000-10000 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.

Benefit: Possible benefit in differentiation of atopic and non-atopic rhinitis through non-invasive means

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 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[482]	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 vs AR and healthy controls -No difference in FeNO between AR and healthy controls
Choi et al[483]	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 vs healthy controls -FeNO positively correlated to total IgE, number of positive SPTs, and peripheral eosinophils
Bencova et al[480]	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 vs controls -FeNO in atopic individuals increased in allergy season -FeNO decreased with topical steroid and oral antihistamine treatment
Hervas et al[499]	2008	4	Case-control	-Healthy children -Asymptomatic atopy -AR without recent exacerbation	-Allergy sensitization -FeNO -Spirometry	-All groups had statistically higher FeNO vs controls -FeNO higher in patients with active AR, allergic asthma

				-AR with one exacerbation in last month -Allergic asthma without rhinitis -Allergic asthma with rhinitis -All groups, n=15		without rhinitis, and allergic asthma and rhinitis vs asymptomatic atopy and AR without recent exacerbation
Van Asch et al[475]	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 vs control
Franklin et al[473]	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 vs controls -FeNO >18.4 ppb had 81.1% sensitivity and 78.6% specificity for diagnosis of AR
Martin et al[491]	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 10s, breath-holding 60s, and nasal breathing

LOE=level of evidence; AR=allergic rhinitis; IgE=immunoglobulin E; SPT=skin prick test; FeNO=fractional exhaled nitric oxide; NO=nitric oxide; s=seconds

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[494]	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 vs control and NAR -4 studies listed cut-off values to discriminate between AR and health controls
Ambrosino et al[493]	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[492]	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 vs NAR -nNO significantly increased during pollen season in allergic patients
Lee et al[489]	2012	4	Case-control	-AR, n=35 -Healthy controls, n=34	-nNO -FeNO	-nNO significantly higher in AR -FeNO significantly higher in

					-Laboratory evaluation (eosinophils, IgE)	AR
Moody et al[496]	2006	4	Case-control	-Perennial AR -Non-atopic subjects	-Validated symptom questionnaire -FeNO -nNO	-nNO levels were not elevated in subjects with perennial AR vs non-atopics -nNO was higher in HDM and cat allergic subjects
Maniscalco et al[495]	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[497]	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 vs controls -nNO was not different in AR vs controls
Baraldi et al[486]	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 vs controls -Topical steroid significantly decreased nNO -No difference in nNO with antihistamine

LOE=level of evidence; SRMA=systematic review and meta-analysis; nNO=nasal nitric oxide; AR=allergic rhinitis; NAR=non-allergic rhinitis; TNSS=Total Nasal Symptom Score; FeNO=fractional exhaled nitric oxide; IgE=immunoglobulin E; HDM=house dust mite; NO=nitric oxide

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.[500] In resource-poor settings, SPT, serologic testing, or other advanced technologies, may not be available to confirm the diagnosis.[52,131,204,501] Furthermore, VCOS offer a more structured and standardized means of obtaining the clinical history and assessing treatment response.

These patient reported outcome measures focus on varying aspects of AR.[502] 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), 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.[503-508] Recently, VCOS have been adapted for use in smartphone applications that track AR symptomatology and medication use.[509-514]

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.[515-533] The TNSS is typically administered as a daily survey comprised of only 4 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-hour nighttime and 12-hour daytime average (rTNSS). The TNSS score 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.[534] 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.[523] The Respiratory Allergy Prediction (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.[530]

If conjunctivitis is to be assessed simultaneously with rhinitis symptoms, then the Rhinitis Total Symptom Score (RTSS) can be combined with Rescue Medication Score (RMS) to yield the combined score (CS).[531] 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 property of evaluating sexual function in AR patients.[532,533] The SNOT-22 has also been validated for use in AR patients.[535]

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.

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 misdiagnoses 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.

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	Rhinoconjunctivitis	28	Yes	No	0-168	Reflective assessment of previous week's

Quality of Life Questionnaire						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
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

1 AR=allergic rhinitis; AC=allergic conjunctivitis; NAR=non-allergic rhinitis; CRS=chronic rhinosinusitis

[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.

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[536]	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[507]	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[523]	2010	2	Cross-sectional	Adults with AR & 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[520]	2002	2	Cross-sectional	-AR confirmed by physician & SPT -Individuals by telephone interview	SFAR	SFAR value $\geq$7 allowed satisfactory discrimination between AR from those without (sensitivity 74%, specificity 83%, PPV 84%, NPV 74%)
Sousa-Pinto et al[512]	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, & 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[509]	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
Galimberti et al[530]	2015	3	Cohort	AR, AC, asthma	Evaluation of RAP (Respiratory Allergy Prediction) 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[522]	2014	3	Cohort	806 children, adolescents and adults with grass-pollen-induced ARC	MCID of RTSS	-RTSS vs 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[524]	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[526]	2020	4	Case series	Children with comorbid asthma & 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[510]	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[535]	2020	4	Case series	Patients with AR	SNOT-22, EQ-5D, RCAT	SNOT-22 reliable and responsive in patients with AR
Kupczyk et al[537]	2020	4	Case series	Patients with asthma & 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[527]	2020	4	Case series	Children & adolescents from 3 allergy centers	CARAT, CARATkids, ACT, CACT, GINA disease control classification, VAS; & lung function	CARAT and CARATkids are disease-control measurements that give additional information to other tests
Werner et al[538]	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[511]	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[539]	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[508]	2016	4	Case series	AR: children, adolescents, & adults	RTSS, VAS, RQLQ	-Although symptom perception differed in children vs 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[518]	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
Hafner et al[515]	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[521]	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[525]	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

LOE=level of evidence; AR=allergic rhinitis; AIT=allergen immunotherapy; SLIT=sublingual immunotherapy; CARAT=Control of Allergic Rhinitis and Asthma Test; ACT=Asthma Control Test; VAS=visual analog scale; SPT=skin prick test; SFAR= Score For Allergic Rhinitis; PPV=positive predictive value; NPV=negative predictive value; app=application; EQ-5D=EurQol-5 Dimensions; WPAI-AS= Work Productivity and Activity Impairment Allergic Specific Questionnaire; AC=allergic conjunctivitis; RAP= Respiratory Allergy Prediction; PCP=primary care provider; ARC=allergic rhinoconjunctivitis; MCID=minimal clinically important difference; RTSS=Rhinoconjunctivitis Total Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; GCRS= global rating of change scale; RAPP=RhinAsthma Patient Perspective; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; CACT=Childhood Asthma Control Test; HRQOL=health related quality of life; GINA=Global Initiative for Asthma; QOL=quality of life; SNOT-22-Sinonasal Outcome Test (22 item); RCAT=Rhinitis Control Assessment Test; SF-12=Short Form (12 item); GRS=global rating scale; ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; TNSS=Total Nasal Symptom Score

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XI. Management

XI.A. Allergen avoidance and environmental controls

XI.A.1. House dust mites

HDMs are a common trigger of AR.[1] Therefore, reducing exposure to HDM through physical barriers and chemical treatments are potentially important options in the management of AR.[1-5] **[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.[6-12] While several interventions have reduced the concentration of environmental HDM antigens,[6-10] an associated improvement in clinical symptoms has not been reliably demonstrated. Ghazala et al[6] and Terreehorst et al[10] 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[13] 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[14] 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.[7] Using a cross-over study design, Chen et al[15] 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[16] suggest acaricides, either as a single measure or in combination with other measures, are the most effective intervention for reducing HDM levels and improving AR symptoms.

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: Mild 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.

TABLE XI.A.1. Evidence table – Allergen avoidance: house dust mite

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Nurmatov et al[1]	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[16]	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[15]	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 vs placebo group; decline in HDM antigen was reportedly “more obvious” -No severe adverse events reported
Jeon et al[12]	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[11]	2017	2	Pilot, double blind, crossover RCT	-Adults with AR and probiotic	-HDM (Der p 1) concentration -Symptom scores	-No difference in HDM levels between

				impregnated bedding, n=20 -Adults with AR and placebo bedding, n=20	-QOL scores -Use of reliever medication	intervention and placebo bedding -Differences in secondary outcome measures between intervention and placebo not significant
Stillerman et al[17]	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
Brehler and Kniest[18]	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[6]	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[10]	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[8]	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[14]	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[7]	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[13]	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
Reisman et al[9]	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

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; HDM=house dust mite; HEPA=high-efficiency particulate air; QOL=quality of life; AR=allergic rhinitis; PAF=personal air filtration; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; VAS=visual analog scale; PEF=peak expiratory flow; IgE=immunoglobulin E

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 educational-based interventions with physical methods.[19] The greatest challenges in controlling cockroach infestation and reducing allergen concentrations are in densely populated inner-city areas that contain multi-occupant housing.[20,21]

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,[22-30] however some studies included treatments targeted at reducing multiple allergens (e.g., HDM, cockroach, rodent, cat, dog).[31,32] 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.[22-27,31,32] Although Bla g 1 and Bla g 2 allergen levels were reduced below 8U/g in some homes, clinical benefits in sensitized individuals were not achieved.[23,26-29] One study found Bla g 1 concentrations could be decreased below targeted thresholds for most apartments using a building-wide cockroach control program.[30] **[TABLE XI.A.2.]**

The most effective treatment for eliminating infestation and reducing allergen load was professional pest control.[24] 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.[22] Bait traps, including labor and monitoring costs, were estimated to be less expensive than commercially applied insecticide sprays.[22] 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.[24,33] Arbes et al[24] and Sever et al[33] 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.[27]

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.[29] Effectively controlling cockroach infestation and allergen levels within multi-family buildings and apartments requires implementation of a building-wide management program.[30] Thus, it is difficult to dramatically reduce cockroach allergen levels in the home unless a significant reduction in cockroach counts is maintained over time.[22] 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.[31,32] No studies included any assessment of symptoms or clinical endpoints associated with AR.

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 & 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.

TABLE XI.A.2. Evidence table – Allergen avoidance: cockroach

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Le Cann et al[19]	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[22]	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[31]	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[23]	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[24]	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
Morgan et al[32]	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[25]	2003	2	RCT	-Professional cleaning & professional pest control (insecticide bait traps) -Professional cleaning & 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[26]	2001	2	RCT	-Professional cleaning; insecticide bait traps, sodium hypochlorite	No direct clinical endpoints	-Professional extermination treatments reduced CR numbers and

				-Control homes: no cleaning, extermination, or bleach solution		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[27]	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[30]	2020	3	Single group, non-controlled time series	Building-wide cockroach 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 & Bla g 2 concentrations significantly reduced from 0-6 months and 6-12 months
Williams et al[29]	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 & Bla g 2 allergen concentration -No significant difference between active and placebo homes
Eggleston et al[28]	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

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; HDM=house dust mite; CR=cockroach; HEPA=high-efficiency particulate air

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.[5,34-36] 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.[34] 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.[37,38] **[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.[39] However, single-modality environmental control has not been associated with improved symptoms despite identified reductions in environmental antigens. Wood et al[40] 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.[41,42]

Aggregate grade of evidence: C (Level 2: 2 studies, level 3: 2 studies, level 4: 1 study; **TABLE XI.A.3.**)

Benefit: Decreased environmental antigen 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.

TABLE XI.A.3. Evidence table – Allergen avoidance: pets

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bjornsdottir et al[39]	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[40]	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[42]	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[41]	1996	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[34]	2015	4	Cohort	Patients with diagnosed allergy	-Sensitization to household animals -Compliance with avoidance	Avoidance recommendations may be impractical with high rates of sensitization, indirect

					recommendations and EC	exposure, and low rates of compliance

LOE=level of evidence; RCT=randomized controlled trial; EC=environmental controls; HEPA=high-efficiency particulate air

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.[31,43-47] 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.[48] **[TABLE XI.A.4.]**

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.[49-52] 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.[48,53]

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.[34,54] 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.[55] 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.[55]

Integrated pest management for rodent infestation. Integrated pest management (IPM) encompasses the initial removal of allergen reservoirs and habit modifications to reduce the risk of infestation recurrence.[48] These interventions include home-based education, rodent 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.[48] *(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.[31,43-47] 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 one 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.[44]

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.[31,43-47] 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.

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.

TABLE XI.A.4. Evidence table – Allergen avoidance: rodents

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Matsui et al[43]	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[47]	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 vs. sham -No change in medication requirements or other asthma clinical measures
Pongracic et al[45]	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[31]	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[46]	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 vs. control
Grant et al[44]	2020	3	RCT*	-Professional integrated pest management + education -Education alone	Lung function	Mouse allergen reduction was related to an increase in prebronchodilator FEV_1
Jacobs et al[51]	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
Kellberger et al[50]	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[49]	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[54]	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[34]	2015	4	Observational ambispective cohort**	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[48]	2012	4***	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[55]	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[52]	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[53]	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

LOE=level of evidence; RCT=randomized controlled trial; HDM=house dust mite; CR=cockroach; FEV_1=forced expiratory volume in 1 second; FeNO=fractional exhaled nitric oxide; QOL=quality of life; HEPA=high-efficiency particulate air; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval

*****LOE downgraded due to selective outcome reporting

**LOE downgraded due to selective sampling

***LOE upgraded due to established methodology, several rounds of review, long history of EBM guideline development

XI.A.5. Pollen

For pollen sensitized patients, avoidance or environmental control measures are often the first recommended intervention to decrease exposure and symptoms.[56] This approach is derived from the experience in which nasal or inhalational allergen challenges induce inflammatory changes and clinical symptoms after exposure.[57] 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.[58] A more realistic goal is a reduction in exposure to pollens rather than complete elimination[59] 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.[60] Cabin air filters in cars, pollen screens, eyeglasses, and mouth-nose covering masks may reduce exposures.[61] Pollen counts tend to be higher on sunny, windy days with lower humidity.[56] 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.[62] 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.[63] While allergen avoidance is endorsed by national and international guidelines,[64,65] 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.[66] 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.[67] 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.[68] 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.]**

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.

TABLE XI.A.5. Evidence table – Allergen avoidance: pollen

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chen et al[68]	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 vs. control
Chen et al[69]	2020	2	RCT, double-blind	90 patients with *Artemisia* (mugwort) sensitization randomized to HEPA air purifier use vs. placebo air filter	-Symptom severity and QOL -RQLQ	Allergy symptom scores significantly improved with HEPA air filter use
Comert et al[66]	2016	2	RCT	70 patients with seasonal AR randomized to medical therapy alone vs. medical therapy + wraparound eyeglasses	-Symptom scores -Rescue medication use -RQLQ	Wraparound eyeglasses improved symptoms, QOL, and rescue medication use vs medical therapy alone
Kenney et al[67]	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 vs placebo

LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; QOL=quality of life; HEPA=high-efficiency particulate air; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; AR=allergic rhinitis; TNSS=Total Nasal Symptom Score

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.[57] Early diagnosis is crucial not only for managing rhinitis symptoms but also potentially preventing the development of coexisting occupational asthma.[70,71] 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.[72]

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. Nasal provocation tests may be pursued but the validity of this testing is often poorly defined.[56] 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 exposure may be an acceptable alternative.[73] 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.[70]

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, acrylates) were assessed at diagnosis and follow up, with a mean time interval of 4.7±1.3 years.[74] 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.[75] 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.[76] 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 compared to high exposure areas.[77] 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.[78]

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.)*

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.

TABLE XI.A.6. Evidence table – Allergen avoidance: occupational

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions

Castano et al[74]	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[75]	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[76]	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	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[78]	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

LOE=level of evidence; OR=occupational rhinitis; QOL=quality of life

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.[79] Antihistamines are inverse agonists of histamine and cause histamine receptors to convert to an inactive state.[80] 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.[81,82] These side

effects can be more pronounced in the elderly, so first generation antihistamines should be used with caution.[83] Newer-generation antihistamines (e.g., bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, 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.[82]

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.[84] 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 also recommended newer-generation antihistamines over first-generation antihistamines for the management of AR.[81,85]

The ARIA guidelines 2010 revision made a strong recommendation for newer-generation antihistamines that are non-sedating and do not interact with cytochrome p450.[86] 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.[87] 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.[88] 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.[88] 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 1 in 5 prescriptions was not redeemed.[89] 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.[90] 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.[79,82,90] The indirect costs amongst newer-generation oral antihistamines are similar given the similar side effect profiles.

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.

TABLE XI.B.1.a.-1 List of commonly used newer-generation antihistamines[85]

Antihistamine	Onset (h)	Duration (h)	Drug Interactions	Elimination (h)	Dosage	
					Adults	Children
Bilastine	2 h	24 h	Unlikely	14.5 h	20 mg QD	N/A
Cetirizine (Zyrtec)	0.7 h	>24 h	Unlikely	6.5-10 h	5-10 mg QD	2-5 y; 2.5 mg or 5 mg QD 6-12 y: 5-10 mg QD
Desloratadine (Clarinex)	2-2.6 h	>24 h	Unlikely	27 h	5 mg QD	2-5 y: 1.25 mg QD 6-11 y: 2.5 mg QD

Fexofenadine (Allegra)	1-3 h	>24 h	Unlikely	11-15 h	60 mg BID or 180 mg QD	2-11 y: 30 mg BID
Levocetirizine (Xyzal)	0.7 h	>24 h	Unlikely	7 h	5 mg QD	2-5 y: 1.25 mg QD 6-11 y: 2.5 mg QD ≥ 12 y: 2.5-5 mg QD
Loratadine (Claritin)	2 h	>24 h	Unlikely	7.8 h	10 mg QD or 5 mg BID	2-5y; 5 mg QD ≥ 6 y; 10 mg QD

h=hours; QD=daily; BID=twice daily

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
Miligkos et al[91]	2021	1	SR of 45 RCTs	Children ≤12 years old on: -OAH -Montelukast -Placebo	-Adverse event -Drug-related adverse events -Treatment discontinuations	Newer-generation OAHs have a favorable safety and tolerability profile
Zhang et al[92]	2021	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
Sastre[93]	2020	1	SR of 15 RCTs	Adolescent and adult patients treated with ebastine	-Relief of allergy symptoms -Safety & tolerability	Ebastine is an effective and well-tolerated newer-generation antihistamine for the treatment of AR
Mullol et al[94]	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[95]	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[96]	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[97]	2013	1	SR of 10 clinical trials	Patients (n=140,853;	-TSS -TNSS	Second-generation levocetirizine

				≥12 years old) treated with: -Desloratadine -Ebastine -Fexofenadine -Levocetirizine		significantly improved symptom scores, especially in severe AR
Compalati et al[98]	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 vs placebo
Ferrer[99]	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 reactions	-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
Mosges et al[100]	2011	1	SR of 7 RCTs	AR patients (n=2238; ≥6 years old treated with: -Levocetirizine -Loratadine	-TSS -DNS -DES	Improvement in TSS, total 5 symptoms score, daytime nasal symptoms, and QOL
Bachert[101]	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 & obstruction	OAH efficacious for improving subjective and objective measures, effective in relieving nasal congestion associated with AR
Katiyar & Prakash[102]	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 & van Cauwenberge[103]	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	Desloratadine is well tolerated and efficacious for intermittent and persistent AR with

					-TNNSS -PNIF -Intermittent, persistent, seasonal, perennial AR	reductions in congestion, TSS, TNSS, TNNSS, and improved QOL
Canonica et al[104]	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[105]	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[106]	2005	1	SR of 7 RCT	Adult patients treated with OAH or placebo	Nasal obstruction	OAH improve nasal obstruction by 22% over placebo
Passalacqua & Canonica[107]	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
Greisner[108]	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[109]	2003	1	SR of 9 RCTs	Patients (≥12 years old) treated with desloratadine	-TSS -TNSS -TNNSS -Nasal congestion & 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[110]	2019	4	Cross sectional	Patients using INCS and/or OAH who completed a mobile allergy diary and (n=9122)	VAS	-Increased medication use associated with increased symptoms -Patients treat themselves as needed for symptoms despite physicians recommending long-term treatment
Scadding[111]	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[85]	2015	4	SR with guideline (9 CPGs, 81 SR & 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[86]	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[84]	2004	4	ARIA/EAACI criteria for antihistamines	Desloratadine	ARIA/EAACI criteria efficacy, safety, pharmacology	Desloratadine recommended for treating patients with AR

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; OAH=oral antihistamine; INCS=intranasal corticosteroid; AIT=allergen-specific immunotherapy; TNSS=Total Nasal Symptom Score; VAS=visual analog scale; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; PNIF=peak nasal inspiratory flow; AR=allergic rhinitis; ARIA=Allergic Rhinitis and its Impact on Asthma; TSS=Total Symptom Score; QOL=quality of life; ESS=Epworth Sleepiness Scale; QT= measure of time between the onset of ventricular depolarization and completion of ventricular repolarization on electrocardiogram; DNS=daytime nasal symptoms; DES=daytime eye symptoms; TSSC=Total Symptom Severity Complex; DTSSm=Mean Total Daily Symptom Score; DSSm=Mean Daily Symptom Score; TNNSS=Total Non-Nasal Symptom Score; TASS=Total Asthma Symptom Score; CS=consensus statement; EAACI=European Academy of Allergy and Clinical Immunology; CPG=clinical practice guideline

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)[112] 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[113] 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[114] found similar improvement in nasal airway resistance between cetirizine and ranitidine, but a significant improvement with the use of combination therapy. Wang et al[115] also showed improvement in nasal airflow with combination therapy of cimetidine and cetirizine. Havas et al[116] measured the nasal airflow resistive response to topical histamine and also found that combined histamine antagonism with diphenhydramine 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.[117,118] 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.[115,117-119] 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[119] randomized 23 subjects with known late-summer AR to receive alternating two-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 eight 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.[113-116] However, the clinical significance of this mechanism is not clear, particularly in the context of modern treatment algorithms.[115-119] 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.

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 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 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.

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[114]	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 & Bende[117]	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[115]	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[113]	1996	2	RCT	Allergy challenge with premedication:	-Nasal lavage fluid protein	-Ranitidine improved nasal resistance more than

				-PO cetirizine -PO ranitidine	concentration -Nasal airway resistance	cetirizine -Cetirizine decreased total protein and albumin more than ranitidine
Havas et al[116]	1985	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[119]	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 & medication scores in chlorpheniramine-cimetidine
Brooks et al[118]	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

LOE=level of evidence; RCT=randomized controlled trial; PO=per os (by mouth)

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[120-143] and 29 studies with an inactive placebo arm.[123,124,128-130,132,134,136,138,140,141,144-161] Monotherapy with azelastine was reported in 37 studies[120,121,123,125-132,134-144,147-152,156-164] while monotherapy with olopatadine was reported in 10 studies.[122,124,145,146,149,151,153-155,163] 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 (7 studies), the Total Ocular Symptom Score (TOSS, 5 studies), the Caregiver Treatment Satisfaction Questionnaire (2 studies), the Pediatric RQLQ (1 study), the SF-36 (1 study), the ESS (1 study), the Rhinitis Severity Score (1 study) and a Subjective Global Assessment (1 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 (3 studies), response to methacholine challenge (2 studies), nasal flow rate (2 studies), and rhinomanometry (1 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, [123,124,128-130,132,134,136,138,140,141,144-161] 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.[120-143] The intranasal antihistamine spray treatment group consistently had a more rapid onset of action than the treatment comparator, occurring as early as 15 minutes after administration, although this was not reported in all studies. Azelastine and olopatadine were directly compared in 3 studies, with no significant difference in symptom relief between agents.[149,151,163] Azelastine was compared with an experimental formulation of intranasal levocabastine in 2 additional studies, with either comparable or superior results for azelastine.[162,164] 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 2 studies,[123,124] INCS in 3 studies,[130,132,159] and showing equivalency in 7 studies.[120-122,136,140,141,143] Superiority of the antihistamine for treating ocular symptoms was found in 2 studies, one of which was nearly 30 years old.[121,141] The 3 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 8 studies, with superiority of intranasal antihistamine in 3 studies,[125,127,135] and equivalency in 5 studies.[129,137-139,142] One study included a treatment arm with oral chlorpheniramine as a positive control without intent to compare efficacy with azelastine.[134] Azelastine monotherapy was at least as effective as combination therapy in a single study comparing azelastine spray versus oral loratadine plus intranasal beclomethasone.[131] Combination therapy with intranasal azelastine plus oral antihistamine was not found to confer additional benefit in 2 studies compared to intranasal azelastine monotherapy.[128,129] An overall dose-response relationship was found in 11 studies that included comparison of multiple dose concentrations of intranasal antihistamine. [134,138,146-148,151-155,161]

Most of the included studies set a minimum enrollment age of 12 years or older. Three studies that included children aged between 6-12 years old found superiority of intranasal antihistamine to placebo in improving symptoms and QOL.[145,146,158]

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.[147] Olopatadine was reported to have better sensory attributes than azelastine in one study.[163] 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.

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.

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[120]	2012	2	DBRCT (post-hoc analysis)	-Azelastine 0.28mg BID -Fluticasone propionate 0.1mg spray BID	-rTNSS -rTOSS -RQLQ	Fluticasone superior to azelastine for improving rhinorrhea; comparable symptom and QOL improvement
Han et al[162]	2011	2	DBRCT	-Azelastine 0.1% -Levocabastine hydrochloride 0.05% spray	rTNSS	Comparable symptom improvement
Howland et al[144]	2011	2	DBRCT	-Azelastine 0.82mg BID -Placebo	-rTNSS -rTOSS -RQLQ	Azelastine superior to placebo for nasal and eye symptoms and QOL
Meltzer et al[145]	2011	2	DBRCT	-Olopatadine 1.33mg BID -Placebo	-rTNSS -rTOSS -PRQLQ -CGTSQ-AR	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers
Kalpaklioglu & Kavut[121]	2010	2	Single-blind RCT	-Azelastine 0.56mg BID -Triamcinolone acetonide 0.22mg 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[146]	2009	2	DBRCT	-Olopatadine 1.33mg BID -Olopatadine 2.66mg 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[147]	2009	2	DBRCT	-Azelastine 0.28mg BID -Reformulated azelastine 0.28mg BID -Azelastine 0.56mg BID -Reformulated azelastine 0.56mg 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[122]	2009	2	DBRCT	-Olopatadine 2.66mg BID -Fluticasone 0.2mg spray QD	-rTNSS -rTOSS	Both treatments improve symptoms; faster onset for olopatadine
Shah et al[148]	2009	2	DBRCT	-Azelastine 0.82mg BID -Azelastine 0.56mg BID	TNSS	Both azelastine doses superior to placebo;

				-Placebo		greater improvement with higher dose
Shah et al[149]	2009	2	DBRCT	-Olopatadine 2.66mg BID -Azelastine 0.56mg BID -Placebo	TNSS	Both treatments superior to placebo; no difference between treatments; less bitter taste with olopatadine
van Bavel et al[150]	2009	2	DBRCT	-Azelastine 0.82mg QD -Placebo	TNSS	Azelastine superior to placebo
Meltzer et al[163]	2008	2	DBRCT	-Olopatadine 2.66mg BID -Azelastine 0.56mg BID	Sensory perception	Olopatadine favored for taste, aftertaste, and likelihood of use
Pipkorn et al[151]	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[152]	2007	2	DBRCT	-Azelastine 0.28mg QD -Azelastine 0.28mg BID -Placebo	TNSS	Azelastine both doses superior to placebo
Patel et al[123]	2007	2	DBRCT	-Azelastine 0.56mg QD -Mometasone furoate 0.2mg spray QD Placebo	TNSS	Azelastine superior to mometasone and placebo
Patel et al[124]	2007	2	DBRCT	-Olopatadine 2.66mg QD -Mometasone furoate 0.2mg spray QD -Placebo	-TNSS -Patient satisfaction	Olopatadine superior to placebo and mometasone in reducing symptoms; faster onset for olopatadine
Berger et al[125]	2006	2	DBRCT	-Azelastine 0.56 mg BID, -Cetirizine 10mg tablet QD	-TNSS -RQLQ	Azelastine superior for sneezing and nasal congestion; azelastine superior for QOL
Hampel et al[153]	2006	2	DBRCT	-Olopatadine 2.66mg BID -Olopatadine 1.77mg BID -Placebo	-Total symptom score -RQLQ	Olopatadine (both doses) superior to placebo in majority of domains for QOL improvement
Horak et al[126]	2006	2	DBRCT	-Azelastine 0.4mg QD -Desloratadine 5mg tablet QD -Placebo spray	TNSS	Azelastine superior to desloratadine and placebo
Corren et al[127]	2005	2	DBRCT	-Azelastine 0.56mg BID -Cetirizine 10mg tablet QD	-TNSS -RQLQ	Azelastine superior cetirizine for symptoms and QOL
Meltzer et al[154]	2005	2	DBRCT	-Olopatadine 2.66mg BID -Olopatadine 1.77mg BID -Placebo	-TNSS -RQLQ	Olopatadine (both doses) superior to placebo for symptoms and QOL improvement
Ratner et al[155]	2005	2	DBRCT	-Olopatadine 2.66mg BID -Olopatadine 1.77mg BID -Placebo	TNSS	Olopatadine (both doses) superior to placebo

LaForce et al[128]	2004	2	DBRCT	-Azelastine 0.56mg BID -Azelastine 0.56mg BID + fexofenadine 60mg tablet BID -Placebo spray + placebo tablet	TNSS	Azelastine superior to placebo; no additional benefit of adding oral fexofenadine to azelastine monotherapy
Berger et al[129]	2003	2	DBRCT	-Azelastine 0.56mg BID -Azelastine 0.56mg BID + loratadine 10mg tablet -Desloratadine 5mg 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[156]	2002	2	DBRCT	-Azelastine 0.28mg 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[164]	2001	2	DBRCT	-Azelastine 0.56mg BID -Levocabastine 0.2mg spray BID	-10-item symptom score -Global assessment	Azelastine superior to levocabastine
Berlin et al[130]	2000	2	DBRCT	-Azelastine 0.56mg BID -Flunisolide 0.116mg spray BID -Placebo	9-item symptom score	Flunisolide superior to azelastine; both treatments superior to placebo
Golden et al[157]	2000	2	DBRCT	-Azelastine 0.56mg BID -Placebo	-RSS -ESS	Azelastine superior to placebo for improving rhinorrhea and sleep quality
Berger et al[131]	1999	2	DBRCT	-Azelastine 0.56mg BID -Loratadine 10mg tablet QD + beclomethasone dipropionate 0.168mg spray BID	-5-item symptom score -Global evaluation	Azelastine at least as effective as combination therapy with loratadine plus beclomethasone spray
Stern et al[132]	1998	2	DBRCT	-Azelastine 0.28mg BID -Budesonide 0.256mg spray QD -Placebo	3-item symptom score	Budesonide superior to azelastine; both treatments superior to placebo
Herman et al[158]	1997	2	DBRCT	-Azelastine 0.28mg BID -Placebo	TNSS	Azelastine superior to placebo for children
Newson-Smith et al[159]	1997	2	DBRCT	-Azelastine 0.56mg BID, -Beclomethasone 0.2mg 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 & Meltzer[160]	1997	2	DBRCT	-Azelastine 0.56mg spray BID + azelastine 0.5mg tablet BID	13-item symptom score	Azelastine spray showed limited benefit over placebo in patients already

				-Placebo spray + azelastine 0.5mg tablet BID		treated with systemic azelastine
LaForce et al[134]	1996	2	DBRCT	-Azelastine 0.56mg QD -Azelastine 0.56mg BID -Chlorpheniramine 12mg tablet BID -Placebo	8-item symptom score	Azelastine superior to placebo at both doses; no comparison with chlorpheniramine
Charpin et al[135]	1995	2	DBRCT	-Azelastine 0.28mg BID -Cetirizine 10mg tablet QD	8-item symptom score	Azelastine superior for nasal stuffiness and rhinorrhea; no difference in other symptoms
Pelucchi et al[136]	1995	2	DBRCT	-Azelastine 0.28mg BID -Beclomethasone dipropionate 0.1mg 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[137]	1994	2	DBRCT	-Azelastine 0.28mg QD -Terfenadine 60mg tablet QD	13-item symptom score	Comparable symptom improvement
Meltzer et al[138]	1994	2	DBRCT	-Azelastine 0.28mg QD -Azelastine 0.28mg BID -Chlorpheniramine 12mg tablet BID -Placebo	11-item symptom score	Azelastine comparable to chlorpheniramine and superior to placebo at both doses
Passali & Piragine[139]	1994	2	DBRCT	-Azelastine 0.28mg BID -Cetirizine 10mg tablet QD	13-item symptom score	Azelastine at least as effective as cetirizine
Ratner et al[161]	1994	2	DBRCT	-Azelastine 0.28mg QD -Azelastine 0.28mg BID -Placebo	8-item symptom score	Azelastine twice-daily superior to placebo
Davies et al[140]	1993	2	DBRCT	-Azelastine 0.28mg BID -Beclomethasone dipropionate 0.1mg spray BID -Placebo	-TNSS -Rhinomanometry	Azelastine superior to beclomethasone and placebo for symptoms; no change in airway resistance with either treatment
Dorow et al[141]	1993	2	DBRCT	-Azelastine 0.28mg BID -Budesonide 0.10mg 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[142]	1993	2	DBRCT	-Azelastine 0.28mg BID -Loratadine 10mg tablet QD	-12-item symptom score -Global assessment	Azelastine at least as effective as loratadine
Gastpar et al[143]	1993	2	DBRCT	-Azelastine 0.28mg BID	-10-item symptom score	Azelastine at least as effective as budesonide for

				-Budesonide 0.10mg spray BID	-Nasal flow rate	symptoms; flow rate improved in both treatment groups

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; BID=twice daily; r=reflective; TNSS=Total Nasal Symptom Score; TOSS=Total Ocular Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; QOL=quality of life; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; CGTSQ-AR=Caregiver Treatment Satisfaction Questionnaire for Allergic Rhinitis; RCT=randomized controlled trial; QD=daily; PNIF=peak nasal inspiratory flow; ESS=Epworth Sleepiness Scale; SF=36=Short Form (36-item); mRQLQ=mini-Rhinoconjunctivitis Quality of Life Questionnaire; SGA=Subject Global Assessment

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[165] 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[166,167] 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 60mg 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[168] demonstrated that 15 days of cortisone (25mg QID [four times daily]) during the ragweed season resulted in significant relief of symptoms in 21 of 25 patients. Schiller and Lowell[169] showed that cortisone (100mg 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.[169] Oral hydrocortisone (40-80mg daily) has been shown to reduce symptoms of ragweed allergies.[170] In a placebo-controlled study performed during the ragweed season, Brooks et al[171] compared the efficacy of methylprednisolone (6, 12, or 24mg 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 6mg and 12mg 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[172] performed a parallel, double

blind study comparing betamethasone 1mg 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.,[57] 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.[173] 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[174] 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 10mg daily alone, loratadine with intranasal mometasone furoate (200μg once daily), or loratadine with oral betamethasone 0.25mg 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.

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.

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[172]	2004	2	Parallel, double-blind, active controlled multicenter study	Patients with severe AR treated for 5-7 days (n=299): -Betamethasone 1.0mg -Betamethasone 1.0mg + loratadine 10mg -Betamethasone 0.5mg + loratadine 10mg -Loratadine 10mg	-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[171]	1993	2	Placebo-controlled, parallel group study	Patients with SAR during the season (n=31): methylprednisolone 6, 12, 24mg QD x 5 days	Symptom scores	All doses more effective than placebo in reducing symptoms; highest dose was most effective
Bascom et al[167]	1989	2	Placebo-controlled, cross over, nasal challenge study	SAR out of season (n=13): prednisone 60mg 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[166]	1988	2	Placebo-controlled, cross over, nasal challenge study	SAR out of season (n=10): prednisone 60mg 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[165]	1987	2	Placebo-controlled, cross over, nasal challenge study	SAR out of season (n=13): prednisone 60mg 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[173]	1985	2	Multicenter, randomized, double-blind, placebo-controlled	Patients with SAR during season (n=99): -Oral flunisolide 500μg BID -Intranasal flunisolide 50μg per nostril BID x 4 weeks	Symptom scores	Intranasal preparation only one to show efficacy in reducing rhinitis symptoms.

Karaki et al[174]	2013	3	Open label, parallel, randomized trial	Patients with SAR during season (n=72): -Loratadine 10mg daily -Loratadine + intranasal MF (200μg QD) -Loratadine + PO betamethasone 0.25mg BID x 1 week.	Symptom scores	-Groups on steroids had lower symptoms compared to loratadine alone -No significant difference between steroid groups
Schwartz[170]	1954	4	Observational case series	Patients with SAR during season (n=10): hydrocortisone 40 to 80mg QD	Symptom relief	7/10 patients reported symptom relief
Schiller & Lowell[169]	1953	4	Observational case series	Patients with SAR during season (n=51): cortisone 100mg QD x 4 days	Symptom relief	42/51 patients reported symptom relief
Schwartz et al[168]	1952	4	Observational case series	Patients with SAR during season (n=25): cortisone 100mg QD x 15 days	Symptom relief	21/25 patients reported symptom relief

LOE=level of evidence; AR=allergic rhinitis; SAR=seasonal allergic rhinitis; QD=daily; PO=per os (by mouth); MBP=major basic protein; EDN=eosinophil derived neurotoxin; TAME= N-a-p-tosyl-L-arginine methyl ester; PGD2=prostaglandin D2; LTC4/D4= leukotriene C4/D4; MF=mometasone furoate; BID=twice daily

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 mucosa.[175-179] INCS also reduce the antigen-induced hyperresponsiveness of the nasal mucosa to subsequent challenge.[176,180,181]

Clinical trials in adults and children have demonstrated the effectiveness of INCS in the reduction of nasal symptoms in AR.[182-184] INCS also significantly improve patients' QOL[183,185,186] and sleep.[187-191] Onset of action starts at time points ranging from 3-5 hours to 60 hours after dosing.[192-195] Although the continuous daily use of INCS is overall superior,[196,197] studies have demonstrated the superiority of as needed use of intranasal fluticasone propionate over placebo[198,199] and one study showed equivalence of as needed to continuous dosing.[200] **[TABLE XI.B.2.b.i.-1]**

INCS have beneficial effects on allergic eye symptoms,[201-204] secondary to a reduction in the naso-ocular reflex.[205] This effect is not equal among preparations.[206] Some, but not all, studies have suggested that INCS improve asthma control measures and asthma exacerbations.[207-209] **[TABLE XI.B.2.b.i.-2]**

In comparative studies there are no significant differences in efficacy between the available agents,[185] and one study shows an advantage of using double dosing.[210] 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.[211-213] However, for fast relief of nasal congestion (one hour after dosing) a combination of loratadine-pseudoephedrine was superior to intranasal fluticasone propionate.[214] INCS are more effective than LTRAs.[213,215,216] **[TABLE XI.B.2.b.i.-3]**

Different preparations of INCS are comparable in efficacy, making sensory attributes an important factor in patient preference.[217] These include aftertaste, nose runout, throat rundown, and odor; there are minor differences between preparations.[218] Two intranasal nonaqueous preparations with hydrofluoroalkane aerosols, beclomethasone dipropionate and ciclesonide, address some of these concerns.[219-224]

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.[225,226] In studies carried over one year, epistaxis is as high as 20%.[227,228] Septal perforations are rare complications of INCS.[229] 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.[230] Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis and adrenal insufficiency show no clinically relevant adverse effects.[228,231-243] Although there exists a report of association between INCS use and development of posterior subcapsular cataracts,[244] 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.[245,246] 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 8 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).[247] 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 (2 studies show growth increase and 2 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]**

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**, **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 have known undesirable local adverse effects such as epistaxis with some 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.

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[186]	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 & OSA
Rodrigo & Neffen[183]	2011	1	SRMA	-16 trials, n=5348 patients -FFNS vs placebo -Seasonal AR (7 studies), perennial AR (9 studies) -Adolescents & 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 vs placebo in patients with seasonal and perennial AR -FFNS led to greater improvements in QOL -FFNS had a favorable safety profile
Penagos et al[182]	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 & congestion, rhinorrhea, sneezing, nasal itching

Thongngarm et al[200]	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[184]	2019	2	Post-hoc analysis of 2 RCTs	-Patients with seasonal AR and moderate-severe nasal congestion, n=684 -MFNS vs 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 vs first
Yamada et al[191]	2012	2	DBRCT, crossover	-Patients with perennial AR, n=57 -MFNS vs 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
Meltzer et al[190]	2010	2	DBRCT, parallel group	-Adults with moderate perennial AR & disturbed sleep, n=30 -MFNS 200μg daily vs 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, & 2 of 5 WPAI-AS domains
Kaiser et al[194]	2007	2	DBRCT, parallel group	-Patients ≥12 years old with fall seasonal AR, n=299 -FFNS 110μg daily vs placebo	-Nasal and ocular symptoms -rTNSS, iTNSS, rTOSS	FFNS produced significantly greater improvements in daily rTNSS & rTOSS, morning pre-dose iTNSS, and patient-rated overall response to therapy
Craig et al[188]	2003	2	DBRCT	-Patients with perennial AR, n=32 -Fluticasone NS 100μg per nostril daily vs placebo	Questionnaires, QOL instruments, daily diary, ESS, polysomnography	-Fluticasone improved subjective sleep vs placebo -No difference in the AHI in treated subjects
Dykewicz et al[199]	2003	2	DBRCT	-Patients ≥12 years old with seasonal AR in the fall, n=241 -FPNS 200μg as needed x4 weeks	TNSS	FPNS group had significantly greater reduction in TNSS & individual symptoms

Hughes et al[189]	2003	2	DBRCT, crossover	-Patients with perennial AR, n=22 -Budesonide 128μg/day vs 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 vs placebo
Fokkens et al[193]	2002	2	DBRCT, parallel group	-Patients 6-16 years old with perennial AR, n= 202 -BANS 128μg daily vs 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 hours for symptoms and within 48 hours for PNIF
Day et al[192]	2000	2	DBRCT, parallel group	-Ragweed-sensitive subjects, n=217 -BANS (64μg and 256μg) vs 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 hours, BANS better than placebo in reducing combined nasal & blocked nose symptoms -For PNIF, time to onset of action was shortest for BANS 256μg
Jen et al[198]	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 & level of eosinophilic cationic protein in nasal lavage	-Nasal symptom score reduced and QOL improved with FPNS vs placebo -Eosinophil number significantly lower with FPNS vs placebo at final visit
Craig et al[187]	1998	2	DBRCT	Patients with perennial AR treated with INCS vs 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 & Carrillo[195]	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 vs placebo -Adverse events were mild and transient
Juniper et al[196]	1990	2	DBRCT, parallel group	-Ragweed-sensitive adults, n=60 -Aqueous BDNS 200μg BID -Aqueous BDNS 100μg as needed, up to 400μg 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 vs to the as-needed group

Herman[185]	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 & adverse event profiles -Based on sensory attributes, patients preferred BANS and TANS
Juniper et al[197]	1993	3	Unblinded RCT, parallel group	-Adults with ragweed pollen-induced rhinitis, n=60 -BDNS 400μg 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

LOE=level of evidence; AR=allergic rhinitis; INCS=intranasal corticosteroid; OSA=obstructive sleep apnea; SRMA=systematic review and meta-analysis; FFNS=fluticasone furoate nasal spray; r=reflective; TNSS=Total Nasal Symptom Score; i=instantaneous; TOSS=Total Ocular Symptom Score; QOL=quality of life; DBRCT=double-blind randomized controlled trial; MFNS=mometasone furoate nasal spray; TNNSS=Total Non-Nasal Symptom Score; RCT=randomized controlled trial; PNIF=peak nasal inspiratory flow; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; ESS=Epworth Sleepiness Scale; AHI=apnea-hypopnea index; WPAI-AS=Work Productivity and Activity Impairment-Allergy Specific; FPNS=fluticasone propionate nasal spray; BANS=budesonide aqueous nasal spray; BDNS=beclomethasone dipropionate nasal spray; BID=twice daily; TANS=triamcinolone aqueous nasal spray

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[204]	2020	1	Meta-analysis of 8 RCTs	Patients with seasonal AR (n=1727) treated for ≥2 weeks: -TANS 220μg daily, n=859 -FPNS 200μg 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 vs placebo -No significant difference between TANS and FPNS for total ocular symptoms
Lohia et al[208]	2013	1	SRMA	Patients with AR and asthma, 18 trials, n=2162 patients	Pulmonary function, bronchial reactivity, asthma symptom scores, asthma specific	-INCS spray significantly improved FEV_1, bronchial challenge, asthma symptom scores, morning/evening peak

					QOL, rescue medication use	expiratory flow, and rescue medication use -No significant changes in asthma outcomes with addition of INCS spray to orally inhaled corticosteroids
Bielory et al[202]	2011	1	Meta-analysis of 10 RCTs	-Patients with seasonal AR (6 studies) and perennial AR (4 studies), n=3132 -MFNS 200μg 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[201]	2003	1	Pooled data from 7 multicenter DBRCTs	Each study evaluated the efficacy of FPNS 200μg 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 vs placebo at both time points
Taramarcaz et al[207]	2003	1	Meta-analysis of RCTs	-Subjects with asthma and AR, 14 trials, n=477 -INCS vs 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[203]	2015	2	DBRCT	-Patients with seasonal AR, n=614 -FPNS 200μg x14 days -Placebo	rTOSS	FPNS more efficacious in reducing the ocular symptoms of AR vs placebo
Baroody et al[205]	2009	2	DBRCT	-Subjects with seasonal AR outside of their allergy season, n=20, underwent allergen challenge after 1 week of treatment -FFNS 110μg daily -Placebo	Nasal and ocular symptoms after allergen challenge	Pretreatment with FFNS significantly reduced eye symptoms following nasal allergen challenge
Yu et al[209]	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 years and 7-18 years

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; TANS=triamcinolone acetonide nasal spray; FPNS=fluticasone propionate nasal spray; SRMA=systematic review and meta-analysis; QOL=quality of life; INCS=intranasal corticosteroid; FEV_1=forced expiratory volume in one second; DBRCT=double-blind randomized controlled trial; TOSS=Total Ocular Symptom Score; r=reflective; FFNS=fluticasone furoate nasal spray

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
Khattiyawit-tayakun et al[210]	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- vs 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[213]	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[215]	2004	1	SRMA	-11 studies on seasonal AR -8 evaluating LTRA alone or with other treatments vs 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 & Rodrigo[212]	2002	1	SR of RCTs	-9 studies, AR patients, n=648 -INCS vs topical antihistamines	Total nasal symptoms, sneezing, rhinorrhea, itching, nasal blockage	-INCS produced greater relief of nasal symptoms vs topical antihistamines -No difference in relief of the ocular symptoms
Weiner et al[211]	1998	1	Meta-analysis of RCTs	-16 trials, subjects with AR, n=2267 -INCS vs oral antihistamines	Nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, nasal discomfort, total nasal symptoms,	-INCS had greater relief than oral antihistamines in nasal blockage, discharge, sneezing, nasal itch, postnasal drip, total nasal symptoms

					nasal resistance, eye symptoms, global ratings	-No significant differences between treatments for nasal discomfort, nasal resistance, eye symptoms
Ng et al[214]	2021	2	DBRCT, crossover	-Patients with ragweed AR challenged in environmental exposure chamber -Randomized to receive 1 of 4 treatment sequences (loratadine 5mg-pseudoephedrine 120mg [LP] tablet, placebo tablet, FPNS 2 sprays in each nostril, placebo spray), n=82	Percent change in PNIF from baseline to 4 hours after dosing	Average change in PNIF was 31% with LP, significantly greater than with placebo and FPNS (12% and 15%, respectively)
Bhattachan et al[216]	2020	2	Prospective, randomized, parallel, cross-sectional	-Patients with AR treated for 1 month, n=126 -MFNS -Oral montelukast	TNSS	-Significant reduction of TNSS vs baseline in both groups -MFNS significantly more effective than montelukast

LOE=level of evidence; SRMA=systematic review and meta-analysis; INCS=intranasal corticosteroid; TNSS=Total Nasal Symptom Score; TOSS=Total Ocular Symptom Score; SR=systematic review; RCT=randomized controlled trial; AR=allergic rhinitis; US=United States; LTRA=leukotriene receptor antagonist; DBRCT=double-blind randomized controlled trial; LP=loratadine-pseudoephedrine; FPNS=fluticasone propionate nasal spray; PNIF=peak nasal inspiratory flow; MFNS=mometasone furoate nasal spray

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[243]	2021	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[246]	2019	1	SRMA	-10 studies for qualitative synthesis, 4 studies for meta-analysis, n=2226, years of 1947-2018 -INCS vs. placebo for rhinitis and their effect on IOP, cataracts, or glaucoma	Increased IOP above 20mm Hg, or formation of posterior subcapsular cataracts	-RR of elevated IOP with INCS was 2.24 vs 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[245]	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 vs control
Mener et al[247]	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 vs placebo -Stadiometry: no significant growth difference in INCS vs placebo
Verkerk et al[230]	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
Hampel et al[242]	2015	2	DBRCT	Patients with perennial AR (6-11 years old) treated for 6 weeks: -BDP nasal aerosol 80μg/day, n = 67 -Placebo, n=32	Change from baseline in 24-hour 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[226]	2009	2	Sub-analysis of 3 DBRCTs	-Children (6-11 years old) with AR, n=948 -Once-daily treatment with either FFNS 55μg, FFNS 110μg, or placebo	Adverse event monitoring, nasal examinations, ophthalmic examinations, 24-hour 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[228]	2009	2	RCT	-Children (6-11 years old) with perennial AR treated for 12 months, n=255 -MFNS 100μg daily	Symptom control and safety	-Appropriate symptom control in both groups

				-BDPNS 168μg daily		-Incidence of epistaxis was 12.7% with MFNS and 9.4% for BDPNS
Tripathy et al[241]	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-hour serum and urine cortisol	-FFNS non-inferior to placebo for 24-hour serum cortisol change from baseline -24-hour urine cortisol excretion similar between groups
Weinstein et al[240]	2009	2	DBRCT, parallel group	-Children (2-5 years old) with perennial AR treated for 4 weeks, n=474 -TANS 110μg 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[225]	2008	2	DBRCT	Children (2-11 years old) with perennial AR treated for 12 weeks, n=558 -FFNS 110μg daily -FFNS 55μg 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 55μg reduced nasal symptoms significantly vs placebo
Patel et al[239]	2008	2	DBRCT, parallel group	-Patients (12-65 years old) with perennial AR, n=112 -FFNS 110μg daily for 6 weeks -Prednisone 10mg daily for last 7 days of study -Placebo	Change in 24-hour serum cortisol and 24-hour 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-hour urinary cortisol excretion similar in FFNS and placebo groups -Plasma levels of FF undetectable after 6 weeks of treatment
Chervinsky et al[238]	2007	2	DBRCT	Patients (≥12 years old) with perennial AR treated up to 52 weeks, n=663) -Ciclesonide 200μg daily -Placebo	Adverse events and exam findings, 24-hour urine free cortisol, morning plasma cortisol, IOP, lens opacification	No clinically relevant differences between ciclesonide and placebo groups
Kim et al[237]	2007	2	Two phase 3 RCTs,	-Children (2-5 years old) with perennial AR treated for 6 or 12 weeks	-Cortisol levels -Systemic exposure of ciclesonide	-Changes in plasma

			parallel group	-Ciclesonide 200μg daily	and its active metabolite, des-CIC, examined at end of 6-week study	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[227]	2007	2	DBRCT, parallel group	-Patients with perennial AR treated for 12 months, n=806 -FFNS 110μg -Placebo	Adverse events, 24-hour 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[236]	2003	2	DBRCT	Children (2-3 years old) with AR treated for 6 weeks, n=65 -FPNS 200μg daily -Placebo	12-hour creatinine-corrected urine free cortisol	No significant difference between FPNS and placebo

LOE=level of evidence; SRMA=systematic review and meta-analysis; INCS=intranasal corticosteroids; AI-adrenal insufficiency; IOP=intraocular pressure; RR=relative risk; SR=systematic review; RCT=randomized controlled trial; AR=allergic rhinitis; CRS=chronic rhinosinusitis; DBRCT=double-blind randomized controlled trial; FFNS=fluticasone furoate nasal spray; HPA=hypothalamic-pituitary axis; MFNS=mometasone furoate nasal spray; BDPNS=beclomethasone dipropionate nasal spray; TANS=triamcinolone acetonide nasal spray; FF=fluticasone furoate; FPNS=fluticasone propionate

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[248] conducted a prospective, single center double-blind RCT in 52 patients with AR Patients received buffered hypertonic saline nasal irrigation (60ml each nostril twice daily) with either a placebo or a budesonide respule (0.5mg/2ml) 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[249] investigated the effect of budesonide administered by nebulization in patients with perennial AR. Patients received either budesonide (0.25mg) 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[250] 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.[251] Active treatment did improve FEV_1 and asthma symptoms. In a similar study, Camargos et al[252] randomized patients with AR and asthma to either fluticasone propionate hydrofluoroalkane (FP-HFA) (100-150μg) 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[253] 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, 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[254] or iatrogenic Cushing syndrome.[255] In a study comparing fluticasone

propionate administered as nasal drops or aqueous spray, the drops had 8 times more systemic bioavailability than the spray.[256]

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 above were not performed in patients with AR or were case reports so are not summarized in the table below.
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.

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[248]	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 (60ml/nostril) with budesonide (0.5mg/2ml)	-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[249]	2014	2	DBRCT, parallel pilot study	Patients with perennial AR (n=40) treated with NasoNeb daily for 26 days: -Budesonide (0.25mg) -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[250]	2013	2	DBRCT	Children with grass AR/asthma (n=40):	-Nasal and oral FeNO	-Nasal IL-5 significantly reduced & nasal pH

				-Nebulized BDP (400μg BID) -Placebo *Treatment for 4 weeks after a 2-week run-in *Inhalation via nose and mouth	-PFTs -Nasal and oral pH and IL-5 -Nasal and bronchial symptom scores	significantly increased with BDP -Reduction in nasal obstruction, sneezing, rhinorrhea with BDP, no change with placebo, no significant difference between groups
Camargos et al[252]	2007	2	RCT	Patients with AR/asthma (n=60, 6-18 years old) treated BID x8 weeks: -FP-HFA (100-150μg) 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
Shaikh[253]	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 & 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 ($p<0.001$)

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; BID=twice daily; SNOT-22=Sinonasal Outcome Test (22 item); VAS=visual analog scale; r=reflective; TNSS=Total Nasal Symptom Score; PNIF-peak nasal inspiratory flow; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; BDP=beclomethasone dipropionate; FeNO=fraction of exhaled nitric oxide; PFT=pulmonary function test; IL=interleukin; PCT=randomized controlled trial; FP-HFA=fluticasone propionate hydrofluoroalkane; FEV_1=forced expiratory volume in 1 second; MDI=metered dose inhaler

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.[257-260] **[TABLE XI.B.2.c.]**

Studies comparing different intramuscular steroid preparations have showed improvement of symptoms with all variations but some differences in efficacy among them.[261-264] 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[265] and more effective than daily intranasal beclomethasone dipropionate in controlling nasal itching, congestion, rhinorrhea and eye symptoms.[260] In another seasonal study, a single injection of methylprednisolone was as effective as intranasal budesonide over a 3 week treatment period.[266] 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.[267]

Injectable corticosteroid preparations have significant potential side effects which can include adrenal suppression and growth retardation.[268] **[TABLE II.C.]** Injectable corticosteroids affected adrenal function in 2 out of 4 relevant studies.[262,266] **[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 3 consecutive years during the allergy season compared to those receiving AIT.[269] Laursen et al[265] 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[261] 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.[270-274] 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.[275]

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;[276] blurred vision and temporary blindness;[277] and temporary distorted vision, decreased visual acuity, and paresis of the medial rectus.[277] Martin reported on the rapid onset of ocular pain, blurred vision, and decreased visual acuity after an intra-turbinate injection of triamcinolone acetonide.[278] Symptoms were caused by choroidal and retinal arterial embolization and resolved completely within 24 hours. A more recent report detailed progression of glaucoma-related optic neuropathy after intra-turbinate injection associated with chorioretinal microvascular embolism.[279] 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).[278] Moss et al[280] reported on personal experience with 152 turbinate and 85 intrapolyp injections of triamcinolone acetonide, noting one transient subjective decrease in vision after intrapolyp 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% (3 instances), with a 0.00% (0 instances) rate of permanent visual complications.

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.

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[267]	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 vs placebo or other therapies -4 studies showed equal efficacy outcomes vs. controls -SR judged inconclusive because of the epidemiological high risk of bias and older studies
Yang et al[275]	2008	2	Randomized, placebo-controlled single-blind	Patients with perennial AR (n=39) received intraturbinate injections: -Botox A (25 units each turbinate) -Triamcinolone (20mg each turbinate) -Isotonic saline (1cc 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[260]	1988	2	Double blind, double dummy, placebo-controlled	Patients with SAR during season (n=30): -Intranasal beclomethasone dipropionate (400μg daily x4 weeks) -IM injection of 2ml 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[266]	1988	2	Double blind, comparative	Patients with SAR (n=30) treated x3 weeks: -Budesonide nasal spray (400μg/d) -Methylprednisolone acetate IM 80mg	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[258]	1987	2	Double-blind, placebo-controlled, parallel	Patients with SAR during 2 consecutive allergy seasons (n=24), received injections each season:	-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

				-Methylprednisolone IM 80mg -Placebo		-Effect obtained irrespective of timing of therapy -Best to administer as soon as symptoms start during the season
Laursen et al[265]	1987	2	Randomized, double-blind comparative	Patients with SAR during season (n=37): -Oral prednisolone 7.5mg PO daily x3 weeks -Single IM injection of 2ml 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[262]	1980	2	Prospective, randomized, parallel group	Patients with SAR during season (n=60) received one of 3 long-acting injections: -Betamethasone dipropionate (5mg) -Betamethasone disodium phosphate-acetate (3mg-3mg) -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[261]	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 (40mg/ml)	Weekly nasal and ocular symptoms x5 weeks	-Both preparations significantly reduced nasal and ocular symptoms -Betamethasone combination was more effective
Axelsson & Lindholm[259]	1972	2	RCT	Patients with allergic & vasomotor rhinitis (n=38): -Triamcinolone acetonide 40mg -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[263]	1969	2	Randomized trial	Patients with perennial AR (n=70) given IM: -Dexamethasone (8 or 16mg) -Cortisone acetate (10mg)	Subjective symptom relief (complete, marked, moderate, slight, no relief)	More complete and marked relief with dexamethasone preparations vs cortisone acetate
Chervinsky[264]	1968	2	Randomized, comparative	Patients with SAR (n=97) poorly responsive to	Patient satisfaction (none, poor, fair,	All treatments were beneficial with no difference between them

				hyposensitization or with no previous treatment received single injection: -Methylprednisone 80mg -Betamethasone phosphate-acetate (6mg-6mg) -Dexamethasone acetate-phosphate disodium (16mg-4mg) -Dexamethasone acetate 16mg	good, excellent) at 2 weeks	
Brown et al[257]	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 (80mg) -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[280]	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, 3 with visual complications (0.003%); all resolved spontaneously, no permanent visual deficits
Aasbjerg et al[269]	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 & diabetes were higher in allergic individuals receiving at least one depot corticosteroid injection during the allergy season vs those receiving AIT

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; IM=intramuscular; SAR=seasonal allergic rhinitis; AR=allergic rhinitis; ACTH=adrenal corticotropic hormone; PO=per os (by mouth); PNIF=peak nasal inspiratory flow; AIT=allergen immunotherapy

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.[281] 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.[85,282-284] **[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.[284-288] 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.[283] With regard to the comparison of pseudoephedrine monotherapy 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.[283-288]

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[289] and more effective than placebo[290,291] in treating primary outcomes. One study showed that pseudoephedrine monotherapy was less effective than a combination therapy of an oral antihistamine and pseudoephedrine,[290] while another study showed no difference in outcome.[291] 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,[285,290] other studies have had different findings.[284-286,288,292] Nonetheless, either monotherapy (i.e., pseudoephedrine or antihistamine) was more effective than placebo.[283,285,290,291] Interestingly, an analysis of the effectiveness of phenylephrine compared to placebo has shown that phenylephrine (up to doses of 40mg six times daily) is not superior to placebo in relieving nasal congestion symptoms in AR patients.[293]

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.

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[293]	2015	2	Open-label RCT	SAR during season (n=539, 18-77 years old): -PE HCL 10mg -PE HCL 20mg -PE HCL 30mg -PE HCL 40mg -Placebo Study protocol: every 4 hours, up to 6 tablets/24h	Daily reflective nasal congestion score	PE HCL is not significantly better than placebo at relieving nasal congestion in adults with SAR
Grubbe et al[286]	2009	2	DBRCT	SAR during season (n=598, 12-76 years old): -Desloratadine 2.5mg + PSE 120mg BID -Desloratadine 5.0mg + placebo tablet daily -PSE 120mg 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 vs baseline
Mucha et al[289]	2005	2	DBRCT	SAR during season (n=58, 18-45 years old): -Montelukast 10mg daily -PSE HCL 240mg 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[294]	2005	2	DBRCT	SAR during season (n=1047, 12-78 years old): -Desloratadine 5mg + PSE 240mg	-Total symptom score (excluding nasal congestion)	-Desloratadine-PSE provided additional

				sustained release daily -Desloratadine 5mg daily -PSE 240mg sustained release daily	-Nasal congestion score	benefit over individual components alone -Monotherapies were equally effective and led to improved symptom scores vs baseline
Sussman et al[288]	1999	2	RCT	SAR during season (n = 651, 12-66 years old): -Fexofenadine HCL 60mg BID -PSE HCL 120mg BID -Fexofenadine HCL 60mg + PSE HCl 120mg 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 vs baseline
Grosclaude et al[284]	1997	2	DBRCT	SAR during season (n=687, 9-66 years old): -Cetirizine 5mg BID -PSE retard 120mg BID -Cetirizine 5mg + PSE retard 120mg 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 vs baseline
Bertrand et al[287]	1996	2	DBRCT	Perennial AR (n=215, 12-65 years old): -Cetirizine 5mg + PSE retard 120mg BID -Cetirizine 5mg BID -PSE retard 120mg BID	Severest symptom score	-Cetirizine-PSE was more effective than treatment with each individual agent -Cetirizine monotherapy was more effective than PSE in relieving sneezing, nasal, ocular pruritus
Dockhorn et al[285]	1996	2	DBRCT	SAR during season (n=702, 12-73 years old): -Acrivastine 8mg + PSE HCL 60mg QID -Acrivastine 8mg QID -PSE HCL 60mg 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 & nasal symptom scores, equally effective in reducing allergy symptom score -Both monotherapies were more effective than placebo

Bronsky et al[283]	1995	2	DBRCT	SAR season (n=879, 12-82 years old): -Loratadine 10mg + PSE sulfate 240mg extended release daily -Loratadine 10mg daily -PSE sulfate 120mg 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 -3 active treatment groups had better therapeutic response than placebo
Howarth et al[292]	1993	2	DBRCT, cross-over	Allergen challenge with premedication: *First part -- AR (n=12, 12-40 years old) -PSE 60mg -Placebo, pretreatment Study protocol: 6 tablets on two days before challenge, 1 tablet on the morning of challenge day *Second part – perennial AR (n=17, 19-56 years old) -PSE 120mg -Terfenadine 60mg -PSE 120mg + terfenadine 60mg -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
Henauer et al[290]	1991	2	RCT, cross-over	Allergen challenge with premedication, SAR (n=13, mean age 13 years): -Terfenadine 60mg rapid release + PSE 120mg controlled release -Terfenadine 60mg rapid release -PSE 120mg 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[291]	1984	2	DBRCT, cross-over	Allergen challenge with premedication, SAR (n=18, 19-38 years old): -Triprolidine 2.5mg + PSE 60mg -Triprolidine 2.5mg -PSE 60mg -Placebo	Nasal airway resistance	Tripolidine-PSE and its individual components were superior to placebo in reducing the increase in nasal resistance after histamine challenge

LOE=level of evidence; RCT=randomized controlled trial; SSAR=seasonal allergic rhinitis; PE=phenylephrine;
HCL=hydrochloride; DBRCT=double-blind randomized controlled trial; PSE=pseudoephedrine; BID=twice daily;

RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; PNIF=peak nasal inspiratory flow; QOL=quality of life; AR=allergic rhinitis; QID=four times daily

XI.B.3.b. Intranasal decongestants

INDC – oxymetazoline, xylometazoline, and phenylephrine – are alpha-adrenergic agonists acting as topical vasoconstrictors reducing edema/tissue thickness.[65] The highest level of evidence consists of 7 RCTs[295-301] looking at short-term effects of INDC. There are also 3 RCTs[302-304] and 2 cohort studies[305,306] 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.[295,296,298,299] Onset of action is within 10 minutes,[297] and duration of the effect lasts up to 12 hours.[301] There are also improvements in objective measures of nasal congestion/blockage, including nasal airway resistance, measures of nasal cavity volume for airflow, and PNIF.[296-300] Measures of nasal cavity volume for airflow exhibit a clear dose-response relationship across doses ranging from 6.25 to 50μg, with nasal airway resistance requiring a higher threshold dose of 25μg before significant changes in nasal patency are seen.[298] Despite oxymetazoline's vasoconstrictive effects, it does not seem to affect histamine-induced plasma exudation.[295] The majority of studies compared INDC to placebo,[295-298,300] but Barnes et al[299] found that the decongestant response was stronger for intranasal xylometazoline after 15 minutes than daily administration of intranasal mometasone furoate after 28 days. It is worth noting that only 3 studies included patients with AR,[299-301] the remainder consisted of healthy participants.[295-298]

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.[303,305,306] Another study, however, noted development of rhinitis medicamentosa after as little as 3 days of use.[302] This may be due to nasal hyperreactivity and mucosal swelling. Additionally, Graf et al[304] 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 1000μg/mL, but no significant difference at 500μg/mL.[307] The 500μg/mL (0.5 mg/mL, 0.05%) 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.[302]

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.

TABLE XI.B.3.b. Literature summary – Intranasal decongestants for allergic rhinitis*

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Druce et al[301]	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 hours post-treatment, there was a significant improvement in subjective nasal congestion and objective nasal flow rate vs control
Gomez-Hervas et al[297]	2015	2	DBRCT, cross-over	Healthy participants (n=8): -Intranasal oxymetazoline -Placebo	-PNIF during exercise -Parameters of exercise performance (e.g., oxygen consumption, ventilatory pattern, efficiency)	10 minutes after use, nasal airflow trended towards improvement with oxymetazoline, but this did not translate to improvements in exercise performance
Pritchard et al[300]	2014	2	RCT	Nasal congestion due to upper respiratory	-Inferior turbinate total volume	Up to and including 12 hours post-treatment,

				infection or hay fever (n=21): -Intranasal oxymetazoline -Placebo	-Middle turbinate total volume	there was a significant reduction in inferior and middle turbinate volumes with oxymetazoline vs placebo
Barnes et al[299]	2005	2	DBRCT, cross-over	AR (n=36): -Intranasal xylometazoline -Intranasal mometasone furoate (daily x28 days)	-PNIF -Nasal forced inspiratory volume in 1 second -Nasal blockage score	Xylometazoline 15-minute response was stronger for all endpoints than mometasone furoate 28-day response
Watanabe et al[303]	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 vs placebo
Bickford et al[296]	1999	2	DBRCT, cross-over	Healthy participants (n=20): -Intranasal oxymetazoline -Placebo	-Nasal airway resistance -Nasal cavity cross-sectional area and volume -Subjective congestion	Up to 120 minutes after treatment, all endpoints were significantly improved with oxymetazoline vs placebo
Taverner et al[298]	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 minutes after treatment, all endpoints except subjective nasal congestion were significantly improved with oxymetazoline vs placebo
Morris et al[302]	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 & Hallen[304]	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[295]	1992	2	DBRCT, cross-over	Healthy participants (n=12): -Intranasal oxymetazoline -Placebo	-Nasal symptoms (sneezing, nasal secretion, blockage) -Histamine-induced plasma exudation	Up to 130 minutes after treatment, there was a significant decrease in nasal blockage but not any of the other endpoints
Yoo et al[305]	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[306]	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

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; PNIF=peak nasal inspiratory flow; RCT=randomized controlled trial; TID=three times daily

*Limitation – only 3 of the listed studies specifically addressed the use of intranasal decongestants in patients with AR

XI.B.4. Leukotriene receptor antagonists

LTRAs have been studied and used 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 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,[308] 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[309-313] 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[314] which showed no difference between the two. Yoshihara et al[315] 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.[216,316,317] In a RCT by Chen et al,[316] 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[318] found 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,[319-321] with recent studies favoring oral antihistamines. Comparing diurnal symptoms of AR, Feng et al[319] 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.[309,322] Li et al[323] 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.[324]

In their 2015 guidelines for AR, the American Academy of Otolaryngology-Head and Neck Surgery recommended against LTRA monotherapy, as it was less effective than other first-line medications and more costly.[85] In 2020, this guideline was endorsed by the American Academy of Family Physicians.[325] 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.[65]

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.[308] 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.

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.

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[319]	2021	1	SR of RCTs	-LTRA -OAH	-Symptoms -QOL -Adverse events	-LTRA superior for nighttime symptoms -OAH superior for daytime symptoms
Meltzer et al[309]	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 -Ped SAR: LTRA superior to INCS, intranasal antihistamine (alone and with INCS), SLIT
Krishnamoorthy et al[310]	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[313]	2016	1	Pooled analysis	-Montelukast -OAH -INCS -SLIT -Placebo	TNSS	-LTRA superior to placebo -LTRA inferior to OAH, INCS, SLIT
Wei[312]	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[320]	2016	1	Network meta-analysis	-Montelukast -OAH	Symptoms	LTRA inferior to OAH
Devillier et al[322]	2014	1	SR of RCTs	-LTRA -SLIT -Placebo	Symptoms	-SLIT superior to LTRA -LTRA superior to placebo
Xu et al[321]	2014	1	SR of RCTs	-Montelukast -OAH	Symptoms	In SAR, OAH superior for daytime symptoms and LTRA superior for nighttime symptoms
Goodman et al[326]	2008	1	SR of RCTs	-Montelukast -Levocetirizine -Desloratadine -Fexofenadine	-Symptoms -Cost	Montelukast has higher incremental cost-effectiveness ratio than levocetirizine and desloratadine
Grainger & Drake-Lee[327]	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 & Yanez[328]	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[215]	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 & Partisan[329]	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[216]	2020	2	RCT	-Montelukast -INCS	TNSS	INCS superior to LTRA for symptom reduction
Li et al[323]	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[316]	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[314]	2018	2	RCT	-Montelukast -Placebo	Symptoms	No difference in LTRA vs placebo
Dalgic et al[318]	2017	2	RCT	-Montelukast -INCS -Montelukast + INCS	Olfactory testing	-No change with LTRA monotherapy -Combination therapy was superior to INCS

Okubo et al[311]	2017	2	RCT	-ONO-4053 (anti-PGD2) -Pranlukast -Placebo	Symptoms	-Pranlukast superior to placebo -ONO-4053 superior to pranlukast
Yoshihara et al[315]	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[317]	2016	2	RCT	-Montelukast -INCS	Symptoms	INCS superior to LTRA
Endo et al[330]	2012	2	RCT	-Pranlukast -Placebo	Symptoms	Following artificial introduction of allergen, pranlukast prevented and reduced symptoms vs placebo
Wakabayashi et al[331]	2012	2	RCT	-Pranlukast -Placebo	Symptoms	Following artificial introduction of allergen in children, pranlukast prevented and reduced symptoms vs placebo
Day et al[332]	2008	2	RCT	-Montelukast -Levocetirizine -Placebo	Symptoms	-Both montelukast and levocetirizine improved symptoms following artificial allergen exposure -Levocetirizine was more effective than montelukast
Jiang[333]	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[289]	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[334]	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[335]	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
Philip et al[336]	2004	2	RCT	-Montelukast -Placebo	-Symptoms -Rhinitis QOL -Asthma QOL	Montelukast improved symptoms, rhinitis QOL, and asthma QOL vs placebo in patients with SAR and asthma
Ratner et al[337]	2003	2	RCT	-Montelukast -Fluticasone	-Symptoms -QOL	Fluticasone was more effective than montelukast in reducing symptoms and improving QOL
van Adelsberg et al[338]	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[339]	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[340]	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[341]	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

LOE=level of evidence; SR=systematic review; RCT-randomized controlled trial; LTRA=leukorience receptor antagonist; OAH=oral antihistamine; QOL=quality of life; INCS=intranasal corticosteroid; SLIT=sublingual immunotherapy; TNSS=Total Nasal Symptom Score; SAR-seasonal allergic rhinitis; AR=allergic rhinitis; IL=interleukin; IFN=interferon; Th=T helper; FeNO=fraction of exhaled nitric oxide; ECP=eosinophil cationic protein; cysLT-cysteinyl leukotriene; PGD2=prostaglandin D2; PNIF=peak nasal inspiratory flow

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.[342,343] 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 hours, taken as 1 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.[344-347]

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.[348,349] Due to its high safety profile, this medication can be considered for very young children and pregnant patients.[350,351]

DSCG has been shown to be more effective than placebo patients with seasonal AR in controlling nasal symptoms of sneezing, rhinorrhea, and nasal congestion as treatment during their peak allergy season.[352-356] The largest double-blinded placebo-controlled trial included 1150 patients with seasonal AR treated for 2 weeks (580 patients on DSCG, 570 treated with placebo).[352] Patients received DSCG as a 4% nasal solution, 1 spray every 4-6 hours, no more than 6 times per day. DSCG was significantly better than placebo in controlling overall symptom relief ($p=0.02$), 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 size.[357-361] In the most recent study that demonstrated a benefit of DSCG in perennial AR (n=14), DCSG resulted in significant improvement in the symptoms scores of runny nose, nasal congestion, sneezing, and nose blowing, when compared to placebo ($p<0.005$).[357] 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.[357] **[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.[362] When compared to intranasal antihistamines[363,364] and INCS,[358,364-373] 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.

Aggregate grade of evidence: A (Level 2 studies: 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.

TABLE XI.B.5. Evidence table – Intranasal cromolyn for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lejeune et al[357]	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[373]	2006	2	RCT	Patients with moderate-severe SAR (12-57 years old): -MF 200µg each nostril daily, n=34 -Nedocromil sodium 1.3mg each nostril TID, n=27	Nasal symptoms	MF was more efficacious than DSCG
Lange et al[364]	2005	2	RCT	Patients with SAR (18-65 years old): -MF 200µg daily, n=41 -Levocabastine HCL 200µg BID, n=40 -DSCG 5.6mg 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[352]	2002	2	DBRCT	Patients with SAR (>12 years old: -DSCG 4% 1 spray q4-6hrs, n=580 -Placebo, n=570	Nasal symptoms	DSCG was more efficacious than placebo
Fisher[365]	1994	2	RCT, blinded	Patients with SAR (6-15 years old): -DSCG 6 times daily (31.2mg per day), n=26 -Budesonide BID (400µg per day), n=30	Nasal symptoms	Budesonide was more efficacious than DSCG
Bousquet et al[366]	1993	2	DBRCT No placebo	Patients with SAR: -FP 200µg QD, n=110 -DSCG 5.2mg 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[362]	1991	2	DBRCT	Patients with AR (12-56 years old): -DSCG 4%, 1 spray each nostril QID -Terfenadine PO BID	Nasal symptoms	No difference between groups

Schata et al[363]	1991	2	DBRCT	Patients with SAR: -Levocabastine HCL 0.5mg/ml, 2 sprays each nostril QID, n=18 -DSCG 20mg/ml, 2 sprays QID, n=19 -Placebo, n=20	Nasal/ocular symptoms	Levocabastine was most efficacious
Schuller et al[374]	1990	2	DBRCT	Patients with SAR (12-65 years old): -Nedocromil 1%, n=80 -DSCG 4%, 1 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[367]	1987	2	RCT	SAR (12-50 years old) -BDP 2 sprays BID (336µg/day), n=26 -Flunisolide 2 sprays BID (200µg/day), n=26 -DSCG 1 spray QID (41.6mg/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 & Illum[368]	1985	2	DBRCT	Patients with SAR (15-55 years old): -Budesonide 200µg BID, n=22 -DSCG 5.2mg 5 times daily, n=21	Nasal symptoms	Budesonide was more efficacious than DSCG
Morrow-Brown et al[369]	1984	2	RCT	Patients with SAR: (11-71 years old): -BDP 2 sprays BID (400 µg/day), n=47 -DSCG 2.6mg, 6 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[353]	1982	2	DBRCT, cross-over	Patients with SAR (n=47, 9-41 years old): -DSCG 4%, 1 spray q3-4 hours -Placebo	-Nasal symptoms -Medication use	DSCG was more efficacious than placebo for all endpoints
Brown et al[370]	1981	2	RCT	Patients with SAR: -DSCG 2.6mg, 6 times daily, n=29 -Flunisolide spray 25µg BID, n=38	Nasal symptoms	Flunisolide was more efficacious than DSCG
Tandon & Strahan[358]	1980	2	DBRCT, cross-over	Perennial AR due to animal dander (n=14, 13-45 years old: -BDP 50µg QID -DSCG 10mg QID	Nasal symptoms	BDP was more efficacious than DSCG
Craig et al[375]	1977	2	DBRCT	Patients with SAR: -DSCG 5.2mg, 6 times daily, n=22 -Placebo, n=17	-Nasal symptoms -Rescue medication use	No difference between groups
Handelman et al[354]	1977	2	DBRCT	Patients with SAR (6-51 years old): -DSCG 62.4mg, 6 times daily, n=45 -Placebo, n=45	-Symptom score -Rescue medication use	DSCG was more efficacious than placebo

McDowell & Spitz[359]	1977	2	DBRCT, cross-over	Patients with perennial AR (n=12, 17-71 years old): -DSCG 2.5mg, 6x daily -Placebo	-Nasal symptoms -Cytology	No significant difference in most patients
Nizami & Baboo[355]	1977	2	DBRCT, cross-over	Patients with SAR (n=92, 7-59 years old): -DSCG 10mg QID -Placebo	Nasal symptoms	DSCG was more efficacious than placebo
Posey & Nelson[376]	1977	2	DBRCT	Patients with SAR (n=32, 12-54 years old): -DSCG 4%, 6 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 & Kapstad[360]	1977	2	DBRCT, cross-over	Perennial AR (n=17, 15-57 years old): -DSCG 10mg QID -Placebo	Nasal symptoms	No difference between groups
Cohan et al[361]	1976	2	DBRCT, cross-over	Perennial AR (n=34, 16-37 years old): -DSCG 4%, 6 times daily -Placebo	-Symptom score -Rescue medication use	DSCG was more efficacious than placebo
Knight et al[356]	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 & Walker[371]	1976	2	RCT	Adults with SAR: -DSCG 10mg QID, n=10 -Beclomethasone valerate 100µg BID, n=10	Nasal symptoms	Beclomethasone was more efficacious than DSCG
Frankland & Walker[372]	1975	2	DBRCT	Adults with SAR: -DSCG 10µg in each nostril 4 times daily (80µg total daily dose), n=14 -Beclomethasone valerate 100µg in each nostril BID (400µg total daily dose), n=19	-Nasal symptoms -PNIF	-Betamethasone was more efficacious for symptom control -No difference between groups for PNIF

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; HDN=house dust mite; DSCG=disodium cromoglycate; QID=four times daily; RCT=randomized controlled trial; SAR=seasonal allergic rhinitis; MF=mometasone furoate; TID=three times daily; HCL=hydrochloride; BOD=twice daily; PNIF=peak nasal inspiratory flow; FP=fluticasone propionate; BDP=beclomethasone dipropionate

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 and was found to reduce rhinorrhea and sneezing with no effects on nasal airway resistance.[377,378] 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.[379] IPB is effective in controlling anterior rhinorrhea with no effect on nasal congestion or sneezing.[380-385] 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%).[383,386] It has a quick onset of action and short half-life and can be administered up to 6 times per day, with less than 10% absorption over a range of 84μg/day to 336μg/day.[387]

Intranasal IPB is poorly absorbed, and systemic side effects have not been observed with therapeutic dosing, as plasma concentrations of greater than 1.8ng/ml are needed to produce systemic anticholinergic effects.[387] 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.[388] 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.[386] In the double-blind RCT cross-over 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.[378] 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.[389] No head-to-head studies have

compared IPB to other AR medications.

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.

TABLE XI.B.6. Evidence table – Ipratropium bromide for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dockhorn et al[390]	1999	2	DBRCT	Perennial AR (8-75 years old): -IPB 0.03% (42µg) 2 sprays TID + BDP 82µg BID, n=109 -IPB 0.03% (42µg) 2 sprays TID, n=222 -BDP 82µg 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[389]	1999	2	RCT, blinded, no placebo	Perennial AR, non-allergic perennial rhinitis (6-18 years old): -IPB 0.03% (42µg) 2 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[391]	1998	2	DBRCT, cross-over	Perennial AR, (n=205, 18-75 years old): -IPB 0.03% (42µg) TID + terfenadine 60mg PO BID -Placebo + terfenadine	Nasal symptoms	-Control of rhinorrhea and sneezing better in IPB-terfenadine -No differences in nasal congestion
Kaiser et al[383]	1998	2	DBRCT	Adults with perennial AR: -IPB 0.06% (42µg) TID -IPB 0.06% (84µg) TID -Placebo	Nasal symptoms	High and low dose IPB resulted in significant reduction of nasal hypersecretion
Meltzer et al[388]	1997	2	DBRCT	Perennial AR & non-allergic rhinitis (6-18 years old): -IPB 0.03% (42µg) 2 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[392]	1993	2	DBRCT	Perennial AR (n=18, 23-33 years old): -IPB 80µg QID -Placebo	Sneezing	IPB resulted in increase in nasal reactivity to histamine, increase in number of sneezes

Meltzer et al[393]	1992	2	DBRCT	Perennial AR (18-70 years old): -IPB 21µg (n=48) or 42µg (n=54), 1 spray TID -Placebo (n=53)	Nasal symptoms	IPB effective in controlling rhinorrhea
Sanwikarja et al[378]	1986	2	DBRCT, cross-over	Seasonal or perennial AR (n=14), perennial non-allergic rhinitis (n=14), 18-49 years old: -IPB 80µg QID -Placebo	Nasal symptoms	IPB has suppressive effects on sneezing and hypersecretion but no influence on nasal airway resistance
Schultz Larsen et al[394]	1983	2	RCT, cross-over	Perennial AR (n=20, 23-84 years old): -IPB 80µg QID -Placebo	Nasal symptoms	IPB effective in controlling rhinorrhea
Borum et al[395]	1979	2	RCT, cross-over	Perennial AR (n=20, 18-82 years old): -IPB 20µg 1 puff QID -Placebo	Nasal symptoms	-Significant effect on rhinorrhea -No effect on other symptoms
Kim et al[386]	2005	3	Prospective	Common cold, seasonal/perennial AR (n=230, 2-5 years old): Allergy group -- IPB 0.06% (42µg) 1 spray TID for 14 days, n=187	Nasal symptoms	IPB effective in controlling rhinorrhea
Kaiser et al[384]	1995	3	Prospective	Perennial AR (n=219, 18-75 years old: -First six months: IPB 0.06% (84µg) 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

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; IPB=ipratropium bromide; TIC=three times daily; BDP=beclomethasone dipropionate; RCT=randomized controlled trial; BID=twice daily; QOL=quality of life; PO=per os (by mouth); QID=four times daily; PND=postnasal drainage

XI.B.7. Biologics

The biologics investigated for treating allergic conditions include omalizumab, mepolizumab, dupilumab, benralizumab and reslizumab.[396] 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 alpha subunit (recognized by IL-4 and IL-13); and mepolizumab, benralizumab and reslizumab on IL-5 or its receptor.[396] 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.[397]

Omalizumab interferes with the allergic cascade by binding the serum free IgE molecules and preventing them from attaching to mast cells and basophils.[398] 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 omalizumab.[399,400] The effectiveness of omalizumab monotherapy was assessed for both seasonal and perennial AR.[401-405] 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.[406,407] 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.[408]

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 total serum IgE level (IU/mL) and the body weight (kg) prior to the initiation of treatment where most studies used dosing from 75 to 375mg 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 $10,000-32,000 per year.[409]

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.[410] Dupilumab was shown to be effective when administered as an adjunct treatment in patients with uncontrolled persistent asthma and comorbid AR.[411] 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.[412] 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.[413] These results suggest dupilumab 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.[399]

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 for 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.

TABLE XI.B.7.-1 Evidence table – Omalizumab for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Yu et al[400]	2019	1	SRMA	-Omalizumab -Placebo n=3458	-Symptoms -Rescue medication -QOL	-Omalizumab superior to placebo -Generally, well tolerated
Tsabouri et al[399]	2014	1	SRMA	-Omalizumab -Placebo n=2870	-Symptoms -Rescue medication -QOL	-Omalizumab superior to placebo -Generally, well tolerated
Casale et al[414]	2006	2	RCT	-Omalizumab -Placebo	-Symptoms -Adverse events	-Omalizumab superior to placebo -Well tolerated
Okubo et al[405]	2006	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication	-Omalizumab effective and well tolerated in cedar pollen AR
Chervinsky et al[404]	2003	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	Omalizumab effective and well tolerated in perennial AR
Kuehr et al[415]	2002	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -Adverse events	-Omalizumab superior to placebo -Well tolerated

Casale et al[403]	2001	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	-Dose-finding trial, 300mg dose effective in improving symptoms and QOL vs placebo
Adelroth et al[402]	2000	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	-Omalizumab superior to placebo in improving symptoms and QOL -Well tolerated
Casale et al[401]	1997	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	-First dose-finding study -Safety confirmed

LOE=level of evidence; SRMA=systematic review and meta-analysis; QOL=quality of life; RCT=randomized controlled trial; AR=allergic rhinitis

TABLE XI.B.7.-2 Evidence table – Dupilumab for allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corren et al[413]	2021	2	Phase 2a RCT	-SCIT + dupilumab -SCIT -Placebo n=103	TNSS	-No difference between SCIT-dupilumab vs SCIT alone for TNSS -Reduction of rescue treatment with SCIT-dupilumab vs SCIT alone
Busse et al[412]	2020	3	Post hoc analysis of phase 3 study	-Add on therapy with dupilumab 200mg or 300mg -Placebo n=814	-RQLQ -Total and sIgE	Both dupilumab doses superior to placebo
Weinstein et al[411]	2018	3	Post hoc analysis of phase 2b study	-Dupilumab 200mg or 300 mg -Placebo n=392	SNOT-22	-Dupilumab 300mg superior to placebo -No difference between dupilumab 200mg and placebo -Generally, well tolerated

LOE=level of evidence; RCT=randomized controlled trial; SCIT=subcutaneous immunotherapy; TNSS=Total Nasal Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; sIgE=antigen-specific immunoglobulin E; SNOT=22=Sinonasal Outcome Test (22 item)

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 9 RCTs in adults[416-424] **[TABLE XI.B.8.-1]** and 1 systematic review[425] and 8 RCTs[426-433] in children. **[TABLE XI.B.8.-2]** Three SRMAs[434-436] have been performed including both adults and children. **[TABLE XI.B.8.-3]** Compared to no irrigations, all found nasal symptoms/patient-reported disease severity were significantly better in the saline irrigation group.[434-436] Hermelingmeier et al[434] 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.[416-424] Compared to no intranasal treatment, hypertonic saline was found to significantly improve outcomes, including nasal symptoms, QOL, and oral antihistamine use.[417,419,421] Ural et al[418] 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[416] and Sansila et al[422] found QOL and symptom score were better with hypertonic solutions. Finally, Yata et al[424] 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[420] 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[416] and Lin et al[423] 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.[425-433] Compared to no irrigations, hypertonic and isotonic saline were found to improve outcomes, including nasal symptoms, oral antihistamine use, and QOL.[427,428,433] 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).[425] Further, studies have shown that that hypertonic saline irrigations resulted in a greater improvement in nasal symptom scores in children than isotonic saline.[429,430,432] Finally, Li et al[426] and Chen et al[431] 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 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.]**

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.

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[424]	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[422]	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 vs 0.9% saline formula
Di Berardino et al[421]	2017	2	RCT, no blinding	Patients with SAR: -Hypertonic saline spray TID	-Symptom score -Oral antihistamine use	Symptoms, oral antihistamine use, mucociliary clearance

				-No local or intranasal treatment	-Mucociliary clearance time	times significantly better in hypertonic saline group
Lin et al[423]	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 vs saline irrigation
Chusakul et al[420]	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[419]	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, vs no local therapy
Ural et al[418]	2008	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
Cordray et al[416]	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[417]	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

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; BID=twice daily; VAS=visual analog scale; SBRCT=single-blind randomized controlled trial; QOL=quality of life; Rcq-36=Rhinoconjunctivitis Quality of Life; TNSS=Total Nasal Symptom Score; RCT=randomized controlled trial;

SAR=seasonal allergic rhinitis; TID=three times daily; INCS=intranasal corticosteroid; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; QID=four times daily

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[425]	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 vs control group
Jung et al[433]	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 vs baseline -No significant change differences in any endpoints between groups
Malizia et al[432]	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 vs normal saline group
Chen et al[431]	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[429]	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 vs control group
Satdhabudha & Poachanukoon[430]	2012	2	DBRCT	Patients with AR: -Buffered hypertonic saline BID -Normal saline irrigations BID *all groups allowed to continue to use previous	-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

				medications for control		
Li et al[426]	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
Garavello et al[428]	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 vs no therapy
Garavello et al[427]	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 vs no therapy

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized controlled trial; PC20=provocative concentrations of methacholine causing a 20% decrease in FEV_1; QOL=quality of life; FeNO=fractional exhaled nitric oxide; BID=twice daily; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; INCS=intranasal corticosteroid; SBRCT=single-blind randomized controlled trial; SAR=seasonal allergic rhinitis; DBRCT=double-blind randomized controlled trial; TNSS=Total Nasal Symptom Score; Rcq-36=Rhinoconjunctivitis Quality of Life; TID=three times daily

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[436]	2020	1	SRMA	Patients with AR, multiple comparisons: -Saline vs no irrigations -Saline irrigation vs INCS -Hypertonic vs isotonic saline	Nasal symptom score	-Symptom scores significantly better with saline irrigation vs 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[435]	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 vs no saline irrigation at up to 3 months in adults and children, with no reported adverse effects
Hermelingmeier et al[434]	2012	1	SRMA	Patients with AR: -Saline irrigations	-Nasal symptom score	-Up to 7 weeks, saline irrigations improve nasal

				-No irrigations	-Medicine use -Mucociliary clearance -QOL	symptoms, medicine use, and mucociliary clearance time, vs no therapy -Children benefit less than adults

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; INCS=intranasal corticosteroid; QOL=quality of life

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 over-sensitization. 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.G.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 T regulatory cells via IL-10 and TGF-β. Furthermore, the allergy-associated Th2 pathway is suppressed through downregulation of IL-4, IgE, IgG1, and IgA.[437]

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[438] 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[439] 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, total IgE, or sIgE.

Du et al[440] 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[441] 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, 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.

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 recommendation for treatment.

Policy level: Option.
Intervention: Consider adjuvant use of probiotics for patients with symptomatic seasonal or perennial AR.

TABLE XI.B.9. Evidence table – Probiotics for allergic rhinitis

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Du et al[440]	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[441]	2016	1	SRMA	17 RCTs: -Probiotic, n=2381 -Control, n=2374	Eczema, prevention of asthma & rhinoconjunctivitis	-Lower relative risk for eczema with probiotic vs control -No significant difference in prevention of asthma or rhinoconjunctivitis
Guvenc et al[438]	2015	1	SRMA	22 DBRCTs, 2242 patients	-Total nasal and ocular symptom scores -QOL	Probiotics showed significant reduction of nasal and ocular symptom scores vs placebo
Zajac et al[439]	2015	1	SRMA	21 RCTs, 2 cross-over studies, 1919 patients	-RQLQ -RTSS -Total IgE	-Improvement in RQLQ with probiotic vs placebo -No effect on RTSS or total IgE
Anania et al[442]	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[443]	2019	2	Randomized, cross-over	152 patients with persistent AR	-SF-36 -SNOT-22 -CARAT	-SF-36 improved vs baseline in both groups -Probiotic group showed more reduction in SNOT-22 and CARAT
Sumadiono et al[444]	2018	2	RCT	3 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 vs cetirizine alone
Dennis-Wall et al[445]	2017	2	DBRCT	n=173 participants: probiotic vs 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[446]	2017	2	RCT	-Probiotic vs placebo, n=40 children	-Total symptom score -mRQLQ	Improvement in AR symptoms and QOL with probiotic

LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; AR=allergic rhinitis; SPT=skin prick test; DBRCT=double-blind randomized controlled trial; QOL=quality of life; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; RTSS=Rhinitis Total Symptom Score; IgE=immunoglobulin E; SF-36=Short Form 36 item questionnaire; SNOT-22=Sinonasal Outcome Test (22 item); CARAT=Control of Allergic Rhinitis and Asthma Test; AIT=allergen immunotherapy; mRQLQ=mini Rhinoconjunctivitis Quality of Life Questionnaire; IL=interleukin
*Relevant prior studies included in SRMAs

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.[214,447-449]

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.[283,284,286-288,292,294,449-460] Combination oral antihistamine-oral decongestant medications have also been shown to reduce nasal congestion symptoms vs. oral antihistamine alone or versus oral decongestant alone.[283,284,286-288,292,294,449-460] 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[461,462] and that different antihistamine-decongestant combinations are statistically equivalent in improving symptom scores.[462-466] 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.[214,467,468] In contrast, cetirizine-pseudoephedrine was not superior to xylometazoline nasal decongestant spray alone in improving nasal airflow and nasal obstruction symptoms.[469] **[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.[447,448] 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.[447,448] 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,[447,448] **[TABLE II.C.]**

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 two years or 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 more 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.

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[214]	2021	2	RCT	-Loratadine-PSE -Placebo tablet -Fluticasone propionate nasal spray -Placebo nasal spray	-TSS -PNIF	-Loratadine-PSE improved PNIF vs placebo tablet and vs fluticasone nasal spray

				(n=82)		-PNIF was not significantly different for fluticasone vs placebo nasal spray
North et al[449]	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 vs fexofenadine-PSE -Fexofenadine-PSE significantly reduced congestion and TNSS vs placebo. -PF-03654764-fexofenadine significantly improved TNSS, but not congestion vs placebo
Grubbe et al[286]	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 vs desloratadine-placebo and vs PSE
Chen et al[461]	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[462]	2006	2	RCT	-Cetirizine-PSE -Loratadine-PSE (n=51)	TNSS	Both groups statistically equivalent in symptom scores
Nathan et al[450]	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[451]	2005	2	RCT	-Desloratadine-PSE -Desloratadine -PSE (n=650)	TSS	Desloratadine-PSE significantly reduced TSS and non-nasal symptom scores vs desloratadine or PSE alone
Pleskow et al[294]	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
Zieglmayer et al[467]	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[463]	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[452]	2003	2	RCT	-Clemastine-PSE-acetaminophen -PSE-acetaminophen	Major symptom complex score	Clemastine-PSE-acetaminophen significantly reduced major symptom

				-Placebo (n=298)		complex score vs PSE-acetaminophen or placebo
Berkowitz et al[453]	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[469]	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 vs xylometazoline
McFadden et al[454]	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 vs placebo
Sussman et al[288]	1999	2	RCT	-Fexofenadine-PSE -Fexofenadine -PSE (n=651)	-TSS -Nasal congestion	-Fexofenadine-PSE significantly improved TSS and nasal congestion symptoms vs fexofenadine or PSE alone -Fexofenadine-PSE improved daily activities and work productivity vs fexofenadine or PSE
Horak et al[455]	1998	2	RCT	-Cetirizine-PSE -Placebo (n=24)	-Nasal obstruction -Nasal patency/airflow	Cetirizine-PSE significantly improved nasal airflow and nasal obstruction symptoms vs placebo
Kaiser et al[470]	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[456]	1998	2	RCT	-Loratadine-PSE -Placebo (n=40)	-Nasal symptoms/signs -TSS	-Loratadine-PSE significantly improved signs and TSS vs placebo -Both placebo and loratadine-PSE improved nasal symptoms
Corren et al[457]	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 vs placebo
Grosclaude et al[284]	1997	2	RCT	-Cetirizine-PSE -Cetirizine -PSE (n=687)	Daily congestion, sneezing, rhinorrhea, nasal	Cetirizine-PSE significantly improved symptoms vs cetirizine or PSE alone

					itching, ocular itching	
Bertrand et al[287]	1996	2	RCT	-Cetirizine-PSE -Cetirizine -PSE (n=210)	Daily symptom scores	Cetirizine-PSE significantly reduced symptoms and increased symptom-free days vs cetirizine or PSE alone
Simola et al[464]	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[458]	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
Bronsky et al[283]	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[468]	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[465]	1994	2	RCT	-Loratadine-PSE -Chlorpheniramine-PSE (n=131)	TSS	Loratadine-PSE was equally effective vs chlorpheniramine-PSE in improving TSS
Howarth et al[292]	1993	2	RCT	-Terfenadine-PSE -Terfenadine -PSE -Placebo (n=14)	TSS	Terfenadine-PSE significantly improved all symptoms vs placebo
Segal et al[466]	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[459]	1989	2	RCT	-Loratadine-PSE -Placebo (n=264)	Nasal and non-nasal symptoms	Loratadine-PSE significantly reduced nasal and non-nasal symptoms scores vs placebo
Storms et al[460]	1989	2	RCT	-Loratadine-PSE -Loratadine -PSE -Placebo (n=435)	TSS	Loratadine-PSE more effective than loratadine, PSE, or placebo in reducing TSS

1 LOE=level of evidence; RCT=randomized controlled trial; PSE; pseudoephedrinel TSS=total symptom score;
2 PNIF=peak nasal inspiratory flow; TNSS=Total Nasal Symptom Score; Qday=daily; BID=twice daily; PFT=pulmonary

function test; QOL=quality of life; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; PEF=peak expiratory flow; FEV_1=forced expiratory volume in 1 second; VAS=visual analog scale

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[471] used TNSS, rhinoconjunctivitis scores, and PNIF to compare 4 groups: (1) intranasal mometasone-oral desloratadine, (2) intranasal mometasone-oral montelukast, (3) intranasal mometasone alone, (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[472] 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.[472]

Barnes et al[473] compared RQLQ scores, PNIF, TNSS, and nasal nitric oxide 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[474] evaluated 5 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 three 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[475] 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 NSS. 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[476] 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.]**

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.

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[476]	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 & Zhang[477]	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[478]	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[472]	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[471]	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[473]	2006	2	RCT	-Cetirizine-nasal fluticasone -Placebo-nasal fluticasone (n=27)	-RQLQ -PNIF -TNSS -Nasal nitric oxide	Symptom scores equivalent for cetirizine-fluticasone vs fluticasone-placebo
Benitez et al[479]	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[474]	2004	2	RCT	-Cetirizine-nasal fluticasone -Montelukast-nasal fluticasone -Cetirizine-montelukast	-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

				-Nasal fluticasone -Placebo (n=100)		superior to placebo or cetirizine-montelukast for TSS, nasal congestion on waking, daily nasal congestion -Combination of cetirizine-fluticasone showed no added benefit vs fluticasone alone for TSS
Lanier et al[480]	2002	2	RCT	-Fexofenadine-nasal fluticasone -Nasal fluticasone-olopatadine -Placebo (n=80)	-Ocular itching -Ocular redness -Nasal symptoms	-Fluticasone-olopatadine improved ocular itching vs fexofenadine-fluticasone -Ocular redness scores similar for fluticasone-olopatadine vs fexofenadine-fluticasone -Both treatment groups improved ocular redness vs placebo and had similar efficacy for TNSS
Wilson et al[481]	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
Berger et al[131]	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[475]	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 only 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 vs loratadine alone or placebo -RQLQ improvement statistically equivalent for loratadine-fluticasone vs fluticasone -No significant benefit of loratadine-fluticasone over fluticasone alone
Juniper et al[482]	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 vs 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 vs beclomethasone alone

LOE=level of evidence; SRMA=systematic review and meta-analysis; INCS=intranasal corticosteroid; OAH=oral antihistamine; IAH=intranasal antihistamine; TNSS=Total Nasal Symptom Score; TOSS= Total Ocular Symptom Score; QOL=quality of life; PNIF=peak nasal inspiratory flow; RCT=randomized controlled trial; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; TSS=total symptom score; PSE=pseudoephedrine; PFT=pulmonary function test; FEV_1=forced expiratory volume in 1 second; ECP=eosinophil cationic protein; AR=allergic rhinitis; NSS=nasal symptom score

XI.B.10.c. Oral antihistamine and leukotriene receptor antagonist

The combination of oral antihistamine-LTRA and oral antihistamines in the treatment of AR was reviewed as a therapeutic option in the previous ICAR-Allergic Rhinitis 2018 consensus statement.[308] An updated systematic search revealed an additional 3 systematic reviews and 2 RCTs,[310,312,483-485] 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[483] 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[310] found that oral antihistamine-LTRA therapy was superior to monotherapy with either LTRA or oral antihistamines alone in improving daytime and nighttime symptoms of AR, as well as ocular symptoms. Additional systematic reviews by Liu et al[484] and Wei[312] 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.[215,474,486,487] Comparing different antihistamines with LTRA, Mahatme et al[485] 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[488] found that combination oral antihistamine-LTRA was superior to oral antihistamines alone in reducing nasal resistance on rhinomanometric testing, and Li et al[489] found that the former was superior to the latter in increasing nasal volume as measured by acoustic rhinometry. However, Moinuddin et al[463] 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[474] and equivalent to oral antihistamines alone.[483]

It is important to note that in the Joint Task Force Practice Parameters,[65] 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,[308] 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.[324]

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 LTRA-oral antihistamine therapy be reserved for rare patients with contraindications to alternative treatments.

Aggregate grade of evidence: A (Level 1: 4 studies, level 2: 13 studies; **TABLE XI.B.10.c.**)
Benefit: Combination LTRA and oral antihistamine were superior in symptom reduction and QOL improvement than placebo, and to 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.

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[310]	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[484]	2018	1	SR of RCTs	-Montelukast-OAH -OAH	Symptoms	LTRA-OAH superior to OAH alone
Wei[312]	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[215]	2004	1	SR of RCTs	-LTRA-OAH -LTRA -OAH -INCS	-Symptoms -QOL	-Combination therapy improved symptoms vs LTRA or OAH alone -No difference in standardized QOL measures -No difference in symptoms for combination therapy vs INCS
Kim et al[483]	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[485]	2016	2	RCT	-Montelukast-levocetirizine -Montelukast-fexofenadine	Symptoms	-Both reduced symptoms -LTRA-levocetirizine greater decrease in symptoms -LTRA-fexofenadine more cost effective
Ciebiada et al[490]	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
Yamamoto et al[491]	2012	2	RCT	-Montelukast-loratadine -Montelukast-placebo	Symptoms	Active combination therapy with improved Total Symptom Score, and specifically sneezing and rhinorrhea
Cingi et al[488]	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[489]	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[486]	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[492]	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[474]	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[463]	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

Saengpanich et al[487]	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[493]	2002	2	RCT	-Montelukast-loratadine -Montelukast -Loratadine -Placebo	-Symptoms -QOL -Peripheral eosinophilia	-Combination therapy decreased symptoms and improved QOL vs placebo -Effect did not reach statistical significance vs monotherapy -Combination therapy decreased peripheral eosinophilia vs placebo and loratadine alone
Meltzer et al[494]	2000	2	RCT	-Montelukast-loratadine -Montelukast -Loratadine -Placebo	-Symptoms -QOL	-Combination therapy improved symptoms and QOL vs placebo -Combination therapy not directly compared to monotherapy

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; OAH=oral antihistamine; LTRA=leukotriene receptor antagonist; INCS=intranasal corticosteroid; QOL=quality of life; ICAM=intracellular adhesion molecule; PNIF=peak nasal inspiratory flow; ECP=eosinophil cationic protein

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, 2 non-blinded) evaluated the efficacy of combination therapy against either placebo or active control.[495-512] An additional 3 observational studies reported outcomes of AzeFlu as a single treatment arm.[513-515] This evidence has been summarized in 2 previous systematic reviews.[476,516,517] **[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 (8 studies), VAS (4 studies), the RQLQ (7 studies), the PRQLQ (1 study), and odor threshold/discrimination/identification score (1 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 2 studies with a 3-month duration[512,515] and 1 study with a 52-week duration.[512] The number of subjects in each study ranged from 47 to 3398. AzeFlu as a single formulation was compared to placebo in 7 studies, with primary outcomes showing superiority to placebo in all studies.[501-503,505-508] Superiority of combination therapy with AzeFlu was also demonstrated over active treatment with fluticasone propionate monotherapy in 6 studies.[504-506,508,510,512] Similarly, superiority of combination therapy with AzeFlu was demonstrated over active treatment with azelastine hydrochloride monotherapy in 4 studies.[505,506,508,512] A single study evaluated combination therapy with non-proprietary azelastine hydrochloride and fluticasone propionate applied using 2 separate spray bottles, which found superiority over either azelastine or fluticasone as monotherapy.[510]

OloMom was compared to olopatadine or mometasone monotherapy in 4 studies, all of which showed superiority of the combination therapy.[495,497-499] One study comparing AzeFlu with OloMom found comparable symptom reduction.[499] AzeFlu was directly compared to combination therapy with intranasal olopatadine and fluticasone in 1 study, with no significant difference in symptom relief between treatment groups.[509] 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.[507] 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.[517]

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 between 6-12 years old were evaluated in 2 studies, with superiority of AzeFlu over

placebo in improving symptoms and QOL.[502,512] Several studies reporting 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.[509] Ocular changes such as increased intraocular pressure and cataract formation are unlikely; nonetheless, caution may be warranted in patients with a history of glaucoma.[246] Additional specific patient factors may be considered when selecting options for combination therapy.

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 2 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[516]	2019	1	SR	-AzeFlu -Azelastine -FP -Placebo	TNSS	AzeFlu superior to either spray alone for symptom improvement
Seresirikachorn et al[476]	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[495]	2020	2	DBRCT	-OloMom -Olopatadine -Mometasone -Placebo	-rTNSS -rTOSS -RQLQ	OloMom superior to monotherapy or placebo for symptom and QOL improvement
Gross et al[498]	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[497]	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[511]	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[499]	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[496]	2019	2	DBRCT	-OloMom -Placebo	-rTNSS -PNSS -RQLQ	OloMom superior to placebo for symptom and QOL improvement
Bousquet et al[500]	2018	2	DBRCT	-AzeFlu -Loratadine-FP	-TNSS -TOSS -VAS	AzeFlu superior to loratadine-FP, more rapid onset of action
Kortekaas Krohn et al[501]	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[502]	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
Berger et al[512]	2016	2	Nonblinded RCT	-AzeFlu -FP	Total symptom score	AzeFlu superior to fluticasone for children; faster onset
Meltzer et al[503]	2013	2	DBRCT	-AzeFlu -Placebo	-rTNSS, -rTOSS	AzeFlu superior to placebo for all symptoms
Price et al[504]	2013	2	DBRCT	-AzeFlu -FP	-rTNSS -Symptom-free days	AzeFlu superior to fluticasone for symptom reduction; faster onset
Carr et al[505]	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[506]	2012	2	DBRCT	-AzeFlu -Azelastine -FP -Placebo	-rTNSS -rTOSS -RQLQ	AzeFlu superior to either spray alone for symptom and QOL improvement
Salapatek et al[507]	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[508]	2010	2	DBRCT	-AzeFlu -Azelastine -FP -Placebo	TNSS	AzeFlu superior to either spray alone, all treatments superior to placebo
LaForce et al[509]	2010	2	DBRCT	-AzeFlu -Olopatadine-FP	TNSS	No difference between treatments
Ratner et al[510]	2008	2	DBRCT	-Azelastine-FP -Azelastine -FP	TNSS	Combination superior to either agent alone
Klimek et al[513]	2016	4	Prospective observational	AzeFlu	VAS	76% of subjects had symptom control after 14 days; significant improvement from baseline
Klimek et al[515]	2016	4	Prospective observational	AzeFlu	-TDI score -VAS symptoms	Olfactory function improved after 1 month
Klimek et al[514]	2015	4	Prospective observational	AzeFlu	VAS	Rapid symptom relief across all age groups

LOE=level of evidence; SR=systematic review; AzeFlu=azelastine-fluticasone; FP=fluticasone propionate; TNSS=Total Nasal Symptom Score; INCS=intranasal corticosteroid; DBRCT=double-blind randomized controlled trial; TOSS=Total Ocular Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; QOL=quality of life; OloMom=olopatadine mometasone; r=reflective; i=instantaneous; PNSS=physician0assessed nasal symptom score; RCAT=Rhinitis Control Assessment Test; RCT=randomized controlled trial; EQ-5D=Euro-QOL-5D; VAS=visual analog scale; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; TDI=threshold/discrimination/identification

XI.B.10.e. Intranasal corticosteroid and leukotriene receptor antagonist

LTRAs have been studied and used 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.[324] 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[518] and eight controlled trials[316,318,471,474,519-522] where montelukast was studied as add-on therapy to INCS. The meta-analysis included four studies that used fluticasone propionate and one 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.[518] 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.[316,471,519,520] Chen et al[316] 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[519] showed similar favorable outcomes in all three outcomes categories for combination therapy. Goh et al[520] reported a RCT with fluticasone propionate compared to montelukast-fluticasone propionate; combination therapy demonstrated improvement in symptom scores and QOL. Pinar et al[471] 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.[318,474,521,522] Di Lorenzo et al[474] studied symptoms and eosinophil-specific inflammatory markers in 4 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[521] 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[318] 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[522] 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[324] and variable study outcomes, use of LTRA with INCS should primarily be considered for patients with co-morbid 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.

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 co-morbid 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.

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[518]	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[519]	2021	2	RCT	-Montelukast-budesonide INCS -Budesonide INCS	-Symptoms -Nasal cavity volume -FeNO	Combination therapy had superior improvement
Chen et al[316]	2018	2	RCT	-Montelukast-budesonide INCS -Budesonide INCS	-Symptoms -Nasal cavity volume -FeNO	Combination therapy had superior improvement
Dalgic et al[318]	2017	2	RCT	-Montelukast-mometasone INCS -Montelukast	Olfactory function	No additional benefit to add-on montelukast
Florincescu-Gheorghe et al[522]	2014	2	RCT	-Montelukast-mometasone INCS -Desloratadine-mometasone INCS -Mometasone INCS	-Symptoms -Immune markers	No additional benefit to add-on montelukast
Goh et al[520]	2014	2	RCT	-Montelukast-fluticasone INCS -Fluticasone INCS	-Symptoms -QOL	Combination therapy had superior improvement
Esteitie et al[521]	2010	2	RCT	-Montelukast-fluticasone INCS -Fluticasone INCS	-Symptoms -QOL	No additional benefit to add-on montelukast
Pinar et al[471]	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[474]	2004	2	RCT	-Montelukast-cetirizine -Montelukast-fluticasone INCS -Cetirizine-fluticasone INCS -Fluticasone	-Symptoms -Immune markers	No additional benefit to add-on montelukast

LOE=level of evidence; INCS=intranasal corticosteroid; QOL=quality of life; RCT=randomized controlled trial; FeNO=fraction of exhaled nitric oxide

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 refractory AR. Most INDC (e.g., oxymetazoline, phenylephrine, xylometazoline) are α-receptor agonists, and decrease nasal congestion by reducing nasal mucosal volume through sympathomimetic vasoconstriction of mucosal blood vessels.[523] Prolonged use of INDCs alone has been shown to cause rhinitis medicamentosa,[524] 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.[525-529] Three of these studies also reported no rhinitis medicamentosa in patients receiving combination therapy.[526,527,529] In contrast, Baroody et al,[530] 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[527] 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[531] 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 variations 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.[65] 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.[85]

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 (2 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.

TABLE XI.B.10.f. Evidence table – Combination therapy: intranasal corticosteroid and intranasal decongestant

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Khattiyawittayakun et al[531]	2018	1	SRMA	6 RCTs: -INCS-INDC -INCS	TNSS, rhinorrhea, itching, sneezing	-2 studies in meta-analysis -Combination therapy did not show benefit over INCS alone
Kirtsreesakul et al[525]	2016	2	RCT	68 participants: -Mometasone furoate-oxymetazoline nasal spray -Mometasone furoate-placebo nasal spray	TNSS, PNIF, nasal mucociliary clearance time, total nasal polyps score	Combination therapy significantly more effective in improving blocked nose, hyposmia, mucociliary clearance, and total nasal polyps score
Thongngarm et al[529]	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[527]	2013	2	RCT	705 participants: -Mometasone-oxymetazoline (3 sprays pn Qday nasal spray	TNSS	-Combination therapy significantly more effective in improving nasal congestion than mometasone alone,

				-Mometasone-oxymetazoline (1 spray pn Qday) nasal spray; -Mometasone nasal spray -Oxymetazoline (2 sprays pn BID) nasal spray -Placebo		oxymetazoline alone, and placebo -No dose-dependent relationship seen with oxymetazoline in combination therapy
Matreja et al[526]	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 vs fluticasone alone
Baroody et al[530]	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[528]	2011	3*	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

LOE=level of evidence, SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; INCS=intranasal corticosteroid; INDC=intranasal decongestant; TNSS=Total Nasal Symptom Score; PNIF=peak nasal inspiratory flow; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; AR=allergic rhinitis; pn=per nostril; Qday=daily; BID=twice daily

*Downgraded LOE due to very small size of RCT and lack of AR/non-allergic rhinitis subgroup analysis

XI.B.10.g. Intranasal corticosteroid and intranasal ipratropium

Current treatment algorithms for children[532,533] and adult patients[65,85] with moderate to severe AR with insufficient symptom control or treatment failure based on 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[390] 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%, 42µg per nostril TID and beclomethasone dipropionate, 84µg per nostril BID was superior to either agent alone and 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 two 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.]**

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 benefits 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.

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[390]	1999	2	DBRCT	Perennial AR (n=279), non-allergic rhinitis (n=274); 8-74 years old: -IPB 0.03% [42µg pn TID] + BDP [84µg pn BID], (n=207) -IPB 0.03% [42µg pn TID] + placebo, (n=103) -BDP [84µg 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

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; IPB=ipratropium bromide; pn=per nostril; TID=three times daily; BDP=beclomethasone dipropionate; BID=twice daily

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.[534] 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.[535] Acupuncture involves insertion of thin needles at specific acupoints located along these meridians with the goal of achieving a therapeutic "*de qi*" effect.[536] 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.[537,538] Acupuncture has an excellent safety profile with only mild reported adverse effects.[538,539]

[TABLE SE/AE]

Several SRMAs have been performed on acupuncture for the treatment of AR. In 2008, Roberts et al[539] reviewed 7 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[540] 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[538], 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.[541] In 2020, a systematic review by Wu et al[542] analyzed 15 RCTs and found acupuncture as a useful adjunct to allopathic standard of care or as monotherapy for AR. Yin et al[543] 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.[544]

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 on-going 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.

TABLE XI.B.11.a. Evidence table – Acupuncture for allergic rhinitis

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Wu et al[542]	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[538]	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[540]	2009	1	SR	-Acupuncture -Sham acupuncture	-Nasal symptom scores	Favorable effects of acupuncture on symptom

				-Conventional medication (2 RCTs)	-RQLQ -Rescue medication use	scores for perennial AR, but not for seasonal AR
Roberts et al[539]	2008	1	SRMA	-Acupuncture -Sham acupuncture	-AR symptom scores -Rescue medication use	No overall effect on AR symptom scores or need for relief medications
Yin et al[543]	2020	2**	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

LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; SRMA=systematic review and meta-analysis; AR=allergic rhinitis
*Relevant prior studies are included in the SRMAs
**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

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;[545] (2) acupoint catgut implantation;[546] (3) acupoint herbal patching;[547] (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;[548-551] 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.[543,552,553] 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.]**

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.

TABLE XI.B.11.b. Evidence table – Other complementary medicine treatments for allergic rhinitis

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions

Yin et al[543]	2020	2[a]	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[548]	2019	2[b]	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[553]	2020	3[c]	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[547]	2015	3[d]	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[551]	2020	4[c]	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[546]	2014	4[e]	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 1 included trial
Zhang et al[545]	2010	4[f]	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; AR=allergic rhinitis; SGA=sphenopalatine ganglion acupuncture; TNSS=Total Nasal Symptom Score; VAS=visual analog scale; TFM=thunder fire moxibustion; TNNSS= Total Non-Nasal Symptom Score; SF-36=Short Form-36; SR=systematic review

*Relevant prior studies are included in the SRMAs

[a]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

[b]LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation concealment; attrition bias with incomplete outcome data

[c]LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation concealment; selective reporting bias

[d]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

[e]LOE downgraded since only 1 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

[f]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

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.[554] Primary sources of antigens can include pollen and microflora from the digestive tract of honeybees, which typically contains microorganisms present in dust, air, and flowers.[555] 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,[556-558] while studies in humans have demonstrated various anti-inflammatory properties of honey.[559,560]

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[561] and an additional RCT[562] showed a significant decrease in total symptoms scores in the treatment group compared to control. In contrast, another double-blind RCT[563] 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 (50-80g daily intake) of honey are required to achieve health benefits from honey,[564] and only the trial by Asha'ari et al[561] dosed patients at that level. In addition, the benefit of birch pollen honey in the trial by Saarinen et al[562] might be explained by a specific immunotolerance developed during oral intake of birch pollen with honey acting as a vehicle.

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.

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[561]	2013	2	DBRCT	-Honey -Placebo	AR symptom scores	Improvement in overall and individual AR symptoms with honey
Saarinen et al[562]	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 relief medications -Honey groups had significantly more asymptomatic days
Rajan et al[563]	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 relief medication

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; RCT=randomized controlled trial

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 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.[565] 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.

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.

TABLE XI.B.11.d. Herbs and supplements used in the treatment of allergic rhinitis

Herb	Mechanism of action	Evidence*	Side effects
Apple polyphenols	Inhibits release of histamine from mast cells and basophils	DBRPCT investigated drinking apple polyphenols (50mg or 200mg daily); improvement in sneezing, nasal discharge, turbinate swelling[566]	Rash, soft stool, headache, changes in hematocrit, increased uric acid levels
Astragalus membranaceus	Unknown	DBRPCT comparing 80mg daily x 6 weeks; improvement in rhinorrhea, TSS, QOL[567]	Pharyngitis, rhinosinusitis
Aller-7	Possible antioxidant and anti-inflammatory pathways[568-570]	Two DBRPCTs showed some relief of symptoms with Aller-7, but some contradictory findings present[571]	Dry mouth, gastric discomfort
Benifuuki green tea	Catechins, EGCG and polyphenols inhibit type I and type IV hypersensitivity reactions[572,573]	DBRPCT showed 700mL Benifuuki green tea daily significantly reduced AR symptoms, improved QOL, suppressed peripheral eosinophils[574]	None reported
Biminne	Unknown	DBRPCT showed 12 weeks of Biminne significantly reduced sneezing[575]	None reported

Butterbur (*Petasites hybridus*)	Inhibits leukotriene/histamine synthesis and mast cell degranulation[576]	3 DBRPCTs showed Butterbur was effective in alleviating symptoms, attenuating PNIF recovery, and reducing maximum % PNIF decrease from baseline after adenosine monophosphate challenge; 2 clinical trials showed butterbur was similar to antihistamine for improving QOL and symptom relief;[565,571] 1 DBRPCT demonstrated no benefit for PNIF, symptoms, QOL[571] 6 RCTs reviewed: 5 compared butterbur to placebo; 4 found butterbur to be superior to placebo. 3 RCTs compared butterbur to antihistamines with no difference found between groups.[542]	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 [577-579]	No evidence of a therapeutic effect of intranasal capsaicin in AR[542,579,580]	Mucosal irritation, burning, lacrimation, coughing.
Chlorophyll c2 (*Sargassum horneri*)	Possibly inhibits degranulation of mast cells and basophils	DBRPCT showed 0.7mg Chlorophyll c2 daily significantly decreased the need for rescue medications after 8 weeks, but no difference in QOL[581]	None reported
Cinnamon bark, Spanish needle, acerola (ClearGuard)	Inhibits production of prostaglandin D2[582]	DBRPCT showed 450mg CG TID comparable to loratadine 10mg in symptom reduction; CG prevented increase in prostaglandin D2 release following nasal allergen challenge[582]	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 2g conjugated linoleic acid daily before and during birch pollen season improves sneezing and wellbeing[583]	None reported
Grapeseed extract	Unknown	DBRPCT showed no benefit of 100mg grapeseed extract BID on nasal symptoms, need for rescue medications, QOL[584]	None reported
Isoquercitrin	Flavonoid with anti-allergic and antioxidant effects	DBRPCT demonstrated 100 mg Isoquercitrin significantly improved ocular symptoms but not nasal symptoms[585,586]	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 (500mg) and loratadine, but there was no significant difference between them[587]	Eructation, dry mouth and throat

Methylsulfonylmethane	Organosulfur compound with anti-inflammatory properties and reported to block the formation of inflammasomes	DBRPCT demonstrated that 3 g daily for two weeks provided significant relief of AR symptoms and objective nasal obstruction measurements[588]	None reported
Nigella sativa (Black seed)	-Inhibits histamine release from rat macrophages[589] -Thymoquinone may inhibit Th2 cytokines and eosinophil infiltration in airways[590]	*N. sativa* capsules (2 DBRPCTs) and N. sativa nasal drops (1 DBRPCT) improve AR symptoms; [591-593] 1 DBRPCT did not find significant differences between treatment and placebo[591]	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[594-597]	DBRPCT showed 50 mg or 200 mg *P. fruescens* enriched for rosmarinic acid did not significantly improve symptom scores [598]	None reported
Probiotics	Down-regulation of IL-5 and allergen-specific IgG4[599,600]	*See Section XI.B.9. Probiotics for additional information on this topic.*	
L.RCM-101	Inhibits histamine release and prostaglandin E2 production[601,602]	DBRPCT showed 4 tablets of RCM-101 TID for 8 weeks significantly improved symptom scores and RQLQ[603]	Mild gastrointestinal side effects
Spirulina	-Reduces IL-4 levels, inhibits histamine release from mast cells[604] -Enhanced IgA levels and IFN-y, natural killer cell damage were increased[605]	DBRPCT showed 2000mg daily Spirulina significantly improved sneezing, rhinorrhea, congestion, and nasal itching[606]	None reported
Ten-Cha (*Rubus suavissimus*)	Inhibits cyclooxygenase activity and histamine release by mast cells[607]	DBRPCT showed no significant improvement in symptom scores, RQLQ, or need for antihistamine with 400mg daily of Ten-Cha extract[608]	None reported
TJ-19**	Inhibits histamine signaling and IL-4 and IL-5 expression in a rat model[609]	DBPRCT showed 3g TJ-19 TID significantly improved sneezing, stuffy nose and rhinorrhea[610]	None reported
Tinofend (*Tinospora cordifolia*)	Possibly through anti-inflammatory effects[611]	DBPCRCT showed 300mg Tinofend x8 weeks significantly improved AR symptoms, also decreased eosinophils, neutrophils, goblet cells on nasal smear[611]	Leukocytosis

Tomato extract	Possibly inhibits histamine release	DBRPCT showed 360mg Tomato extract daily x8 weeks decreased sneezing score, rhinorrhea, nasal obstruction[612]	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[613]	-DBRPCT showed symptom improvement over placebo at 1 hour[614] -One systematic review showed no significant intergroup differences[571]	None reported
Vitamin C (ascorbic acid)	Acts as a water-soluble antioxidant with immune modulating effects[615]	DBRPCT showed that 2-week nasal application of ascorbic acid reduced nasal edema, mucus secretion, nasal obstruction[615]	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[616] -*See Section VI.H. Vitamin D for additional information on this topic*	None reported
Vitamin E	Unknown	-One DBRPCT showed that 800mg per day of vitamin E had no effect on ocular symptoms but improved nasal symptoms; no reduction in medications reported[617] -Another DBRPCT showed 400 IU per day of vitamin E had no effect on nasal symptoms or IgE levels[618]	None reported

DBRPCT=double-blind randomized placebo-controlled trial; TSS=Total Symptom Score; QOL=quality of life; EGCG=epigallocatechin-3-O-gallate; AR=allergic rhinitis; PNIF=peak nasal inspiratory flow; TID=three times daily; TNF=tumor necrosis factor; IFN=interferon; IL=interleukin; BID=twice daily; Ig=immunoglobulin; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; Th2=T-helper 2

*All listed studies LOE 2

**Not available in US; contains ephedra

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.

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[85]	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[619]	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[620]	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

AR=allergic rhinitis; EBM=evidence-based medicine; AAP=American Academy of Pediatrics; TCM=Traditional Chinese Medicine; GRADE=Grading of Recommendations, Assessment, Development and Evaluation

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,[621-623] most of the recent literature suggests the contrary,[624-633] with overall low complication rates.[634,635] Kim et al[636] 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. 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.[637] 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.[638] 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,[638] can reduce the distance between IT and lateral nasal wall and enlarge the dimensions of the nasal airway when performed alone[639,640] or in conjunction with other techniques.[641,642] IT surgery via energy-related techniques[641-700] and via direct tissue removal[629,633,636,640,644,647,668,669,672,673,675,681,701-713] 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[714-716] and high-intensity focused ultrasound may also provide symptomatic relief,[717,718] though there remains limited evidence for 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 towards volumetric reduction to improve airflow. Though ablation of the swell body (whether through radiofrequency, laser, or coblation) has shown promise in reducing symptoms,[719-723] 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.[723] 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.[712,724-727] A RCT and another non-randomized controlled trial of patients with both AR and chronic rhinosinusitis with nasal polyps found similar results, as well as improvement on pulmonary functions tests.[728,729] There remains some concern that symptom recurrence may be high based on earlier studies,[730] 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.[731] Though recent evidence suggests that the properly selected patient does not experience symptomatic dry eye postoperatively,[732] newer, more directed techniques targeting distal nerve segments have been developed. Specifically, the posterior nasal nerve (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 patients, PNN neurectomy has been similarly shown to be effective for reducing symptoms,[711,733-739] though one non-randomized controlled trial did not find a benefit to adding PNN neurectomy to microdebrider-assisted turbinoplasty.[740] 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[741] in 1983. Studies utilizing cryoablation, including a randomized, sham-controlled trial, have shown improvement in symptoms and QOL.[742-748] 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.[749,750] In-office endoscopic laser ablation of the PNN has also been reported with positive improvement.[751] These procedures seem to be well-tolerated, with minimal complication risk.[752] There is also evidence to suggest that appropriate response to ipratropium nasal spray seems to correlate with improved cryotherapy treatment response.[748]

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]**

Aggregate grade of evidence – septoplasty/septorhinoplasty: 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.

Aggregate grade of evidence – inferior turbinate surgery: 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.

Aggregate grade of evidence – neurectomy (vidian neurectomy, posterior nasal neurectomy): 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.

Aggregate grade of evidence – cryotherapy/radiofrequency ablation of posterior nasal nerve: 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, 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.

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[629]	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[628]	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[636]	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 & Rhinasthma score for those that also underwent septoplasty -No difference in rescue med use
Karatzanis et al[622]	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[635]	2021	5*	Retrospective case series	Heterogenous case series of patients undergoing septoplasty or septorhinoplasty +/-	Septal perforation rates	No AR patient had a septal perforation

				turbinoplasty, including those with AR		
Kim et al[632]	2021	5**	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/hour 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[631]	2019	5*	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[630]	2019	5*	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[627]	2018	5*	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
Bugten et al[626]	2016	5*	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[623]	2012	5*	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[634]	2011	5***	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[625]	2004	5*	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[621]	1988	5*	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-op compared to non-AR patients, and had unchanged nasal secretion
Stoksted & Gutierrez[624]	1983	5*	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

LOE=level of evidence; NOSE=Nasal Obstruction Symptom Evaluation; AR=allergic rhinitis; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; VAS=visual analog scale; OSA=obstructive sleep apnea; IT=inferior turbinate; AHI=apnea hypopnea index; UPSIT=University of Pennsylvania Smell Identification Test; SNOT-20=Sinonasal Outcome Test (20 items); RhinoQOL=Rhinosinusitis Quality of Life Survey

*****LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR patients

**LOE downgraded due to inclusion criteria of a unique population and low sample size

*** 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

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[672]	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[668]	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 & Coatesworth[753]	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[648]	2009	1	SR	RFA turbinoplasty	-Symptom questionnaires	Nasal RFA reduced IT mucous membrane volume and may decrease

					-Acoustic rhinometry -Rhinomanometry	subjective symptoms and nasal blockage, with only minor discomfort and side effects
Ghosh et al[633]	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[678]	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[708]	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
Banhiran et al[671]	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[641]	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 vs RFA alone
Abtahi et al[715]	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
Lee[701]	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[718]	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 submucosal glands
Lavinsky-Wolff et al[660]	2012	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
Chusakul et al[689]	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[653]	2010	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[647]	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
Unal et al[716]	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[681]	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[629]	2019	3	Prospective cohort	IT reduction (via microdebrider) with septoplasty in AR 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[709]	2019	3	Case-control	-Submucosal turbinoplasty with resection of PNN branches in IT	Nasal obstruction, sneezing, nose blowing, mouth breathing, hyposmia	Rhinorrhea severity, detection threshold, and recognition threshold significantly lower after resection of the posterior

				-Submucosal turbinoplasty alone		nasal nerves with turbinoplasty
Zhong et al[677]	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[702]	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[713]	2015	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[670]	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[654]	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
Tan et al[712]	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 & El-Hakim[754]	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[755]	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[706]	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[646]	2008	3	Case-control	-Coblation-assisted -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[688]	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[686]	2005	3	Case-control	Septoplasty or nasal polypectomy with vs without RFA turbinoplasty	Nasal obstruction, rhinitis symptoms via Haikou standard	First group (with RFA) had significantly higher improvement in nasal obstruction
Takeno et al[697]	2003	3	Prospective cohort	CO2 laser on AR allergic to house dust mites and Japanese cedar pollen vs 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[695]	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
Passali et al[644]	1999	3	Retrospective cohort	-Electrocautery vs cryotherapy vs laser vs submucosal resection -With vs without lateral displacement -Turbinectomy	-Rhinomanometry -Acoustic rhinometry -Mucociliary transport time -Secretory IgA -Symptoms	Submucosal resection with lateral displacement of the inferior turbinate had the greatest improvement in nasal respiratory function with the lowest long-term complications
LOE 4* studies [639,640,642,643,645,649-652,655-659,661-667,669,673-676,679,680,682-685,687,690-694,696,698-700,703-705,707,710,711,714,718]						

LOE=level of evidence; SR=systematic review; RFA=radiofrequency ablation; SRMA=systematic review and meta-analysis; IT=inferior turbinate; NOSE=Nasal Obstruction Symptom Evaluation; RCT=randomized controlled trial; AR=allergic rhinitis; QOL=quality of life; INCS=intranasal corticosteroid; PNN=posterior nasal nerve; SNOT-22=Sinonasal Outcome Test (22 item); VAS=visual analog scale

*LOE 4 studies referenced due to extensive number of studies in this group and multiple higher LOE studies included in the table

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[728]	2020	2	RCT	Patients with AR + CRSwNP who underwent nasal	-VAS: nasal symptoms -TNSS	-Vidian neurectomy group had greater improvement in VAS nasal obstruction &

				polypectomy, sinus surgery, and septoplasty (when indicated): -No further treatment -Vidian neurectomy	-PFT, methacholine challenge	rhinorrhea, but not sneezing or itching -TNSS was significantly improved in vidian neurectomy group vs controls -Number of patients with PFT impairment reduced more significantly in vidian neurectomy group
Qi et al[729]	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 cores -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[712]	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[727]	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
Ai et al[726]	2018	4	Retrospective cohort	Patient with AR and asthma who has received: -Conservative medical treatment	-RQLQ -VAS -TASS -AQLQ -Medication scores	-Neurectomy group experienced significant improvement in RQLQ, VAS, AQLQ, and medication scores vs medical management

				-Bilateral endoscopic vidian neurectomy		-No difference in pre- and post-treatment TASS was noted in either group
Su et al[725]	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[724]	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

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; CRSwNP=chronic rhinosinusitis with nasal polyposis; VAS=visual analog scale; TNSS=Total Nasal Symptom Score; PFT=pulmonary function test; QOL=quality of life; TASS=Total Asthma Symptom Score; AQLQ=Asthma Quality of Life Questionnaire

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[734]	2021	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 vs PNN alone
Marshak et al[739]	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[736]	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[740]	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[756]	2011	3	Non-randomized controlled trial	AR patients that underwent: -Selective resection of peripheral branches of posterior nasal nerve via submucous turbinectomy (local anesthesia) -Total resection of posterior nasal nerve + 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)
Wang et al[735]	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[738]	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[737]	2017	4	Retrospective case series	AR patients that underwent PNN neurectomy after submucous inferior turbinectomy	TNSS	TNSS significantly improved
Ogawa et al[711]	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[733]	2021	5	Retrospective case series	AR patients that underwent: -PNN trunk resection in an underwater environment	-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

				-Resection of peripheral branches of PNN **All patients also underwent submucous inferior turbinectomy		medication scores, sneezing symptoms & rhinorrhea symptoms (but not nasal obstruction)

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; NN=posterior nasal nerve; VAS=visual analog scale; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; SR=systematic review; SNOT-22=Sinonasal Outcome Test (22 item); CRSwNP=chronic rhinosinusitis with nasal polyps; FESS=functional endoscopic sinus surgery; TNSS=Total Nasal Symptom Score

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[744]	2021	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 1 category)	-Cryotherapy had significantly greater improvement in all three categories vs sham surgery -Presence of AR did not affect whether cryotherapy led to improvement
Stolovitzky et al[749,750]	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 vs sham surgery -No subgroup analysis on AR patients
Ehmer et al[749]	2021	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
Ow et al[745]	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[747]	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[742]	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[746]	2021	5*	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[751]	2020	5*	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
Yen et al[743]	2020	5*	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[748]	2020	5*	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[741]	1983	5*	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

LOE=level of evidence; AR=allergic rhinitis; PNN=posterior nasal nerve; r=reflective; TNSS=Total Nasal Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; NOSE=Nasal Obstruction Symptom Evaluation; CGI-I=Clinical Global Impressions-Improvement Scale; SNOT-22=Sinonasal Outcome Test (22 item); VAS=visual analog scale

*****LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR patients

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.[757] 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.[757,758] 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.[759] 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.[760,761]

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.[762-764] In a double-blind, placebo-controlled RCT, there was no difference in symptom scores in patients who discontinued AIT after four years of use and those who continued it.[762]

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.[765] 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.[766,767] 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 vs 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.[768]

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.[769,770] 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.[771] 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.[772] 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.[758] AIT can also be provided in the sublingual form [SLIT]; dissolvable tablets are FDA approved for a limited number of allergens.[773]

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 blocking antibodies; generation of allergen-specific regulatory T and B cells and suppression of allergen-specific effector T cell subsets and innate lymphoid cells; and reduction in tissue mast cells and eosinophils accompanied by a decrease in type I skin test reactivity.[774,775] The clinically evident changes occur earlier with SCIT, and more pronounced allergen-specific IgG4 responses are observed compared with SLIT.[776]

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.[777-779] 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.[308]

The severity and duration of AR symptoms, as well as coexisting medical conditions such as asthma, should considered in assessing the need for AIT.[758] 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.[65] 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.[65]

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.[765] 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 beta 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.[780] Most fatal reactions were associated with bronchospasm and/or respiratory failure.[780,781]

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% 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.[782] 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.[783,784] Thus, the lack of effect of typical subcutaneous epinephrine dosing in a β-blocked patient creates the treatment dilemma.

Although there is some variability, many guidelines generally consider active systemic autoimmune diseases and active malignancy as contraindications to AIT.[785] 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.[786] Similarly, the theoretical concerns in autoimmune disease are offset by several case series demonstrating relative safety and effectiveness.[787] 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.[788]

Initiating AIT during pregnancy is contraindicated although most consensus documents state that continuing maintenance immunotherapy during pregnancy is not contraindicated.[757,758] 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.[789] A more recent study demonstrated the relative safety of SLIT initiated during pregnancy.[790]

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.[791] SLIT tablets are also contraindicated in patients with EoE.[791-794]

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 venom immunotherapy is a relative contraindication, but not for AIT.[785] 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)[794]. 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.[795,796] 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.[797]

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.[798,799] Impurities in the source materials, such as mold growing on pollen granules or bacteria on cat pelts, may

affect immunogenicity.[800] Variation also occurs in the raw material collection[799] and in the extraction process.[797,798,801,802] 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.[797] Given that the antigenic 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 leads 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.[803] 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 gram 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.[797] 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.[797]

In Europe, many manufactures use proprietary units and internal quality controls which must utilize a validated assay.[798] This European manufacturer based quality control is known as "In House Reference

Preparation" or "IHRP".[799] However, the European Medical Agency has been developing a standardized framework based on protein homology rather than source species.[804] The European Union is also developing additional allergen standards with the WHO starting with Bet v 1 and Phl p 5a.[804] 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 manufacturer 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.[804]

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-degree (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 50mm ($ID_{50}EAL$) 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 3-fold dilutions is defined as 100,000 BAUs/mL and twelve 3-fold dilutions 10,000 BAUs/mL.[804] Manufactures 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.[803] 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.[800]

Some allergen extracts in Europe use the Nordic method where 10,000 biologically standardized units/mL is comparable to a skin prick test response elicited by 10 mg/mL of histamine.[804] Most allergen extracts in Europe are proprietary; however, the European effort to develop cross-product comparability is summarized nicely by Zimmer et al.[800] 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".[805,806]

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.[807] Adjuvants are chemicals and proteins that may enhance the safety, convenience and immunological effects of AIT.[808-814] Effective AIT attenuates pro-inflammatory Th2 responses in favor of tolerogenic T reg 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.[815,816] Early studies with alum-

precipitated extracts demonstrated an augmented immunologic response but with some undesirable IgE mediated response that hindered its therapeutic application.[815,817] Microcrystalline tyrosine has been tested as an alternative with less IgE production.[810,816] 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.[813,818-820] Tversky et al[821,822] showed that traditional SCIT alone results in 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[823] 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.[824] In 2021, Leonard et al[825] 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.[826]

A TLR-4 adjuvant has also been in clinical development (Pollinex Quattro™, Allergy Therapeutics).[827] 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.[828] A brief ragweed trial also showed positive clinical effect.[829]

Nanoparticle based constructs. Synthetic nanoparticles have been proffered since 1959 to deliver a host physiologically active substances including vaccines.[830,831] 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.[832,833] One example is vitamin D3 which has been shown to reduce effector T cell stimulation and cytokine production and promote the effect of AIT in both mice and humans.[834-836] One mouse immunotherapy study successfully employed the use of Fel d 1 covalently bound to vitamin D3.[837] *(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), induces levels of IL-10, IFN-γ and Foxp3 in response to environmental allergens.[838] Like TLR ligands, ASHMI has shown some limited effectiveness in treating certain allergic diseases by itself without the presence of an allergen.[839] 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.

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

Category	Adjuvant	Examples and comments
	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 increasing 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.

Category	Adjuvant	Examples and comments
	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

Ig=immunoglobulin; TLR=toll-like receptor; TSLP=thymic stromal lymphopoietin; ASHMI= Anti-Asthma Simplified Herbal Medicine Intervention

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.[840] 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.[841] 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.[842] 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.[843,844] 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.[845,846] 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,[847] and ragweed peptide therapy improved symptom scores compared to natural extract and placebo.[848] Birch pollen pre-seasonal treatment induced immunologic changes, but clinical symptoms were not significantly improved.[849] 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.[850-853] 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.[854-856]

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.[857] While immediate hypersensitivity reactions are reduced, late phase adverse reactions can still occur.[858] Allergoid preparations have been evaluated to several different allergens. Initially utilized in ragweed allergic patients, allergoid preparations reduced symptom scores and increased blocking antibodies.[859,860] Subsequent studies with grass pollen allergoid also showed effectiveness in reducing clinical symptom scores and medication use.[817,861,862] Allergoids in HDM allergic patients also demonstrated improved symptom scores, in both subcutaneous and sublingual routes.[863,864] 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.[865] 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.[866] 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.[867] Most of the research involving encapsulated allergens has yet to be evaluated in human trials.[809] 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.[868] 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.[869] Limited human trial data suggest that encapsulated allergens may induce immune responses but further understanding of their role in AIT is needed.[814]

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,[870] multiple RCTs have supported the therapeutic efficacy of SCIT for AR.[758] SCIT efficacy is contingent upon an appropriate treatment duration and dose, with an optimal target maintenance dose between 5-20µg of major allergen for each clinically relevant aeroallergen.[758] SCIT has been associated with effective symptom amelioration and potential disease modification that can persist after stopping treatment.[758]

Evidence suggests that a SCIT treatment duration of 3-5 years is appropriate.[758] A clinically significant relapse rate has been observed with SCIT discontinuation prior to 3 years.[871] 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.[872]

SCIT is efficacious for AR sensitive to pollen, mold, HDM, and animal allergens.[758,872-878] Such efficacy has been demonstrated based on rigorous RCTs for pollens (e.g., ragweed, grass, 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.[758,873-877]

The majority of RCTs supporting SCIT for AR have been studies of single aeroallergens.[758] 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.[758] Evidence indicates local reactions do not reliably predict occurrence of subsequent systemic reactions; dosage adjustment is not typically required after their occurrence.[758] 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.[758] Severe grade 4 anaphylactic reactions occur in approximately 1 per million injections, and fatal reactions in approximately 1 in 23 million injection visits.[879,880]

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.[758,879-881] 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.[880]

***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.[882,883] 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]).[884]

***Evidence*.** Dhami et al,[777] 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]; 6 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, 9 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[885,886] and new allergen sensitivities.[887,888] However, data meta-analyzed by Dhami et al[777] 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.[889-891] Arroabarren et al[764] 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[892] reported 77% reduction in TNSS in children with a similar decrease in medication scores. In an elderly cohort, Bozek et al[893] 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.[764,893-897] Kim et al[896] 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,[764] systemic adverse effects were noted in 2.5% of patients overall, while Scadding et al[889] 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[308] 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;[898] recommendations for SLIT in Europe include tablet formulations and sublingual drops.[757] 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.

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 appropriately. 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.

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[896]	2021	1	Network meta-analysis	-SCIT -SLIT	-Symptoms -Medication use	All forms of AIT were effective, with SCIT providing greater benefit
Dhami et al[777]	2017	1	SRMA	-SCIT -Comparator	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Corren et al[413]	2021	2	DBRCT	-Pollen SCIT -Pollen SCIT + dupilumab	Symptom scores following nasal challenge	-Dupilumab did not provide additional symptom benefit to SCIT

				-Dupilumab -Placebo		-Fewer dupilumab patients required epinephrine
Shamji et al[899]	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[891]	2020	2	DBRCT	-HDM SCIT -HDM SLIT -Placebo	Combined symptom and medication scores	Patients receiving SCIT experienced improvement in symptoms and medications vs placebo
Worm et al[890]	2018	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[894]	2017	2	DBRCT	-HDM SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Pfaar et al[895]	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[889]	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[900]	2016	2	DBRCT	-HDM SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Kleine-Tebbe et al[901]	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[902]	2014	2	DBRCT	-Grass pollen SCIT -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Tworek et al[903]	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
Patel et al[850]	2012	2	DBRCT	-Fel d 1 antigen SCIT -Placebo	Symptom scores	SCIT group had improvement in symptom scores
James et al[904]	2011	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptoms

Kuna et al[905]	2011	2	DBRCT	-*Alternaria* SCIT -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Hoiby et al[906]	2010	2	DBRCT	-Birch pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Pfaar et al[907]	2010	2	DBRCT	-Tree pollen SCIT -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Riechelmann et al[863]	2010	2	DBRCT	-Glutaraldehyde-modified HDM SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Tabar et al[908]	2008	2	DBRCT	-*Alternaria* SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Charpin et al[909]	2007	2	DBRCT	-Tree pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Powell et al[910]	2007	2	DBRCT	-Grass pollen immunotherapy -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Colas et al[911]	2006	2	DBRCT	-Tree pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Alvarez-Cuesta et al[912]	2005	2	RCT	-Pollen SCIT -Placebo	-QOL -Skin test response	Symptom scores and medication scores were significantly reduced, QOL improved
Corrigan et al[817]	2005	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use -sIgG	SCIT group had improvement in symptom and medication scores
Dokic et al[913]	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[914]	2005	2	DBRCT	-Parietaria pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Tabar et al[915]	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[916]	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[917]	2004	2	DBRCT	-Ambrosia pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Radcliffe et al[918]	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[919]	2003	2	DBRCT	-HDM SCIT -Placebo	-Symptoms -Medication use -Skin test reactivity	SCIT group had improvement in symptom and medication scores
Arvidsson et al[920]	2002	2	DBRCT	-Birch pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Bodtger et al[921]	2002	2	DBRCT	-Birch pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Drachenberg et al[922]	2002	2	DBRCT	-Tree pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Drachenberg et al[818]	2001	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use -Skin testing -IgG	SCIT group had improvement in symptom and medication scores
Leynadier et al[923]	2001	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Walker et al[924]	2001	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Durham et al[762]	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[925]	1998	2	DBRCT	-Tree pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Zenner et al[926]	1997	2	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Olsen et al[927]	1995	2	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Ortolani et al[928]	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[929]	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[930]	1991	2	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Grammer et al[931]	1983	2	DBRCT	-Grass pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Grammer et al[860]	1982	2	DBRCT	-Ragweed pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptom scores
Weyer et al[932]	1981	2	DBRCT	-Grass pollen SCIT -Placebo	Combined symptoms and medication scores	SCIT group had improvement in symptom and medication scores
Schmid et al[897]	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
Wang & Shi[892]	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[893]	2016	3	RCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Moreno et al[933]	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[764]	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[934]	2012	3*	DBRCT	-Grass pollen SCIT -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
DuBuske et al[935]	2011	3	Placebo-controlled study	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Ceuppens et al[936]	2009	3*	DBRCT	-Birch pollen SCIT -Placebo	-Symptoms -sIgG	SCIT group had reduced symptom scores
Pauli et al[845]	2008	3*	DBRCT	-Birch pollen SCIT -Placebo	-Symptoms -Medication use -Skin testing	SCIT group had improvement in symptom and medication scores
Chakraborty et al[937]	2006	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use -sIgE and IgG, total IgE	SCIT group had improvement in symptom and medication scores

					-Skin test response -FEV_1	
Frew et al[938]	2006	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Jutel et al[843]	2005	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Rak et al[939]	2001	3*	DBRCT	-Pollen SCIT -Nasal steroid	-Symptoms -Medication use	Nasal steroid was more effective than a short course of pre-seasonal SCIT in improving symptoms
Ariano et al[940]	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[941]	1997	3*	DBRCT	-Parietaria pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Dolz et al[942]	1996	3*	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[943]	1992	3*	DBRCT	-Ragweed pollen SCIT -Placebo	-Symptoms -Nasal provocation -sIgE and sIgG -Basophil histamine release	SCIT group had reduced symptom scores
Bousquet et al[944]	1991	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Iliopoulos et al[945]	1991	3*	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[861]	1990	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Fell & Brostoff[946]	1990	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Nasal challenge	SCIT group had improvement in symptom scores
Horst et al[947]	1990	3*	DBRCT	-*Alternaria* SCIT -Placebo	-Global symptom and medication scores -Skin tests -sIgG	SCIT group had improvement in symptom and medication scores
Juniper et al[948]	1990	3*	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[862]	1989	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had reduced symptoms and decreased medications but a higher rate of adverse reactions
Ewan et al[949]	1988	3*	DBRCT	-HDM SCIT -Placebo	-Symptoms -Nasal challenge -Skin test response	SCIT group had improvement in symptom scores
Bousquet et al[950]	1987	3*	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[951]	1987	3*	DBRCT	-Ragweed pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Grammer et al[952]	1984	3	Placebo-controlled study	-Ragweed pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptoms
Metzger et al[953]	1981	3*	DBRCT	-Ragweed pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptoms

LOE=level of evidence; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; AIT=allergen immunotherapy; SRMA=systematic review and meta-analysis; DBRCT=double-blind randomized controlled trial; s=antigen-specific; Ig=immunoglobulin; HDM=house dust mite; RCT=randomized controlled trial; QOL=quality of life; SPT=skin prick test; FEV_1=forced expiratory volume in 1 second

*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

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.[954] 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).[955]

Efficacy and safety. Aeroallergen rush SCIT has demonstrated effectiveness for AR and asthma.[954] The majority of double-blind RCTs utilized single-allergen extracts, primarily grass pollen.[934,942,950,956] Other allergens investigated include ragweed, various tree pollens, *Alternaria*, cat, dog, and HDM.[414,944,947,957-961] 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.[954] This improves to 12-38% when using routine premedication.[962] Depigmented-polymerized extracts have a significantly better safety profile with systemic reactions occurring in less than 2% of patients.[934,956,958,963] Local reactions do not appear to predict systemic reactions and delayed systemic reactions are reported rarely with rush SCIT.[958] Only one double-blind RCT specifically evaluated safety and efficacy of rush versus conventional SCIT.[959] 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.[964]

***Rush, ultra-rush, and modified rush*.** Rush SCIT has traditionally been defined as achieving target therapeutic dose within 1 to 3 days;[308,758] 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 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.[934,956,958,963] 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.[965,966] 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% versus 73%, respectively).[965] 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.[966] 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.[414,957] A 5-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.

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.

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[956]	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 vs placebo -Higher rates of mild SRs in therapy arm but none required specific treatment
Pfaar et al[934]	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 vs placebo -Higher rates of mild SRs in treatment arm but no grade 3 or 4 reactions
Klunker et al[957]	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[414]	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 5-fold decrease in risk of rush SCIT associated anaphylaxis -Combination therapy associated with significant reduction in symptom severity vs AIT alone
Cox[954]	2006	2	Systematic review	-AR, asthma, Hymenoptera, imported fire ant	-Combined symptom-medication score	-SR rate significantly higher for rush SCIT (27-100%)

				-Adults and children -RCTs, observational cohorts, case series	-SR rate -Cutaneous testing -Provocation challenges -sIgE and sIgG	-Baseline FEV_1 <80% and high skin test reactivity are predictive of SR -Premedication reduced risk of SRs with rush SCIT
Akmanlar et al[959]	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 -3 had mild SRs -No severe reactions
Dolz et al[942]	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 systemic reactions during build-up requiring epinephrine
Portnoy et al[965]	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[944]	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[947]	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 vs 0 in the placebo arm
Lilja et al[960]	1989	2	DBRCT	-Animal-dander rush SCIT -Placebo (transferred to active arm after 1 year)	-Skin prick test -Allergen and histamine	Improvement in skin prick test and bronchial challenges for treatment

					bronchial challenges	group at 1 year and 2 year follow up periods
Bousquet et al[950]	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 vs placebo -Nearly 2-fold increase in SRs for patients treated with allergoid
Morais-Almeida et al[958]	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 -2 cases of mild SRs out of 100 patients
Casanovas et al[963]	2005	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 2 injections on day 1 without the need for premedication
Hejjaoui et al[966]	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[961]	1989	3	Observational cohort	-HDM-allergic patients with asthma -Adults and children	SR rate and severity	38% SRs in cohort with 8 cases of anaphylactic shock
Winslow et al[962]	2018	4	Case series	-AR and asthma -Adults and children	SR rate and severity	Per-patient incidence of SRs was 4-fold higher in rush SCIT patients compared to conventional and cluster protocols despite premedication use
Cook et al[964]	2017	4	Case series	Rush SCIT	SR rate	Increased rate of SRs on subsequent doses after initial rush SCIT
Cox et al[758]	2011	4*	Evidence-based search	-Allergen immunotherapy -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
More et al[955]	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

LOE=level of evidence; DBRCT=double-blind randomized controlled trial; SCIT=subcutaneous immunotherapy; SR=systemic reaction; IgE=immunoglobulin E; mAb=monoclonal antibody; s=antigen-specific; IgG=immunoglobulin G; AIT=allergen immunotherapy; AR=allergic rhinitis; RCT=randomized controlled trial; FEV_1=forced expiratory volume in 1 second; HDM=house dust mite

*Upgraded from LOE 5 due to established methodology, several rounds of review, long history of evidence-based guideline development

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 2 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.[967-969]

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 predication regimens. One SRMA evaluated the cluster SCIT efficacy for single allergen extracts and included 8 RCTs comparing cluster SCIT to conventional SCIT or placebo.[967] 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.[970,971] 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.[902,921] Compared to conventional SCIT, cluster SCIT demonstrates similar efficacy for multiple extracts including pollens and HDM.[915,967,972-974] 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.[967,968] 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[968] 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 designed 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.[962,973] Minimal data is available on delayed reactions with cluster SCIT and no conclusions can be drawn.[968,975]

Factors that affect systemic reactions with cluster SCIT. Only one RCT specifically assessed the use of premedication in cluster SCIT with standardized pollen extracts.[976] Use of loratadine prior to cluster dosing showed a decline in systemic reactions from 79% of patients to 33% for the study duration.[976] 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.[954]

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.[954] 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.[962,968,972] 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.

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.

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[968]	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 vs conventional SCIT
Yu et al[972]	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[969]	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 vs conventional SCIT -No conclusive difference in SR rate
Feng et al[967]	2014	2*	SRMA	Efficacy and safety of cluster SCIT vs	Not applicable	-Similar efficacy and safety of cluster SCIT vs conventional SCIT

				conventional SCIT or placebo		-Improved QOL for cluster SCIT versus placebo -Nonsignificant trend for improved symptom and medication scores
Klimek et al[902]	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 vs placebo
Wang et al[974]	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[973]	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[971]	2008	2	RCT	-Grass mix cluster SCIT -Placebo	Nasal provocation test	Significant increase in threshold concentration for positive provocation
Cox[954]	2006	2**	Systematic review	-Adults & 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 vs conventional SCIT
Tabar et al[915]	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[970]	2004	2	DBRCT	Cat hair and dander: -Cluster SCIT 0.6µg Fel d 1 -Cluster SCIT 3µg Fel d 1 -Cluster SCIT 15µg 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[921]	2002	2	DBRCT	Depot birch extract: -Cluster SCIT -Placebo	-Symptom score -Medication score -Conjunctival sensitivity -SPT	Treatment group showed improvement in all categories versus placebo,

					-SRs	with similar rates of adverse events
Nielsen et al[976]	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
Winslow et al[962]	2018	4	Case series	-AR and asthma -Adults and children	SR rate and severity	Per-patient incidence of SRs was 4-fold higher in rush SCIT patients compared to conventional and cluster SCIT protocols, despite premedication use
Cook et al[975]	2015	4	Case series	Timing of SRs to aeroallergen immunotherapy	Rate of SRs	52.8% of SRs occurred after at least 30 minutes from the injection time

LOE=level of evidence; SRMA=systematic review and meta-analysis; SCIT=subcutaneous immunotherapy; SPT=skin prick test; RCT=randomized controlled trial; SR=systemic reaction; HDM=house dust mite; QOL=quality of life; DBRCT=double-blind randomized controlled trial; Ig=immunoglobulin; s=antigen-specific; AR=allergic rhinitis; TGF=transforming growth factor; IL=interleukin; IFN=interferon
*LOE downgraded due to heterogenicity of included studies included
**LOE downgraded due to inconsistency of results

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,[796,977] the first double-blind placebo-controlled trial of SLIT dates from 1986 by Scadding and Brostoff.[978] 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. [979,980] Since then, a wealth of high-quality SLIT trials have been conducted.[981]

In ICAR-Allergic Rhinitis 2018,[308] 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 RCT 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 between 0.3-0.5 indicates mild effect, 0.5-0.8 moderate effect, and above 0.8 a large effect of the intervention on the disease.[982]

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).[760] 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.[983] In addition to the ICAR-Allergic Rhinitis 2018 evidence demonstrating moderate efficacy for symptom relief in pollen and HDM liquid SLIT[984] and grass pollen tablet SLIT,[985] there is additional evidence for a moderate reduction in symptoms and medication scores in pediatric perennial AR.[986,987] 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.[313] An additional study showed that the 5-grass tablet had the highest relative clinical impact on symptom score over all other pharmacotherapy treatments.[322] 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.[988-993] Most meta-analyses show superiority of SCIT over SLIT, but they are of low grade evidence as they are based on indirect comparisons.[994] 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.[889] In children, SCIT seems more effective than SLIT, but the quality of evidence is low.[984] 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 two years off-treatment.[765] 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,[765] while another systematic review found only low-grade evidence.[995] 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,[994] found SLIT to be safer than SCIT. In the complete dataset of systemic reviews, there were 7 reports of the use of epinephrine in the SLIT group.[996] 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[997,998] 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 minutes following the initial dose.[999] Starting SLIT in-season seemed to be safe. Although there were 2 serious treatment related adverse events with co-seasonal SLIT initiation, none needed epinephrine administration.[1000]

Grass pollen SLIT tablets were noted to be equally safe in AR patients with and without mild asthma.[1001] 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.[1002] There have been a few case-reports of eosinophilic esophagitis after a course of grass pollen SLIT tablets.[1003] 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.[1004]

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.[1005,1006] 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,[1007] 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.[1008]

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 ($p<0.001$).[1009] A post-hoc analysis demonstrated symptom and medication reduction with the birch SLIT tablet during the oak pollen season in adults with allergic rhinoconjunctivitis.[1010]

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.[899]

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 vs aqueous SLIT vs 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.

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[1011]	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- vs poly-sensitized AR
Chen et al[986]	2020	1	SRMA	-SLIT for HDM tablet vs 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[777]	2017	1	SRMA	-AIT for AR and ARC -Antigens vs 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[987]	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 vs 1025), oral pruritis most common
Kristiansen et al[765]	2017	1	SRMA	-SLIT, SCIT, oral AIT -Numerous antigens vs 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 y): 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[1012]	2021	2	SRMA	-AR in adults -Grass pollen SLIT vs 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

Ji et al[994]	2019	2	SRMA	-SCIT vs 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[1013]	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[896]	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 to -0.127) -Tablet: symptoms -0.329 (95% CI, -0.426 to -0.231) -In network metanalysis SCIT more effective than aqueous SLIT & tablets
Dhami et al[777]	2017	1	SRMA	-AIT for AR and ARC -Antigens vs 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[989]	2015	1	Network meta-analysis of RCTs	Grass pollen allergy: -SLIT tablets vs placebo -SLIT aqueous vs placebo -SCIT vs placebo	ARC symptoms & medication use	Symptom and medication scores with SCIT, SLIT aqueous and tablets all reduced vs. placebo, except for symptom score with SLIT aqueous
Di Bona et al[988]	2012	1	MA-based comparison	Grass pollen seasonal AR: -SCIT vs placebo -SLIT vs placebo	-Symptoms -Medication use	Indirect modest evidence of SCIT more effective for seasonal AR than SLIT (aqueous) and SLIT (tablet) for symptom and medication score reduction
Radulovic et al[1014]	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 (95% CI -0.05, 0.04) -Tablets: SMD -0.33 (95% CI -0.46, -0.2)

						-SLIT appears safe for AR
Di Bona et al[1015]	2010	1	MA of RCTs	Grass pollen: SLIT vs 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[1016]	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[1017]	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[1018]	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[984]	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[1019]	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 vs placebo -Significant improvement in inflammatory markers in monotherapy group
Moreno-Ancillo et al[1020]	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- vs single-allergen group
Lee et al[1021]	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[309]	2021	1	SRMA of DBRCT	Seasonal or perennial AR in adults & adolescents: -INCS -INCS + INAH -oral AH -LTRA -Tablet-SLIT	-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)

				-Placebo-controlled		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[986]	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[1022]	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[996]	2015	1	MA of RCTs	Seasonal AR: Grass pollen SLIT tablets vs placebo	-Symptoms -Medication use	-Small improvement in symptom and medication scores vs 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[322]	2014	1	MA of RCTs	Pollen SLIT vs pharmacotherapy vs placebo for seasonal AR	Relative clinical impact	Clinical impact: 5 grasses tablet > INCS > Timothy grass tablet > montelukast > antihistamines
Nelson[875]	2018	2*	SR of 15 DBRCTs	-HDM SCIT (3 trials) -SLIT tablets (12 trials)	-Symptoms -Medication use	Effectiveness of SCIT and SLIT tablets established
Durham et al[313]	2016	2	Pooled analysis from RCTs	-Seasonal AR: grass or ragweed SLIT tablet vs pharmacotherapy** -Perennial AR: HDM SLIT tablet vs pharmacotherapy**	TNSS vs 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[1001]	2015	2	Pooled analysis from RCTs	-Grass SLIT tablet vs 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 & Ellis[990]	2014	2	SR of RCTs	Grass pollen for seasonal AR: -Tablet (Timothy only) -Tablet (5 grasses) -SCIT -Placebo -Indirect comparison	-Efficacy -Safety -Cost for Canadian setting	-Symptoms: All AIT treatments < placebo -Costs for 5 grasses tablet < costs Timothy grass tablet and SCIT

LOE=level of evidence; SR=systematic review; SLIT=sublingual immunotherapy; HDM=house dust mite; AR=allergic rhinitis; RCT=randomized controlled trial; QOL=quality of life; SRMA=systematic review and meta-analysis; AIT=allergen immunotherapy; ARC=allergic rhinoconjunctivitis; SCIT=subcutaneous immunotherapy; SMD=standardized mean difference; MA=meta-analysis; VAS=visual analog scale; CI=confidence interval; DBRCT=double-blind randomized controlled trial; PFT=pulmonary function test; INCS=intranasal corticosteroid; IAH=intranasal antihistamine; AH=antihistamine; LTRA=leukotriene receptor antagonist; TNSS=Total Nasal Symptom Score; TMS=Total Medication Score; IgE=immunoglobulin E; MFNS=mometasone furoate nasal spray; TEAS=treatment emergent adverse events; TRAE=treatment related adverse event
*LOE downgraded due to no meta-analysis, not limited to SLIT or AR alone
**Antihistamines, montelukast, mometasone furoate nasal spray

TABLE XI.D.6.a.-2 Established aggregate grade of evidence from ICAR-Allergic Rhinitis 2018[308]

	Aggregate grade of evidence	Direction of impact	Magnitude of impact*	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,[1016] Radulovic,[1014] Di Bona,[996,1015] Nelson,[989] Calderon[993]			
SLIT is effective for the reduction of symptoms of AR in children	B	Yes	Low impact	Recommendation
	Kim,[984] Larenas-Linnemann;[985] not enough evidence: Roder[1023]			
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[1002] -- same drop-out rates SLIT vs placebo			
SLIT is safe for the treatment of AR in children	B	Yes	---	Safety profile is very good
	-Systematic reviews (Kim,[984] Larenas-Linnemann,[985] Roder[1023]) all included safety evaluation -Makatsori[1002] -- same drop-out rates SLIT vs placebo			
SCIT is more effective than SLIT	A	Yes	Weak evidence	Recommendation
	-Chelladurai,[991] Dretzke,[1024] Calderon (HDM),[993] Kim (children)[984 29] -Grass pollen tablets/drops vs SCIT: Di Bona[988] -SCIT equivalent to grass pollen tablets only, drops less effective: Nelson[989]			
SLIT is safer than SCIT	B	Yes	Weak evidence	Recommendation
	Aasbjerg[992]			
Total cost of SLIT is less than SCIT	A	Yes	Moderate evidence	Recommendation
	Meadows (UK setting),[1007] Dranitsaris (Canadian setting)[990]			

It is safe to continue SLIT during pregnancy	B	No added risk	Moderate evidence	Recommendation
	Oykhman[1004]			
It is safe to start SLIT during the season	B	Sightly added risk	Moderate evidence	Option
	Creticos[1000]			
Tablet SLIT is more effective than pharmacotherapy	A	Yes	-Moderate: antihistamines, montelukast -Weak: INCS	Recommendation
	-Devillier (pollen tablet SLIT),[322] Durham (grass pollen or ragweed tablet SLIT)[313] -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,[1007] Dranitsaris[990]			
SLIT is cost-effective after several years of treatment	B	Yes	Weak-moderate evidence	Recommendation
	Meadows,[1007] Dranitsaris[990]			
SLIT has a long-term effect beyond 3-years' application	B	Yes	Moderate evidence	Recommendation
	Durham,[1025] Didier[1026]			
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[765] (New evidence since ICAR-Allergic Rhinitis 2018)			
SLIT with grass pollen is effective for seasonal AR	A	Yes	Low impact	Strong recommendation**
	Di Bona,[996,1015] Nelson,[989] Durham[313]			
SLIT with tree pollen is effective for seasonal AR	A	Yes	Moderate effect	Strong recommendation**
	Valovirta[1027]			
	A	Yes	Moderate effect	Strong recommendation**

SLIT with ragweed pollen is effective for seasonal AR	Durham,[313] Nolte,[1028] Creticos,[1029] Skoner[1030]			
SLIT with HDM is effective for AR	A	Yes	Low impact	Strong recommendation**
	Nolte,[1031] Bergmann,[1032] Mosbech,[1033] Calderon[993]			
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[1034]			

SLIT=sublingual immunotherapy; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; INCS=intranasal corticosteroid; HDM=house dust mite; SRMA=systematic review and meta-analysis
*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.
**Considering the added long-term post-treatment effect and the possible preventive effects on the development of asthma and new 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,[765,777,986,987,994,1011-1013] six presented aqueous and tablet SLIT separately,[777,896,988,989,1014,1015] and nine reported on tablet SLIT alone.[309,313,322,875,986,990,996,1001,1022] 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[309] 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.[986] A similar study of HDM SLIT tablets in adults[1022] showed improvement in symptom scores and QOL compared to placebo. Nelson et al[875] published a systematic review of 12 double-blind RCTs for HDM SLIT tablets and concluded that efficacy was established with all twelve 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,[980] Horak et al,[1035] Malling et al,[1036] and Bergmann et al.[1032] Dose-finding studies aim to identify effective therapeutic doses while minimizing adverse effects.

The efficacy findings from 2017-2022 SLIT tablet studies are consistent with the findings reported in the first ICAR-Allergic Rhinitis 2018.[308] 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 in children reduce symptoms of AR.

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 7 of 2259 patients on grass pollen SLIT tablets were given epinephrine for treatment related adverse effects.[996] Presence of mild asthma did not affect adverse reactions for grass pollen SLIT tablets.[1001] Starting SLIT in-season is generally deemed to be safe; although there were 2 serious treatment related adverse events with co-season SLIT initiation, none needed epinephrine.[1000]

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[1011] 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.[1001] Simultaneous co-administration within 5 minutes did not result in severe swelling, systemic allergic reactions, asthma attacks, or reactions requiring epinephrine. Gotoh et al[1037] 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.

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.[1038]

Aqueous SLIT has a mild to moderate effect on improving patient symptoms and reducing medication usage.[777,984,988,1015,1016] 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.[777,989]

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.[1015] However, most of the included studies included had a low monthly allergen dose that has been shown to be ineffective in subsequent meta-analyses.[777,988,989,1016] Lack of dosing standardization across multiple studies in different countries using extracts from various manufacturers has led to heterogeneity in aqueous SLIT data.[1039]
[TABLE XI.D.6.a.-1]

Leatherman et al[1038] 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.[1038] There is expert opinion that for allergens without current effective ranges, daily SLIT dose equal to the monthly SCIT dose may be in the effective dose range; further studies should validate this.[758]

While single allergen SLIT has been shown to be effective in both monosensitized and polysenstized patients,[1011,1018,1021] 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.[1040] 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 9 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.[1019] Another study randomized polysensitized patients to single, pauci, or multi-allergen SLIT.[1017] Symptom scores

significantly improved in all groups, yet there was no significant efficacy difference shown for single vs pauci- vs 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[1014,1016] except for one meta-analysis of SCIT and SLIT for grass allergens[988] 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.[988] There were no cases of anaphylaxis or life-threatening events in children.[984] **[TABLE II.C.]**

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.

TABLE XI.D.6.c. Recommended SLIT dosing (µg/day)[1038]

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

XI.D.7. Subcutaneous versus sublingual allergen immunotherapy for allergic rhinitis – comparison table

TABLE XI.D.7. Comparison – subcutaneous vs sublingual immunotherapy

	Subcutaneous immunotherapy	Sublingual immunotherapy
Efficacy	Significant efficacy over placebo[829,909,923,1041]	Significant efficacy over placebo[1042-1044]
	-Both demonstrate efficacy over placebo for allergic rhinoconjunctivitis and other allergic conditions, but head-to-head data are lacking[761,984,994,1024,1045-1048, 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[758]	-Decreased risk of systemic reactions compared with SCIT -Epinephrine autoinjector mandated in the US by the FDA for tablet SLIT[1049, b]
	At office visits, consider peak expiratory flow tests or spirometry in patients with asthma (no treatment or testing if exacerbation)[758]	
Cost[c]	-Lower direct cost to patient, but may be comparable or higher in total (e.g., indirect) costs[990,1050,1051, d] -Lower initial ICER (e.g., first 6 years)[1007]	-Higher direct cost to patient, but may be comparable or lower in total (e.g., indirect) costs[990,1050,1051, d] -Higher initial ICER (e.g., first 6 years)[1007]
	Cost-effectiveness threshold: £20,000-30,000 / QALY by year 6[1007,1008]	
Covered by insurance?[1050, c]	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)[758]	-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[758]	-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[1046,1052-1055]	
Adherence to therapy	-More easily monitored (in office) -Most common reason for discontinuation is inconvenience[1056]	-Less easily monitored (at home) -Adherence may be improved with more frequent clinic visits, improving therapy availability, and mitigating concerns about clinical efficacy[1057,1058]
	-Overall adherence rates are similar, but conflicting data depends on how adherence is measured[1056,1059-1061, g] - Patients should be re-evaluated at least every 6-12 months while receiving immunotherapy[758, h]	
Mechanism of action	-Subcutaneous (systemic) injection -IgG, IgG4 antibody induction[899]	-Sublingual (local) administration[1062] -IgA1, IgA2 antibody induction[899]
	Allergen extracts presented to immune system induce allergen desensitization and immunologic tolerance[1046,1052,1053]	
FDA-approved allergens[1063,1064, c, 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[1046,1053]	-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[1046,1053]	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)	

SLIT=sublingual immunotherapy; SCIT=subcutaneous immunotherapy; US=United States; FDA=Food and Drug Administration; IECR=incremental cost-effectiveness ratio; QALY=quality adjusted life year; SPT=skin prick test; IDT=intradermal dilutional test; MQT=modified quantitative test; Ig=immunoglobulin

[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,[988,991] but the most recent meta-analyses did not demonstrate superiority of one over the other.[761,994] 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.[1060] Controversy exists regarding whether epinephrine autoinjectors are warranted for patients on SLIT due to factors such as the rarity of systemic allergic reactions,[1065] costs exceeding that of SLIT therapy, and poor compliance with purchasing/carrying autoinjectors.[1049,1066] 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.[990]

[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.[970,1067,1068]

[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 b-blockers.

[g]Conflicting studies have shown SCIT to have higher adherence,[1069,1070] SLIT to have higher adherence,[1071,1072] or both to have comparable compliance.[1061,1073]

[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.[1074,1075] May use SCIT extracts off label for SLIT.

[j]Contraindication for SLIT. Limited evidence suggests SCIT should not be typically recommended for patients with eosinophilic esophagitis. However, SCIT may benefit some patients with eosinophilic esophagitis.[1076]

[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.[758,1053]

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. Allergen is applied through patches kept on the skin for several hours. The epidermal barrier is usually impermeable to molecules larger than 500 Da.[1077] 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.[809,1078] 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).[1079] 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.[1080] **[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.[1081] 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.[1082] 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).[1083] 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.[1084] 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.[1085] 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 (RR [relative risk] 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.

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 2009-2015.
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[1085]	2020	2*	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[1084]	2015	2	DBRCT	Adults, 6 weekly patches kept on for 8 hours: -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 7 treatment (14.6%) and 1 control patients
Senti et al[1083]	2012	2	DBRCT	Adults, 6 weekly patches kept on for 8 hours: -Placebo patches, n=33 -Low dose grass patches, n=33 -Medium 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%

				-High dose grass patches, n=33		
Agostinis et al[1082]	2010	2	DBRCT	Children, 12 weekly patches kept on for 24 hours: -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[1081]	2009	2	DBRCT	Adults, 12 weekly patches kept on for 48 hours, 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

LOE=level of evidence; SR=systematic review; RR=relative risk; DBRCT=double-blind randomized controlled trial; CPT=conjunctival provocation test; SPT=skin prick test; NPT=nasal provocation test
*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.[871] 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 eight weeks.[1086] The cumulative dose for ILIT is dramatically lower than that used for conventional AIT and there are significantly fewer adverse events.[1087]

Thus far, two systematic reviews are available. **[TABLE XI.D.8.]** The first systematic review included eleven trials and two cohorts in a qualitative and quantitative analyses of 483 participants with the average age of 33 years.[1087] The second systematic review involved quantitative analysis of eleven trials with 452 participants aged 15 years and above.[1088] 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.[1089-1099] In one pilot study, the cervical lymph nodes

were used as the injected site.[1100] Single allergen was evaluated in seven trials,[1090-1093,1097-1099] two different allergens assessed simultaneously in four trials,[1089,1094-1096] and one trial assessed two different allergens individually.[1095] Grass pollen extract was injected in eight trials,[1089,1090,1092-1097] cedar pollen extract in two trials,[1098,1099] birch pollen extract in four trials,[1089,1094-1096] and cat dander allergen extract (MAT-Fel d 1) in one trial.[1091] Placebo injections were used in all but two trials[1089,1090] which used SCIT as control groups.

All trials performed three injections at four-week intervals except for one trial which used a two-week interval. Short-term relief of the combined symptoms and medication score was achieved in the four-week but not for the two-week interval.[1087] Increased sIgG4 levels have been associated with the effectiveness of AIT.[1101] While a short-term increase of sIgG4 level has been documented following ILIT, there has not been any medium-term or long-term effects.[1087] The reduction of sIgE in the short, medium, and long-term is frequently reported with SCIT; however, this has been notably absent with ILIT.[1087,1090]

ILIT was shown to confer short-term relief of AR symptoms in one review.[1087] Despite being safe and well tolerated, both meta-analyses determined that the efficacy of ILIT for long-term relief of AR symptoms was inconclusive.[1087,1088] 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.[1087] The major advantage in favor of ILIT compared to SCIT is fewer adverse effects of local and systemic reactions[1090] compared to SCIT. At present, there is no trial comparing ILIT vs SLIT with regard to adverse effects. Overall, two anaphylactic events have been reported for ILIT but no deaths.[1102] 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 four-week (vs. two-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.[1095] 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.

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.

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[1088]	2021	1	SRMA	-ILIT -Placebo -SCIT	-CSMS -Symptoms -Medication use -Overall improvement score -QOL -Adverse events	-No difference vs placebo -Generally well-tolerated -ILIT had fewer adverse events vs SCIT
Hoang et al[1087]	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 vs SCIT
Konradsen et al[1096]	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

Skaarup et al[1097]	2020	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
Terada et al[1099]	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[1098]	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[1095]	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
Hylander et al[1094]	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[1093]	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[1089]	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[1092]	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[1091]	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 3 injections
Senti et al[1090]	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	-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

				-54 subcutaneous injections over 3 years (cumulative dose of 4,031,540 SQU).		
Wang et al[1100]	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[1102]	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[1103]	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

LOE=level of evidence; SRMA-systematic review and meta-analysis; ILIT=intralymphatic immunotherapy; SCIT=subcutaneous immunotherapy; CSMS=combined symptom-medication score; VAS=visual analog scale; QOL=quality of life; IgE=immunoglobulin E; IgG4=immunoglobulin G4; RCT=randomized controlled trial; NPT=nasal provocation test; AR=allergic rhinitis; SQU=standardized quality units; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; SPT=skin prick test; SNOT-20=Sinonasal Outcome Test

XI.D.9. Other forms of immunotherapy – oral, nasal, inhaled

Oral, nasal, and inhaled (intra-bronchial) routes of AIT administration 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.[758]

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,[1104] cat,[1105] and ragweed[1106] 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.[758,1105] In contrast to AR, the efficacy of oral/gastrointestinal immunotherapy has been demonstrated for the treatment of food hypersensitivity.[1107] **[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.[1108] Theoretical benefits include induction of immune tolerance using lower antigen concentrations, decreased local side effects and higher adherence versus SLIT.[1109] 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 six months of treatment.[1110] No adverse events were reported, and there were no significant differences between outcome measures for both treatment arms.[1110] 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.[1111,1112] 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.[1069] 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.[1113]

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 represents a possible alternative to SCIT/SLIT warranting further study.

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.

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[1106]	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 vs placebo
Oppenheimer et al[1105]	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 vs placebo
Taudorf et al[1104]	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[1110]	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[1111]	1995	3*	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 vs placebo -Symptom scores were significantly reduced with local nasal AIT
Andri et al[1112]	1993	3*	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

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; AIT=allergen-specific immunotherapy; NPT=nasal provocation test; sIgG=specific immunoglobulin G; SPT=skin prick test; sIgE=specific immunoglobulin E; CPT=conjunctival provocation test; OMIT=oral mucosal immunotherapy; SLIT=sublingual immunotherapy; IgE=immunoglobulin E; QOL=quality of life; ICAM=intracellular adhesion molecule; ECP=eosinophil cationic protein
*LOE downgraded due to small sample size

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.[1114]

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 to 3 SCIT injections weekly to approximately 20µg 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.[413] **[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.[403,404]

The first clinical trial that investigated the effects of omalizumab plus AIT was conducted by Kuehr et al.[415] 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 omalizumab or placebo lasted 24 weeks. Combination therapy with omalizumab reduced symptom load over the 2 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.[1115] Subgroup analysis of grass allergic patients confirmed the primary study results.[1116]

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.[1117,1118] Casale et al[414] conducted a 3-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 1.2-4.0mug 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.[957]

Kopp et al performed a double-blind, placebo-controlled, multicenter RCT of omalizumab vs 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.[1119,1120]

Massanari et al[1121] 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 eight weeks, after which they received SCIT to at least 1 of 3 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.

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 cost benefits 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 with 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.

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[413]	2021	2	RCT	Adults, grass pollen induced AR: -SCIT -Dupilumab (300mg 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[1121]	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[1119,1120]	2009/ 2013	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[414]	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 5-fold decreased risk of rush SCIT associated anaphylaxis -Combination therapy associated with reduction in symptom severity versus SCIT alone
Kuehr et al[415]	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

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; AUC=area under the curve; TNSS=Total Nasal Symptom Score; QOL=quality of life

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.[799,800]

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.[840] 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.[1122] 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% to 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.[799,840]

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 unitage 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.[800] 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.[840] 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.[806]

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.[809] 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.[758,1123] 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-minute intervals.[1124,1125] 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.[1126]

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.[1127] The multi-allergen approach is scientifically supported by four double-blind placebo-controlled RCTs from the 1960s to 1980s (2 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.[1128-1131] More recent studies based in Spain have also supported multi-allergen immunotherapy.[1132,1133] A SR in 2009 evaluated 13 multi-allergen immunotherapy studies (11 SCIT, 1 SLIT and 1 both) and corroborated that co-administration of two extracts is in fact clinically effective.[1134] 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 6 US and Canadian practices reported a mean of 18 extracts in their mixtures.[1135,1136]

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.[1019] Ortiz et al[1017] 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 (3-6 antigens) or multi-allergen SLIT in polysensitized patients. Additionally, Wang and Shi[892] concluded that single-allergen SLIT response is comparable to multi-allergen SCIT in children with AR secondary to HDM.[20] 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.[1011,1018,1021,1036,1137-1139]

A clear knowledge gap is the need for further evidence to support the use of multi-allergen immunotherapy in polysensitized patients.[1123] 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 (5 SCIT, 2 SLIT, 1 both SCIT and SLIT and 3 ILIT).[1140] 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.[1125,1141] 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.[1142,1143]

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 IgG_4 levels.[893,894,1042,1144] These effects remained durable 3 years after completing a 3-year course of SCIT.[1145]

In children, several studies have demonstrated AIT has short-term and long-term effectiveness, including decreasing the dose of inhaled corticosteroids in asthmatic patients.[1146-1151] Literature supports the efficacy of both SCIT and SLIT in the pediatric population.[777] 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 PAT [Preventive Allergy Treatment] 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.[1152,1153] SLIT using a grass tablet was shown to have a similar asthma prevention effect in the GAP [Grass immunotherapy tablet Asthma Prevention] trial.[768] 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.[1154] 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.[765]

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.[1155] 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.[1156] 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.[758] 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.[1157] 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.[1158] 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.[1125,1159,1160]

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 2 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.[1161] New technologies focused on component

resolved diagnostics may prove useful in determining whether cross-reactive allergens are the cause of polysensitization, and may help to direct AIT decisions.[1162]

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.[1123]

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 2 homologous allergens may be used, and for the polyallergic patient sensitized to allergens which are not homologous, AIT should be limited to 1 or 2 of the clinically most important allergens administered separately at distinct anatomic locations and separated by 30-60 minutes.[757] 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.[1124] The Practice Parameter Third Update guidelines developed by the Joint Task Force[758] 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 two and optimally three 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.[1163]

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 three-year regimen of grass SLIT tablets. The authors found that only 55% of patients completed the three-year treatment period.[1164] These data are similar to many retrospective analyses of adherence to SLIT at the end of a 3-year regimen, ranging 10-61%[1165-1167] 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 three years.[1168] A retrospective cohort analysis of a German longitudinal prescription database indicated that at the end of three years, adherence to SCIT was 35-37%, and higher than that reported for SLIT (10-18%).[1169] A data management retrospective study compared adherence to SCIT and SLIT at the end of three years and found that SLIT patients had a higher dropout rate (39%) versus SCIT (32.4%).[1167] In a retrospective analysis of a community pharmacy database, only 18% of 6486 patients starting AIT reached a minimal duration of three years, 23% for SCIT and 7% for SLIT.[1070] 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.[1170] Another

retrospective analysis comparing SLIT versus SCIT adherence found that only about 30% of patients completed a three-year course of either therapy.[1171]

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.[1172] One-third of these women will suffer from worsening symptoms during pregnancy[1173] and up to 20% will experience exacerbations of asthma resulting in hospitalization or even death.[1174] 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.[758]

The first study to assess the safety of AIT in pregnancy was published in 1978 by Metzger et al.[1175] 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 a 1993 study, Shaikh et al[789] 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[1175] study were analyzed, and when compared to the control group of 60 patients (82 pregnancies) who refused AIT, the incidence of prematurity, gestational hypertension, and proteinuria were actually lower. Of note, only 7 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[790] 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.[898]

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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.[1] 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.[2] The future development of AR should be considered in children exhibiting signs of the "allergic march".[3] 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.[4-8] 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.[2]

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.[7] Other comorbidities include rhinosinusitis, SDB, ETD, otitis media, and oral allergy syndrome.[1,9-11] Oral allergy syndrome may be suspected in patients with mouth itching or swelling after eating raw fruits or vegetables.[9]

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.[10,12,13] *(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.[10,11,14-16] *(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.[2,4]

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.[2] Some physical exam findings are similar to the adult population including posterior pharyngeal cobblestoning, clear drainage, serous middle ear effusions, and enlarged/boggy ITs.[2,4] 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."[17] "Allergic shiners" are caused by infraorbital venous stasis and "Dennie-Morgan lines" are folds below the lower eyelids suggesting allergic conjunctivitis.[2-4,6,18] Voice changes including hoarseness and hyponasality are common in pediatric AR.[5] Anterior rhinoscopy can reveal IT bogginess, paleness and/or hypertrophy.[2] 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.[19] 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.[20] Non-allergic rhinitis, viral URI, and anatomical causes of nasal obstruction should be on the differential diagnosis in children evaluated for AR.[4]

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.[21] 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.[22]

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.[10] 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.[18] 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.[2]

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.[23-26] Additionally, nasal basophilic metachromic cells have shown high sensitivity for AR.[2,27] 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.[28]

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.[6,29,30]

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

six 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.[29-32] Intranasal antihistamines have been recommended over oral antihistamines in the appropriate patient population.[22,29]

For *persistent or moderate-to-severe symptoms*, INCS are recommended as the best single therapy in the treatment of allergic symptoms affecting QOL.[6,22,29,30] The effectiveness of INCS in the reduction of nasal symptoms including sneezing, itching, rhinorrhea, and congestion in children with AR has been demonstrated.[33-36] 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.[6,29,30,37-39] 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.[22]

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 3-6 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.[30,40,41]

Ipratropium bromide nasal spray has been shown to decrease rhinorrhea. It has a quick but short-lasting 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.[42] 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.[30,43,44] 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.[45] 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 of SLIT tablets variable depending on the individual 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.[46]

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,[47-49] and both SCIT and SLIT have resulted in improved control of comorbid conditions such as asthma and allergic conjunctivitis.[22] Of particular importance 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.[50-52]

In all populations, absolute contraindications to AIT (SCIT and SLIT) include uncontrolled or poorly controlled asthma, active autoimmune disorders, and malignancy.[53] EoE is also a contraindication to SLIT.[54-57] 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.[45]

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.[58]

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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.[1] The definition of asthma has appreciably changed over time.[2] 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'*.[3]

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.[3] In clinical practice patients have a variety of clinical presentations, and when patients are well, most tests show no abnormalities.[4] 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.[5] Most patients have mild or moderate disease. A small proportion (up to 10%) have severe disease that is refractory to standard inhaled medications. These patients have more severe symptoms, frequent exacerbations and need more intensive treatment regimens.[6]

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 towards conceptualizing multimorbid chronic upper airway inflammation and asthma as a single 'unified airway' pathology affecting both the upper and lower airway.

The prevalence of comorbid AR and asthma varies. Recent population-based studies have shown rates between 20.3% and 93.5%.[7-12] 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).[12] 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.[13-16] Interestingly, the association of allergy with asthma weakens with more severe asthma.[17] **[TABLE XIII.A.2.]**

Non-allergic rhinitis is also commonly associated with comorbid asthma.[18,19] Increasingly, asthma is being considered a multifactorial disease with variable endotype and phenotypic presentations, particularly with regards to aberrant type 2 inflammation, which may or may not be allergic.[20,21] 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.[22]
ii. Nasal obstruction results in mouth breathing, which leads to reduced filtration and humidification of inspired air, facilitating reactive lower airways.[23]
iii. Nasal blockage resulting in mouth breathing can be associated with breathing pattern disorders and increased breathlessness in patients with asthma.[22,23]

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.[24] Moreover, gene expression analyses suggest that type 2 mediated inflammation has a similar molecular basis across disease types.[25] These findings underscore the proposed 'one airway' model, which recognizes similar disease mechanisms occurring in both the upper airway and the lower airway.[26]

In summary, upper airway symptoms can impact asthma disease control and patient QOL.[27] Assessment and treatment via a multidisciplinary approach, encompassing pulmonologists, allergists, immunologists, otolaryngologists/rhinologists, should be considered.

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.**)

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[28]	2019	1	Meta-analysis of cross-	General public, asthma patients, n=3182	Asthma+AR prevalence	-Asthma and AR are often comorbid diseases

			sectional studies			-Asthma+AR prevalence 39%
Tohinidik et al[8]	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[29]	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[9]	2020	2	Cross-sectional	Mild vs. 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[10]	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[11]	2017	2	Cross-sectional	Pediatric AR patients vs. 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[30]	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[18]	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
Tosca et al[31]	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
Kisiel et al[32]	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[7]	2020	4	Cross-sectional	General public, n=7,275	Prevalence of rhinitis and asthma	-7% asthma and 4% rhinitis prevalence -Higher prevalence of rhinitis in asthma patients vs without (20.3% vs. 2.9%, OR 8.39) -Atopic disease burden high -Asthma and rhinitis strongly associated with each other
Heffler et al[33]	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[34]	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
Ji et al[35]	2019	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
Ozoh et al[12]	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[36]	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[37]	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.
LOE=level of evidence; AR=allergic rhinitis; OR=odds ratio; NAR=non-allergic rhinitis

XIII.A.3. Allergic rhinitis and asthma – association of risk factors

Up to 30% of patients with AR develop asthma.[38] 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.[39] **[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.[40] Rhinitis is also a significant risk factor for adult-onset asthma whether patients are atopic or non-atopic.[41-44] In contrast, in childhood, asthma is frequently associated with allergy.[40,45] Limited data fail to demonstrate a relationship between a diagnosis of AR and severity of comorbid asthma.[46] Nevertheless, data on whether the severity of AR itself impacts the prevalence of comorbid asthma remains conflicting.[47,48]

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.[39,49,50] Indeed, most inhaled allergens are associated with both nasal and bronchial hyperresponsiveness.[51] Occupational rhinitis is also a risk factor for occupational asthma caused by high-molecular-weight agents.[52] 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.[53]

There is growing evidence that exposure to traffic related air pollutants, (i.e., black carbon, NO_2, NO, SO_2, CO, CO_2, 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.[54-56] *(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.[57] *(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.

Aggregate grade of evidence: C (Level 2: 3 studies, level 3: 19 studies; **TABLE XIII.A.3.**)

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[42]	2006	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[50]	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[40]	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[58]	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[56]	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[49]	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[55]	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 NO2, urbanization and traffic exhaust increased risk of developing asthma and AR

Lipiec et al[39]	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[54]	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
Panganiban et al[53]	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[59]	2013	3	Cross-sectional	Children with AR	Associated diseases	Asthma present in 49.5% of AR patients
Jarvis et al[60]	2012	3	Cross-sectional	General population	Self-reported current asthma	Asthma associated with chronic rhinosinusitis
Rochat et al[45]	2010	3	Cohort	Birth cohort	Development of wheezing	AR is a predictor for subsequent wheezing onset
Polosa et al[57]	2008	3	Cross-sectional	Adult smokers with AR vs 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[19]	2008	3	Cohort	Population-based study	Frequency of asthma	Rhinitis (+/- atopy) is a powerful predictor of adult-onset asthma
Burgess et al[61]	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[44]	2007	3	Cohort	General population	Changes in bronchial hyperresponsiveness in non-asthmatic subjects	AR associated with increased onset bronchial hyperresponsiveness
Bodtger et al[62]	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[63]	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[43]	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
Plaschke et al[64]	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[41]	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

LOE=level of evidence; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval; RHINESSA=Respiratory Health in Northern Europe, Spain and Australia study; NO2=nitrogen dioxide; TRAP=traffic related air pollutants; IgE=immunoglobulin E

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.[65-69] Indeed, there is a body of evidence to suggest that the following AR therapies may benefit both conditions: INCS,[70-73] intranasal antihistamine,[74] oral antihistamines,[75,76] LTRAs,[77] and AIT.[78-80] AIT has shown promising results in altering the course of the allergic inflammation seen in both AR and asthma.[81-83] 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.[84]

Allergen avoidance

Allergen avoidance is often recommended for allergies, specifically for AR and allergic asthma.[85-87] 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.[88] 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).[88-90] Nevertheless, there is theoretical benefit of reducing allergen exposure, a paucity of data 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.[91-96] 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.[97] 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.[95,98,99] Antihistamines may also have a preventive effect on the development of asthma in atopic patients.[100] 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.[101] They are also effective for symptoms of rhinitis.[102] Due to the side-effect profile associated with these medications, especially with increasing duration of use,[103] 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.[104,105] 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.[70,71,73,74,106-116] 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.[106] 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.[71] 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.[117] Finally, intranasal azelastine-fluticasone propionate spray is a known effective treatment for AR alone. Recently, a pre-post historical cohort also demonstrated its potential utility in asthmatics with AR, demonstrating a significant reduction in acute respiratory events and rescue inhaler medication usage, as well as an increase in the overall number of well-controlled asthmatics.[74] *(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".[118] 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 beta agonist use.[89] The 2010 ARIA 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. [119] A more recent review in 2015 also identified some utility of LTRAs for patients with concomitant AR and asthma.[120] 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.[119] *(See Section XI.B.4. Leukotriene Receptor Antagonists for additional information on this topic)* **[TABLE XIII.A.4.-3]**

Aggregate grade of evidence for pharmacotherapy treatment of AR and its effect on asthma: 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.[121] Omalizumab has demonstrated effectiveness separately for asthma as well as AR.[121-125] There are several published studies evaluating omalizumab in AR or asthma,[121,126] with one RCT specifically evaluating the efficacy of omalizumab in patients with concomitant moderate-to-severe asthma and persistent AR.[127] Omalizumab as an adjunct to SCIT has also been evaluated.[128] Both studies show a reduction in symptoms as well as an improvement in QOL measures.[127,128] 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]**

Aggregate grade of evidence for biologic treatment of AR and its effect on asthma: 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.[129-133] Several studies indicate that AIT, often in addition to traditional antihistamine pharmacotherapies, may help halt the progression of allergic disease, including preventing new allergic sensitivities and the development of asthma.[81-83,134-139] However, several systematic reviews have concluded that the evidence for AIT preventing further allergic sensitization is low, due to limited analyses of asthma exacerbations, mixed population recruitment, and a focus on mild disease only.[140-142] Further evaluation is required to assess safety in patients with uncontrolled asthma.[142] Of note, the 2010 ARIA statement recommended both SCIT and SLIT for the treatment of asthma in patients with AR and asthma.[119] 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.[143] 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.[144] *(See Section XI.D. Allergen Immunotherapy for additional information on this topic.)* **[TABLE XIII.A.4.-5]**

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.-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[91]	2006	2	RCT	Persistent AR and asthma, n=50: -Levocetirizine 5mg -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[92]	2003	2	RCT	Seasonal AR and asthma, n=924: -Desloratadine 5mg -Montelukast 10mg -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[93]	2002	2	RCT	AR and asthma, n=326: -Desloratadine 5mg -Placebo	-TSS -Asthma symptom scores -β-agonist use	-Desloratadine reduced rhinitis symptoms & asthma TSS -Desloratadine reduced β-agonist use
Grant et al[94]	1995	2	RCT	AR and asthma, n=186: -Cetirizine 10mg -Placebo	-Rhinitis and asthma symptoms -Spirometry	-Cetirizine improved asthma symptoms -No differences in objective measures
Aubier et al[95]	2001	3*	RCT	Seasonal AR and asthma, n=12: -Cetirizine crossover to placebo -Placebo crossover to cetirizine	-BHR[a] -NBI[b]	-Cetirizine increased BHR -Cetirizine reduced NBI vs placebo at 6 hours
Aaronson[96]	1996	3*	RCT	AR and perennial asthma, n=28: -Cetirizine 20mg -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

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; QOL=quality of life; SF-36=Short Form Health Survey; TASS= Total Asthma Symptom Score; FEV_1= forced expiratory volume in 1 second; TSS=Total Symptom Score; BHR=bronchial hyperresponsiveness; NBI=nasal blocking index; PEFR=peak expiratory flow rate; PC_{20} and PD_{20}= provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV_1; PFT=pulmonary function test

[a]BHR measured as methacholine PD_{20}

[b]NBI measured using peak expiratory flow meter and calculated as (oral peak flow – nasal peak flow) / (oral peak flow)

*LOE downgraded due to small sample size, no power analysis or power calculation, which limits interpretation of negative findings

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[71]	2013	1	SRMA	18 RCTs, n=2162: -INCS vs placebo -INCS spray + oral ICS vs oral ICS alone -Nasal INH steroid vs 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 plus oral ICS vs oral ICS alone -Nasal INH steroid improved PEF
Taramarcaz & Gibson[106]	2003	1	SRMA	14 RCTs: -INCS vs placebo -INCS vs conventional asthma treatment -INCS plus conventional vs conventional alone	-Asthma symptoms -β-agonist use -Asthma exacerbations -QOL -FEV_1, PEF, PC_{20}, PD_{20} -Inflammatory markers	-Non-significant symptom improvement INCS vs placebo -No difference in FEV_1, PEF, PC_{20}, PD_{20}
Jindal et al[107]	2016	2	RCT	AR and asthma, n=120: -FP INCS 200µg BID -MON 10mg PO QHS	-Symptom scores of rhinitis and asthma -PEF	-Reduction in asthma symptom severity score with FP vs MON -Increase in PEF with FP vs MON
Dahl et al[108]	2005	2	RCT	Pollen-induced AR and asthma, n=262: -INFP 200µg daily + IHFP 250µg BID -INFP + inhaled placebo -Intranasal placebo + IHFP -Intranasal placebo + inhaled placebo	-Asthma and AR symptoms -PFTs -Methacholine BHR -PEF	-Increased PEF for IHFP + INFP vs other groups -PEF increase for IHFP vs no IHFP -FEV_1 higher with IHFP -Increased BHR with INFP; no increase with IHFP
Nathan et al[109]	2005	2	RCT	Seasonal AR and persistent asthma, n=863; all received FSC: -INFP 200µg and FSC daily -MON 10mg + 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[110]	2005	2	RCT	Perennial AR and mild-to-moderate persistent asthma, n=59: -Nasal Bdp 400µg + placebo MDI	-Asthma and AR symptom scores -PEF -FEV_1 and BHR (PC_{20}) -Proxy indicators of asthma-related	-Reductions of AR and asthma symptoms in all groups -No change PEF or BHR

				-Placebo nasal spray + Bdp MDI 1000µg -Bdp nasal spray 400µg + Bdp MDI 1000µg daily	morbidity (work absence, emergency visits, etc)	-Increased FEV_1 with nasal Bdp alone and for Bdp MDI alone -Asthma morbidity reduced for all
Thio et al[111]	2000	2	RCT	Two grass pollen seasons of treatment (season 1, n=21; season 2, n=67): -FP nasal spray 200µg -Bdp nasal spray 400µg -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[74]	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 vs 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[70]	2012	3*	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[112]	2010	3*	RCT	Moderate/severe persistent AR with intermittent asthma, n=47: -MFNS nasal spray 200µg 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 vs placebo for rescue meds
Nair et al[113]	2010	3*	RCT	Persistent AR and asthma, n=25: -INH FP, INH placebo, placebo nasal spray -INH FP 100µg, INH placebo, FP INCS -INH FP, INH placebo, placebo nasal spray daily	-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 vs INH FP alone -No change in asthma QOL -FeNO and PNIF reduced only with INCS
Agondi et al[114]	2008	3*	RCT	AR and asthma, n=33: -Bdp nasal spray 400µg per day -Placebo nasal spray	-Rhinitis and asthma symptom scores -Rescue medication use -BHR (histamine provocation)	Changes with Bdp vs placebo: -Asthma symptoms reduced -Medication use decreased

						-BHR reduced
Pedroletti et al[115]	2008	3*	RCT	Perennial rhinitis and allergic asthma, n=40: -MFNS -Placebo	-FeNO -ECP in nasal lavage -PEF -FEV_1	-No difference in FeNO for MFNS vs placebo -Nasal ECP reduced -No difference in PEF or FEV_1
Watson et al[116]	1993	3*	RCT	AR and controlled asthma, n=21: -Intranasal Bdp 100µg twice daily, then placebo -Placebo nasal spray, then intranasal Bdp 100µg twice daily	-Asthma and rhinitis symptoms -PC_{20} -Bdp deposition**	-No difference in asthma symptoms with Bdp -PC_{20} improved with Bdp -Evening asthma symptoms reduced with Bdp
Corren et al[73]	1992	3*	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; INCS=intranasal corticosteroid; ICS=inhaled corticosteroid; INH=inhaled; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; PC_{20} and PD_{20}= provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV_1; QOL=quality of life; AR=allergic rhinitis; FP=fluticasone propionate; BID=twice daily; MON=montelukast; PO=per os (taken orally); QHS=each night; INFP=inhaled fluticasone propionate; PFT=pulmonary function test; BHR=bronchial hyperresponsiveness; FSC=inhaled fluticasone propionate and salmeterol; Bdp=beclomethasone dipropionate; MDI=metered dose inhaler; AUC=area under the curve; ACQ=Asthma Control Questionnaire; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; FeNO=fraction of exhaled nitric oxide; MFNS=mometasone furoate nasal spray; GS=Rhinasthma global summary; RAI=respiratory allergy impact; LA=lower airway; UA=upper airway; PNIF=peak nasal inspiratory flow; ECP=eosinophil cationic protein; NBI=nasal blocking index (based on PEF and calculated as (oral peak flow – nasal peak flow) / (oral peak flow))

*LOE downgraded due to small sample size

**Radiolabeled Bdp < 2% deposition in lungs, 20%-50% in nasal cavity, and 48%-78% swallowed

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[145]	2018	2	RCT	Perennial AR and mild to moderate asthma, n=228: -MON 10mg -MON 10mg + levocetirizine 5mg	-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[107]	2016	2	RCT	AR and asthma, n=120: -FP INCS 200µg BID -MON 10mg PO QHS	-Symptom scores of rhinitis and asthma -PEF	-Reduction in asthma symptom severity score with FP vs MON -Increase in PEF with FP vs MON
Katial et al[146]	2010	2	RCT	Seasonal AR and asthma, n=1385: -FSC 100/50µg BID -FSC BID + FPNS 200µg daily -FSC BID + MON, 10mg daily -MON 10mg daily	-PEF -Rescue albuterol use -Asthma and rhinitis symptoms	-No additional improvements in asthma with MON-FSC -FSC improved all outcome measures vs MON
Price et al[147]	2006	2	RCT	Asthma symptoms despite ICS, subgroup with coexistent AR, n=889: -MON + budesonide -Double-dose budesonide	Improvement in AM PEF vs baseline	PEF had greater increase from baseline in MON-budesonide vs double-dose budesonide*
Nathan et al[109]	2005	2	RCT	Seasonal AR and persistent asthma, n=863; all received FSC: -INFP 200µg and FSC daily -MON 10mg + 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[148]	2004	2	RCT	Seasonal AR and asthma, n=831: -MON 10mg 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[92]	2003	2	RCT	Seasonal AR and asthma, n=924: -Desloratadine 5mg -MON 10mg -placebo	-TASS -FEV_1 -β-agonist use	Desloratadine vs placebo: -Reduction in mean TASS -Improvement in FEV_1 -Reduction in β-agonist use -Desloratadine versus montelukast: No differences

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; MON=montelukast; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FP=fluticasone propionate; INCS=inhaled corticosteroid; BID=twice daily; PO=per os (by mouth); QHS=each night; PEF=peak expiratory flow; FSC= inhaled fluticasone propionate and salmeterol; FPNS=fluticasone propionate nasal spray; ICS=inhaled corticosteroid; INFP= inhaled fluticasone propionate; 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[128]	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[127]	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

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; PEF=peak expiratory flow; GETE=global evaluation of treatment effectiveness; ACQ=Asthma Control Questionnaire; QOL=quality of life; AQLQ=Asthma Quality of Life Questionnaire; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; PFT=pulmonary function test; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; FVC=forced vital capacity

TABLE XIII.A.4.-5 Evidence table – Evidence for allergen immunotherapy for asthma treatment in coexistent asthma and allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Fortescue et al[142]	2020	1	Systematic review	Systematic review of 66 RCTs (mild or intermittent asthma +/- AR)	-Asthma exacerbations & QOL -Adverse effects -Asthma symptoms & 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[132]	2018	1	Systematic review	Systematic review of 112 RCTs: -AR with or without 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 & medication usage -SLIT reduced ICS dose & 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[140]	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 vs 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[141]	2017	1	Systematic review	Systematic review of 8 studies (1 RCT, 7 prospective): monosensitized children +/- asthma with HDM sensitivity, treated with AIT vs not treated with AIT	New allergic sensitization	Low evidence that AIT prevents further allergic sensitization among children monosensitized to HDM
Kristiansen et al[139]	2017	1	Systematic review	Systematic review of 32 studies (17 RCTs, 15 controlled-before-after studies): SLIT or SCIT vs no intervention, placebo, or comparator	Development 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
Erekosima et al[129]	2014	1	Systematic review	Systematic review of 61 RCTs (26 specifically asthma and rhinitis): -SCIT vs placebo -SCIT vs pharmacotherapy	-Asthma and RC symptoms & medication use -Safety of SCIT	-Asthma plus rhinitis/RC symptoms & medications reduced with SCIT[a] -Most adverse reactions mild
Lin et al[149]	2013	1	Systematic review	Systematic review of 63 RCTs: -SLIT vs placebo -SLIT vs 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[81]	2008	2	RCT	Rhinitis +/- intermittent asthma, n=216: -Standard drug therapy control group -Standard drug therapy plus SLIT*	-Development of persistent asthma (not at baseline) -Symptom and medication scores of allergic symptoms -Daily medication use -New sensitization	-Persistent asthma incidence lower with SLIT vs control -Methacholine-positive patients after 3 years reduced with SLIT -Lower symptom and medication scores with SLIT

Novembre et al[83]	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 vs SLIT
Moller et al[82]	2002	2	RCT	RC with or without 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[133]	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[135]	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
Grembiale et al[78]	2000	3**	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 med use and visits with placebo -No difference in asthma incidence

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; QOL=quality of life; SLIT=sublingual immunotherapy; ICS=inhaled corticosteroid; AIT=allergen immunotherapy; HDM=house dust mite; SCIT=subcutaneous immunotherapy; RC=rhinoconjunctivitis; BHR=bronchial hyperreactivity; PC_{20} and PD_{20}= provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV_1; VAS=visual analog scale; IgE=immunoglobulin E

[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

*SLIT administered as sublingual drops of standardized allergen for a build-up phase and then continued for maintenance phase

**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.[150] 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.[150,151] 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.[152,153] 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.[152,153] 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.[150,154] The Wilson et al[155] 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.[150,155] **[TABLE XIII.B.1.-1]**

Aggregate grade of evidence (AR and CRSsNP): 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.[155]

Allergic rhinitis and chronic rhinosinusitis with nasal polyposis. The pathogenesis of CRSwNP is strongly associated with type 2 inflammation.[150,151] Additionally, nasal polyps have high levels of tissue eosinophils, as well as mast cells and basophils.[150,151] AR follows a similar inflammatory pathway and this suggests there may be a pathophysiologic similarities between CRSwNP and AR.[150,151,154] However, the clinical evidence for or against an association between AR and CRSwNP has been mixed.[150,154] Similar to CRSsNP, there have been no new studies specifically examining CRSwNP and AR since ICAR-Allergic Rhinitis 2018.[154] 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.[155] Hypersensitivity to HDM, cockroach, and *Candida* have been associated with CRSwNP. Despite the overlapping pathophysiologic features between allergy and CRSwNP, conflicting evidence exists regarding and association between AR and CRSwNP. Allergy testing remains an option in

CRSwNP patients based on the theoretical benefit of identifying and treating comorbid allergic disease, especially since allergy may be seen in these patients.[150,155] **[TABLE XIII.B.1.-2]**

Aggregate grade of evidence (AR and CRSwNP): D (Level 3: 5 studies, level 4: 16 studies, conflicting evidence; **TABLE XIII.B.1.-2**) Table adapted from Wilson et al.[155]

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[155] review and the ICAR-Allergic Rhinitis 2018[154] 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 risk of allergic rhinosinusitis treatment and the theoretical benefits of reducing allergic sinonasal inflammation.[150]

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[156]	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[155]	2014	3	Systematic review	CRSsNP with or without allergy	Association between CRSsNP and allergy	Conflicting evidence, no clear association
Tan et al[157]	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[158]	2009	4	Prospective case series	CRSsNP with or without allergy, n=115	CT scores	No difference in CT scores
Gelincik et al[159]	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 & Ruttanaphol[160]	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[161]	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[162]	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[163]	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[164]	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

LOE=level of evidence; RCT=randomized controlled trial; CRSsNP=chronic rhinosinusitis without nasal polyps; CT=computed tomography; URTI=upper respiratory tract infection

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[165]	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[166]	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[155]	2014	3	Systematic review	CRSwNP with or without allergy	Association between CRSwNP and allergy	Conflicting evidence, no clear association
Houser & Keen[167]	2008	3	Retrospective case series	CRSwNP with or without allergy, n=373	Nasal polyposis	AR associated with the development of nasal polyposis
Kirtsreesakul[168]	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[169]	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[170]	2011	4	Prospective case-control	CRSwNP compared to controls, n=50	Rates of food sensitivity	Higher rate of milk sensitivity in CRSsNP
Tan et al[157]	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[171]	2009	4	Prospective case-control	CRSwNP compared to controls, n=190	Rates of allergy compared to control	Higher rates of allergy in CRSwNP vs control
Pearlman et al[158]	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 & Malinvaud[172]	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[173]	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[174]	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[175]	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[163]	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 & Bottazzi[176]	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
Vogels et al[177]	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 & Bottazzi[178]	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[179]	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[180]	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[181]	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 increases symptom scores and serum levels

LOE=level of evidence; CRSwNP=chronic rhinosinusitis with nasal polyps; CT=computed tomography
AR=allergic rhinitis

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.[182,183] 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[184] 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.[185]

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.[186-188] Additionally, it has been determined that most AFRS patients have detectable fungal sIgE in their allergic mucin.[189,190] Wise et al[191] 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 1 hypersensitivity in AFRS, even in the absence of positive serum sIgE to fungal allergens, has also been demonstrated.[192,193] **[TABLE XIII.B.2.]**

Although generally both CRSsNP and CRSwNP have been found to have an equivocal association with allergy,[155] 100% of AFRS patients in a study by Marcus et al[194] demonstrated positive allergy testing. Allergy testing and treatment is not recommended in CRS unless there are concurrent AR symptoms and sensitivities, respectively,[195] 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.[196,197] Still, a systematic review by Gan et al[198] 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.[199,200] Pant et al[200] 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[201] 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 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. [199,202-204] Despite these debates, there is evidence demonstrating the important role allergy and type 2 inflammation play in the pathophysiology, diagnosis, and treatment of AFRS.[205]

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 9 studies, level 4: 5 studies; **TABLE XIII.B.2.**)

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[198]	2014	2*	Systematic review	Adults, AFRS (Bent and Kuhn[184] criteria), post-sinus surgery, clearly defined endpoint	Efficacy of 6 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 & Fang[192]	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[191]	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 -Antigen-sIgE to 14 common antigens	-More IgE staining in AFRS sinus epi-/subepithelium vs controls and CRSsNP -AFRS sinus tissue had more sIgE vs control for 7 of 14 antigens ($p<0.05$) and total IgE ($p=0.004$)
Saravanan et al[185]	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[200]	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 vs healthy controls but not vs diseased controls -Fungal-specific IgG3 levels elevated in all EMCRS subgroups vs controls ($p<0.0001$) -Fungal-sIgE levels not significantly different between fungal-allergic EMCRS and diseased controls
Collins et al[190]	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 & Hunsaker[188]	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 5 molds versus 0.1 mold in those without AFRS
Ponikau et al[202]	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[197]	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[196]	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 (2 patients), methylprednisone (1 patient) -Control group: 2 patients with frequent use of oral steroids and recommendation for revision surgery, 1 patient with recurrent disease at 4 months post-op
Marcus et al[194]	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[201]	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 vs non-AFRS group (63.2% vs 24.1%, p = 0.005)
Hutcheson et al[186]	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 vs CRS patients
Cody et al[203]	1994	4	Retrospective cohort	789 histologic specimens, 44 had allergic mucin: -AFRS based on fungal hyphae in mucin or positive fungal culture, n=26	Culture results of 31 of the 44 AFRS patients	19 of the 31 had negative culture results

				-AFRS-like mucin, n=18		
Manning et al[187]	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

LOE=level of evidence; AFRS=allergic fungal rhinosinusitis; AIT=allergen immunotherapy; INCS=intranasal corticosteroid; CRSwNP=chronic rhinosinusitis with nasal polyps; CRS=chronic rhinosinusitis; sIgE=specific immunoglobulin E; CRSsNP=chronic rhinosinusitis without nasal polyps; Ig=immunoglobulin; M=allergic mucin; F=fungal/mycelial element; EMCRS= eosinophilic mucin chronic rhinosinusitis; CRP=C-reactive protein; ECP=eosinophilic cationic protein; RAST=radioallergosorbent test; EMSS=endoscopic mucosal staging system; QOL=quality of life; CSS=Chronic Sinusitis Survey; AERD=aspirin exacerbated respiratory disease; CCAD=central compartment atopic disease; NOS=not otherwise specified; CC=central compartment
*LOE downgraded due to inclusion of cohort studies primarily

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.[206] In 2014 White et al[207] first described the association between allergy and isolated MT polypoid edema, with 16/16 patients having allergen sensitization. Hamizan et al[208] 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[209] 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[206] 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.[206] To further characterize CCAD, Roland et al[210] 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[194] 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[211] noted a significantly higher association with allergen sensitization compared to the non-CCAD group ($p=0.03$). Abdullah et al[212] 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[213] 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.[214] 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,[214] 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.[206] 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.[215-217]

Aggregate grade of evidence: C (Level 3: 2 studies, level 4: 11 studies; **TABLE XIII.B.3.**)

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[213]	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 vs non-CCAD -Higher prevalence of allergen sensitization in

						CCAD (87.1%) vs non-CCAD (62.4%) (p=0.008)
Hamizan et al[208]	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[214]	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 & MT/polyp IL-5 cs non-CC CRS -No difference in allergen sensitization in CC and non-CC CRS
Makary et al[216]	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<.0001)
Abdullah et al[212]	2020	4	Case-control	CRSwNP, n=38	-Allergen sensitivity -CT and endoscopy pattern of disease	-Increased allergen sensitivity in CCAD (100%) vs 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[194]	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
Roland et al[210]	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[217]	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[215]	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[211]	2018	4	Case series	CRS, n=112	-CT disease pattern: diffuse vs. central -Allergen sensitivity	-CCAD higher association with allergen sensitization vs non-CCAD (73.53% vs. 53.16%, p=0.03) -Central disease was associated with allergen sensitization (p=0.03, specificity 90.82%, PPV 73.53%).
Brunner et al[209]	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 vs diffuse paranasal sinus polyposis (83% vs. 34%, p<0.001) -Isolated MT polypoid patients: more commonly female, younger, lower L-M score, lower incidence of CRS
DelGaudio et al[206]	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[207]	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

LOE=level of evidence; CRS=chronic rhinosinusitis; eos=eosinophils; tIgE=total immunoglobulin E; CT=computed tomography; IgE=immunoglobulin E; CCAD=central compartment atopic disease; MT=middle turbinate; ROC=receiver-operating characteristic curve; CC=central compartment; SNOT=Sinonasal Outcome Test; L-M=Lund-Mackay CT score; IL=interleukin; AERD=aspirin exacerbated respiratory disease; AFRS=allergic fungal rhinosinusitis; eCRSwNP=eosinophilic chronic rhinosinusitis with nasal polyps; CRSwNP=chronic rhinosinusitis with nasal polyps; NOS=not otherwise specified; REAH=respiratory epithelioid adenomatous hamartoma; PPV=positive predictive value; AR=allergic rhinitis; NOSE=Nasal Obstruction Symptom Evaluation

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.[218]

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.[219] However, recent evidence supports a higher atopic rate in AERD.[220-223] In one cohort, 200 of 300 (66%) AERD subjects had a history of positive SPT,[221] and in a latent class analysis of AERD sub-phenotypes, 105 of 201 (52.2%) patients had positive aeroallergen SPT responses,[220] with the most common allergen being HDM (29.6%).[223] In another study that evaluated personal atopic history, SPT, and elevated total and specific IgE, AERD subjects had a higher rate of atopy than controls (53.9% versus 14%, p<0.001).[224] **[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).[225] 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 versus 1.1% non-atopic subjects).[226]

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.[227] Similarly, serum tIgE is often elevated in AERD patients but does not discriminate atopic from non-atopic AERD populations.[220]

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.[228] 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%.[229] 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.[230] However, AIT may only be highest yield for candidates with obvious seasonal variation to their symptoms and identifiable environmental triggers.

Aggregate grade of evidence: C (Level 3: 3 studies, level 4: 3 studies; **TABLE XIII.B.4.**)

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[226]	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[225]	2017	3	Retrospective cohort	1059 US patients with CRSwNP: -AERD, n=171 -CRSwNP + asthma, n=171 -CRSwNP, n=459	-Clinical characteristics in AERD patients vs CRSwNP patients +/- comorbid asthma -Atopy defined by physician-diagnosed AR on chart review + SPT	-AR: AERD (85%) vs CRSwNP (66%) -SPT positivity: AERD (83%) vs CRSwNP (66%)
Bochenek et al[224]	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 vs controls
Jakiela et al[222]	2021	4*	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	-36% of AERD patients with positive SPT -SPT positivity did not differ

					-SPT, spirometry, nasal lavage, bronchoscopy -Cytokine and eicosanoid levels in bronchoalveolar lavage	between eosinophilic and non-eosinophilic AERD endotypes of AERD
DelGaudio et al[215]	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)
Dona et al[223]	2018	4**	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%)

LOE=level of evidence; CRS=chronic rhinosinusitis; AERD=aspirin exacerbated respiratory disease; IgE=immunoglobulin E; SPT=skin prick test; CRSwNP=chronic rhinosinusitis with nasal polyposis; AR=allergic rhinitis; NASID=non-steroidal anti-inflammatory drug; tIgE=total immunoglobulin E; sIgE=specific immunoglobulin E; US=United States; CC=central compartment

*LOE downgraded due to very limited study sample

**LOE downgraded due to poor inclusion criteria

XIII.C. Conjunctivitis

Although the association between AR and allergic conjunctivitis (AC) is well recognized, accurate insight into ocular allergy prevalence is complicated by multiple factors.[231,232] 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.[233,234] 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.[235] 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,[236-241] with higher rates noted in some studies. In one report, 95% of 187 Australian patients with allergist-diagnosed AR reported ocular allergy.[242] A Swiss survey of hay fever patients showed 85% prevalence of concomitant nasal and eye symptoms.[243] A cross-sectional Italian study of 2150 adolescents determined that more than half of the respondents with AR also had AC.[240] Comorbid AC also conferred an increased risk of asthma (OR 5.23) versus AR alone (OR 2.28).[240]

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, ISSAC studies support the frequent association of AR with itchy/watery eyes; Phase I results revealed that ocular symptoms affect 33-50% of children with AR.[244] ISAAC Phase 3 analyzed temporal trends in prevalence of allergic rhinoconjunctivitis over 7 years in 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.[233]

Recently, the Global Asthma Network used ISAAC methodology to update the prevalence of pediatric atopic diseases.[234] 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%.[245] 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,[246] AC is often underrecognized and undertreated except when severe.[231] More than half of AR patients endorsed that red/itchy/watery eyes were moderately to extremely bothersome in the Allergies in America Survey.[247] Another survey of allergic rhinoconjunctivitis patients (n=2765) ranked red/itchy eyes as the second most bothersome symptom after nasal obstruction.[248]

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.[248] 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.[249] 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.[250]

Aggregate grade of evidence: C (Level 2: 4 studies, level 3: 8 studies; **TABLE XIII.C.**)

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[234]	2022	2*	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[238]	2016	2*	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[239]	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[235]	2010	2*	Cross-sectional survey	NHANES III participants (n=33,994), 1988-1994	Describe the epidemiology of AC in the United States	-40% adults with AC -Isolated ocular symptoms reported by 6% -30% prevalence of concomitant AR and AC
Sanchez-Hernandez et al[245]	2021	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)
Williams et al[242]	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
Alexandropoulos et al[251]	2012	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[252]	2010	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
Navarro et al[236]	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 & Wolthers[241]	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
Kosrirukvongs et al[237]	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[243]	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%

LOE=level of evidence; RC=rhinoconjunctivitis; ISAAC=International Study of Asthma and Allergies in Childhood; AR=allergic rhinitis; AC=allergic conjunctivitis; OR=odds ratio; CI=confidence interval; sIgE=specific immunoglobulin E; NHANES=National Health and Nutrition Examination Survey
*LOE upgraded due to very large sample size

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.[253] AD is the leading cause of the global burden from skin disease.[254] AD is associated with increased risk of multiple allergic comorbidities, including food allergy, asthma, and AR.[253,255] 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.[256,257]

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.[255] 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 example, less than half of all patients reporting AR had a physician-confirmed diagnosis of AR.[258] Therefore, the link between AR and AD remains poorly defined due to methodologic differences and limitations of the studies that have examined this association.[7,259-270] **[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.[271] 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 5-20%.[271] 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 15-61%.[272-275]

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 2-4-fold increase in AR among people with AD.[7,259-269,276] 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.[269]

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.[263]

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).[265]

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.[7,259-269]

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[267]	2021	2	Prospective longitudinal cohort	Children with AD/eczema in Cincinnati	-SPT -Symptoms upon allergen exposure	AD associated with AR (-asthma) in White (3x risk) and Black (6x risk) children

				enrolled ≤2 years old, n=601		
Schoos et al[262]	2021	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[7]	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[259]	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[263]	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[265]	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[275]	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[276]	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[277]	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 & Jarzab[278]	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[279]	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)
Karaman et al[280]	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[281]	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[282]	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[283]	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 & Ho[284]	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[261]	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 & Chiang[264]	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[266]	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[285]	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)
Peroni et al[286]	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[287]	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[288]	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[289]	2003	3	Cross-sectional	Preschool children aged 3-5 years, n=1402	-ISAAC questionnaire -SPT	-Prevalence of AR in prior 12 months 16.8% -AD significantly associated with AR (22.9%) vs. non-AR (13.9%), p<0.001
Rhodes et al[273]	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[274]	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[290]	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[291]	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[270]	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
Bekic et al[260]	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[268]	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%)

LOE=level of evidence; AD=atopic dermatitis; SPT=skin prick test; AR=allergic rhinitis; ISAAC= International Study of Asthma and Allergies in Childhood; sIgE=specific immunoglobulin E; OR=odds ratio; tIgE=total immunoglobulin E; HDM=house dust mite; RR=relative risk; 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]).[292,293] 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.[294] **TABLE XIII.E.1.-1** lists common pollen allergens with plant-derived foods that may demonstrate cross-reactivity.[295] A 2018 review by Carlson et al[296] 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.[297,298] **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.[299] The estimated rates of systemic and anaphylactic reactions from a pollen-food allergy are 10% and 2-10%,[300,301] 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.[302] 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.[303] Oral food challenge, SPT, and food sIgE levels have also been used to diagnose PFAS or food allergy.[296,304-306] Another technique that has also shown promise in accurate diagnosis of PFAS and food allergy is component-resolved testing utilizing pure and potentially cross-reactive allergenic components in certain foods.[307] 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.[308]

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.[301] Some 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 cooked apple, carrot, or celery in patients with AD and birch pollen allergy, who reported OAS and dermatologic symptoms upon ingestion of the raw foods.[309] 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.[309-312] However, one RCT failed to demonstrate any improved tolerance to apple in birch allergic patients treated with birch specific AIT compared to placebo.[302] 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.[311] 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]**

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.-1 Pollen-food allergy cross-reactivity[313]

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[304]	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[297]	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[302]	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[314]	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[305]	2019	4	Cross-sectional	Korean adults with suspected FA, including many PFAS, n=812	Clinical features and culprit food allergens	-77.8% FA patients had comorbid allergic diseases (AR was most common at 53.4% of all patients) -One-third of FA patients had accompanying PFAS -94.8% of PFAS patients had accompanying AR

Thong et al[315]	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[300]	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[294]	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
Diaz-Cabrera et al[316]	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[317]	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[318]	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[296]	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[293]	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

LOE=level of evidence; AR=allergic rhinitis; PFAS=pollen-food allergy syndrome; IgE=immunoglobulin E; FA=food allergy; OR=odds ratio; CI=confidence interval

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[312]	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[309]	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[310]	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[311]	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

LOE=level of evidence; RCT=randomized controlled trial; AIT=allergen immunotherapy; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; PFAS=pollen-food allergy syndrome

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.[319] 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.[314,317,318,320-332] **[TABLE XIII.E.2.]** In an analysis of over 8000 families, Alm et al[327] 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[326] found that a diagnosis of FA 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.[326,333-335] Similarly, AR is a relatively more common atopic condition among people with allergies to shellfish,[315,326,336,337] and specifically shrimp.[315,336,338] Identifying infants at high risk of peanut allergy and introducing peanuts to them early can significantly decrease the frequency of developing peanut allergy;[339,340] however, it is currently unclear whether such measures

can have a protective effect on developing AR in the future.[341] 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.[342]

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.[343,344] 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.[345] 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, T reg), regulatory B cells, innate lymphoid cells, dendritic cells, mast cells, eosinophils, and basophils.[345] When studied separately, AIT treatment has been shown to lead to several years of symptomatic remission in AR[346,347] or sustained responsiveness for various food allergies.[348,349]

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.**)

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[342]	2016	1	SRMA	Infants at risk of allergic or autoimmune disease, n=1915 across 5 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[334]	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[323]	2020	2	Cross-sectional survey	Nationally representative sample	Prevalence of shellfish food	History of AR independently associated

				of US children, n=38,408	allergy, associated factors	with shellfish allergy (OR 2.0; 95% CI 1.4-2.9)
Alm et al[327]	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[338]	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[331]	2020	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[329]	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[325]	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)
Scott et al[335]	2019	3	Retrospective cohort	Patients with peanut allergy vs controls, n=50,483	Incidence and prevalence of peanut allergy, atopic comorbidities, anaphylaxis	-Peanut allergy patient with had 8% prevalence of AR vs 3% AR in controls -RR of experiencing AR along with peanut allergy 2.6 (95% CI 2.4-3.0)
Taylor-Black & Wang[337]	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% vs 44% in patients without shellfish allergy)
Tong et al[320]	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)

Blaiss et al[333]	2021	4*	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 peanut allergy-free children (66% vs 21%)
Huang et al[328]	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)
Bilaver et al[322]	2020	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)
Ruffner et al[324]	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[332]	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)
Walter & Kalicinsky[330]	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[326]	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 4 foods)
Celakovska & Bukac[321]	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[336]	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

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; OR=odds ratio; CI-confidence interval; US=United States; HDM=house dust mite; IgE=immunoglobulin E; RR=relative risk; FPIES= food protein-induced enterocolitis syndrome
*LOE downgraded due to peripheral focus of study

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.[350,351]

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.[352] Similarly, Dogru et al[353] found a relatively high rate (21.2%) of AH amongst 566 children with AR. Modrynksi and Zawisza[354] 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[355] 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[356] 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[353] 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[351] reported that inhalant allergen sensitization decreased as AH size increased. Karaca et al[357] compared allergy sensitization to radiographic adenoid

size in 82 children and found no association. Ameli et al[358] 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[359] 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 ($r=-0.208$, $p=0.009$)[360] and ($p=0.04$).[361] 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[362] found a higher Th17/Treg ratio in adenoid tissue from children with AR versus non-allergic controls. Masieri et al[363] 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[364] 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.[365] Independently, Shin et al[366,367] 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.[368,369] Whether INCS reduce adenoid size is unclear.[370] One retrospective study (n=47) reported improvement in rhinitis symptoms in similar percentages of AR (86%) and non-allergic rhinitis (76%) after adenoidectomy.[371] At least one study suggests that AR is a risk factor for refractory nasal symptoms after adenoidectomy.[372]

In summary, AH occurs in allergic children more often than non-allergic controls.[352-354] A recent systematic review concluded that clinical and biomarker evidence favored an association between

allergy and AH.[373] However, in children referred to otolaryngology for nasal obstruction, the association between allergic sensitivity and AH is inconsistent.[351,357,358,360,361] 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,[374] 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).

Aggregate grade of evidence: C (Level 2: 1 study, level 4: 12 studies; **TABLE XIII.F.**)

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[373]	2021	2*	Systematic review	-Allergy -Adenotonsillar disease	-Clinical evidence -Biomarkers	Qualitative link between allergy and AH/ATH
Karabulut et al[361]	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[353]	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[355]	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[360]	2015	4	Consecutive cohort	Children referred from pediatric allergy to otolaryngology	-Endoscopic adenoid size -SPT	AH negatively correlated with (+) allergy testing
Evcimik et al[352]	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[374]	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[358]	2013	4	Consecutive cohort	Children with persistent upper airway obstruction	-Endoscopic adenoid size -SPT	Adenoid volume and % not associated with allergy
Karaca et al[357]	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[359]	2011	4	Retrospective cohort	-ATH -No ATH	SPT for food, inhalant, and latex	-ATH & positive SPT 70.3% -No ATH & positive SPT 10%
Mordrzynski & Zawisza[354]	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
Cassano et al[351]	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 & Giannoni[356]	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

LOE=level of evidence; AH=adenoid hypertrophy; ATH=adenotonsillar hypertrophy; SPT=skin prick test; AR=allergic rhinitis; IgE=immunoglobulin E; RAST=radioallergosorbent test; LRTI=lower respiratory tract infection
*LOE downgraded due to low quality of included studies

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.[375,376] 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, 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.[377-379]

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[380-383] and without AR,[378] as well as in animal models,[384-386] although ET responses have not been found to correlate with IgE levels.[379] **[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.[387,388] 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.[389] Similarly, a pediatric population study found that significantly more children with AR had abnormal tympanograms compared to those without AR.[390] Histologically, increased levels of allergic cytokines such as IL-4, IL-5, and eosinophils have been found at both ends of the ET,[376] 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[391] 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.[392] On the other hand, Pollock et al[393] found that ETD could be prevented in sensitized rats when pre-treated with IL-4 receptor decoys, and Derebery et al[394] 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.

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 12 studies, level 4: 3 studies; **TABLE XIII.G.1.**)

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[391]	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 2 groups per patient (19% vs 32%; p=0.18) or per ear (22% vs 35%; p=0.15) -No difference in symptom score between the 2 groups (p=0.27)
Ebert et al[385]	2002	3*	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) vs controls -MCTTs were 2.4 times longer in histamine group vs control
Pollock et al[393]	2002	3*	Randomized observational	-Treatment groups: sIL-4R/OVA sensitized rats injected with sIL-4R 1 hour 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[384]	2001	3*	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 vs intranasal histamine -Increase in MCTT after transtympanic histamine compared with transtympanic PBS control

Hardy et al[386]	2001	3*	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
Knight et al[388]	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[378]	1991	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[387]	1989	3	Cohort	Children with ragweed sensitivity, n=15	Nine-step tympanometric ET function test	60% of cases developed ET obstruction following natural pollen exposure
Skoner et al[379]	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 vs 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[382]	1987	3**	Double-blind crossover	-Adults with AR, n=5 -Adults without AR, n=5	-Nine-step tympanometric ET function test	-All AR subjects had ET obstruction after histamine provocation (56% at 0.1mg, 100% at 0.5mg) -Two non-AR subjects developed ET obstruction following a much higher dose (20% at 5mg) -Remainder did not develop ET obstruction (up to 10mg)

Skoner at al[381]	1986	3	Cohort	Adults with AR sensitive to house dust mite, normal ET function (n=23 subjects, 40 ears)	-Nine-step tympanometric ET function test	55% of ears developed ET obstruction after provocation
O'Connor et al[383]	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
Friedman et al[380]	1983	3**	Double-blind crossover	Adult patients with AR sensitive to ragweed, grass pollen, or both; n=8	Nine-step tympanometric ET function test	All subjects experienced bilateral ET obstruction following pollen provocation
Juszczak et al[389]	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[390]	2015	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[395] for children younger than 11 months	-Adults with AR demonstrated a significant difference in tympanogram peak admittance vs controls -15.5% of children with AR and 0% of controls had abnormal tympanograms (p=0.03)
Derebery et al[394]	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%

LOE=level of evidence; RDBPCT=randomized double-blind placebo-controlled trial; TAA-AQ=triamcinolone acetonide aqueous; ETD=Eustachian tube dysfunction; PBS=phosphate buffered saline; ET=Eustachian tube; MCTT=mucociliary clearance time of the tubotympanum; IL=interleukin; OVA=ovalbumin; OME=otitis media with effusion; SC=subcutaneous; AR=allergic rhinitis; PG=prostaglandin; IgE=immunoglobulin E; OR=odds ratio

*LOE downgraded due to animal study

**LOE downgraded due to small sample size

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.[396] 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,[397,398] to varying degrees of difference,[399-406] to a near universal association.[407-412] However, cross-sectional studies and one recent SRMA have reported that AR and atopy are independent risk factors for OME.[413-415] 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[416] or OME phenotype.[417] **[TABLE XIII.G.2.]**

Proposed pathogenic mechanisms of the development of OME center around Eustachian tube dysfunction;[418] 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 on this topic.)* Some have proposed that the middle ear itself can be a site of targeted allergic reaction.[419] Several cohort studies suggest that the middle ear is capable of developing a local IgE-mediated inflammatory reaction irrespective of a systemic inflammatory reaction.[420-423] 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.[424-426] 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.[425,427-430] 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.[430]

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.[431,432] Two Cochrane reviews have demonstrated the statistical ineffectiveness of antihistamines, decongestants, antihistamine/decongestant combinations, and INCS in resolution of OME.[433,434] In two RCTs of children with OME, LTRAs provided no benefit over placebo in resolution of effusions.[435,436] 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.[411]

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.

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.**)

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[414]	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 & Flynn[433]	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[434]	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[412]	2020	2	Cross-sectional	Children with OME, n=130	-Prevalence of AR at baseline -Prevalence of AR for pts with	Prevalence of AR in OME children was 52.3% and 80.3% for those with persistent OME

					persistent OME after 3 months	
Byeon[415]	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) vs children without AR
Roditi et al[416]	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[436]	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[403]	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[435]	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
Williamson et al[432]	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[431]	1982	2	RCT	70 children (4-14 years old) with MEE	-Tympanometry -Hearing improvement after 1 month of intranasal beclomethasone spray vs placebo	Beclomethasone nasal spray is no more effective than placebo for MEE resolution
Songu et al[406]	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[405]	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[417]	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[404]	2013	4	Case-control	-Children with OME, n=370 -Controls, n=100	History of allergy	Incidence of AR higher in OME (33.8%) vs controls (16%)
Kreiner-Moller et al[413]	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[411]	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[398]	2007	4	Case-control	-Children with OME, n=123 -Controls, n=141	-History of AR -Skin prick tests	-AR in 28% of OME group vs 24% of control
Chantzi et al[402]	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[430]	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
Jang & Kim[429]	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[428]	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[425]	2002	4	Case series	26 OME patients	-Skin prick tests -Effusion immunocytochemistry	Higher levels of eosinophils and T lymphocytes in effusions of atopics than non-atopics
Alles et al[410]	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 & Venge[424]	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 vs non-atopic -No difference in serum tIgE
Wright et al[427]	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 vs controls

Hurst et al[423]	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[397]	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[409]	1996	4	Cohort	-Patients with OME, n=73 -Controls, n=16	-Allergy tests -Effusion ECP	Positive allergies in 97% of COME
Corey et al[401]	1994	4	Case-control	-Children with OME, n=89 -Controls, n=59	RAST	61% positive RAST in OME group vs 41% in controls
Tomonaga et al[400]	1988	4	Cohort	-Children with OME, n=259 -Nasal allergies, n=605 -Controls, n=104	-Allergy testing	50% of OME patients had nasal allergy vs 17% controls
Bernstein et al[422]	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[421]	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[399]	1983	4	Case-control	-Patients with SOM, n=89 -Controls, n=67	-Allergy history -Allergy testing	41% of SOM patients had perennial rhinitis vs 11% of controls
Bernstein et al[420]	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[407]	1981	4	Case series	Patients with COME, n=119	-RAST	93% of COME patients tested positive to inhalants

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; OME= otitis media with effusion; OR=odds ratio; CI=confidence interval; CHL=conductive hearing loss; INCS=intranasal corticosteroid; MEE=middle ear effusion; tIgE=total immunoglobulin E; RAOM=recurrent acute otitis media; IgE=immunoglobulin E; AIT=allergen immunotherapy; IL=interleukin; RANTES= regulated upon activation, normal T cell expressed and secreted; ECP=eosinophil cationic protein; TNF=tumor necrosis factor; MPO=myeloperoxidase; CD=cluster of differentiation; MBP=major basic protein; sIgE=specific immunoglobulin E; COME=chronic otitis media with effusion; RAST=radioallergosorbent test; SOM=serous otitis media

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.[437] 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.[438] 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[439] and have increased odds of allergies versus controls.[440] Similar patient-reported data suggests higher rates of allergy and migraine in Meniere's disease patients.[441] Overall, these studies generally provide low grade evidence. **[TABLE XIII.G.3.]**

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,[442,443] as well as in patients with acute low frequency SNHL compared to those with sudden SNHL.[444] However, in another small study, there was no difference in serum tIgE levels between Meniere's disease and controls.[445] In two small studies, electrocochleographic summation potential/action potential [SP/AP] ratios increased in response to allergen challenge in Meniere's disease patients,[446,447] 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.[444] 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).[448,449] 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.[450] 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.

Aggregate grade of evidence: C (Level 2: 1 study, level 3: 1 study, level 4: 10 studies; **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[440]	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[449]	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[444]	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[443]	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[451]	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[441]	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[442]	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 & Berliner[439]	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[447]	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 & Valenzuela[448]	1992	4	Cohort	MD patients with suspected allergy, n=93	-Allergy skin test -In vitro allergy tests -Serum IgE	-82% had normal serum IgE -AIT improved vertigo in 62%

					-Provocative food testing -AIT response	
Viscomi & Bojrab[446]	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[445]	1990	4	Case-control	-MD patients, n=42 -Controls, n=18	-Serum tIgE	No difference in serum tIgE between groups

LOE=level of evidence; MD=Meniere's disease; OR=odds ratio; AIT=allergen immunotherapy; SNHL=sensorineural hearing loss; tIgE=total immunoglobulin E; sIgE=specific IgE; ECoG=electrocochleography; SP/AP=summation potential/action potential ratio; IgE=immunoglobulin E; AR=allergic rhinitis; OAE=otoacoustic emissions; ABR=auditory brainstem response

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.[452] AR has been associated with cough. Allergens may stimulate the nasal mucosa, resulting in the rhinobronchial reflex and bronchospasm.[453] 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.[453] 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.[119] 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.[119] Krzych-Falta et al[454] 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[455] 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.[456] In an animal model, HDM-sensitized guinea pigs had a significantly enhanced cough response compared to non-sensitized animals.[457] 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.[458,459] In addition, combined respiratory disease may be seen; this occurred in 33.5%, with the most common combination being AR and asthma.[458,459] 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.[460] 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[461] found the prevalence of comorbidities, including cough, to gradually increase with increasing AR severity and frequency.

Publications from 2020-2021 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% and 20% of patients.[462] Kim et al[463] 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.[455-457] 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.[464,465] 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.[466,467]

It is not clear if treatment of AR with INCS improves the associated cough,[463,468] but an RCT by Kim et al[463] 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.[469]

Aggregate grade of evidence: C (Level 2: 3 studies, level 3: 3 studies, level 4: 11 studies, level 5: 1 study; **TABLE XIII.H.**)

TABLE XIII.H. Evidence table – Association between allergic rhinitis and cough

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dicpinigiatis et el[462]	2021	2	Secondary analysis of RCTs	Patients ≥18 years with refractory/unexplained cough in COUGH-1 and COUGH-2 RCTs of the P2X3 receptor antagonist gefapixant, n=2044	Concurrent AR	AR was present in 20% of COUGH-1 and 15% in COUGH-2 participants
Hua et al[469]	2020	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 vs nasal neurectomy alone
Lin et al[470]	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[468]	2019	3*	SR	RCTs evaluating effect of INCS of secondary symptoms of AR, including cough	Cough severity	2 studies identified: 1 showed improvement on daytime cough, 1 showed no difference in cough
He et al[461]	2016	3	Prospective, nonrandomized	Serum sIgE from patients with AR symptoms from 2011-2014, 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[453]	2011	3	Cohort	Patients from otolaryngology and pulmonary centers, n=159	Analysis of rhino-bronchial syndrome signs & symptoms	-Increased frequency of the Rhino-Bronchial Syndrome in allergic disease (37.9% vs 20.9%) -Cough in 96%

Chen et al[466]	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[465]	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 vs non-AR
Kim et al[463]	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[467]	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[464]	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 55.03; 95% CI 1.88-13.49)
Cho et al[460]	2016	4	Case series	Adults with primary diagnosis of asthma, AR, COPD, or rhinosinusitis, n=5250	Respiratory disease & demographics questionnaire completed by participants & 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[459]	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[458]	2016	4	Case series	Adults with primary diagnosis of asthma, AR, COPD, or rhinosinusitis, n=1001	Respiratory disease questionnaire completed by participants & 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[454]	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
Chakir et al[455]	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[456]	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[457]	2016	5	Bench research	30 guinea pigs: -HDM group (sensitized by HDM aerosol, then challenged, sensitization	-Symptoms of AR induced by intranasal application of 15µl 0.5 % HDM -Cough challenge with	-HDM and OVA-sensitized groups showed a significantly enhanced nasal reactivity and cough response vs controls

				confirmed via skin test) -OVA group -Control group	citric acid performed -Airway resistance measured in vivo by Pennock's method.	-Airway resistance data did not show significant differences.

LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; HDM=house dust mite; INCS=intranasal corticosteroid; sIgE=specific immunoglobulin E; CVA=cough variant asthma; FeNO=fraction of exhaled nitric oxide; MMEF=maximum mid-expiratory flow; CPA=cough predominant asthma; FEF_{25-75}= forced expiratory flow at 25% to 75% of pulmonary volume; NAEB=non-asthmatic eosinophilic bronchitis; UACS=upper airway cough syndrome; GERC=gastroesophageal reflux-related cough; OR=odds ratio; CI=confidence interval; COPD=chronic obstructive pulmonary disease; IL=interleukin; OVA=ovalbumin
*Downgraded due to low number of included studies, inconsistent results

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.[471] 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 at al[472] found an association between the diagnosis of chronic laryngitis and AR in a Korean nationwide cohort. Subsequently, Wang et al[473] 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.[474-477] Ohlsson et al[478] 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[479] 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.[480] The likelihood of AR increased as the number of vocal symptoms increased.[480]

The adverse effects of AR on voice-related QOL have also been reported,[474,476,481] and Turley et al[481] 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.[477] Overall, there is a higher than anticipated incidence of AR in patients with vocal dysfunction and vice versa.[477,480-482]

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.[476,483] 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.[484] However, the opposite may be true in professional voice users presenting with dysphonia.[479] Randhawa et al[483] 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.[485,486] Eren et al[486] demonstrated no significant difference in laryngeal appearance between allergy-positive and LPR-positive subjects. However, thick endolaryngeal mucus may predict allergy.[487]

Several studies have evaluated the direct effect of allergens on the larynx. Belafsky et al[488] and Mouadeb et al[489] 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.[471,490] In the first study, Reidy et al[471] 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[490] used increased allergen concentration for the challenge and noted an increase in endolaryngeal mucus, throat clearing, and coughing. Roth et al[491] 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[492] 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.[492] 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.[471]

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[472]	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[491]	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[477]	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[490]	2009	2	RCT	HDM-sensitive adults: -*D. pteronyssinus* challenge -Placebo	Effect of allergen on laryngeal findings	Laryngeal abnormalities secondary to lower respiratory stimulation
Krouse et al[476]	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
Simberg et al[482]	2007	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
Reidy et al[471]	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[473]	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 vs those without AR
Alharethy et al[484]	2018	3	Cohort	Patients presenting to otolaryngology clinic with LPR symptoms	SFAR in patients with positive and negative 24-hour oropharyngeal pH monitoring	-LPR patients based on pH testing had higher SFAR scores -Higher Ryan score associated with higher SFAR score
Velickovic et al[479]	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[492]	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[493]	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[478]	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[494]	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[486]	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[475]	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[481]	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 vs controls -Patients with worse rhinitis symptoms had worse voice-related QOL and more severe chronic laryngeal symptoms
Randhawa et al[483]	2010	4	Case series	Patients diagnosed with primary voice disorder or globus sensation	Prevalence of AR and LPR	3 times as many patients had allergies vs LPR, not statistically significant
Hamdan et al[480]	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

Millqvist et al[474]	2006	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
Jackson-Menaldi et al[487]	1997	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[488]	2015	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[489]	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 vs saline

LOE=level of evidence, IgE=immunoglobulin E; VHI=Voice Handicap Index; RCT=randomized controlled trial; HDM=house dust mite; LPR=laryngopharyngeal reflux; GERD=gastroesophageal reflux disease; AIT=allergen immunotherapy; AR=allergic rhinitis; ICD=International Classification of Diseases; SFAR=Score for Allergic Rhinitis; ARIA=Allergic Rhinitis and its Impact on Asthma; RSI=Reflux Symptom Index; SPT=skin prick test; NAR=non-allergic rhinitis; HDMA=house dust mite allergen

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.[495]

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.[496-512] There is also evidence for a higher prevalence of AR among EoE patients compared with the general population.[495,513,514] 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[257] 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.[515-522] AIT has also demonstrated efficacy in the treatment of EoE in one case-control study and two case reports.[523-525] 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.[526] However other studies, including a systematic review by Lucendo et al,[527] demonstrated no seasonal variation in EoE diagnosis or exacerbations, suggesting a limited role for aeroallergens as a relevant trigger for initiating or aggravating EoE.[527-529] Therefore, there is limited observational data suggesting a potential association between aeroallergens and EoE pathogenesis, with some conflicting data.

Aggregate grade of evidence: C (Level 3: 6 studies, level 4: 29 studies; **TABLE XIII.J.**)

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[497]	2017	3	Population-based database	Pediatric and adult EoE patients	Demographic and clinical characteristics	45% had AR
Gonzalez-Cervera et al[513]	2017	3	Systematic review	Pediatric and adult EoE patients	Demographic and clinical characteristics	AR significantly more common among EoE patients vs controls (OR 5.09)
Furuta et al[496]	2007	3	Systematic review	Pediatric and adult EoE patients	Demographic and clinical characteristics	50-80% had AR and sensitization to aeroallergens
Ancellin et al[499]	2020	4	Case series	Pediatric EoE patients, n=49	Demographic and clinical characteristics	78% were atopic; 64% sensitized to aeroallergens
Azzano et al[498]	2020	4	Case series	Pediatric EoE patients, n=108	Demographic and clinical characteristics	63% sensitized to aeroallergens; 51% had AR
Imamura et al[514]	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% vs 11%)
Leigh & Spergel[495]	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% vs 3.5%)
Alves Marcelino et al[501]	2017	4	Case series	Pediatric EoE patients, n=25	Demographic and clinical characteristics	92% sensitized to aeroallergens
Mohammad et al[500]	2017	4	Case series	Pediatric and adult EoE patients, n=449	Demographic and clinical characteristics	62% had AR
Olson et al[502]	2016	4	Case series	Adult EoE patients, n=257	Demographic and clinical characteristics	79% had AR
Castro Jimenez et al[505]	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[504]	2014	4	Case series	Pediatric EoE patients, n=311	Demographic and clinical characteristics	86% were atopic; 67% had AR
Vernon et al[503]	2014	4	Case series	Pediatric and adult EoE patients, n=100	Demographic and clinical characteristics	65% had AR
Spergel et al[506]	2009	4	Case series	Pediatric EoE patients, n=562	Demographic and clinical characteristics	68% were atopic; 43% had AR
Roy-Ghanta et al[507]	2008	4	Case series	Adult EoE patients, n=23	Demographic and clinical characteristics	78% had AR; 86% sensitized to aeroallergens
Assa'ad et al[508]	2007	4	Case series	Pediatric EoE patients, n=89	Demographic and clinical characteristics	79% sensitized to environmental allergens
Plaza-Martin et al[509]	2007	4	Case series	Pediatric EoE patients, n=14	Demographic and clinical characteristics	93% had AR and sensitization to aeroallergens
Sugnanam et al[510]	2007	4	Case series	Pediatric EoE patients, n=45	Demographic and clinical characteristics	93% had AR
Remedios et al[511]	2006	4	Case series	Adult EoE patients, n=26	Demographic and clinical characteristics	77% were atopic; 54% had AR
Guajardo et al[512]	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[515]	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[523]	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[527]	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[524]	2021	4	Case report	Pediatric patients with EoE and multiple environmental	Clinicohistologic remission	EoE remission observed after treatment with multiallergen SCIT as monotherapy

				allergies treated with AIT		
Reed et al[516]	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[257]	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[517]	2017	4	Case series	Pediatric EoE patients, n=38	Season of EoE diagnosis	Correlation between onset of EoE symptoms and peak grass pollen levels
Elias et al[528]	2015	4	Case series	Adult EoE patients, n=372	Season of EoE diagnosis	Increased presentation of EoE in winter months
Ram et al[518]	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[529]	2014	4	Retrospective cohort	Pediatric and adult EoE patients	Season of EoE diagnosis	Incidence of EoE consistent across all seasons
Ramirez & Jacobs[525]	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[519]	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[520]	2009	4	Case series	Adult EoE patients, n=41	Season of EoE diagnosis	68% diagnosed in spring/summer vs 32% in fall/winter
Wang et al[521]	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 vs spring, summer, and fall; least intense esophageal eosinophilia in winter
Fogg et al[522]	2003	4	Case report	Pediatric EoE patient	Seasonal biopsy findings	Increased esophageal eosinophilia during pollen seasons

LOE=level of evidence; EoE=eosinophilic esophagitis; AR=allergic rhinitis; OR=odds ratio; AIT=allergen immunotherapy; SCIT=subcutaneous immunotherapy

XIII.K. Sleep disturbance and obstructive sleep apnea

AR negatively impacts sleep and is a risk factor for OSA.[530] 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.[531-542] This may be due to increased nasal obstruction during the night with a peak in the early morning.[543] 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.[544-546] Histamine plays a role in the regulation of the sleep-wake cycle and arousal, and cysteinyl leukotrienes are involved in sleep disruption.[547,548] Excessive histamine results in insomnia and inadequate amounts cause hypersomnolence.[547,549] 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.[550-552] Patients with OSA also have increased mediators which activate Th2 cells, such TNF, IL-1 and IL-6, further exacerbating symptoms of AR and potentiating the severity of OSA.[553] 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.[554-559] 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.[560] **[TABLE XIII.K.]**

Sleep is critical for mood, cognitive function, immune function, and endocrine functions.[544] OSA is associated with hypertension, coronary artery disease, cerebrovascular disease, arrhythmias, insulin resistance, congestive heart failure, pulmonary hypertension, and behavioral problems in children.[561-566] Further, in children, SDB may negatively impact brain development, impair psychomotor and cognitive performance, and contribute to hyperactivity.[567-569] REM sleep is associated with memory, cognition, dreams, and restorative sleep.[570,571] As the nasal cycle is prolonged, worsening nasal obstruction, people with AR have impaired REM sleep.[570-574] 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.[575]

CPAP treatment for OSA may present a non-allergic trigger to AR patients with OSA and worsen nasal symptoms.[576] Further, persistent nasal symptoms are a common reason for early CPAP non-compliance.[576-578] However, correction of nasal obstruction can improve CPAP compliance/tolerance,[579-581] though there is typically no direct impact on OSA severity.[582]

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.[583] 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.[584-588] INCS may improve sleep in patients with AR due to improvement in nasal obstruction, but also due to reduction in local inflammatory cytokines.[547,548] A recent RCT and case series found significant improvements in sleep parameters following AR treatment with HDM SLIT.[589,590] 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, second generation H_1 antagonists are favored, such as fexofenadine and loratadine, which are lipophobic and do not cross the blood-brain barrier.[591-593] 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.[594,595] Nasal decongestants may result in stimulatory effects causing insomnia.[546] Nasal decongestant sprays do not significantly improve AHI.[596] A cross-over 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.[596] 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 Rhinitis Disease Burden – Sleep Disturbance for additional information on this topic)*

Aggregate grade of evidence: B (Level 2: 3 studies, level 3: 4 studies, level 4: 9 studies; **TABLE XIII.K.**)

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[597]	2020	2%	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 vs control -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[589]	2019	2	RCT, double blind, placebo-controlled	Moderate-severe HDM AR treated with SLIT, n=656	RQLQ	SLIT resulted in improvement in sleep quality vs placebo
Chen et al[594]	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 & nasal smear eosinophil count -Nasal airway resistance	Montelukast superior to cetirizine for night sleep quality
Liu et al[544]	2020	3*	Cross-sectional	Children with snoring from adenotonsillar hypertrophy,	-PSG -Sleep questionnaire	-Prevalence of AR in SDB (25.8%), OSA (19.4%) -Regardless of OSA status, AR children had more daytime

				aged 3-14 years, n=660		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[598]	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[576]	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 -AR group improved significantly less vs control.
Chuang et al[599]	2019	3	Controlled cohort	AR patients, age/sex-matched controls, n=412,074	OSA	-Incidence of OSA significantly higher in AR patients vs controls -AR was significant risk factor for OSA
Kim et al[584]	2021	4**	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[600]	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[575]	2020#	4***	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 vs controls -AR patients more likely to have REM-AHI in moderate-severe range vs controls
Bosnic-Anticevich et al[601]	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 vs controls
Giraldo-Cadavid et al[602]	2020	4****	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[530]	2020	4*****	Prospective controlled cohort	60 participants: -NARES -AR -Control	-Home sleep study -VAS -STOP-BANG -ESS	-OSA present in: NARES 60%, AR 35% AR, control 10% -No significant difference in OSA between NARES vs AR, or AR vs control -No difference in OSA severity across groups
Wongvilairat et al[603]	2019	4******	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
Berson et al[571]	2018	4***	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
Novakova et al[590]	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)

LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized controlled trial; HDM=house dust mite; SLIT-sublingual immunotherapy; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; TNSS=Total Nasal Symptoms Score; IgE=immunoglobulin E; ECP=eosinophil cationic protein; PSG=polysomnography; SDB=sleep disordered breathing; OSA=obstructive sleep apnea; REM=rapid eye movement; CPAP=continuous positive airway pressure; SFAR=Score for Allergic Rhinitis; NOSE=Nasal Obstruction Symptom Evaluation; SNOT=Sinonasal Outcome Test; VAS=visual analog scale; IT=inferior turbinate; ESS=Epworth Sleepiness Scale; AHI=apnea-hypopnea index; RDI=respiratory disturbance index; sIgE=specific immunoglobulin E; STOP-BANG= Snoring, Tiredness, Observed breathing cessation, Pressure, BMI, Age, Neck circumference, Gender

Questionnaire; ESPRINT-15=validated health-related quality of life questionnaire for adults with AR; PSQ=Pediatric Sleep Questionnaire; NARES=non-allergic rhinitis with eosinophilia syndrome
[%]LOE downgraded; not a SRMA of RCTs
*LOE downgraded due to significant difference in group sizes
**LOE downgraded due to small number of AR patients (n=8) and only 1 female patient included
***diagnosis of AR based on skin prick or serum testing
****LOE downgraded as diagnosis of AR based on symptoms only
*****LOE downgraded as OSA diagnosed on home sleep study and AHI values only
******LOE downgraded as OSA diagnosed on questionnaires, not PSG (probability of OSA calculated)
same patient group as 2018 study

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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.[1] 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.[2] 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.[3,4] However, as case rates fell, it was necessary to find ways to evaluate patients for AR.[5,6] Telemedicine, using phone or video where available, was rapidly implemented and provided significant access to specialty care while limiting exposure for patients and providers.[2-4,7,8] However, implementation of telemedicine practices may exacerbate gaps in access for populations already at risk for health disparities.[9]

Another evident issue became the similarities in presentation between AR and COVID-19, and it was important to identify ways to differentiate the diseases.[2,4] AR was not a risk factor for severe COVID-19 infection.[10-17] 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.[18] Patients scored validated questionnaires like the SNOT-22 and mini-RQLQ differently.[19,20] 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).[19] In patients with allergic rhinoconjunctivitis with COVID-19 infection, mini-RQLQ scores were lower in COVID-19 infection compared to their allergies.[20] 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.[21,22] However, in general, AR symptoms and medication use decreased.[23-26] 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.[2,27] 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.[25,28] The COVID pandemic also led to increased exposure to indoor respiratory irritants such as tobacco, cooking smoke, and cleaning products.[29] And although use of face masks were reliably associated with fewer nasal symptoms compared to no mask, the effect on ocular symptoms was mixed.[30,31] Finally, patients who discontinued their therapies for AR due to pandemic concerns expectedly reported loss of symptom control.[32]

Comorbid mental health diagnoses including depression and anxiety are commonly reported in patients with AR and positively correlated with symptom scores.[33] 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[24] than non-atopic patients.[34]

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.[6,35] 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.[3] Additionally, there was often national, regional, and/or institutional guidance for in person visits and procedures.[3,6,35-40] 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.[5]

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[4,5,41] and, in some countries, body temperature screening and epidemiologic tracking via smartphone.[38,41] Social distancing of at least 6 feet was recommended when possible.[4,38,42] This was

important in clinical spaces and the waiting room. Visitor limitations (with 1 adult allowed for children and none for adult patients when possible) were enacted.[43,44] 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.[5] 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.[4,8,35,41,42]

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.[45,46] Initial studies by two research groups using cadaveric heads did not demonstrate aerosol generation during cold instrumentation[47,48] although further studies in live patients undergoing nasal endoscopy detected increased airborne particles.[49,50] 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.[51] There is also concern that nasal endoscopy can induce behaviors including sneezing, breathing, speaking, and possibly coughing that are aerosol generating.[47,49,52] However, some modifications including nasal endoscopy using modified surgical or N95 masks could prevent aerosol generation,[47,49,50] as well as repositioning at the back of the patient[53] or using a tower with camera, screen, and light source.[6] Local anesthetics and decongestants could be applied with actuated pump sprays or soaked pledgets rather than atomized forms to avoid aerosol generation.[37,47,52] Immediate decontamination of equipment, especially the endoscope, was also recommended.[35] Expert groups generally recommended against certain procedures including nasal provocation, nasal cytology, anterior rhinomanometry, and PNIF.[37,54,55] If supplies were not constrained, rapid and accurate pre-procedural screening for SARS-CoV-2 was also recommended.[5] For personal protective equipment, the WHO recommended an N95 face mask, full eye protection, and full body protective clothing.[4,37,54] Techniques to improve donning and doffing included one-step glove and gown removal, double-gloving, spoken instructions during doffing, and glove disinfection.[54]

Aerosol clearance depends on ventilation and air exchange.[54] 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 minutes. 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.[56,57]

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.[6,27,39,55,58] 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.[38] 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.[59-61]

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.[27] 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.[2,4,10,55,62] Systemic corticosteroids may be a concern although this is not a standard therapy for AR.[63] 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.[64] Montelukast has also been associated with a reduction in COVID-infection in a small retrospective cohort study of elderly asthmatics.[65]

AIT has been shown to improve symptom control with a decrease in respiratory infections and antibiotic use.[66] Prior studies with viral infections including influenza, cytomegalovirus (CMV), and HIV have not shown changes in the efficacy or safety of AIT.[32] 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.[3,39,43,55] 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.[4] 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.[7,67-70] 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.[8,39,55] In case of COVID-associated quarantine, an adequate supply of SLIT should be maintained at home.[6,32] Finally, home SCIT in selected patients was cost effective under pandemic considerations alone.[2,71] Of note, this is not currently approved and is not the standard of care.[3]

Finally, anti-IgE therapy has been approved for severe cases of Japanese cedar pollinosis.[55] 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.[72-74] 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.[75-77] However, as there is limited evidence, physician judgment is recommended.

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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 many of the 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,[1] but the cause of hyposmia in AR is unclear.[2,3] 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.[4,5] 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. 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 Rhinitis 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.

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