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 studie s, level 4: 2 studies)

Benefit: Exposure to pets at birth and in the first year of life has potential benefits of decreasing risk of AR.

Harm: Pet keeping in childhood could have a negative effect, especially in Asians.

Cost: Various.

Benefits-harm assessment: Difficulty distinguishing between benefits and harm.

Value judgment: There is conflicting evidence that childhood pet exposure prevents the developme nt 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

	2018	46	B	Recommendation	improve sleep.

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-	2023	16	B	Recommendation	Serum sIgE testing is recommended for

specific IgE	2018	7	B	Recommendation	allergy testing.
Correlation between skin and *in vitro* testing	2023	19	B	-----	Studies differ regarding the concordance of various allergy testing methods.
	2018	19	B	-----	
Nasal sIgE	2023	36	C	Option	Nasal sIgE is an option in patients with suspected AR.
	2018	24	C	Option	
Basophil activation test	2023	19	C	Option	BAT may be used for diagnosis when first-line tests are discordant, and for monitoring response to AIT.
	2018	12	B	Option	
Component resolved diagnostic testing	2023	18	C	Option	May improve selection of allergens for AIT, especially in polysensitized patients.
	2018	n/a	n/a	n/a	
Nasal provocation testing	2023	8	C	Option	Option for diagnostic testing for AR. Recommended for diagnosis of occupational rhinitis and local AR.
	2018	4	C	n/a	
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

	2018	18	C	between AR and laryngeal disease.
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

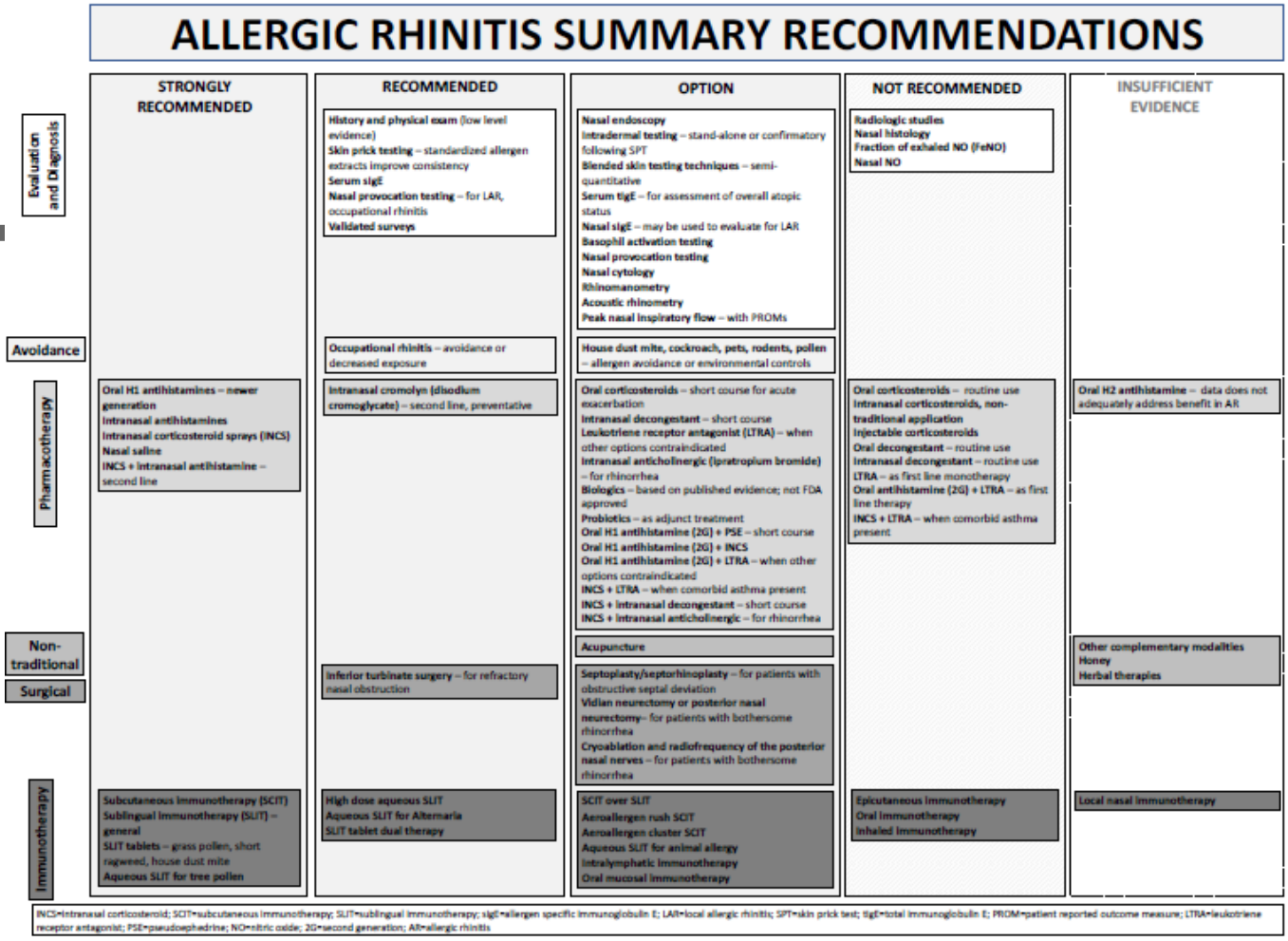
*Studies included in systematic reviews were not separately listed in tables

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.



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.

REFERENCES

1. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

2. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. Nov-Dec 2011;1(6):431-7. doi:10.1002/alr.20095

3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med*. 2009;3(3):e123-30.

4. American Academy of Pediatrics Steering Committee on Quality I, Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. Sep 2004;114(3):874-7. doi:10.1542/peds.2004-1260

5. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. Nov 2001;108(5 Suppl):S147-334. doi:10.1067/mai.2001.118891

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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
ACEI	angiotensin converting enzyme inhibitors
AD	atopic dermatitis
AERD	aspirin-exacerbated respiratory disease
AFRS	allergic fungal rhinosinusitis
AH	adenoid hypertrophy
AHI	apnea-hypopnea index
AIDS	acquired immunodeficiency syndrome
AIT	allergen-specific immunotherapy
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
AP	activator protein
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ARS	acute rhinosinusitis
ASHMI	Anti-Asthma Simplified Herbal Medicine Intervention
ATH	adenotonsillar hypertrophy
AU	allergy units
BAT	basophil activation test
BAU	biologic allergy units
CBER	Center for Biologics Evaluation and Research
CC	central compartment

CCAD	central compartment atopic disease
CCL5	C-C chemokine ligand-5
CD	cluster of differentiation
CDC	Centers for Disease Control
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related protein
CI	confidence interval
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVID	coronavirus disease
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CPT	conjunctival provocation test
CRD	component-resolved diagnostics
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	combined score
CSF	cerebrospinal fluid
CT	computed tomography
DAMP	damage-associated molecular pattern
dsDNA	double stranded DNA
DSCG	disodium cromoglycate
EAACI	European Academy of Allergy and Clinical Immunology
EBRR	evidence-based review with recommendations
ECP	eosinophil cationic protein
EGPA	eosinophilic granulomatosis with polyangiitis
EGR	early growth response
ECHRS	European Community Respiratory Health Survey
EEC	environmental exposure chamber
ELISA	enzyme-linked immunosorbent assay
eNOS	endothelial nitric oxide synthase

ENS	empty nose syndrome
EoE	eosinophilic esophagitis
ET	Eustachian tube
ETD	Eustachian tube dysfunction
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FITC	fluorescein isothiocyanate
FOXP3	forkhead-box P3
GA^2LEN	Global Allergy and Asthma European Network
GATA	GATA binding protein
GINA	Global Initiative for Asthma
GITRL	glucocorticoid-induced TNF receptor ligand
GM-CSF	granulocyte-macrophage colony stimulating factor
GPA	granulomatosis with polyangiitis
GWAS	genome-wide association studies
HDM	house dust mite
HEPA	high-efficiency particulate air [filtration]
HIV	human immunodeficiency virus
HMGB-1	high mobility group box-1
HMW	high molecular weight
HSP	heat shock protein
ICAM	intracellular adhesion molecule
ICAR	International Consensus Statement on Allergy and Rhinology
ICD	International Classification of Disease
IDT	intradermal dilutional testing
IFN	interferon
Ig	immunoglobulin
IgE	immunoglobulin E
IL	interleukin
ILC	innate lymphoid cell
ILIT	intralymphatic immunotherapy
IMAP	inferior meatus augmentation procedure
INCS	intranasal corticosteroid
INDC	intranasal decongestant
iNOS	inducible nitric oxide synthase
IPB	ipratropium bromide
IPM	integrated pest management
ISAAC	International Studies of Asthma and Allergies in Childhood
IT	inferior turbinate
ITAM	immunoreceptor tyrosine-based activation motif

KNHANES	South Korean National Health and Nutrition Examination Survey
LAR	local allergic rhinitis
LMW	low molecular weight
LOE	level of evidence
LPR	laryngopharyngeal reflux
LSR	lipolysis-stimulated lipoprotein receptor
LTRA	leukotriene receptor antagonist
MBP	major basic protein
MCP	monocyte chemoattractant protein
MD	molecular diagnostics
MEE	middle ear effusion
MMP	matrix metalloproteinase
MQT	modified quantitative testing
mRQLQ	mini-Rhinoconjunctivitis Quality of Life Questionnaire
MT	middle turbinate
NARES	non-allergic rhinitis with eosinophilia syndrome
NC	nasal cytology
NF	nuclear factor
NFAT	nuclear factor of activated T cells
NGF	neural growth factor
NH	nasal histology
NHANES	National Health and Nutrition Examination Survey
NK	natural killer
nNO	nasal nitric oxide
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
NOSE	Nasal Obstruction Symptom Evaluation
NPT	nasal provocation test
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OAS	oral allergy syndrome

OME	otitis media with effusion
OMIT	oral mucosal immunotherapy
OR	odds ratio
OSA	obstructive sleep apnea
PAMD@	precision allergy molecular diagnostic applications
PAMP	pathogen-associated molecular pattern
PDE	phosphodiesterase
PEF	peak expiratory flow
PFAS	pollen food allergy syndrome
PFT	pulmonary function test
PG	prostaglandin
PM	particulate matter
PNEF	peak nasal expiratory flow
PNIF	peak nasal inspiratory flow
PNN	posterior nasal nerve
PO	per os (by mouth)
Ppb	parts per billion
PPV	positive predictive value
PROM	patient reported outcome measure
PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PSG	polysomnogram
QALY	quality adjusted life year
QID	four times daily
QOL	quality of life
RANTES	regulated upon activation, normal T cell expressed and presumably secreted
RAP	Respiratory Allergy Prediction
RAPP	RhinAsthma Patient Perspectives
RARS	recurrent acute rhinosinusitis
RAST	radio allegro-sorbent test

RCT	randomized controlled trial
RDI	respiratory disturbance index
REM	rapid eye movement
RMS	rescue medication score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RR	relative risk
RSDI	Rhinosinusitis Disability Index
RTSS	Rhinitis Total Symptom Score
SARS-CoV-2	virus that causes COVID-19
SCIT	subcutaneous immunotherapy
SDB	sleep disordered breathing
SES	socioeconomic status
sIgE	allergen-specific immunoglobulin E
sIgG	allergen-specific immunoglobulin G
SLIT	sublingual immunotherapy
SMA	smooth muscle actin
SMD	standardized mean difference
SNHL	sensorineural hearing loss
SNOT	SinoNasal Outcome Test
SNP	single nucleotide polymorphism
SPT	skin prick test
SRMA	systematic review and meta-analysis
STAT	signal transducer and activator of transcription
TARC	thymus and activation-regulated chemokine
TGF	transforming growth factor
TCM	Traditional Chinese Medicine
Th	T helper
tIgE	total immunoglobulin E
TJ	tight junction
TL1A	tumor necrosis factor-like cytokine 1A
TLR	toll-like receptor
TNF	tumor necrosis factor
TNSS	Total Nasal Symptom Score

TOSS	Total Ocular Symptom Score
TPRV	transient receptor potential vanilloid
Treg	T regulatory cell
TRP	transient receptor potential
TSLP	thymic stromal lymphopoietin
TSS	total symptom score
UK	United Kingdom
US	Unites States
VAS	visual analog scale
VCAM	vascular cell adhesion molecule
VCOS	validated clinical outcome survey
VD3	vitamin D
VDR	vitamin D receptor
VHI	voice handicap index
WAO	World Allergy Organization
WHO	World Health Organization
ZO	zonula occludens

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

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

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.

REFERENCES

1. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

2. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. Nov-Dec 2011;1(6):431-7. doi:10.1002/alr.20095

3. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. Feb 2016;6 Suppl 1:S22-209. doi:10.1002/alr.21695

4. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. Mar 2021;11(3):213-739. doi:10.1002/alr.22741

5. Wang EW, Zanation AM, Gardner PA, et al. ICAR: endoscopic skull-base surgery. *Int Forum Allergy Rhinol*. Jul 2019;9(S3):S145-S365. doi:10.1002/alr.22326

6. Patel ZM, Holbrook EH, Turner JH, et al. International consensus statement on allergy and rhinology: Olfaction. *Int Forum Allergy Rhinol*. Apr 2022;12(4):327-680. doi:10.1002/alr.22929

7. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. Jan 13 1996;312(7023):71-2. doi:10.1136/bmj.312.7023.71

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

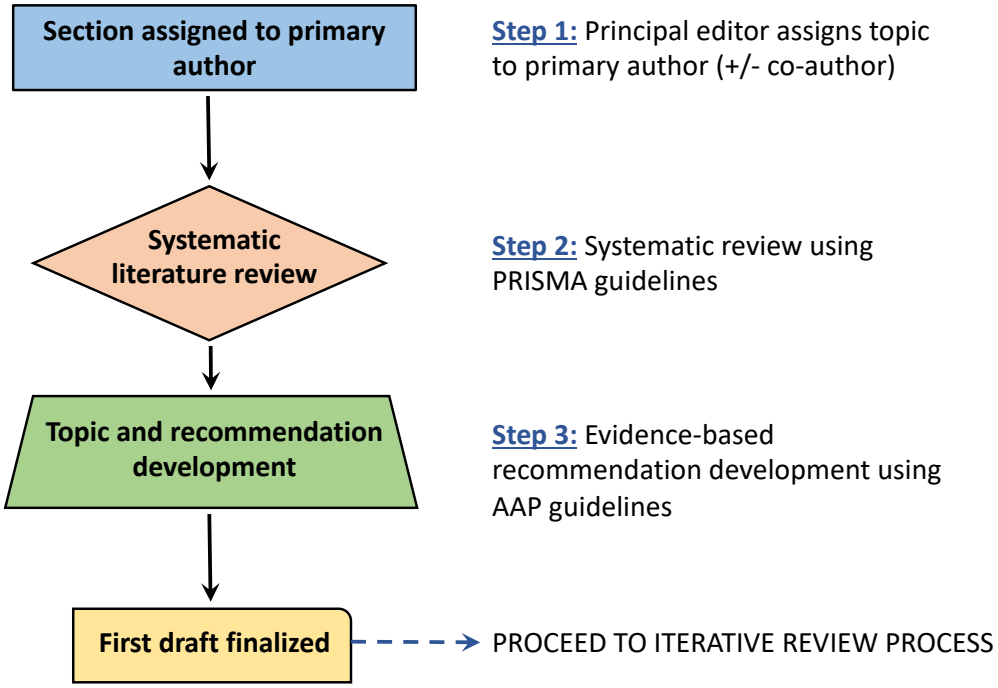
RCT=randomized controlled trial

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
A. Well-designed RCT's	*Strong recommendation*	*Option*	*Strong recommendation against*
B. RCT's with minor limitations; overwhelmingly consistent evidence from observational studies	*Recommendation*		
C. Observational studies (case-control and cohort design)			*Recommendation against*
D. Expert opinion, case reports, reasoning from first principles	*Option*	*No recommendation*	

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)

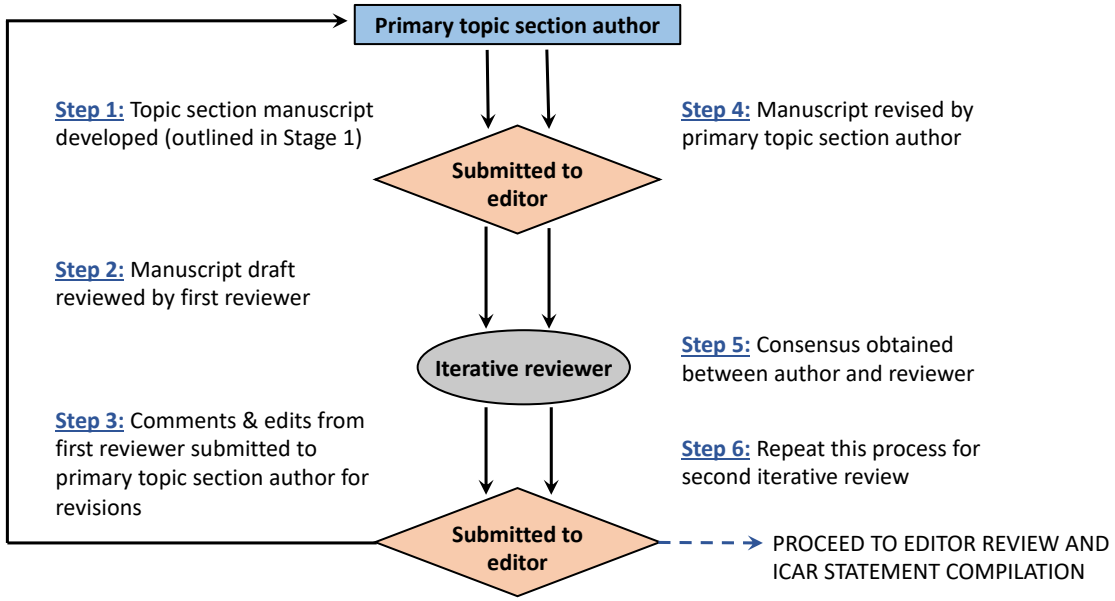
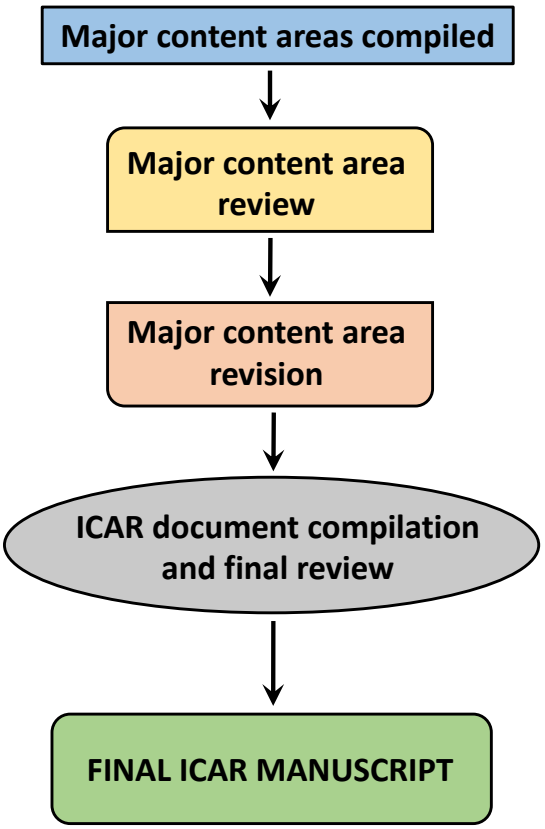


Figure IV.C. ICAR-Allergic Rhinitis 2023 statement development (Stage 3)



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

REFERENCES

1. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. Feb 2016;6 Suppl 1:S22-209. doi:10.1002/alr.21695

2. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. Mar 2021;11(3):213-739. doi:10.1002/alr.22741

3. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

4. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. Nov-Dec 2011;1(6):431-7. doi:10.1002/alr.20095

5. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med*. 2009;3(3):e123-30.

6. OCEBM Levels of Evidence Working Group: The Oxford 2011 Levels of Evidence. Accessed April 4, 2019, http://www.cebm.net/index.aspx?o=5653

7. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach, updated October 2013. Accessed April 2, 2019, https://gdt.gradepro.org/app/handbook/handbook.html

8. American Academy of Pediatrics Steering Committee on Quality I, Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. Sep 2004;114(3):874-7. doi:10.1542/peds.2004-1260

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.

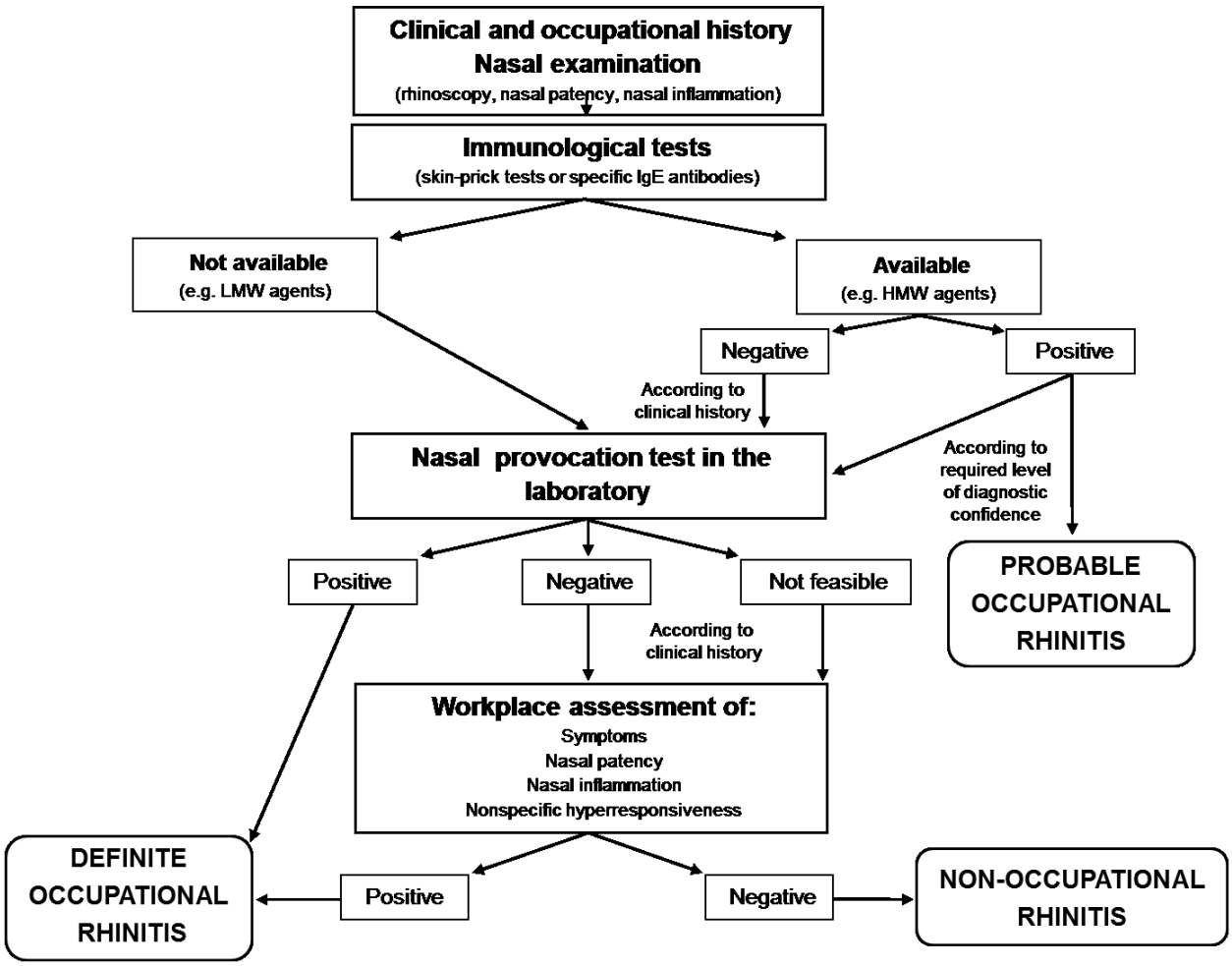
Occupational rhinitis has both medical and socioeconomic implications,[144] and may be the cause of leaving work.[145] Since occupational rhinitis is acknowledged as a risk factor for the development of occupational asthma, the prevention and early identification of occupational rhinitis of exposed workers 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)	Unilateral nasal obstruction Unilateral rhinorrhea Mucopurulent rhinorrhea Progressive worsening of symptoms Epistaxis Hypoesthesia Visual changes

	Carcinomas Melanomas Lymphomas	Epiphora Trismus Dental changes
Other	Cerebrospinal fluid Retained foreign bodies Rhinolithiasis Primary ciliary dyskinesia Cystic fibrosis Gastroesophageal reflux disease Laryngopharyngeal reflux disease	Unilateral rhinorrhea Positional rhinorrhea Purulent nasal drainage Systemic organ dysfunction Retrosternal burning Globus Dysphagia

REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. Nov 2001;108(5 Suppl):S147-334. doi:10.1067/mai.2001.118891

2. Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*. Sep 2009;124(3):428-33. doi:10.1016/j.jaci.2009.06.027

3. Bousquet JJ, Schunemann HJ, Togias A, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. *Clin Transl Allergy*. 2019;9:44. doi:10.1186/s13601-019-0279-2

4. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. Aug 26 2006;368(9537):733-43. doi:10.1016/S0140-6736(06)69283-0

5. Vinke JG, KleinJan A, Severijnen LW, Hoeve LJ, Fokkens WJ. Differences in nasal cellular infiltrates between allergic children and age-matched controls. *Eur Respir J*. Apr 1999;13(4):797-803. doi:10.1034/j.1399-3003.1999.13d17.x

6. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. Nov 2004;24(5):758-64. doi:10.1183/09031936.04.00013904

7. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy*. Mar 2005;60(3):350-3. doi:10.1111/j.1398-9995.2005.00751.x

8. Ciprandi G, Buscaglia S, Pesce G, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. *J Allergy Clin Immunol*. Dec 1995;96(6 Pt 1):971-9. doi:10.1016/s0091-6749(95)70235-0

9. Platts-Mills TA, Hayden ML, Chapman MD, Wilkins SR. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. *J Allergy Clin Immunol*. May 1987;79(5):781-91. doi:10.1016/0091-6749(87)90211-9

10. Connell JT. Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. *J Allergy*. Jan 1969;43(1):33-44. doi:10.1016/0021-8707(69)90018-5

11. Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. *J Allergy Clin Immunol*. Oct 1989;84(4 Pt 1):492-501. doi:10.1016/0091-6749(89)90362-x

12. Juliusson S, Bende M. Priming effect of a birch pollen season studied with laser Doppler flowmetry in patients with allergic rhinitis. *Clin Allergy*. Nov 1988;18(6):615-8. doi:10.1111/j.1365-2222.1988.tb02913.x

13. Naito K, Ishihara M, Senoh Y, Takeda N, Yokoyama N, Iwata S. Seasonal variations of nasal resistance in allergic rhinitis and environmental pollen counts. II: Efficacy of preseasonal therapy. *Auris Nasus Larynx*. 1993;20(1):31-8. doi:10.1016/s0385-8146(12)80208-2

14. Koh YY, Lim HS, Min KU, Min YG. Airways of allergic rhinitics are 'primed' to repeated allergen inhalation challenge. *Clin Exp Allergy*. Apr 1994;24(4):337-46. doi:10.1111/j.1365-2222.1994.tb00244.x

15. Assing K, Bodtger U, Poulsen LK, Malling HJ. Grass pollen symptoms interfere with the recollection of birch pollen symptoms - a prospective study of suspected, asymptomatic skin sensitization. *Allergy*. Apr 2007;62(4):373-7. doi:10.1111/j.1398-9995.2006.01280.x

16. Knani J, Campbell A, Enander I, Peterson CG, Michel FB, Bousquet J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. *J Allergy Clin Immunol*. Dec 1992;90(6 Pt 1):880-9. doi:10.1016/0091-6749(92)90460-j

17. Ricca V, Landi M, Ferrero P, et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol*. Jan 2000;105(1 Pt 1):54-7. doi:10.1016/s0091-6749(00)90177-5

18. Riediker M, Monn C, Koller T, Stahel WA, Wuthrich B. Air pollutants enhance rhinoconjunctivitis symptoms in pollen-allergic individuals. *Ann Allergy Asthma Immunol*. Oct 2001;87(4):311-8. doi:10.1016/S1081-1206(10)62246-6

19. Bousquet J, Annesi-Maesano I, Carat F, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy*. Jun 2005;35(6):728-32. doi:10.1111/j.1365-2222.2005.02274.x

20. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. Aug 2008;122(2 Suppl):S1-84. doi:10.1016/j.jaci.2008.06.003

21. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy*. Jun 2006;61(6):705-11. doi:10.1111/j.1398-9995.2006.01057.x

22. Demoly P, Allaert FA, Lecasble M, Bousquet J, Pragma. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy*. Jul 2003;58(7):672-5. doi:10.1034/j.1398-9995.2003.t01-1-00202.x

23. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy*. Jun 2006;61(6):693-8. doi:10.1111/j.1398-9995.2006.01054.x

24. Todo-Bom A, Loureiro C, Almeida MM, et al. Epidemiology of rhinitis in Portugal: evaluation of the intermittent and the persistent types. *Allergy*. Sep 2007;62(9):1038-43. doi:10.1111/j.1398-9995.2007.01448.x

25. Custovic A, Henderson J, Simpson A. Does understanding endotypes translate to better asthma management options for all? *J Allergy Clin Immunol*. Jul 2019;144(1):25-33. doi:10.1016/j.jaci.2019.05.016

26. Akar-Ghibril N, Casale T, Custovic A, Phipatanakul W. Allergic Endotypes and Phenotypes of Asthma. *J Allergy Clin Immunol Pract*. Feb 2020;8(2):429-440. doi:10.1016/j.jaip.2019.11.008

27. Saglani S, Wisnivesky JP, Charokopos A, Pascoe CD, Halayko AJ, Custovic A. Update in Asthma 2019. *Am J Respir Crit Care Med*. Jul 15 2020;202(2):184-192. doi:10.1164/rccm.202003-0596UP

28. Thien F, Beggs PJ, Csutoros D, et al. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. *Lancet Planet Health*. Jun 2018;2(6):e255-e263. doi:10.1016/S2542-5196(18)30120-7

29. Thien F. Melbourne epidemic thunderstorm asthma event 2016: Lessons learnt from the perfect storm. *Respirology*. Nov 2018;23(11):976-977. doi:10.1111/resp.13410

30. O'Hehir RE, Varese NP, Deckert K, et al. Epidemic Thunderstorm Asthma Protection with Five-Grass Pollen Tablet Sublingual Immunotherapy: A Clinical Trial. *Am J Respir Crit Care Med*. Jul 1 2018;198(1):126-128. doi:10.1164/rccm.201711-2337LE

31. Custovic A, Custovic D, Kljaic Bukvic B, Fontanella S, Haider S. Atopic phenotypes and their implication in the atopic march. *Expert Rev Clin Immunol*. Sep 2020;16(9):873-881. doi:10.1080/1744666X.2020.1816825

32. Oksel C, Custovic A. Development of allergic sensitization and its relevance to paediatric asthma. *Curr Opin Allergy Clin Immunol*. Apr 2018;18(2):109-116. doi:10.1097/ACI.0000000000000430

33. Shtessel M, Tversky J. Reliability of allergy skin testing. *Ann Allergy Asthma Immunol*. Jan 2018;120(1):80-83. doi:10.1016/j.anai.2017.10.015

34. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol*. Oct 2005;116(4):744-9. doi:10.1016/j.jaci.2005.06.032

35. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. *Allergy*. Apr 2007;62(4):385-93. doi:10.1111/j.1398-9995.2006.01294.x

36. Marinho S, Simpson A, Marsden P, Smith JA, Custovic A. Quantification of atopy, lung function and airway hypersensitivity in adults. *Clin Transl Allergy*. Dec 12 2011;1(1):16. doi:10.1186/2045-7022-1-16

37. Roberts G, Ollert M, Aalberse R, et al. A new framework for the interpretation of IgE sensitization tests. *Allergy*. Nov 2016;71(11):1540-1551. doi:10.1111/all.12939

38. Eguiluz-Gracia I, Testera-Montes A, Gonzalez M, et al. Safety and reproducibility of nasal allergen challenge. *Allergy*. Jun 2019;74(6):1125-1134. doi:10.1111/all.13728

39. Ramchandani R, Linton S, Hossenbaccus L, Ellis AK. Comparing the nasal allergen challenge and environmental exposure unit models of allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2021;127(2):163-164. doi:10.1016/j.anai.2021.04.012

40. Custovic A, Sonntag HJ, Buchan IE, Belgrave D, Simpson A, Prosperi MCF. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol*. Dec 2015;136(6):1645-1652 e8. doi:10.1016/j.jaci.2015.03.041

41. Howard R, Belgrave D, Papastamoulis P, Simpson A, Rattray M, Custovic A. Evolution of IgE responses to multiple allergen components throughout childhood. *J Allergy Clin Immunol*. Oct 2018;142(4):1322-1330. doi:10.1016/j.jaci.2017.11.064

42. Simpson A, Lazic N, Belgrave DC, et al. Patterns of IgE responses to multiple allergen components and clinical symptoms at age 11 years. *J Allergy Clin Immunol*. Nov 2015;136(5):1224-31. doi:10.1016/j.jaci.2015.03.027

43. Prosperi MC, Marinho S, Simpson A, Custovic A, Buchan IE. Predicting phenotypes of asthma and eczema with machine learning. *BMC Med Genomics*. 2014;7 Suppl 1:S7. doi:10.1186/1755-8794-7-S1-S7

44. Prosperi MC, Belgrave D, Buchan I, Simpson A, Custovic A. Challenges in interpreting allergen microarrays in relation to clinical symptoms: a machine learning approach. *Pediatr Allergy Immunol*. Feb 2014;25(1):71-9. doi:10.1111/pai.12139

45. Fontanella S, Frainay C, Murray CS, Simpson A, Custovic A. Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: A cross-sectional analysis within a population-based birth cohort. *PLoS Med*. Nov 2018;15(11):e1002691. doi:10.1371/journal.pmed.1002691

46. Roberts G, Fontanella S, Selby A, et al. Connectivity patterns between multiple allergen specific IgE antibodies and their association with severe asthma. *J Allergy Clin Immunol*. Oct 2020;146(4):821-830. doi:10.1016/j.jaci.2020.02.031

47. Niespodziana K, Borochova K, Pazderova P, et al. Toward personalization of asthma treatment according to trigger factors. *J Allergy Clin Immunol*. Jun 2020;145(6):1529-1534. doi:10.1016/j.jaci.2020.02.001

48. Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. *Clin Exp Allergy*. Mar 2010;40(3):381-4. doi:10.1111/j.1365-2222.2009.03450.x

49. Settipane RA, Kaliner MA. Chapter 14: Nonallergic rhinitis. *Am J Rhinol Allergy*. May-Jun 2013;27 Suppl 1:S48-51. doi:10.2500/ajra.2013.27.3927

50. Agnihotri NT, McGrath KG. Allergic and nonallergic rhinitis. *Allergy Asthma Proc*. Nov 1 2019;40(6):376-379. doi:10.2500/aap.2019.40.4251

51. Walgama ES, Hwang PH. Aspirin-Exacerbated Respiratory Disease. *Otolaryngol Clin North Am*. Feb 2017;50(1):83-94. doi:10.1016/j.otc.2016.08.007

52. Laidlaw TM, Levy JM. NSAID-ERD Syndrome: the New Hope from Prevention, Early Diagnosis, and New Therapeutic Targets. *Curr Allergy Asthma Rep*. Mar 14 2020;20(4):10. doi:10.1007/s11882-020-00905-9

53. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. *Allergy*. Jan 2019;74(1):28-39. doi:10.1111/all.13599

54. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med*. Nov 7 2002;347(19):1493-9. doi:10.1056/NEJMoa013508

55. Barnes PJ. Neurogenic inflammation in the airways. *Respir Physiol*. Mar 2001;125(1-2):145-54. doi:10.1016/s0034-5687(00)00210-3

56. Kaliner MA, Baraniuk JN, Benninger M, et al. Consensus Definition of Nonallergic Rhinopathy, Previously Referred to as Vasomotor Rhinitis, Nonallergic Rhinitis, and/or Idiopathic Rhinitis. *World Allergy Organ J*. Jun 15 2009;2(6):119-20. doi:10.1097/WOX.0b013e3181a8e15a

57. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. *Clin Allergy Immunol*. 2007;19:23-34.

58. Mah GT, Tejani AM, Musini VM. Methyldopa for primary hypertension. *Cochrane Database Syst Rev*. Oct 7 2009;(4):CD003893. doi:10.1002/14651858.CD003893.pub3

59. Boswell-Smith V, Spina D, Page CP. Phosphodiesterase inhibitors. *Br J Pharmacol*. Jan 2006;147 Suppl 1:S252-7. doi:10.1038/sj.bjp.0706495

60. Andersson KE. PDE5 inhibitors - pharmacology and clinical applications 20 years after sildenafil discovery. *Br J Pharmacol*. Jul 2018;175(13):2554-2565. doi:10.1111/bph.14205

61. Kiroglu AF, Bayrakli H, Yuca K, Cankaya H, Kiris M. Nasal obstruction as a common side-effect of sildenafil citrate. *Tohoku J Exp Med*. Mar 2006;208(3):251-4. doi:10.1620/tjem.208.251

62. Motamed M, Sandhu D, Murty GE. Sildenafil and nasal obstruction. *J Otolaryngol*. Aug 2003;32(4):259-61. doi:10.2310/7070.2003.41631

63. Cingi C, Ozdoganoglu T, Songu M. Nasal obstruction as a drug side effect. *Ther Adv Respir Dis*. Jun 2011;5(3):175-82. doi:10.1177/1753465811403348

64. Ahmed WS, Geethakumari AM, Biswas KH. Phosphodiesterase 5 (PDE5): Structure-function regulation and therapeutic applications of inhibitors. *Biomed Pharmacother*. Feb 2021;134:111128. doi:10.1016/j.biopha.2020.111128

65. Togias A. Unique mechanistic features of allergic rhinitis. *J Allergy Clin Immunol*. Jun 2000;105(6 Pt 2):S599-604. doi:10.1067/mai.2000.106885

66. Pinargote P, Guillen D, Guarderas JC. ACE inhibitors: upper respiratory symptoms. *BMJ Case Rep*. Jul 17 2014;2014doi:10.1136/bcr-2014-205462

67. Riccio MM, Proud D. Evidence that enhanced nasal reactivity to bradykinin in patients with symptomatic allergy is mediated by neural reflexes. *J Allergy Clin Immunol*. Jun 1996;97(6):1252-63. doi:10.1016/s0091-6749(96)70193-8

68. Shirasaki H, Kanaizumi E, Himi T. Immunohistochemical localization of the bradykinin B1 and B2 receptors in human nasal mucosa. *Mediators Inflamm*. 2009;2009:102406. doi:10.1155/2009/102406

69. Trimarchi M, Miluzio A, Nicolai P, Morassi ML, Bussi M, Marchisio PC. Massive apoptosis erodes nasal mucosa of cocaine abusers. *Am J Rhinol*. Mar-Apr 2006;20(2):160-4.

70. Tan TH, Stevenson B, Yip D. Docetaxel-induced nasal septal perforation. *Intern Med J*. Jul 2006;36(7):471-2. doi:10.1111/j.1445-5994.2006.01105.x

71. Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. *Ann Allergy Asthma Immunol*. Dec 2007;99(6):473-9; quiz 480-1, 521. doi:10.1016/S1081-1206(10)60373-0

72. Alexander D, Alexander K, Valentino J. Intranasal hydrocodone-acetaminophen abuse induced necrosis of the nasal cavity and pharynx. *Laryngoscope*. Nov 2012;122(11):2378-81. doi:10.1002/lary.23542

73. Wang SH, Wang HW, Wang JY. Effects of cocaine on human nasal mucosa. *Eur Arch Otorhinolaryngol*. 1993;250(4):245-8. doi:10.1007/BF00171534

74. Snyder RD, Snyder LB. Intranasal cocaine abuse in an allergists office. *Ann Allergy*. Jun 1985;54(6):489-92.

75. Hall LJ, Jackson RT. Effects of alpha and beta adrenergic agonists on nasal blood flow. *Ann Otol Rhinol Laryngol*. Dec 1968;77(6):1120-30. doi:10.1177/000348946807700610

76. Walker JS. Rhinitis medicamentosa. *J Allergy*. Mar 1952;23(2):183-6. doi:10.1016/0021-8707(52)90093-2

77. Kim D, Steinhart B. Seizures induced by recreational abuse of bupropion tablets via nasal insufflation. *CJEM*. Mar 2010;12(2):158-61. doi:10.1017/s1481803500012203

78. Sataloff RT, Gullane PJ, Goldstein DP. *Sataloff's comprehensive textbook of otolaryngology, head and neck surgery*. Jaypee Brothers Medical Publishing; 2016.

79. Daws LC, Callaghan PD, Moron JA, et al. Cocaine increases dopamine uptake and cell surface expression of dopamine transporters. *Biochem Biophys Res Commun*. Feb 8 2002;290(5):1545-50. doi:10.1006/bbrc.2002.6384

80. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. *Addiction*. Aug 2011;106(8):1460-73. doi:10.1111/j.1360-0443.2011.03424.x

81. Zhang H, Prisinzano TE, Donovan MD. Permeation and metabolism of cocaine in the nasal mucosa. *Eur J Drug Metab Pharmacokinet*. Dec 2012;37(4):255-62. doi:10.1007/s13318-012-0085-x

82. Lin RJ, Smith LJ. Laryngeal Manifestation of Intranasal Acetaminophen Abuse and Review of Literature. *Ear Nose Throat J*. Apr-May 2019;98(4):192-194. doi:10.1177/0145561319836807

83. Hardison SA, Marcum KK, Lintzenich CR. Severe necrosis of the palate and nasal septum resulting from intranasal abuse of acetaminophen. *Ear Nose Throat J*. Oct-Nov 2015;94(10-11):E40-2.

84. Lin Y, Lu JY, Pinheiro-Neto CD, Jones DM, Gildener-Leapman N. Intranasal Acetaminophen Abuse and Nasal, Pharyngeal, and Laryngotracheal Damage. *Cureus*. Aug 19 2019;11(8):e5432. doi:10.7759/cureus.5432

85. Morrison DA, Wise SK, DelGaudio JM, Chowdhury NI, Levy JM. Intranasal tissue necrosis associated with opioid abuse: Case report and systematic review. *Laryngoscope*. Aug 2018;128(8):1767-1771. doi:10.1002/lary.27069

86. Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. *J Investig Allergol Clin Immunol*. 2006;16(3):148-55.

87. Graf PM. Rhinitis medicamentosa. *Clin Allergy Immunol*. 2007;19:295-304.

88. Min YG, Kim HS, Suh SH, Jeon SY, Son YI, Yoon S. Paranasal sinusitis after long-term use of topical nasal decongestants. *Acta Otolaryngol*. May 1996;116(3):465-71. doi:10.3109/00016489609137874

89. Mortuaire G, de Gabory L, Francois M, et al. Rebound congestion and rhinitis medicamentosa: nasal decongestants in clinical practice. Critical review of the literature by a medical panel. *Eur Ann Otorhinolaryngol Head Neck Dis*. Jun 2013;130(3):137-44. doi:10.1016/j.anorl.2012.09.005

90. Zucker SM, Barton BM, McCoul ED. Management of Rhinitis Medicamentosa: A Systematic Review. *Otolaryngol Head Neck Surg*. Mar 2019;160(3):429-438. doi:10.1177/0194599818807891

91. Graf P, Juto JE. Sustained use of xylometazoline nasal spray shortens the decongestive response and induces rebound swelling. *Rhinology*. Mar 1995;33(1):14-7.

92. Vicks Sinex. Thompson PDR; 2004.

93. Fleece L, Mizes JS, Jolly PA, Baldwin RL. Rhinitis medicamentosa. Conceptualization, incidence, and treatment. *Ala J Med Sci*. Apr 1984;21(2):205-8.

94. Knipping S, Holzhausen HJ, Goetze G, Riederer A, Bloching MB. Rhinitis medicamentosa: electron microscopic changes of human nasal mucosa. *Otolaryngol Head Neck Surg*. Jan 2007;136(1):57-61. doi:10.1016/j.otohns.2006.08.025

95. Marple B, Roland P, Benninger M. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. *Otolaryngol Head Neck Surg*. Jan 2004;130(1):131-41. doi:10.1016/j.otohns.2003.07.005

96. Graf P. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. *Clin Ther*. Oct 1999;21(10):1749-55. doi:10.1016/S0149-2918(99)80053-8

97. Graf P. Rhinitis medicamentosa: a review of causes and treatment. *Treat Respir Med*. 2005;4(1):21-9. doi:10.2165/00151829-200504010-00003

98. Graf P. Benzalkonium chloride as a preservative in nasal solutions: re-examining the data. *Respir Med*. Sep 2001;95(9):728-33. doi:10.1053/rmed.2001.1127

99. Kawabata M, Ohori J, Kurono Y. Effects of benzalkonium chloride on histamine H1 receptor mRNA expression in nasal epithelial cells. *Auris Nasus Larynx*. Dec 2016;43(6):685-8. doi:10.1016/j.anl.2016.02.003

100. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ. An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion. *Am J Rhinol*. Mar-Apr 1997;11(2):109-15. doi:10.2500/105065897782537197

101. Chodirker WB. Rhinitis medicamentosa. *Can Med Assoc J*. Feb 15 1981;124(4):370, 372.

102. May M, West JW. The "stuffy" nose. *Otolaryngol Clin North Am*. Oct 1973;6(3):655-74.

103. Graf P, Hallen H, Juto JE. The pathophysiology and treatment of rhinitis medicamentosa. *Clin Otolaryngol Allied Sci*. Jun 1995;20(3):224-9. doi:10.1111/j.1365-2273.1995.tb01853.x

104. Elwany S, Abdel-Salaam S. Treatment of rhinitis medicamentosa with fluticasone propionate--an experimental study. *Eur Arch Otorhinolaryngol*. Mar 2001;258(3):116-9. doi:10.1007/s004050000309

105. Tas A, Yagiz R, Yalcin O, et al. Use of mometasone furoate aqueous nasal spray in the treatment of rhinitis medicamentosa: an experimental study. *Otolaryngol Head Neck Surg*. Apr 2005;132(4):608-12. doi:10.1016/j.otohns.2005.01.010

106. Stephens AL, Jr., Boggs PB. Intranasal dexamethasone: an adjunct in the treatment of chemical rhinitis. *Ann Allergy*. Nov 1968;26(11):612-3.

107. Elwany SS, Stephanos WM. Rhinitis medicamentosa. An experimental histopathological and histochemical study. *ORL J Otorhinolaryngol Relat Spec*. 1983;45(4):187-94. doi:10.1159/000275642

108. Settipane RA. Other causes of rhinitis: mixed rhinitis, rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis. *Immunol Allergy Clin North Am*. Aug 2011;31(3):457-67. doi:10.1016/j.iac.2011.05.011

109. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol*. Nov 1998;81(5 Pt 2):478-518. doi:10.1016/s1081-1206(10)63155-9

110. Akerlund A, Bende M. Sustained use of oxymetazoline nose drops aggrevates vasomotor rhinitis. *Amer J Rhinol*. 1991;5:157-160.

111. Fowler J, Chin CJ, Massoud E. Rhinitis medicamentosa: a nationwide survey of Canadian otolaryngologists. *J Otolaryngol Head Neck Surg*. Dec 9 2019;48(1):70. doi:10.1186/s40463-019-0392-1

112. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. *Laryngoscope*. Jan 1997;107(1):40-3. doi:10.1097/00005537-199701000-00010

113. Moscato G, Vandenplas O, Van Wijk RG, et al. EAACI position paper on occupational rhinitis. *Respir Res*. Mar 3 2009;10:16. doi:10.1186/1465-9921-10-16

114. Kotz S, Pechtold L, Jorres RA, Nowak D, Chaker AM. Occupational rhinitis. *Allergol Select*. 2021;5:51-56. doi:10.5414/ALX02165E

115. Vandenplas O, Hox V, Bernstein D. Occupational Rhinitis. *J Allergy Clin Immunol Pract*. Nov - Dec 2020;8(10):3311-3321. doi:10.1016/j.jaip.2020.06.047

116. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

117. Tarlo SM, Lemiere C. Occupational asthma. *N Engl J Med*. Feb 13 2014;370(7):640-9. doi:10.1056/NEJMra1301758

118. Ronsmans S, Steelant B, Backaert W, Nemery B, Van Gerven L. Diagnostic approach to occupational rhinitis: the role of nasal provocation tests. *Curr Opin Allergy Clin Immunol*. Apr 2020;20(2):122-130. doi:10.1097/ACI.0000000000000608

119. Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. *Clin Exp Allergy*. Nov 2000;30(11):1519-34. doi:10.1046/j.1365-2222.2000.00946.x

120. Pala G, Pignatti P, Perfetti L, et al. Occupational rhinitis and asthma due to cabreuva wood dust. *Ann Allergy Asthma Immunol*. Mar 2010;104(3):268-9. doi:10.1016/j.anai.2010.01.009

121. Lopata AL, Jeebhay MF. Airborne seafood allergens as a cause of occupational allergy and asthma. *Curr Allergy Asthma Rep*. Jun 2013;13(3):288-97. doi:10.1007/s11882-013-0347-y

122. Siracusa A, De Blay F, Folletti I, et al. Asthma and exposure to cleaning products - a European Academy of Allergy and Clinical Immunology task force consensus statement. *Allergy*. Dec 2013;68(12):1532-45. doi:10.1111/all.12279

123. Siracusa A, Folletti I, Moscato G. Non-IgE-mediated and irritant-induced work-related rhinitis. *Curr Opin Allergy Clin Immunol*. Apr 2013;13(2):159-66. doi:10.1097/ACI.0b013e32835e12e7

124. Folletti I, Zock JP, Moscato G, Siracusa A. Asthma and rhinitis in cleaning workers: a systematic review of epidemiological studies. *J Asthma*. Feb 2014;51(1):18-28. doi:10.3109/02770903.2013.833217

125. Szeszenia-Dabrowska N, Swiatkowska B, Wilczynska U. Occupational diseases among farmers in Poland. *Med Pr*. 2016;67(2):163-71. Choroby zawodowe rolnikow w Polsce. doi:10.13075/mp.5893.00303

126. Rodier F, Gautrin D, Ghezzo H, Malo JL. Incidence of occupational rhinoconjunctivitis and risk factors in animal-health apprentices. *J Allergy Clin Immunol*. Dec 2003;112(6):1105-11. doi:10.1016/j.jaci.2003.08.011

127. Ruoppi P, Koistinen T, Susitaival P, Honkanen J, Soininen H. Frequency of allergic rhinitis to laboratory animals in university employees as confirmed by chamber challenges. *Allergy*. Mar 2004;59(3):295-301. doi:10.1046/j.1398-9995.2003.00204.x

128. Schyllert C, Ronmark E, Andersson M, et al. Occupational exposure to chemicals drives the increased risk of asthma and rhinitis observed for exposure to vapours, gas, dust and fumes: a cross-sectional population-based study. *Occup Environ Med*. Oct 2016;73(10):663-9. doi:10.1136/oemed-2016-103595

129. Krop EJ, Heederik DJ, Lutter R, et al. Associations between pre-employment immunologic and airway mucosal factors and the development of occupational allergy. *J Allergy Clin Immunol*. Mar 2009;123(3):694-700, 700 e1-3. doi:10.1016/j.jaci.2008.12.021

130. Phipatanakul W, Matsui E, Portnoy J, et al. Environmental assessment and exposure reduction of rodents: a practice parameter. *Ann Allergy Asthma Immunol*. Dec 2012;109(6):375-87. doi:10.1016/j.anai.2012.09.019

131. Pignatti P, Pala G, Pisati M, Perfetti L, Banchieri G, Moscato G. Nasal blown secretion evaluation in specific occupational nasal challenges. *Int Arch Occup Environ Health*. Feb 2010;83(2):217-23. doi:10.1007/s00420-009-0459-9

132. Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in daily practice. *Allergy*. Feb 2016;71(2):162-74. doi:10.1111/all.12778

133. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. *J Allergy Clin Immunol*. May 1999;103(5 Pt 1):773-9. doi:10.1016/s0091-6749(99)70419-7

134. Nam YH, Lee SK. Comparison between skin prick test and serum immunoglobulin E by CAP system to inhalant allergens. *Ann Allergy Asthma Immunol*. May 2017;118(5):608-613. doi:10.1016/j.anai.2017.03.005

135. Raulf M, Quirce S, Vandenplas O. Addressing Molecular Diagnosis of Occupational Allergies. *Curr Allergy Asthma Rep*. Feb 14 2018;18(1):6. doi:10.1007/s11882-018-0759-9

136. Amirneni A, Tversky J. High Histamine Control Concentration Leads to False Negative Allergy Skin Testing. *Am J Rhinol Allergy*. Nov 2021;35(6):854-860. doi:10.1177/19458924211008685

137. Tversky JR, Chelladurai Y, McGready J, Hamilton RG. Performance and Pain Tolerability of Current Diagnostic Allergy Skin Prick Test Devices. *J Allergy Clin Immunol Pract*. Nov-Dec 2015;3(6):888-93. doi:10.1016/j.jaip.2015.07.022

138. Tversky J, MacGlashan D. Short-wave infrared camera as a novel solution to allergy skin testing. *Allergy*. Apr 2020;75(4):965-968. doi:10.1111/all.14089

139. Kim YH, Jang TY. Nasal provocation test using allergen extract versus cold dry air provocation test: which and when? *Am J Rhinol Allergy*. Mar-Apr 2013;27(2):113-7. doi:10.2500/ajra.2013.27.3870

140. Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy*. Jul-Aug 2015;29(4):e100-4. doi:10.2500/ajra.2015.29.4214

141. Gomez F, Rondon C, Salas M, Campo P. Local allergic rhinitis: mechanisms, diagnosis and relevance for occupational rhinitis. *Curr Opin Allergy Clin Immunol*. Apr 2015;15(2):111-6. doi:10.1097/ACI.0000000000000150

142. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. Apr 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

143. Moscato G, Pala G, Sastre J. Specific immunotherapy and biological treatments for occupational allergy. *Curr Opin Allergy Clin Immunol*. Dec 2014;14(6):576-81. doi:10.1097/ACI.0000000000000105

144. Moscato G, Rolla G, Siracusa A. Occupational rhinitis: consensus on diagnosis and medicolegal implications. *Curr Opin Otolaryngol Head Neck Surg*. Feb 2011;19(1):36-42. doi:10.1097/MOO.0b013e328341e228

145. Gerth van Wijk R, Patiwael JA, de Jong NW, de Groot H, Burdorf A. Occupational rhinitis in bell pepper greenhouse workers: determinants of leaving work and the effects of subsequent allergen avoidance on health-related quality of life. *Allergy*. Jul 2011;66(7):903-8. doi:10.1111/j.1398-9995.2011.02556.x

146. Foss-Skiftesvik MH, Winther L, Johnsen CR, et al. High occurrence of rhinitis symptoms in hairdressing apprentices. *Int Forum Allergy Rhinol*. Jan 2017;7(1):43-49. doi:10.1002/alr.21834

147. Rouadi PW, Idriss SA, Naclerio RM, et al. Immunopathological features of air pollution and its impact on inflammatory airway diseases (IAD). *World Allergy Organ J*. Oct 2020;13(10):100467. doi:10.1016/j.waojou.2020.100467

148. Moscato G, Pala G, Folletti I, Siracusa A, Quirce S. Occupational rhinitis affects occupational asthma severity. *J Occup Health*. Jun 16 2016;58(3):310-3. doi:10.1539/joh.15-0067-BR

149. Tai CF, Baraniuk JN. Upper airway neurogenic mechanisms. *Curr Opin Allergy Clin Immunol*. Feb 2002;2(1):11-9. doi:10.1097/00130832-200202000-00003

150. Meggs WJ. RADS and RUDS--the toxic induction of asthma and rhinitis. *J Toxicol Clin Toxicol*. 1994;32(5):487-501. doi:10.3109/15563659409011053

151. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest*. Sep 1985;88(3):376-84. doi:10.1378/chest.88.3.376

152. Bello A, Quinn MM, Perry MJ, Milton DK. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. *Environ Health*. Mar 27 2009;8:11. doi:10.1186/1476-069X-8-11

153. Chary A, Hennen J, Klein SG, Serchi T, Gutleb AC, Blomeke B. Respiratory sensitization: toxicological point of view on the available assays. *Arch Toxicol*. Feb 2018;92(2):803-822. doi:10.1007/s00204-017-2088-5

154. Kimber I, Dearman RJ, Basketter DA. Diisocyanates, occupational asthma and IgE antibody: implications for hazard characterization. *J Appl Toxicol*. Oct 2014;34(10):1073-7. doi:10.1002/jat.3041

155. Kimber I, Dearman RJ. Chemical respiratory allergy: role of IgE antibody and relevance of route of exposure. *Toxicology*. Dec 27 2002;181-182:311-5. doi:10.1016/s0300-483x(02)00299-8

156. Wisnewski AV. Developments in laboratory diagnostics for isocyanate asthma. *Curr Opin Allergy Clin Immunol*. Apr 2007;7(2):138-45. doi:10.1097/ACI.0b013e3280895d22

157. Christensen DN, Franks ZG, McCrary HC, Saleh AA, Chang EH. A Systematic Review of the Association between Cigarette Smoke Exposure and Chronic Rhinosinusitis. *Otolaryngol Head Neck Surg*. May 2018;158(5):801-816. doi:10.1177/0194599818757697

158. Eriksson J, Ekerljung L, Sundblad BM, et al. Cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men. *Allergy*. Mar 2013;68(3):347-54. doi:10.1111/all.12095

159. Yao TC, Chang SW, Chang WC, et al. Exposure to tobacco smoke and childhood rhinitis: a population-based study. *Sci Rep*. Feb 16 2017;7:42836. doi:10.1038/srep42836

160. Lee A, Lee SY, Lee KS. The Use of Heated Tobacco Products is Associated with Asthma, Allergic Rhinitis, and Atopic Dermatitis in Korean Adolescents. *Sci Rep*. Nov 27 2019;9(1):17699. doi:10.1038/s41598-019-54102-4

161. Phulka JS, Howlett JW, Hu A. Cannabis related side effects in otolaryngology: a scoping review. *J Otolaryngol Head Neck Surg*. Sep 27 2021;50(1):56. doi:10.1186/s40463-021-00538-6

162. Abramson MJ, Schindler C, Schikowski T, et al. Rhinitis in Swiss adults is associated with asthma and early life factors, but not second hand tobacco smoke or obesity. *Allergol Int*. Apr 2016;65(2):192-198. doi:10.1016/j.alit.2015.11.004

163. Pallasaho P, Kainu A, Juusela M, Meren M, Sovijarvi A. High prevalence of rhinitis symptoms without allergic sensitization in Estonia and Finland. *Eur Clin Respir J*. 2015;2doi:10.3402/ecrj.v2.25401

164. Shargorodsky J, Garcia-Esquinas E, Galan I, Navas-Acien A, Lin SY. Allergic Sensitization, Rhinitis and Tobacco Smoke Exposure in US Adults. *PLoS One*. 2015;10(7):e0131957. doi:10.1371/journal.pone.0131957

165. Hisinger-Molkanen H, Piirila P, Haahtela T, Sovijarvi A, Pallasaho P. Smoking, environmental tobacco smoke and occupational irritants increase the risk of chronic rhinitis. *World Allergy Organ J*. 2018;11(1):6. doi:10.1186/s40413-018-0184-5

166. Gleich GJ, Welsh PW, Yunginger JW, Hyatt RE, Catlett JB. Allergy to tobacco: an occupational hazard. *N Engl J Med*. Mar 13 1980;302(11):617-9. doi:10.1056/NEJM198003133021107

167. Burrows B, Halonen M, Lebowitz MD, Knudson RJ, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. *J Allergy Clin Immunol*. Sep 1982;70(3):199-204. doi:10.1016/0091-6749(82)90042-2

168. Bascom R, Kesavanathan J, Fitzgerald TK, Cheng KH, Swift DL. Sidestream tobacco smoke exposure acutely alters human nasal mucociliary clearance. *Environ Health Perspect*. Nov 1995;103(11):1026-30. doi:10.1289/ehp.951031026

169. Andre E, Campi B, Materazzi S, et al. Cigarette smoke-induced neurogenic inflammation is mediated by alpha,beta-unsaturated aldehydes and the TRPA1 receptor in rodents. *J Clin Invest*. Jul 2008;118(7):2574-82. doi:10.1172/JCI34886

170. Meggs WJ. Neurogenic inflammation and sensitivity to environmental chemicals. *Environ Health Perspect*. Aug 1993;101(3):234-8. doi:10.1289/ehp.93101234

171. Bascom R, Kulle T, Kagey-Sobotka A, Proud D. Upper respiratory tract environmental tobacco smoke sensitivity. *Am Rev Respir Dis*. Jun 1991;143(6):1304-11. doi:10.1164/ajrccm/143.6.1304

172. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. Oct 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

173. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. Feb 20 2020;58(Suppl S29):1-464. doi:10.4193/Rhin20.600

174. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: Establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg*. Dec 2004;131(6 Suppl):S1-62. doi:10.1016/j.otohns.2004.09.067

175. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl*. Mar 2012;23:3 p preceding table of contents, 1-298.

176. Aring AM, Chan MM. Current Concepts in Adult Acute Rhinosinusitis. *Am Fam Physician*. Jul 15 2016;94(2):97-105.

177. Canonica GW, Ciprandi G, Pesce GP, Buscaglia S, Paolieri F, Bagnasco M. ICAM-1 on epithelial cells in allergic subjects: a hallmark of allergic inflammation. *Int Arch Allergy Immunol*. May-Jun 1995;107(1-3):99-102. doi:10.1159/000236943

178. Ciebiada M, Gorska-Ciebiada M, Gorski P. sICAM-1 and TNF-alpha in asthma and rhinitis: relationship with the presence of atopy. *J Asthma*. Sep 2011;48(7):660-6. doi:10.3109/02770903.2011.604886

179. Tantilipikorn P. The relationship between allergic rhinitis and viral infections. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2014;22(3):249-52. doi:10.1097/MOO.0000000000000049

180. Gorska-Ciebiada M, Ciebiada M, Gorska MM, Gorski P, Grzelewska-Rzymowska I. Intercellular adhesion molecule 1 and tumor necrosis factor alpha in asthma and persistent allergic rhinitis: relationship with disease severity. *Ann Allergy Asthma Immunol*. Jul 2006;97(1):66-72. doi:10.1016/S1081-1206(10)61372-5

181. Shiota Y, Wilson JG, Marukawa M, Ono T, Kaji M. Soluble intercellular adhesion molecule 1 (ICAM-1) antigen in sera of bronchial asthmatics. *Chest*. Jan 1996;109(1):94-9. doi:10.1378/chest.109.1.94

182. Gosset P, Tillie-Leblond I, Janin A, et al. Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. *Int Arch Allergy Immunol*. Jan 1995;106(1):69-77. doi:10.1159/000236892

183. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev*. Jun 4 2013;(6):CD000247. doi:10.1002/14651858.CD000247.pub3

184. Kaper NM, Breukel L, Venekamp RP, Grolman W, van der Heijden GJ. Absence of evidence for enhanced benefit of antibiotic therapy on recurrent acute rhinosinusitis episodes: a systematic review of the evidence base. *Otolaryngol Head Neck Surg*. Nov 2013;149(5):664-7. doi:10.1177/0194599813505841

185. Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AI. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev*. Oct 17 2012;10:CD006089. doi:10.1002/14651858.CD006089.pub4

186. van den Broek MF, Gudden C, Kluijfhout WP, et al. No evidence for distinguishing bacterial from viral acute rhinosinusitis using symptom duration and purulent rhinorrhea: a systematic review of the evidence base. *Otolaryngol Head Neck Surg*. Apr 2014;150(4):533-7. doi:10.1177/0194599814522595

187. Stjarne P, Odeback P, Stallberg B, Lundberg J, Olsson P. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. *Prim Care Respir J*. Jun 2012;21(2):174-9; quiz 10p following 179. doi:10.4104/pcrj.2012.00011

188. Jaume F, Quinto L, Alobid I, Mullol J. Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: a population-based study (the PROSINUS study). *BMJ Open*. Jan 31 2018;8(1):e018788. doi:10.1136/bmjopen-2017-018788

189. Seresirikachorn K, Snidvongs K, Chitsuthipakorn W, et al. EPOS2012 has better specificity compared to IDSA2012 for diagnosing acute bacterial rhinosinusitis. *Rhinology*. Sep 1 2018;56(3):241-244. doi:10.4193/Rhin17.261

190. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. Apr 2012;54(8):e72-e112. doi:10.1093/cid/cir1043

191. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. Apr 2015;152(2 Suppl):S1-S39. doi:10.1177/0194599815572097

192. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med*. Mar 1996;28(3):183-8.

193. Ellegard EK. Pregnancy rhinitis. *Immunol Allergy Clin North Am*. Feb 2006;26(1):119-35, vii. doi:10.1016/j.iac.2005.10.007

194. Ellegard EK. Clinical and pathogenetic characteristics of pregnancy rhinitis. *Clin Rev Allergy Immunol*. Jun 2004;26(3):149-59. doi:10.1385/CRIAI:26:3:149

195. Ellegard E, Karlsson G. Nasal congestion during pregnancy. *Clin Otolaryngol Allied Sci*. Aug 1999;24(4):307-11. doi:10.1046/j.1365-2273.1999.00264.x

196. Baudoin T, Simunjak T, Bacan N, Jelavic B, Kuna K, Kosec A. Redefining Pregnancy-Induced Rhinitis. *Am J Rhinol Allergy*. May 2021;35(3):315-322. doi:10.1177/1945892420957490

197. Ellegard E, Hellgren M, Toren K, Karlsson G. The incidence of pregnancy rhinitis. *Gynecol Obstet Invest*. 2000;49(2):98-101. doi:10.1159/000010223

198. Philpott CM, Conboy P, Al-Azzawi F, Murty G. Nasal physiological changes during pregnancy. *Clin Otolaryngol Allied Sci*. Aug 2004;29(4):343-51. doi:10.1111/j.1365-2273.2004.00815.x

199. Toppozada H, Michaels L, Toppozada M, El-Ghazzawi I, Talaat M, Elwany S. The human respiratory nasal mucosa in pregnancy. An electron microscopic and histochemical study. *J Laryngol Otol*. Jul 1982;96(7):613-26. doi:10.1017/s0022215100092902

200. Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. *Ann Allergy*. Mar 1993;70(3):225-30.

201. Kumar R, Hayhurst KL, Robson AK. Ear, nose, and throat manifestations during pregnancy. *Otolaryngol Head Neck Surg*. Aug 2011;145(2):188-98. doi:10.1177/0194599811407572

202. Orban N, Maughan E, Bleach N. Pregnancy-induced rhinitis. *Rhinology*. Jun 2013;51(2):111-9. doi:10.4193/Rhino12.045

203. Hamano N, Terada N, Maesako K, et al. Expression of histamine receptors in nasal epithelial cells and endothelial cells--the effects of sex hormones. *Int Arch Allergy Immunol*. Mar 1998;115(3):220-7. doi:10.1159/000023904

204. Ellegard E, Oscarsson J, Bougoussa M, et al. Serum level of placental growth hormone is raised in pregnancy rhinitis. *Arch Otolaryngol Head Neck Surg*. Apr 1998;124(4):439-43. doi:10.1001/archotol.124.4.439

205. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Chest*. Jan 2000;117(1):137-41. doi:10.1378/chest.117.1.137

206. Favilli A, Laurenti E, Stagni GM, Tassi L, Ricci G, Gerli S. Effects of Sodium Hyaluronate on Symptoms and Quality of Life in Women Affected by Pregnancy Rhinitis: A Pilot Study. *Gynecol Obstet Invest*. 2019;84(2):159-165. doi:10.1159/000493137

207. Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. Nov 2017;72(11):1657-1665. doi:10.1111/all.13200

208. Ellegard EK, Karlsson NG, Ellegard LH. Rhinitis in the menstrual cycle, pregnancy, and some endocrine disorders. *Clin Allergy Immunol*. 2007;19:305-21.

209. Navarrete-Palacios E, Hudson R, Reyes-Guerrero G, Guevara-Guzman R. Correlation between cytological characteristics of the nasal epithelium and the menstrual cycle. *Arch Otolaryngol Head Neck Surg*. Apr 2003;129(4):460-3. doi:10.1001/archotol.129.4.460

210. Proetz AW. Further observations of the effects of thyroid insufficiency on the nasal mucosa. *Laryngoscope*. Jul 1950;60(7):627-33. doi:10.1288/00005537-195007000-00004

211. Kulekci Ozturk S, Sakci E, Kavvasoglu C. Rhinitis in patients with acquired hypothyroidism. *Eur Arch Otorhinolaryngol*. Jan 2021;278(1):87-92. doi:10.1007/s00405-020-06254-7

212. Skinner DW, Richards SH. Acromegaly--the mucosal changes within the nose and paranasal sinuses. *J Laryngol Otol*. Dec 1988;102(12):1107-10. doi:10.1017/s0022215100107455

213. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. Nov 2014;134(5):1016-25 e43. doi:10.1016/j.jaci.2014.05.013

214. Jovancevic L, Georgalas C, Savovic S, Janjevic D. Gustatory rhinitis. *Rhinology*. Mar 2 2010;48(1):7-10. doi:10.4193/Rhin07.153

215. Waibel KH, Chang C. Prevalence and food avoidance behaviors for gustatory rhinitis. *Ann Allergy Asthma Immunol*. Mar 2008;100(3):200-5. doi:10.1016/S1081-1206(10)60443-7

216. Raphael G, Raphael MH, Kaliner M. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. *J Allergy Clin Immunol*. Jan 1989;83(1):110-5. doi:10.1016/0091-6749(89)90484-3

217. Georgalas C, Jovancevic L. Gustatory rhinitis. *Curr Opin Otolaryngol Head Neck Surg*. Feb 2012;20(1):9-14. doi:10.1097/MOO.0b013e32834dfb52

218. Seki N, Shirasaki H, Kikuchi M, Sakamoto T, Watanabe N, Himi T. Expression and localization of TRPV1 in human nasal mucosa. *Rhinology*. Jun 2006;44(2):128-34.

219. Marshak T, Yun WK, Hazout C, Sacks R, Harvey RJ. A systematic review of the evidence base for vidian neurectomy in managing rhinitis. *J Laryngol Otol*. Jul 2016;130 Suppl 4:S7-S28. doi:10.1017/S0022215116008008

220. Nihlen U, Greiff LJ, Nyberg P, Persson CG, Andersson M. Alcohol-induced upper airway symptoms: prevalence and co-morbidity. *Respir Med*. Jun 2005;99(6):762-9. doi:10.1016/j.rmed.2004.11.010

221. Glicksman JT, Parasher AK, Doghramji L, et al. Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. Oct 2018;8(10):1093-1097. doi:10.1002/alr.22168

222. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. Mar-Apr 2014;2(2):208-13. doi:10.1016/j.jaip.2013.12.003

223. De Schryver E, Derycke L, Campo P, et al. Alcohol hyper-responsiveness in chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy*. Feb 2017;47(2):245-253. doi:10.1111/cea.12836

224. Lomholt FK, Nielsen SF, Nordestgaard BG. High alcohol consumption causes high IgE levels but not high risk of allergic disease. *J Allergy Clin Immunol*. Nov 2016;138(5):1404-1413 e13. doi:10.1016/j.jaci.2016.05.022

225. Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome. *Curr Allergy Asthma Rep*. May 2006;6(3):215-20. doi:10.1007/s11882-006-0037-0

226. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome). Clinical and immunologic presentation. *J Allergy Clin Immunol*. Apr 1981;67(4):253-62. doi:10.1016/0091-6749(81)90019-1

227. Simola M, Malmberg H. Sense of smell in allergic and nonallergic rhinitis. *Allergy*. Feb 1998;53(2):190-4. doi:10.1111/j.1398-9995.1998.tb03869.x

228. Moneret-Vautrin DA, Jankowski R, Bene MC, et al. NARES: a model of inflammation caused by activated eosinophils? *Rhinology*. Sep 1992;30(3):161-8.

229. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy*. Jun 2001;31(6):864-72. doi:10.1046/j.1365-2222.2001.01106.x

230. Berger G, Goldberg A, Ophir D. The inferior turbinate mast cell population of patients with perennial allergic and nonallergic rhinitis. *Am J Rhinol*. Jan-Feb 1997;11(1):63-6. doi:10.2500/105065897781446775

231. De Corso E, Baroni S, Battista M, et al. Nasal fluid release of eotaxin-3 and eotaxin-2 in persistent sinonasal eosinophilic inflammation. *Int Forum Allergy Rhinol*. Aug 2014;4(8):617-24. doi:10.1002/alr.21348

232. De Corso E, Baroni S, Lucidi D, et al. Nasal lavage levels of granulocyte-macrophage colony-stimulating factor and chronic nasal hypereosinophilia. *Int Forum Allergy Rhinol*. Jun 2015;5(6):557-62. doi:10.1002/alr.21519

233. Kramer MF, Burow G, Pfrogner E, Rasp G. In vitro diagnosis of chronic nasal inflammation. *Clin Exp Allergy*. Jul 2004;34(7):1086-92. doi:10.1111/j.1365-2222.2004.01989.x

234. Groger M, Klemens C, Wendt S, et al. Mediators and cytokines in persistent allergic rhinitis and nonallergic rhinitis with eosinophilia syndrome. *Int Arch Allergy Immunol*. 2012;159(2):171-8. doi:10.1159/000336169

235. Marcella R, Croce A, Moretti A, Barbacane RC, Di Giocchino M, Conti P. Transcription and translation of the chemokines RANTES and MCP-1 in nasal polyps and mucosa in allergic and non-allergic rhinopathies. *Immunol Lett*. Dec 15 2003;90(2-3):71-5. doi:10.1016/s0165-2478(03)00163-9

236. Peric A, Sotirovic J, Spadijer-Mirkovic C, Matkovic-Jozin S, Peric AV, Vojvodic D. Nonselective chemokine levels in nasal secretions of patients with perennial nonallergic and allergic rhinitis. *Int Forum Allergy Rhinol*. Apr 2016;6(4):392-7. doi:10.1002/alr.21684

237. Becker S, Rasp J, Eder K, Berghaus A, Kramer MF, Groger M. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Otorhinolaryngol*. Jun 2016;273(6):1469-75. doi:10.1007/s00405-015-3769-4

238. Eckrich J, Hinkel J, Fischl A, et al. Nasal IgE in subjects with allergic and non-allergic rhinitis. *World Allergy Organ J*. Jun 2020;13(6):100129. doi:10.1016/j.waojou.2020.100129

239. Zhang M, Yan B, Wang Y, Wang C, Zhang L. Charcot-Leyden Crystal Protein in Nasal Secretions of Patients with Nonallergic Rhinitis with Eosinophilia Syndrome. *Int Arch Allergy Immunol*. 2020;181(11):888-896. doi:10.1159/000509252

240. Meng Y, Yan B, Wang Y, Wu D, Zhang L, Wang C. Diagnosis and management of nonallergic rhinitis with eosinophilia syndrome using cystatin SN together with symptoms. *World Allergy Organ J*. Jul 2020;13(7):100134. doi:10.1016/j.waojou.2020.100134

241. Numao T, Agrawal DK. Neuropeptides modulate human eosinophil chemotaxis. *J Immunol*. Nov 15 1992;149(10):3309-15.

242. Kramer MF, de la Chaux R, Fintelmann R, Rasp G. NARES: a risk factor for obstructive sleep apnea? *Am J Otolaryngol*. May-Jun 2004;25(3):173-7. doi:10.1016/j.amjoto.2003.12.004

243. Wang Q, Ji J, Xie Y, et al. Lower airway inflammation and hyperresponsiveness in non-asthmatic patients with non-allergic rhinitis. *J Thorac Dis*. Oct 2015;7(10):1756-64. doi:10.3978/j.issn.2072-1439.2015.10.26

244. Settipane RA, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol*. May 2001;86(5):494-507; quiz 507-8. doi:10.1016/S1081-1206(10)62896-7

245. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med*. Jun 11 1987;316(24):1506-10. doi:10.1056/NEJM198706113162403

246. Webb DR, Meltzer EO, Finn AF, Jr., et al. Intranasal fluticasone propionate is effective for perennial nonallergic rhinitis with or without eosinophilia. *Ann Allergy Asthma Immunol*. Apr 2002;88(4):385-90. doi:10.1016/S1081-1206(10)62369-1

247. Bachert C, van Cauwenberge P, Khaltaev N, World Health O. Allergic rhinitis and its impact on asthma. In collaboration with the World Health Organization. Executive summary of the workshop report. 7-10 December 1999, Geneva, Switzerland. *Allergy*. Sep 2002;57(9):841-55. doi:10.1034/j.1398-9995.2002.23625.x

248. Banov CH, Lieberman P, Vasomotor Rhinitis Study G. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol*. Jan 2001;86(1):28-35. doi:10.1016/S1081-1206(10)62352-6

249. De Corso E, Anzivino R, Galli J, et al. Antileukotrienes improve naso-ocular symptoms and biomarkers in patients with NARES and asthma. *Laryngoscope*. Mar 2019;129(3):551-557. doi:10.1002/lary.27576

250. Settipane RA. Epidemiology of vasomotor rhinitis. *World Allergy Organ J*. Jun 15 2009;2(6):115-8. doi:10.1097/WOX.0b013e3181ac91ae

251. Mullarkey MF, Hill JS, Webb DR. Allergic and nonallergic rhinitis: their characterization with attention to the meaning of nasal eosinophilia. *J Allergy Clin Immunol*. Feb 1980;65(2):122-6. doi:10.1016/0091-6749(80)90196-7

252. Enberg RN. Perennial nonallergic rhinitis: a retrospective review. *Ann Allergy*. Dec 1989;63(6 Pt 1):513-6.

253. Nozad CH, Michael LM, Betty Lew D, Michael CF. Non-allergic rhinitis: a case report and review. *Clin Mol Allergy*. Feb 3 2010;8:1. doi:10.1186/1476-7961-8-1

254. Pattanaik D, Lieberman P. Vasomotor rhinitis. *Curr Allergy Asthma Rep*. Mar 2010;10(2):84-91. doi:10.1007/s11882-010-0089-z

255. Campo P, Rondon C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in non-allergic rhinitis. *Clin Exp Allergy*. May 2015;45(5):872-881. doi:10.1111/cea.12476

256. James LK, Durham SR. Rhinitis with negative skin tests and absent serum allergen-specific IgE: more evidence for local IgE? *J Allergy Clin Immunol*. Nov 2009;124(5):1012-3. doi:10.1016/j.jaci.2009.09.029

257. Hamizan AW, Rimmer J, Alvarado R, et al. Positive allergen reaction in allergic and nonallergic rhinitis: a systematic review. *Int Forum Allergy Rhinol*. Sep 2017;7(9):868-877. doi:10.1002/alr.21988

258. Eifan AO, Durham SR. Pathogenesis of rhinitis. *Clin Exp Allergy*. Sep 2016;46(9):1139-51. doi:10.1111/cea.12780

259. Bernstein JA, Hastings L, Boespflug EL, Allendorfer JB, Lamy M, Eliassen JC. Alteration of brain activation patterns in nonallergic rhinitis patients using functional magnetic resonance imaging before and after treatment with intranasal azelastine. *Ann Allergy Asthma Immunol*. Jun 2011;106(6):527-32. doi:10.1016/j.anai.2011.02.014

260. Segboer C, Gevorgyan A, Avdeeva K, et al. Intranasal corticosteroids for non-allergic rhinitis. *Cochrane Database Syst Rev*. Nov 2 2019;2019(11)doi:10.1002/14651858.CD010592.pub2

261. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin*. Apr 2005;21(4):611-8. doi:10.1185/030079905X41408

262. Grossman J, Banov C, Boggs P, et al. Use of ipratropium bromide nasal spray in chronic treatment of nonallergic perennial rhinitis, alone and in combination with other perennial rhinitis medications. *J Allergy Clin Immunol*. May 1995;95(5 Pt 2):1123-7. doi:10.1016/s0091-6749(95)70216-4

263. Yan CH, Hwang PH. Surgical Management of Nonallergic Rhinitis. *Otolaryngol Clin North Am*. Oct 2018;51(5):945-955. doi:10.1016/j.otc.2018.05.010

264. Ikeda K, Yokoi H, Saito T, Kawano K, Yao T, Furukawa M. Effect of resection of the posterior nasal nerve on functional and morphological changes in the inferior turbinate mucosa. *Acta Otolaryngol*. 2008;128(12):1337-41. doi:10.1080/00016480801935525

265. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol*. Oct 2017;7(10):952-956. doi:10.1002/alr.21991

266. Kompelli AR, Janz TA, Rowan NR, Nguyen SA, Soler ZM. Cryotherapy for the Treatment of Chronic Rhinitis: A Qualitative Systematic Review. *Am J Rhinol Allergy*. Nov 2018;32(6):491-501. doi:10.1177/1945892418800879

267. Sahin-Yilmaz AA, Corey JP. Rhinitis in the elderly. *Clin Allergy Immunol*. 2007;19:209-19.

268. Edelstein DR. Aging of the normal nose in adults. *Laryngoscope*. Sep 1996;106(9 Pt 2):1-25. doi:10.1097/00005537-199609001-00001

269. Lindemann J, Sannwald D, Wiesmiller K. Age-related changes in intranasal air conditioning in the elderly. *Laryngoscope*. Aug 2008;118(8):1472-5. doi:10.1097/MLG.0b013e3181758174

270. Pinto JM, Jeswani S. Rhinitis in the geriatric population. *Allergy Asthma Clin Immunol*. May 13 2010;6(1):10. doi:10.1186/1710-1492-6-10

271. Rodriguez K, Rubinstein E, Ferguson BJ. Clear anterior rhinorrhea in the population. *Int Forum Allergy Rhinol*. Nov 2015;5(11):1063-7. doi:10.1002/alr.21583

272. Parashar R, Amir M, Pakhare A, Rathi P, Chaudhary L. Age Related Changes in Autonomic Functions. *J Clin Diagn Res*. Mar 2016;10(3):CC11-5. doi:10.7860/JCDR/2016/16889.7497

273. Hotta H, Uchida S. Aging of the autonomic nervous system and possible improvements in autonomic activity using somatic afferent stimulation. *Geriatr Gerontol Int*. Jul 2010;10 Suppl 1:S127-36. doi:10.1111/j.1447-0594.2010.00592.x

274. Lal D, Corey JP. Vasomotor rhinitis update. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2004;12(3):243-7. doi:10.1097/01.moo.0000122310.13359.79

275. Kimmelman CP, Ali GH. Vasomotor rhinitis. *Otolaryngol Clin North Am*. Feb 1986;19(1):65-71.

276. Georgitis JW. Prevalence and differential diagnosis of chronic rhinitis. *Curr Allergy Asthma Rep*. May 2001;1(3):202-6. doi:10.1007/s11882-001-0006-6

277. Baptist AP, Nyenhuis S. Rhinitis in the Elderly. *Immunol Allergy Clin North Am*. May 2016;36(2):343-57. doi:10.1016/j.iac.2015.12.010

278. Janzen VD. Rhinological disorders in the elderly. *J Otolaryngol*. Aug 1986;15(4):228-30.

279. Ciftci Z, Catli T, Hanci D, Cingi C, Erdogan G. Rhinorrhoea in the elderly. *Eur Arch Otorhinolaryngol*. Oct 2015;272(10):2587-92. doi:10.1007/s00405-014-3182-4

280. Bozek A. Pharmacological Management of Allergic Rhinitis in the Elderly. *Drugs Aging*. Jan 2017;34(1):21-28. doi:10.1007/s40266-016-0425-7

281. Ho JC, Chan KN, Hu WH, et al. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. *Am J Respir Crit Care Med*. Mar 2001;163(4):983-8. doi:10.1164/ajrccm.163.4.9909121

282. Mirza N, Kroger H, Doty RL. Influence of age on the 'nasal cycle'. *Laryngoscope*. Jan 1997;107(1):62-6. doi:10.1097/00005537-199701000-00014

283. Slavin RG. Treating rhinitis in the older population: special considerations. *Allergy Asthma Clin Immunol*. Dec 1 2009;5(1):9. doi:10.1186/1710-1492-5-9

284. Schrodter S, Biermann E, Halata Z. Histological evaluation of age-related changes in human respiratory mucosa of the middle turbinate. *Anat Embryol (Berl)*. Jul 2003;207(1):19-27. doi:10.1007/s00429-003-0326-5

285. Milgrom H, Huang H. Allergic disorders at a venerable age: a mini-review. *Gerontology*. 2014;60(2):99-107. doi:10.1159/000355307

286. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. Jan 29 2015;372(5):456-63. doi:10.1056/NEJMcp1412282

287. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis executive summary. *Otolaryngol Head Neck Surg*. Feb 2015;152(2):197-206. doi:10.1177/0194599814562166

288. Slavin RG. Special considerations in treatment of allergic rhinitis in the elderly: role of intranasal corticosteroids. *Allergy Asthma Proc*. May-Jun 2010;31(3):179-84. doi:10.2500/aap.2010.31.3342

289. Bozek A, Cudak A, Walter Canonica G. Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis. *Allergy Asthma Proc*. Jul 1 2020;41(4):271-277. doi:10.2500/aap.2020.41.200035

290. Jain T, Sanju Kumar H, Guerrieri M, Ralli M, Di Mauro R. Primary atrophic rhinitis: ozeana and other infective forms. In: Di Girolamo S, ed. *Atrophic Rhinitis*. Springer, Cham; 2020:3-12.

291. Wright J. Atrophic rhinitis in its historical, etiological and histological aspects. *Laryngoscope*. 1913;23:641-666.

292. Ruskin S. A differential diagnosis and therapy of atrophic rhinitis and ozena. *Arch Otolaryngol*. 1932;15:222-257.

293. Bunnag C, Jareoncharsri P, Tansuriyawong P, Bhothisuwan W, Chantarakul N. Characteristics of atrophic rhinitis in Thai patients at the Siriraj Hospital. *Rhinology*. Sep 1999;37(3):125-30.

294. Moore EJ, Kern EB. Atrophic rhinitis: a review of 242 cases. *Am J Rhinol*. Nov-Dec 2001;15(6):355-61.

295. Bist SS, Bisht M, Purohit JP, Saxena R. Study of histopathological changes in primary atrophic rhinitis. *ISRN Otolaryngol*. 2011;2011:269479. doi:10.5402/2011/269479

296. Bist SS, Bisht M, Purohit JP. Primary atrophic rhinitis: a clinical profile, microbiological and radiological study. *ISRN Otolaryngol*. 2012;2012:404075. doi:10.5402/2012/404075

297. Sinha SN, Sardana DS, Rajvanshi VS. A nine years' review of 273 cases of atrophic rhinitis and its management. *J Laryngol Otol*. Jul 1977;91(7):591-600. doi:10.1017/s0022215100084097

298. Mishra A, Kawatra R, Gola M. Interventions for atrophic rhinitis. *Cochrane Database Syst Rev*. Feb 15 2012;(2):CD008280. doi:10.1002/14651858.CD008280.pub2

299. Gigant L, Zoli A, Guiacomini PG, Zoli A. A secondary atrophis rhinitis: autoimmune and granulomatous forms. In: Di Girolamo S, ed. *Atrophic Rhinitis*. Springer Cham; 2020:13-30.

300. Ly TH, deShazo RD, Olivier J, Stringer SP, Daley W, Stodard CM. Diagnostic criteria for atrophic rhinosinusitis. *Am J Med*. Aug 2009;122(8):747-53. doi:10.1016/j.amjmed.2008.12.025

301. Taylor M, Young A. Histopathological and histochemical studies on atrophic rhinitis. *J Laryngol Otol*. Jun 1961;75:574-90. doi:10.1017/s0022215100058138

302. Zohar Y, Talmi YP, Strauss M, Finkelstein Y, Shvilli Y. Ozena revisited. *J Otolaryngol*. Oct 1990;19(5):345-9.

303. Chand MS, MacArthur CJ. Primary atrophic rhinitis: a summary of four cases and review of the literature. *Otolaryngol Head Neck Surg*. Apr 1997;116(4):554-8. doi:10.1016/s0194-5998(97)70311-5

304. Sibert JR, Barton RP. Dominant inheritance in a family with primary atrophic rhinitis. *J Med Genet*. Feb 1980;17(1):39-40. doi:10.1136/jmg.17.1.39

305. Scheithauer MO. Surgery of the turbinates and "empty nose" syndrome. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2010;9:Doc03. doi:10.3205/cto000067

306. Coste A, Dessi P, Serrano E. Empty nose syndrome. *Eur Ann Otorhinolaryngol Head Neck Dis*. Apr 2012;129(2):93-7. doi:10.1016/j.anorl.2012.02.001

307. Chhabra N, Houser SM. The diagnosis and management of empty nose syndrome. *Otolaryngol Clin North Am*. Apr 2009;42(2):311-30, ix. doi:10.1016/j.otc.2009.02.001

308. Houser SM. Surgical treatment for empty nose syndrome. *Arch Otolaryngol Head Neck Surg*. Sep 2007;133(9):858-63. doi:10.1001/archotol.133.9.858

309. Kuan EC, Suh JD, Wang MB. Empty nose syndrome. *Curr Allergy Asthma Rep*. Jan 2015;15(1):493. doi:10.1007/s11882-014-0493-x

310. Velasquez N, Thamboo A, Habib AR, Huang Z, Nayak JV. The Empty Nose Syndrome 6-Item Questionnaire (ENS6Q): a validated 6-item questionnaire as a diagnostic aid for empty nose syndrome patients. *Int Forum Allergy Rhinol*. Jan 2017;7(1):64-71. doi:10.1002/alr.21842

311. Payne SC. Empty nose syndrome: what are we really talking about? *Otolaryngol Clin North Am*. Apr 2009;42(2):331-7, ix-x. doi:10.1016/j.otc.2009.02.002

312. Chang MT, Nayak JV. In Response to Inferior Meatus Augmentation Procedure (IMAP) for Treatment of Empty Nose Syndrome. *Laryngoscope*. Jun 2022;132(6):E22. doi:10.1002/lary.30119

313. Thamboo A, Velasquez N, Ayoub N, Nayak JV. Distinguishing computed tomography findings in patients with empty nose syndrome. *Int Forum Allergy Rhinol*. Oct 2016;6(10):1075-1082. doi:10.1002/alr.21774

314. Malik J, Li C, Maza G, et al. Computational fluid dynamic analysis of aggressive turbinate reductions: is it a culprit of empty nose syndrome? *Int Forum Allergy Rhinol*. Aug 2019;9(8):891-899. doi:10.1002/alr.22350

315. Bautista DM, Siemens J, Glazer JM, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature*. Jul 12 2007;448(7150):204-8. doi:10.1038/nature05910

316. Zhao K, Blacker K, Luo Y, Bryant B, Jiang J. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. *PLoS One*. 2011;6(10):e24618. doi:10.1371/journal.pone.0024618

317. Zhao K, Jiang J, Blacker K, et al. Regional peak mucosal cooling predicts the perception of nasal patency. *Laryngoscope*. Mar 2014;124(3):589-95. doi:10.1002/lary.24265

318. Willatt DJ, Jones AS. The role of the temperature of the nasal lining in the sensation of nasal patency. *Clin Otolaryngol Allied Sci*. Dec 1996;21(6):519-23. doi:10.1111/j.1365-2273.1996.tb01102.x

319. Kimbell JS, Frank DO, Laud P, Garcia GJ, Rhee JS. Changes in nasal airflow and heat transfer correlate with symptom improvement after surgery for nasal obstruction. *J Biomech*. Oct 18 2013;46(15):2634-43. doi:10.1016/j.jbiomech.2013.08.007

320. Lindemann J, Tsakiropoulou E, Scheithauer MO, Konstantinidis I, Wiesmiller KM. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. *Am J Rhinol*. Jul-Aug 2008;22(4):402-5. doi:10.2500/ajr.2008.22.3194

321. Sozansky J, Houser SM. Pathophysiology of empty nose syndrome. *Laryngoscope*. Jan 2015;125(1):70-4. doi:10.1002/lary.24813

322. Li C, Farag AA, Leach J, et al. Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients. *Laryngoscope*. Jun 2017;127(6):E176-E184. doi:10.1002/lary.26530

323. Li C, Farag AA, Maza G, et al. Investigation of the abnormal nasal aerodynamics and trigeminal functions among empty nose syndrome patients. *Int Forum Allergy Rhinol*. Mar 2018;8(3):444-452. doi:10.1002/alr.22045

324. Malik J, Dholakia S, Spector BM, et al. Inferior meatus augmentation procedure (IMAP) normalizes nasal airflow patterns in empty nose syndrome patients via computational fluid dynamics (CFD) modeling. *Int Forum Allergy Rhinol*. May 2021;11(5):902-909. doi:10.1002/alr.22720

325. Thamboo A, Velasquez N, Habib AR, Zarabanda D, Paknezhad H, Nayak JV. Defining surgical criteria for empty nose syndrome: Validation of the office-based cotton test and clinical interpretability of the validated Empty Nose Syndrome 6-Item Questionnaire. *Laryngoscope*. Aug 2017;127(8):1746-1752. doi:10.1002/lary.26549

326. Talmadge J, Nayak JV, Yao W, Citardi MJ. Management of Postsurgical Empty Nose Syndrome. *Facial Plast Surg Clin North Am*. Nov 2019;27(4):465-475. doi:10.1016/j.fsc.2019.07.005

327. Kanjanawasee D, Campbell RG, Rimmer J, et al. Empty Nose Syndrome Pathophysiology: A Systematic Review. *Otolaryngol Head Neck Surg*. Oct 19 2021:1945998211052919. doi:10.1177/01945998211052919

328. Manji J, Nayak JV, Thamboo A. The functional and psychological burden of empty nose syndrome. *Int Forum Allergy Rhinol*. Jun 2018;8(6):707-712. doi:10.1002/alr.22097

329. Huang CC, Wu PW, Fu CH, Huang CC, Chang PH, Lee TJ. Impact of Psychologic Burden on Surgical Outcome in Empty Nose Syndrome. *Laryngoscope*. Mar 2021;131(3):E694-E701. doi:10.1002/lary.28845

330. Huang CC, Wu PW, Lee CC, Chang PH, Huang CC, Lee TJ. Suicidal thoughts in patients with empty nose syndrome. *Laryngoscope Investig Otolaryngol*. Feb 2022;7(1):22-28. doi:10.1002/lio2.730

331. Tian P, Hu J, Ma Y, et al. The clinical effect of psychosomatic interventions on empty nose syndrome secondary to turbinate-sparing techniques: a prospective self-controlled study. *Int Forum Allergy Rhinol*. Jun 2021;11(6):984-992. doi:10.1002/alr.22726

332. Lemogne C, Consoli SM, Limosin F, Bonfils P. Treating empty nose syndrome as a somatic symptom disorder. *Gen Hosp Psychiatry*. May-Jun 2015;37(3):273 e9-10. doi:10.1016/j.genhosppsych.2015.02.005

333. Borchard NA, Dholakia SS, Yan CH, Zarabanda D, Thamboo A, Nayak JV. Use of intranasal submucosal fillers as a transient implant to alter upper airway aerodynamics: implications for the assessment of empty nose syndrome. *Int Forum Allergy Rhinol*. Jun 2019;9(6):681-687. doi:10.1002/alr.22299

334. Modrzynski M. Hyaluronic acid gel in the treatment of empty nose syndrome. *Am J Rhinol Allergy*. Mar-Apr 2011;25(2):103-6. doi:10.2500/ajra.2011.25.3577

335. Saafan ME. Acellular dermal (alloderm) grafts versus silastic sheets implants for management of empty nose syndrome. *Eur Arch Otorhinolaryngol*. Feb 2013;270(2):527-33. doi:10.1007/s00405-012-1955-1

336. Jiang C, Shi R, Sun Y. Study of inferior turbinate reconstruction with Medpor for the treatment of empty nose syndrome. *Laryngoscope*. May 2013;123(5):1106-11. doi:10.1002/lary.23908

337. Bastier PL, Bennani-Baiti AA, Stoll D, de Gabory L. beta-Tricalcium phosphate implant to repair empty nose syndrome: preliminary results. *Otolaryngol Head Neck Surg*. Mar 2013;148(3):519-22. doi:10.1177/0194599812472436

338. Jung JH, Baguindali MA, Park JT, Jang YJ. Costal cartilage is a superior implant material than conchal cartilage in the treatment of empty nose syndrome. *Otolaryngol Head Neck Surg*. Sep 2013;149(3):500-5. doi:10.1177/0194599813491223

339. Velasquez N, Huang Z, Humphreys IM, Nayak JV. Inferior turbinate reconstruction using porcine small intestine submucosal xenograft demonstrates improved quality of life outcomes in patients with empty nose syndrome. *Int Forum Allergy Rhinol*. Nov 2015;5(11):1077-81. doi:10.1002/alr.21633

340. Chang MT, Bartho M, Kim D, et al. Inferior Meatus Augmentation Procedure (IMAP) for Treatment of Empty Nose Syndrome. *Laryngoscope*. Jun 2022;132(6):1285-1288. doi:10.1002/lary.30001

341. Thamboo A, Dholakia SS, Borchard NA, et al. Inferior Meatus Augmentation Procedure (IMAP) to Treat Empty Nose Syndrome: A Pilot Study. *Otolaryngol Head Neck Surg*. Mar 2020;162(3):382-385. doi:10.1177/0194599819900263

342. Dholakia SS, Yang A, Kim D, et al. Long-Term Outcomes of Inferior Meatus Augmentation Procedure to Treat Empty Nose Syndrome. *Laryngoscope*. Nov 2021;131(11):E2736-E2741. doi:10.1002/lary.29593

343. Malik J, Thamboo A, Dholakia S, et al. The cotton test redistributes nasal airflow in patients with empty nose syndrome. *Int Forum Allergy Rhinol*. Apr 2020;10(4):539-545. doi:10.1002/alr.22489

344. Alobid I, Mullol J, Cid MC. Rhinitis of granulomatous and vasculitic diseases. *Clin Allergy Immunol*. 2007;19:221-39.

345. Afiari A, Gabriel A, Gaiki MR. Concurrent Use of Mepolizumab and Rituximab for Eosinophilic Granulomatosis With Polyangiitis and Multisystem Involvement. *Cureus*. Jul 17 2020;12(7):e9242. doi:10.7759/cureus.9242

346. Falk RJ, Gross WL, Guillevin L, et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Arthritis Rheum*. Apr 2011;63(4):863-4. doi:10.1002/art.30286

347. Sardana K, Goel K. Nasal septal ulceration. *Clin Dermatol*. Nov-Dec 2014;32(6):817-26. doi:10.1016/j.clindermatol.2014.02.022

348. Erickson VR, Hwang PH. Wegener's granulomatosis: current trends in diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2007;15(3):170-6. doi:10.1097/MOO.0b013e3281568b96

349. Nasser M, Cottin V. The Respiratory System in Autoimmune Vascular Diseases. *Respiration*. 2018;96(1):12-28. doi:10.1159/000486899

350. Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol*. Jan 2011;23(1):7-11. doi:10.1097/BOR.0b013e32834115f9

351. Beltran Rodriguez-Cabo O, Reyes E, Rojas-Serrano J, Flores-Suarez LF. Increased histopathological yield for granulomatosis with polyangiitis based on nasal endoscopy of suspected active lesions. *Eur Arch Otorhinolaryngol*. Feb 2018;275(2):425-429. doi:10.1007/s00405-017-4841-z

352. Al-Hussain T, Hussein MH, Conca W, Al Mana H, Akhtar M. Pathophysiology of ANCA-associated Vasculitis. *Adv Anat Pathol*. Jul 2017;24(4):226-234. doi:10.1097/PAP.0000000000000154

353. Lynch JP, 3rd, Derhovanessian A, Tazelaar H, Belperio JA. Granulomatosis with Polyangiitis (Wegener's Granulomatosis): Evolving Concepts in Treatment. *Semin Respir Crit Care Med*. Aug 2018;39(4):434-458. doi:10.1055/s-0038-1660874

354. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. *Lancet*. Feb 15 2003;361(9357):587-94. doi:10.1016/S0140-6736(03)12518-4

355. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med*. Sep 2015;26(7):545-53. doi:10.1016/j.ejim.2015.04.022

356. Chaigne B, Dion J, Guillevin L, Mouthon L, Terrier B. Physiopathologie de la granulomatose eosinophilique avec polyangeite (Churg-Strauss. *Rev Med Interne*. 2016;37:337-342.

357. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med*. May 18 2017;376(20):1921-1932. doi:10.1056/NEJMoa1702079

358. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. Apr 15 2020;201(8):e26-e51. doi:10.1164/rccm.202002-0251ST

359. Cereceda-Monteoliva N, Rouhani MJ, Maughan EF, et al. Sarcoidosis of the ear, nose and throat: A review of the literature. *Clin Otolaryngol*. Sep 2021;46(5):935-940. doi:10.1111/coa.13814

360. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. *Clin Rev Allergy Immunol*. Aug 2015;49(1):63-78. doi:10.1007/s12016-014-8450-y

361. Send T, Tuleta I, Koppen T, et al. Sarcoidosis of the paranasal sinuses. *Eur Arch Otorhinolaryngol*. Jul 2019;276(7):1969-1974. doi:10.1007/s00405-019-05388-7

362. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet*. Nov 22 2014;384(9957):1878-1888. doi:10.1016/S0140-6736(14)60128-8

363. Thong B, Olsen NJ. Systemic lupus erythematosus diagnosis and management. *Rheumatology (Oxford)*. Apr 1 2017;56(suppl_1):i3-i13. doi:10.1093/rheumatology/kew401

364. Samotij D, Reich A. Biologics in the Treatment of Lupus Erythematosus: A Critical Literature Review. *Biomed Res Int*. 2019;2019:8142368. doi:10.1155/2019/8142368

365. Tanaka Y, Tummala R. Anifrolumab, a monoclonal antibody to the type I interferon receptor subunit 1, for the treatment of systemic lupus erythematosus: an overview from clinical trials. *Mod Rheumatol*. Jan 2021;31(1):1-12. doi:10.1080/14397595.2020.1812201

366. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. Mar 2021;11(3):213-739. doi:10.1002/alr.22741

367. Helman SN, Barrow E, Edwards T, DelGaudio JM, Levy JM, Wise SK. The Role of Allergic Rhinitis in Chronic Rhinosinusitis. *Immunol Allergy Clin North Am*. May 2020;40(2):201-214. doi:10.1016/j.iac.2019.12.010

368. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res*. Apr 2010;2(2):65-76. doi:10.4168/aair.2010.2.2.65

369. Kakli HA, Riley TD. Allergic Rhinitis. *Prim Care*. Sep 2016;43(3):465-75. doi:10.1016/j.pop.2016.04.009

370. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg*. Sep 2003;129(3 Suppl):S1-32. doi:10.1016/s0194-5998(03)01397-4

371. Shapiro DJ, Gonzales R, Cabana MD, Hersh AL. National trends in visit rates and antibiotic prescribing for children with acute sinusitis. *Pediatrics*. Jan 2011;127(1):28-34. doi:10.1542/peds.2010-1340

372. Whyte A, Boeddinghaus R. Imaging of adult nasal obstruction. *Clin Radiol*. Sep 2020;75(9):688-704. doi:10.1016/j.crad.2019.07.027

373. Hsu DW, Suh JD. Anatomy and Physiology of Nasal Obstruction. *Otolaryngol Clin North Am*. Oct 2018;51(5):853-865. doi:10.1016/j.otc.2018.05.001

374. Cox DR, Wise SK. Medical Treatment of Nasal Airway Obstruction. *Otolaryngol Clin North Am*. Oct 2018;51(5):897-908. doi:10.1016/j.otc.2018.05.004

375. Villwock JA, Kuppersmith RB. Diagnostic Algorithm for Evaluating Nasal Airway Obstruction. *Otolaryngol Clin North Am*. Oct 2018;51(5):867-872. doi:10.1016/j.otc.2018.05.002

376. Samra S, Steitz JT, Hajnas N, Toriumi DM. Surgical Management of Nasal Valve Collapse. *Otolaryngol Clin North Am*. Oct 2018;51(5):929-944. doi:10.1016/j.otc.2018.05.009

377. Alvo A, Villarroel G, Sedano C. Neonatal nasal obstruction. *Eur Arch Otorhinolaryngol*. Oct 2021;278(10):3605-3611. doi:10.1007/s00405-020-06546-y

378. Harvey RJ, Sheahan PO, Schlosser RJ. Surgical management of benign sinonasal masses. *Otolaryngol Clin North Am*. Apr 2009;42(2):353-75, x. doi:10.1016/j.otc.2009.01.006

379. Kuo MJ, Reid AP, Smith JE. Unilateral nasal obstruction: an unusual presentation of a complication of nasotracheal intubation. *J Laryngol Otol*. Nov 1994;108(11):991-2. doi:10.1017/s0022215100128701

380. Tuluc M, Zhang X, Inniss S. Giant cell tumor of the nasal cavity: case report. *Eur Arch Otorhinolaryngol*. Feb 2007;264(2):205-8. doi:10.1007/s00405-006-0143-6

381. Hongmei Y, Zhe W, Jing W, Daokui W, Peicheng C, Yongjie L. Delayed cerebrospinal fluid rhinorrhea after gamma knife surgery in a patient with a growth hormone-secreting adenoma. *J Clin Neurosci*. Jun 2012;19(6):900-2. doi:10.1016/j.jocn.2011.09.016

382. Marchiano E, Carniol ET, Guzman DE, Raikundalia MD, Baredes S, Eloy JA. An Analysis of Patients Treated for Cerebrospinal Fluid Rhinorrhea in the United States from 2002 to 2010. *J Neurol Surg B Skull Base*. Feb 2017;78(1):18-23. doi:10.1055/s-0036-1584297

383. Tufano RP, Thaler ER, Lanza DC, Goldberg AN, Kennedy DW. Endoscopic management of sinonasal inverted papilloma. *Am J Rhinol*. Nov-Dec 1999;13(6):423-6. doi:10.2500/105065899781329665

384. Taylor MA, Saba NF. Cancer of the Paranasal Sinuses. *Hematol Oncol Clin North Am*. Oct 2021;35(5):949-962. doi:10.1016/j.hoc.2021.05.006

385. Oakley GM, Alt JA, Schlosser RJ, Harvey RJ, Orlandi RR. Diagnosis of cerebrospinal fluid rhinorrhea: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Jan 2016;6(1):8-16. doi:10.1002/alr.21637

386. Kinoshita Y, Wasita B, Akatsuka K, Kambe A, Kurosaki M, Watanabe T. Choroid plexus papilloma presenting with cerebrospinal fluid rhinorrhea and otorrhea: case report. *Neurol Med Chir (Tokyo)*. 2010;50(10):930-3. doi:10.2176/nmc.50.930

387. Kose OD, Kose TE, Erdem MA, Cankaya AB. Large rhinolith causing nasal obstruction. *BMJ Case Rep*. Mar 10 2015;2015doi:10.1136/bcr-2014-208260

388. Sumbullu MA, Tozoglu U, Yoruk O, Yilmaz AB, Ucuncu H. Rhinolithiasis: the importance of flat panel detector-based cone beam computed tomography in diagnosis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. Jun 2009;107(6):e65-7. doi:10.1016/j.tripleo.2009.02.029

389. Okafor S, Kelly KM, Halderman AA. Management of Sinusitis in the Cystic Fibrosis Patient. *Immunol Allergy Clin North Am*. May 2020;40(2):371-383. doi:10.1016/j.iac.2019.12.008

390. Shoemark A, Harman K. Primary Ciliary Dyskinesia. *Semin Respir Crit Care Med*. Aug 2021;42(4):537-548. doi:10.1055/s-0041-1730919

391. Finocchio E, Locatelli F, Sanna F, et al. Gastritis and gastroesophageal reflux disease are strongly associated with non-allergic nasal disorders. *BMC Pulm Med*. Feb 8 2021;21(1):53. doi:10.1186/s12890-020-01364-8

392. Dagli E, Yuksel A, Kaya M, Ugur KS, Turkay FC. Association of Oral Antireflux Medication With Laryngopharyngeal Reflux and Nasal Resistance. *JAMA Otolaryngol Head Neck Surg*. May 1 2017;143(5):478-483. doi:10.1001/jamaoto.2016.4127

393. Lou Z, Lou ZH. Laryngopharyngeal reflux is a potential cause of nasal congestion and obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. Sep 2018;275(9):2409-2411. doi:10.1007/s00405-017-4782-6

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.

REFERENCES

1. Kraft S, Kinet JP. New developments in FcepsilonRI regulation, function and inhibition. *Nat Rev Immunol*. May 2007;7(5):365-78. doi:10.1038/nri2072

2. Acharya M, Borland G, Edkins AL, et al. CD23/FcepsilonRII: molecular multi-tasking. *Clin Exp Immunol*. Oct 2010;162(1):12-23. doi:10.1111/j.1365-2249.2010.04210.x

3. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. *Nat Rev Immunol*. Apr 2014;14(4):247-59. doi:10.1038/nri3632

4. Blank U, Huang H, Kawakami T. The high affinity IgE receptor: a signaling update. *Curr Opin Immunol*. Oct 2021;72:51-58. doi:10.1016/j.coi.2021.03.015

5. Humbert M, Bousquet J, Bachert C, et al. IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy. *J Allergy Clin Immunol Pract*. May - Jun 2019;7(5):1418-1429. doi:10.1016/j.jaip.2019.02.030

6. Paolini R, Jouvin MH, Kinet JP. Phosphorylation and dephosphorylation of the high-affinity receptor for immunoglobulin E immediately after receptor engagement and disengagement. *Nature*. Oct 31 1991;353(6347):855-8. doi:10.1038/353855a0

7. Siraganian RP, de Castro RO, Barbu EA, Zhang J. Mast cell signaling: the role of protein tyrosine kinase Syk, its activation and screening methods for new pathway participants. *FEBS Lett*. Dec 15 2010;584(24):4933-40. doi:10.1016/j.febslet.2010.08.006

8. Costello PS, Turner M, Walters AE, et al. Critical role for the tyrosine kinase Syk in signalling through the high affinity IgE receptor of mast cells. *Oncogene*. Dec 19 1996;13(12):2595-605.

9. Zhang J, Berenstein EH, Evans RL, Siraganian RP. Transfection of Syk protein tyrosine kinase reconstitutes high affinity IgE receptor-mediated degranulation in a Syk-negative variant of rat basophilic leukemia RBL-2H3 cells. *J Exp Med*. Jul 1 1996;184(1):71-9. doi:10.1084/jem.184.1.71

10. Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol Rev*. Mar 2018;282(1):121-150. doi:10.1111/imr.12634

11. Draber P, Halova I, Polakovicova I, Kawakami T. Signal transduction and chemotaxis in mast cells. *Eur J Pharmacol*. May 5 2016;778:11-23. doi:10.1016/j.ejphar.2015.02.057

12. Motakis E, Guhl S, Ishizu Y, et al. Redefinition of the human mast cell transcriptome by deep-CAGE sequencing. *Blood*. Apr 24 2014;123(17):e58-67. doi:10.1182/blood-2013-02-483792

13. Li Y, Gao J, Kamran M, et al. GATA2 regulates mast cell identity and responsiveness to antigenic stimulation by promoting chromatin remodeling at super-enhancers. *Nat Commun*. Jan 21 2021;12(1):494. doi:10.1038/s41467-020-20766-0

14. Cildir G, Pant H, Lopez AF, Tergaonkar V. The transcriptional program, functional heterogeneity, and clinical targeting of mast cells. *J Exp Med*. Sep 4 2017;214(9):2491-2506. doi:10.1084/jem.20170910

15. Jayapal M, Tay HK, Reghunathan R, et al. Genome-wide gene expression profiling of human mast cells stimulated by IgE or FcepsilonRI-aggregation reveals a complex network of genes involved in inflammatory responses. *BMC Genomics*. Aug 16 2006;7:210. doi:10.1186/1471-2164-7-210

16. Anto JM, Bousquet J, Akdis M, et al. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol*. Feb 2017;139(2):388-399. doi:10.1016/j.jaci.2016.12.940

17. Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. *J Clin Invest*. Oct 1999;104(7):829-35. doi:10.1172/JCI8205

18. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med*. May 4 2012;18(5):693-704. doi:10.1038/nm.2755

19. Berger A. Th1 and Th2 responses: what are they? *BMJ*. Aug 12 2000;321(7258):424. doi:10.1136/bmj.321.7258.424

20. Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol*. Feb 2010;125(2 Suppl 2):S3-23. doi:10.1016/j.jaci.2009.12.980

21. Moro K, Yamada T, Tanabe M, et al. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature*. Jan 28 2010;463(7280):540-4. doi:10.1038/nature08636

22. Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature*. Apr 29 2010;464(7293):1367-70. doi:10.1038/nature08900

23. Halim TY, Steer CA, Matha L, et al. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity*. Mar 20 2014;40(3):425-35. doi:10.1016/j.immuni.2014.01.011

24. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. *J Allergy Clin Immunol*. Sep 2014;134(3):499-507. doi:10.1016/j.jaci.2014.06.036

25. Cayrol C, Duval A, Schmitt P, et al. Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat Immunol*. Apr 2018;19(4):375-385. doi:10.1038/s41590-018-0067-5

26. Roan F, Obata-Ninomiya K, Ziegler SF. Epithelial cell-derived cytokines: more than just signaling the alarm. *J Clin Invest*. Apr 1 2019;129(4):1441-1451. doi:10.1172/JCI124606

27. Hammad H, Lambrecht BN. Barrier Epithelial Cells and the Control of Type 2 Immunity. *Immunity*. Jul 21 2015;43(1):29-40. doi:10.1016/j.immuni.2015.07.007

28. Osguthorpe JD. Pathophysiology of and potential new therapies for allergic rhinitis. *Int Forum Allergy Rhinol*. May 2013;3(5):384-92. doi:10.1002/alr.21120

29. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. *Proc Am Thorac Soc*. Mar 2011;8(1):106-14. doi:10.1513/pats.201008-057RN

30. Pawankar R, Mori S, Ozu C, Kimura S. Overview on the pathomechanisms of allergic rhinitis. *Asia Pac Allergy*. Oct 2011;1(3):157-67. doi:10.5415/apallergy.2011.1.3.157

31. Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med*. Feb 20 2006;203(2):269-73. doi:10.1084/jem.20051745

32. Bousquet J, Anto JM, Bachert C, et al. Allergic rhinitis. *Nat Rev Dis Primers*. Dec 3 2020;6(1):95. doi:10.1038/s41572-020-00227-0

33. Geha RS. Regulation of IgE synthesis in humans. *J Allergy Clin Immunol*. Aug 1992;90(2):143-50. doi:10.1016/0091-6749(92)90064-9

34. Nurieva RI, Liu X, Dong C. Yin-Yang of costimulation: crucial controls of immune tolerance and function. *Immunol Rev*. May 2009;229(1):88-100. doi:10.1111/j.1600-065X.2009.00769.x

35. Luna-Gomes T, Magalhaes KG, Mesquita-Santos FP, et al. Eosinophils as a novel cell source of prostaglandin D2: autocrine role in allergic inflammation. *J Immunol*. Dec 15 2011;187(12):6518-26. doi:10.4049/jimmunol.1101806

36. Xue L, Salimi M, Panse I, et al. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol*. Apr 2014;133(4):1184-94. doi:10.1016/j.jaci.2013.10.056

37. Togias A. Systemic effects of local allergic disease. *J Allergy Clin Immunol*. Jan 2004;113(1 Suppl):S8-14. doi:10.1016/j.jaci.2003.09.051

38. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respir Med*. Feb 2014;2(2):131-40. doi:10.1016/S2213-2600(13)70277-7

39. Togias AG. Systemic immunologic and inflammatory aspects of allergic rhinitis. *J Allergy Clin Immunol*. Nov 2000;106(5 Suppl):S247-50. doi:10.1067/mai.2000.110157

40. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy*. Jun 10 2011;1(1):2. doi:10.1186/2045-7022-1-2

41. Rondon C, Bogas G, Barrionuevo E, Blanca M, Torres MJ, Campo P. Nonallergic rhinitis and lower airway disease. *Allergy*. Jan 2017;72(1):24-34. doi:10.1111/all.12988

42. Fuiano N, Fusilli S, Passalacqua G, Incorvaia C. Allergen-specific immunoglobulin E in the skin and nasal mucosa of symptomatic and asymptomatic children sensitized to aeroallergens. *J Investig Allergol Clin Immunol*. 2010;20(5):425-30.

43. Campo P, Rondon C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in non-allergic rhinitis. *Clin Exp Allergy*. May 2015;45(5):872-881. doi:10.1111/cea.12476

44. Rondon C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. Jun 2012;129(6):1460-7. doi:10.1016/j.jaci.2012.02.032

45. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy*. Oct 2003;33(10):1374-9. doi:10.1046/j.1365-2222.2003.01737.x

46. Rondon C, Campo P, Zambonino MA, et al. Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *J Allergy Clin Immunol*. Apr 2014;133(4):1026-31. doi:10.1016/j.jaci.2013.10.034

47. Rondon C, Campo P, Eguiluz-Gracia I, et al. Local allergic rhinitis is an independent rhinitis phenotype: The results of a 10-year follow-up study. *Allergy*. Feb 2018;73(2):470-478. doi:10.1111/all.13272

48. Sennekamp J, Joest I, Filipiak-Pittroff B, von Berg A, Berdel D. Local allergic nasal reactions convert to classic systemic allergic reactions: a long-term follow-up. *Int Arch Allergy Immunol*. 2015;166(2):154-60. doi:10.1159/000380852

49. Coker HA, Durham SR, Gould HJ. Local somatic hypermutation and class switch recombination in the nasal mucosa of allergic rhinitis patients. *J Immunol*. Nov 15 2003;171(10):5602-10. doi:10.4049/jimmunol.171.10.5602

50. Durham SR, Gould HJ, Thienes CP, et al. Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. *Eur J Immunol*. Nov 1997;27(11):2899-906. doi:10.1002/eji.1830271123

51. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol*. Jun 1979;122(6):2218-25.

52. Takhar P, Smurthwaite L, Coker HA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol*. Apr 15 2005;174(8):5024-32. doi:10.4049/jimmunol.174.8.5024

53. Powe DG, Huskisson RS, Carney AS, et al. Mucosal T-cell phenotypes in persistent atopic and nonatopic rhinitis show an association with mast cells. *Allergy*. Feb 2004;59(2):204-12. doi:10.1046/j.1398-9995.2003.00315.x

54. Rondon C, Dona I, Lopez S, et al. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy*. Oct 2008;63(10):1352-8. doi:10.1111/j.1398-9995.2008.01695.x

55. Rondon C, Romero JJ, Lopez S, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol*. Apr 2007;119(4):899-905. doi:10.1016/j.jaci.2007.01.006

56. Wedback A, Enbom H, Eriksson NE, Moverare R, Malcus I. Seasonal non-allergic rhinitis (SNAR)--a new disease entity? A clinical and immunological comparison between SNAR, seasonal allergic rhinitis and persistent non-allergic rhinitis. *Rhinology*. Jun 2005;43(2):86-92.

57. Huggins KG, Brostoff J. Local production of specific IgE antibodies in allergic-rhinitis patients with negative skin tests. *Lancet*. Jul 26 1975;2(7926):148-50. doi:10.1016/s0140-6736(75)90056-2

58. Bozek A, Ignasiak B, Kasperska-Zajac A, Scierski W, Grzanka A, Jarzab J. Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol*. Mar 2015;114(3):199-202. doi:10.1016/j.anai.2014.12.013

59. Klimek L, Bardenhewer C, Spielhaupter M, Harai C, Becker K, Pfaar O. [Local allergic rhinitis to Alternaria alternata : Evidence for local IgE production exclusively in the nasal mucosa]. *HNO*. May 2015;63(5):364-72. Lokale allergische Rhinitis auf Alternaria alternata : Nachweis bei Patienten mit persistierender nasaler Symptomatik. doi:10.1007/s00106-015-0005-x

60. Lopez S, Rondon C, Torres MJ, et al. Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus in local allergic rhinitis. *Clin Exp Allergy*. Jul 2010;40(7):1007-14. doi:10.1111/j.1365-2222.2010.03492.x

61. Samolinski B, Rapiejko P, Krzych-Falta E. Standards of nasal provocation tests. *Postepy Dermatol Alergol*. 2010;27:1669.

62. Rondon C, Fernandez J, Lopez S, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol*. Nov 2009;124(5):1005-11 e1. doi:10.1016/j.jaci.2009.07.018

63. Blanca-Lopez N, Campo P, Salas M, et al. Seasonal Local Allergic Rhinitis in Areas With High Concentrations of Grass Pollen. *J Investig Allergol Clin Immunol*. 2016;26(2):83-91. doi:10.18176/jiaci.0018

64. Campo P, Eguiluz-Gracia I, Bogas G, et al. Local allergic rhinitis: Implications for management. *Clin Exp Allergy*. Jan 2019;49(1):6-16. doi:10.1111/cea.13192

65. Rondon C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy*. Oct 2012;67(10):1282-8. doi:10.1111/all.12002

66. Campo P, Villalba M, Barrionuevo E, et al. Immunologic responses to the major allergen of Olea europaea in local and systemic allergic rhinitis subjects. *Clin Exp Allergy*. Nov 2015;45(11):1703-12. doi:10.1111/cea.12600

67. Gomez E, Campo P, Rondon C, et al. Role of the basophil activation test in the diagnosis of local allergic rhinitis. *J Allergy Clin Immunol*. Oct 2013;132(4):975-6 e1-5. doi:10.1016/j.jaci.2013.07.016

68. Campo P, Salas M, Blanca-Lopez N, Rondon C. Local Allergic Rhinitis. *Immunol Allergy Clin North Am*. May 2016;36(2):321-32. doi:10.1016/j.iac.2015.12.008

69. Reitsma S, Subramaniam S, Fokkens WWJ, Wang Y. Recent developments and highlights in rhinitis and allergen immunotherapy. *Allergy*. Dec 2018;73(12):2306-2313. doi:10.1111/all.13617

70. Shin YS, Jung CG, Park HS. Prevalence and clinical characteristics of local allergic rhinitis to house dust mites. *Curr Opin Allergy Clin Immunol*. Feb 2018;18(1):10-15. doi:10.1097/ACI.0000000000000413

71. Cheng KJ, Xu YY, Liu HY, Wang SQ. Serum eosinophil cationic protein level in Chinese subjects with nonallergic and local allergic rhinitis and its relation to the severity of disease. *Am J Rhinol Allergy*. Jan 2013;27(1):8-12. doi:10.2500/ajra.2013.27.3845

72. Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy*. Jul-Aug 2015;29(4):e100-4. doi:10.2500/ajra.2015.29.4214

73. Zicari AM, Occasi F, Di Fraia M, et al. Local allergic rhinitis in children: Novel diagnostic features and potential biomarkers. *Am J Rhinol Allergy*. Sep 2016;30(5):329-34. doi:10.2500/ajra.2016.30.4352

74. Duman H, Bostanci I, Ozmen S, Dogru M. The Relevance of Nasal Provocation Testing in Children with Nonallergic Rhinitis. *Int Arch Allergy Immunol*. 2016;170(2):115-21. doi:10.1159/000447635

75. Altintoprak N, Kar M, Bayar Muluk N, et al. Update on local allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Aug 2016;87:105-9. doi:10.1016/j.ijporl.2016.06.008

76. Buntarickpornpan P, Veskitkul J, Pacharn P, et al. The proportion of local allergic rhinitis to Dermatophagoides pteronyssinus in children. *Pediatr Allergy Immunol*. Sep 2016;27(6):574-9. doi:10.1111/pai.12606

77. Rondon C, Campo P, Blanca-Lopez N, Torres MJ, Blanca M. More research is needed for local allergic rhinitis. *Int Arch Allergy Immunol*. 2015;167(2):99-100. doi:10.1159/000436970

78. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy*. Jun 2001;31(6):864-72. doi:10.1046/j.1365-2222.2001.01106.x

79. Papadopoulos NG, Bernstein JA, Demoly P, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy*. May 2015;70(5):474-94. doi:10.1111/all.12573

80. Toppila-Salmi S, van Drunen CM, Fokkens WJ, et al. Molecular mechanisms of nasal epithelium in rhinitis and rhinosinusitis. *Curr Allergy Asthma Rep*. Feb 2015;15(2):495. doi:10.1007/s11882-014-0495-8

81. Scadding GK, Scadding GW. Innate and adaptive immunity in allergic airway disease. *Curr Opin Allergy Clin Immunol*. Feb 1 2022;22(1):10-15. doi:10.1097/ACI.0000000000000800

82. Jacquet A, Robinson C. Proteolytic, lipidergic and polysaccharide molecular recognition shape innate responses to house dust mite allergens. *Allergy*. Jan 2020;75(1):33-53. doi:10.1111/all.13940

83. Kortekaas Krohn I, Seys SF, Lund G, et al. Nasal epithelial barrier dysfunction increases sensitization and mast cell degranulation in the absence of allergic inflammation. *Allergy*. May 2020;75(5):1155-1164. doi:10.1111/all.14132

84. Shim JS, Lee HS, Park DE, et al. Aggravation of asthmatic inflammation by chlorine exposure via innate lymphoid cells and CD11c(intermediate) macrophages. *Allergy*. Feb 2020;75(2):381-391. doi:10.1111/all.14017

85. Kim J, Kim YC, Ham J, et al. The effect of air pollutants on airway innate immune cells in patients with asthma. *Allergy*. Sep 2020;75(9):2372-2376. doi:10.1111/all.14323

86. Steelant B, Farre R, Wawrzyniak P, et al. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens-1 expression. *J Allergy Clin Immunol*. Apr 2016;137(4):1043-1053 e5. doi:10.1016/j.jaci.2015.10.050

87. Pat Y, Ogulur I. The epithelial barrier hypothesis: a 20-year journey. *Allergy*. Nov 2021;76(11):3560-3562. doi:10.1111/all.14899

88. van Tongeren J, Golebski K, Van Egmond D, de Groot EJ, Fokkens WJ, van Drunen CM. Synergy between TLR-2 and TLR-3 signaling in primary human nasal epithelial cells. *Immunobiology*. Apr 2015;220(4):445-51. doi:10.1016/j.imbio.2014.11.004

89. Radman M, Golshiri A, Shamsizadeh A, et al. Toll-like receptor 4 plays significant roles during allergic rhinitis. *Allergol Immunopathol (Madr)*. Jul-Aug 2015;43(4):416-20. doi:10.1016/j.aller.2014.04.006

90. Mjosberg JM, Trifari S, Crellin NK, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. *Nat Immunol*. Sep 11 2011;12(11):1055-62. doi:10.1038/ni.2104

91. Matsushita K, Kato Y, Akasaki S, Yoshimoto T. Proallergic cytokines and group 2 innate lymphoid cells in allergic nasal diseases. *Allergol Int*. Jul 2015;64(3):235-40. doi:10.1016/j.alit.2014.12.008

92. Bartemes KR, Kephart GM, Fox SJ, Kita H. Enhanced innate type 2 immune response in peripheral blood from patients with asthma. *J Allergy Clin Immunol*. Sep 2014;134(3):671-678 e4. doi:10.1016/j.jaci.2014.06.024

93. Hong H, Liao S, Chen F, Yang Q, Wang DY. Role of IL-25, IL-33, and TSLP in triggering united airway diseases toward type 2 inflammation. *Allergy*. Nov 2020;75(11):2794-2804. doi:10.1111/all.14526

94. Doherty TA, Scott D, Walford HH, et al. Allergen challenge in allergic rhinitis rapidly induces increased peripheral blood type 2 innate lymphoid cells that express CD84. *J Allergy Clin Immunol*. Apr 2014;133(4):1203-5. doi:10.1016/j.jaci.2013.12.1086

95. Lao-Araya M, Steveling E, Scadding GW, Durham SR, Shamji MH. Seasonal increases in peripheral innate lymphoid type 2 cells are inhibited by subcutaneous grass pollen immunotherapy. *J Allergy Clin Immunol*. Nov 2014;134(5):1193-5 e4. doi:10.1016/j.jaci.2014.07.029

96. Dhariwal J, Cameron A, Trujillo-Torralbo MB, et al. Mucosal Type 2 Innate Lymphoid Cells Are a Key Component of the Allergic Response to Aeroallergens. *Am J Respir Crit Care Med*. Jun 15 2017;195(12):1586-1596. doi:10.1164/rccm.201609-1846OC

97. Xie Y, Ju X, Beaudin S, et al. Effect of intranasal corticosteroid treatment on allergen-induced changes in group 2 innate lymphoid cells in allergic rhinitis with mild asthma. *Allergy*. Sep 2021;76(9):2797-2808. doi:10.1111/all.14835

98. Sugita K, Steer CA, Martinez-Gonzalez I, et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. *J Allergy Clin Immunol*. Jan 2018;141(1):300-310 e11. doi:10.1016/j.jaci.2017.02.038

99. Boguniewicz M, Beck LA, Sher L, et al. Dupilumab Improves Asthma and Sinonasal Outcomes in Adults with Moderate to Severe Atopic Dermatitis. *J Allergy Clin Immunol Pract*. Mar 2021;9(3):1212-1223 e6. doi:10.1016/j.jaip.2020.12.059

100. Orimo K, Tamari M, Saito H, Matsumoto K, Nakae S, Morita H. Characteristics of tissue-resident ILCs and their potential as therapeutic targets in mucosal and skin inflammatory diseases. *Allergy*. Nov 2021;76(11):3332-3348. doi:10.1111/all.14863

101. Akdis M, Aab A, Altunbulakli C, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: Receptors, functions, and roles in diseases. *J Allergy Clin Immunol*. Oct 2016;138(4):984-1010. doi:10.1016/j.jaci.2016.06.033

102. Zheng H, Zhang Y, Pan J, et al. The Role of Type 2 Innate Lymphoid Cells in Allergic Diseases. *Front Immunol*. 2021;12:586078. doi:10.3389/fimmu.2021.586078

103. Schuijs MJ, Willart MA, Vergote K, et al. Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. *Science*. Sep 4 2015;349(6252):1106-10. doi:10.1126/science.aac6623

104. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol*. Jan 2015;16(1):45-56. doi:10.1038/ni.3049

105. Muraro A, Lemanske RF, Jr., Hellings PW, et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. May 2016;137(5):1347-58. doi:10.1016/j.jaci.2016.03.010

106. Nian JB, Zeng M, Zheng J, et al. Epithelial cells expressed IL-33 to promote degranulation of mast cells through inhibition on ST2/PI3K/mTOR-mediated autophagy in allergic rhinitis. *Cell Cycle*. May 2020;19(10):1132-1142. doi:10.1080/15384101.2020.1749402

107. Cheng KJ, Zhou ML, Liu YC, Wang C, Xu YY. The Role of CD40 in Allergic Rhinitis and Airway Remodelling. *Mediators Inflamm*. 2021;2021:6694109. doi:10.1155/2021/6694109

108. KleinJan A, Willart M, van Rijt LS, et al. An essential role for dendritic cells in human and experimental allergic rhinitis. *J Allergy Clin Immunol*. Nov 2006;118(5):1117-25. doi:10.1016/j.jaci.2006.05.030

109. Hammad H, Plantinga M, Deswarte K, et al. Inflammatory dendritic cells--not basophils--are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J Exp Med*. Sep 27 2010;207(10):2097-111. doi:10.1084/jem.20101563

110. Meng Y, Wang C, Zhang L. Advances and novel developments in allergic rhinitis. *Allergy*. Dec 2020;75(12):3069-3076. doi:10.1111/all.14586

111. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol*. Mar 2015;135(3):626-35. doi:10.1016/j.jaci.2014.11.001

112. Durham SR, Ying S, Varney VA, et al. Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/macrophage-colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol*. Apr 15 1992;148(8):2390-4.

113. Sogut A, Yilmaz O, Kirmaz C, et al. Regulatory-T, T-helper 1, and T-helper 2 cell differentiation in nasal mucosa of allergic rhinitis with olive pollen sensitivity. *Int Arch Allergy Immunol*. 2012;157(4):349-53. doi:10.1159/000329159

114. Pawankar RU, Okuda M, Okubo K, Ra C. Lymphocyte subsets of the nasal mucosa in perennial allergic rhinitis. *Am J Respir Crit Care Med*. Dec 1995;152(6 Pt 1):2049-58. doi:10.1164/ajrccm.152.6.8520775

115. Soyka MB, Wawrzyniak P, Eiwegger T, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-gamma and IL-4. *J Allergy Clin Immunol*. Nov 2012;130(5):1087-1096 e10. doi:10.1016/j.jaci.2012.05.052

116. Kubo T, Wawrzyniak P, Morita H, et al. CpG-DNA enhances the tight junction integrity of the bronchial epithelial cell barrier. *J Allergy Clin Immunol*. Nov 2015;136(5):1413-6 e1-8. doi:10.1016/j.jaci.2015.05.006

117. Georas SN, Rezaee F. Epithelial barrier function: at the front line of asthma immunology and allergic airway inflammation. *J Allergy Clin Immunol*. Sep 2014;134(3):509-20. doi:10.1016/j.jaci.2014.05.049

118. Akdis M. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol*. Dec 2006;18(6):738-44. doi:10.1016/j.coi.2006.06.003

119. Akdis M, Akdis CA. Therapeutic manipulation of immune tolerance in allergic disease. *Nat Rev Drug Discov*. Aug 2009;8(8):645-60. doi:10.1038/nrd2653

120. Raedler D, Ballenberger N, Klucker E, et al. Identification of novel immune phenotypes for allergic and nonallergic childhood asthma. *J Allergy Clin Immunol*. Jan 2015;135(1):81-91. doi:10.1016/j.jaci.2014.07.046

121. Akdis M, Verhagen J, Taylor A, et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med*. Jun 7 2004;199(11):1567-75. doi:10.1084/jem.20032058

122. Suarez-Fueyo A, Ramos T, Galan A, et al. Grass tablet sublingual immunotherapy downregulates the TH2 cytokine response followed by regulatory T-cell generation. *J Allergy Clin Immunol*. Jan 2014;133(1):130-8 e1-2. doi:10.1016/j.jaci.2013.09.043

123. Fox EM, Torrero MN, Evans H, Mitre E. Immunologic characterization of 3 murine regimens of allergen-specific immunotherapy. *J Allergy Clin Immunol*. May 2015;135(5):1341-51 e1-7. doi:10.1016/j.jaci.2014.07.052

124. Akdis CA, Akdis M. Advances in allergen immunotherapy: aiming for complete tolerance to allergens. *Sci Transl Med*. Mar 25 2015;7(280):280ps6. doi:10.1126/scitranslmed.aaa7390

125. Jansen K, Cevhertas L, Ma S, Satitsuksanoa P, Akdis M, van de Veen W. Regulatory B cells, A to Z. *Allergy*. Sep 2021;76(9):2699-2715. doi:10.1111/all.14763

126. Hofmann MA, Fluhr JW, Ruwwe-Glosenkamp C, Stevanovic K, Bergmann KC, Zuberbier T. Role of IL-17 in atopy-A systematic review. *Clin Transl Allergy*. Aug 2021;11(6):e12047. doi:10.1002/clt2.12047

127. Yu X, Wang M, Cao Z. Reduced CD4(+)T Cell CXCR3 Expression in Patients With Allergic Rhinitis. *Front Immunol*. 2020;11:581180. doi:10.3389/fimmu.2020.581180

128. Morita H, Arae K, Unno H, et al. An Interleukin-33-Mast Cell-Interleukin-2 Axis Suppresses Papain-Induced Allergic Inflammation by Promoting Regulatory T Cell Numbers. *Immunity*. Jul 21 2015;43(1):175-86. doi:10.1016/j.immuni.2015.06.021

129. Ganzer U, Bachert C. Localization of IgE synthesis in immediate-type allergy of the upper respiratory tract. *ORL J Otorhinolaryngol Relat Spec*. 1988;50(4):257-64. doi:10.1159/000276000

130. KleinJan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J*. Mar 2000;15(3):491-7. doi:10.1034/j.1399-3003.2000.15.11.x

131. Yao Y, Wang N, Chen CL, et al. CD23 expression on switched memory B cells bridges T-B cell interaction in allergic rhinitis. *Allergy*. Oct 2020;75(10):2599-2612. doi:10.1111/all.14288

132. Bentley AM, Jacobson MR, Cumberworth V, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol*. Apr 1992;89(4):877-83. doi:10.1016/0091-6749(92)90444-7

133. Gomez E, Corrado OJ, Baldwin DL, Swanston AR, Davies RJ. Direct in vivo evidence for mast cell degranulation during allergen-induced reactions in man. *J Allergy Clin Immunol*. Oct 1986;78(4 Pt 1):637-45. doi:10.1016/0091-6749(86)90082-5

134. Haenuki Y, Matsushita K, Futatsugi-Yumikura S, et al. A critical role of IL-33 in experimental allergic rhinitis. *J Allergy Clin Immunol*. Jul 2012;130(1):184-94 e11. doi:10.1016/j.jaci.2012.02.013

135. KleinJan A, McEuen AR, Dijkstra MD, Buckley MG, Walls AF, Fokkens WJ. Basophil and eosinophil accumulation and mast cell degranulation in the nasal mucosa of patients with hay fever after local allergen provocation. *J Allergy Clin Immunol*. Oct 2000;106(4):677-86. doi:10.1067/mai.2000.109621

136. Semik-Orzech A, Barczyk A, Wiaderkiewicz R, Pierzchala W. Eotaxin, but not IL-8, is increased in upper and lower airways of allergic rhinitis subjects after nasal allergen challenge. *Allergy Asthma Proc*. May-Jun 2011;32(3):230-8. doi:10.2500/aap.2011.32.3435

137. Kim TH, Lee JY, Lee HM, et al. Remodelling of nasal mucosa in mild and severe persistent allergic rhinitis with special reference to the distribution of collagen, proteoglycans, and lymphatic vessels. *Clin Exp Allergy*. Dec 2010;40(12):1742-54. doi:10.1111/j.1365-2222.2010.03612.x

138. Pawankar R, Yamagishi S, Yagi T. Revisiting the roles of mast cells in allergic rhinitis and its relation to local IgE synthesis. *Am J Rhinol*. Sep-Oct 2000;14(5):309-17. doi:10.2500/105065800781329582

139. Pawankar R. Mast cells in allergic airway disease and chronic rhinosinusitis. *Chem Immunol Allergy*. 2005;87:111-129. doi:10.1159/000087639

140. Powe DG, Hiskisson RS, Carney AS, Jenkins D, Jones NS. Idiopathic and allergic rhinitis show a similar inflammatory response. *Clin Otolaryngol Allied Sci*. Dec 2000;25(6):570-6. doi:10.1046/j.1365-2273.2000.00422-2.x

141. Divekar R, Kita H. Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation. *Curr Opin Allergy Clin Immunol*. Feb 2015;15(1):98-103. doi:10.1097/ACI.0000000000000133

142. Wang W, Li Y, Lv Z, et al. Bronchial Allergen Challenge of Patients with Atopic Asthma Triggers an Alarmin (IL-33, TSLP, and IL-25) Response in the Airways Epithelium and Submucosa. *J Immunol*. Oct 15 2018;201(8):2221-2231. doi:10.4049/jimmunol.1800709

143. Hussain M, Borcard L, Walsh KP, et al. Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy. *J Allergy Clin Immunol*. Jan 2018;141(1):223-234 e5. doi:10.1016/j.jaci.2017.02.035

144. Corren J, Ziegler SF. TSLP: from allergy to cancer. *Nat Immunol*. Dec 2019;20(12):1603-1609. doi:10.1038/s41590-019-0524-9

145. London NR, Jr., Lane AP. Innate immunity and chronic rhinosinusitis: What we have learned from animal models. *Laryngoscope Investig Otolaryngol*. Jun 2016;1(3):49-56. doi:10.1002/lio2.21

146. Pawankar R. Epithelial cells as immunoregulators in allergic airway diseases. *Curr Opin Allergy Clin Immunol*. Feb 2002;2(1):1-5. doi:10.1097/00130832-200202000-00001

147. Peng YQ, Qin ZL, Fang SB, et al. Effects of myeloid and plasmacytoid dendritic cells on ILC2s in patients with allergic rhinitis. *J Allergy Clin Immunol*. Mar 2020;145(3):855-867 e8. doi:10.1016/j.jaci.2019.11.029

148. Kabata H, Moro K, Koyasu S. The group 2 innate lymphoid cell (ILC2) regulatory network and its underlying mechanisms. *Immunol Rev*. Nov 2018;286(1):37-52. doi:10.1111/imr.12706

149. Wilhelm C, Hirota K, Stieglitz B, et al. An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. *Nat Immunol*. Oct 9 2011;12(11):1071-7. doi:10.1038/ni.2133

150. Turner JE, Morrison PJ, Wilhelm C, et al. IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med*. Dec 16 2013;210(13):2951-65. doi:10.1084/jem.20130071

151. Wilson AM, Duong M, Crawford L, Denburg J. An evaluation of peripheral blood eosinophil/basophil progenitors following nasal allergen challenge in patients with allergic rhinitis. *Clin Exp Allergy*. Jan 2005;35(1):39-44. doi:10.1111/j.1365-2222.2004.02072.x

152. Bradding P, Holgate ST. The mast cell as a source of cytokines in asthma. *Ann N Y Acad Sci*. Oct 31 1996;796:272-81. doi:10.1111/j.1749-6632.1996.tb32589.x

153. Pawankar RU, Okuda M, Hasegawa S, et al. Interleukin-13 expression in the nasal mucosa of perennial allergic rhinitis. *Am J Respir Crit Care Med*. Dec 1995;152(6 Pt 1):2059-67. doi:10.1164/ajrccm.152.6.8520776

154. Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitics exhibit increased expression of the Fc epsilonRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest*. Apr 1 1997;99(7):1492-9. doi:10.1172/JCI119311

155. Pawankar R. Inflammatory mechanisms in allergic rhinitis. *Curr Opin Allergy Clin Immunol*. Feb 2007;7(1):1-4. doi:10.1097/ACI.0b013e3280145347

156. Nonaka M, Pawankar R, Fukumoto A, Ogihara N, Sakanushi A, Yagi T. Induction of eotaxin production by interleukin-4, interleukin-13 and lipopolysaccharide by nasal fibroblasts. *Clin Exp Allergy*. May 2004;34(5):804-11. doi:10.1111/j.1365-2222.2004.1954.x

157. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. Mar 5 2009;360(10):985-93. doi:10.1056/NEJMoa0805435

158. Nakamaru Y, Oridate N, Nishihira J, Takagi D, Furuta Y, Fukuda S. Macrophage migration inhibitory factor in allergic rhinitis: its identification in eosinophils at the site of inflammation. *Ann Otol Rhinol Laryngol*. Mar 2004;113(3 Pt 1):205-9. doi:10.1177/000348940411300306

159. Kobayashi H, Gleich GJ, Butterfield JH, Kita H. Human eosinophils produce neurotrophins and secrete nerve growth factor on immunologic stimuli. *Blood*. Mar 15 2002;99(6):2214-20. doi:10.1182/blood.v99.6.2214

160. Pappu R, Ramirez-Carrozzi V, Sambandam A. The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. *Immunology*. Sep 2011;134(1):8-16. doi:10.1111/j.1365-2567.2011.03465.x

161. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. *Int Immunopharmacol*. Nov 2011;11(11):1646-62. doi:10.1016/j.intimp.2011.07.005

162. Kim D, Baraniuk JN. Neural aspects of allergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg*. Aug 2007;15(4):268-73. doi:10.1097/MOO.0b013e328259c372

163. Pfaar O, Raap U, Holz M, Hormann K, Klimek L. Pathophysiology of itching and sneezing in allergic rhinitis. *Swiss Med Wkly*. Jan 24 2009;139(3-4):35-40. doi:smw-12468

164. Singh U, Bernstein JA, Haar L, Luther K, Jones WK. Azelastine desensitization of transient receptor potential vanilloid 1: a potential mechanism explaining its therapeutic effect in nonallergic rhinitis. *Am J Rhinol Allergy*. May-Jun 2014;28(3):215-24. doi:10.2500/ajra.2014.28.4059

165. Singh U, Bernstein JA, Lorentz H, et al. A Pilot Study Investigating Clinical Responses and Biological Pathways of Azelastine/Fluticasone in Nonallergic Vasomotor Rhinitis before and after Cold Dry Air Provocation. *Int Arch Allergy Immunol*. 2017;173(3):153-164. doi:10.1159/000478698

166. Kuruvilla M, Kalangara J, Lee FEE. Neuropathic Pain and Itch Mechanisms Underlying Allergic Conjunctivitis. *J Investig Allergol Clin Immunol*. 2019;29(5):349-356. doi:10.18176/jiaci.0320

167. Gawlik R, Jawor B, Rogala B, Parzynski S, DuBuske L. Effect of intranasal azelastine on substance P release in perennial nonallergic rhinitis patients. *Am J Rhinol Allergy*. Nov-Dec 2013;27(6):514-6. doi:10.2500/ajra.2013.27.3955

168. Baraniuk JN, Kaliner MA. Neuropeptides and nasal secretion. *J Allergy Clin Immunol*. Oct 1990;86(4 Pt 2):620-7. doi:10.1016/s0091-6749(05)80226-x

169. Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S, Levin LS. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2011;107(2):171-8. doi:10.1016/j.anai.2011.05.016

170. Golpanian RS, Smith P, Yosipovitch G. Itch in Organs Beyond the Skin. *Curr Allergy Asthma Rep*. Jun 19 2020;20(9):49. doi:10.1007/s11882-020-00947-z

171. Mosimann BL, White MV, Hohman RJ, Goldrich MS, Kaulbach HC, Kaliner MA. Substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide increase in nasal secretions after allergen challenge in atopic patients. *J Allergy Clin Immunol*. Jul 1993;92(1 Pt 1):95-104. doi:10.1016/0091-6749(93)90043-f

172. Singh U, Bernstein JA. Intranasal capsaicin in management of nonallergic (vasomotor) rhinitis. *Prog Drug Res*. 2014;68:147-70. doi:10.1007/978-3-0348-0828-6_6

173. Sanico AM, Koliatsos VE, Stanisz AM, Bienenstock J, Togias A. Neural hyperresponsiveness and nerve growth factor in allergic rhinitis. *Int Arch Allergy Immunol*. Feb-Apr 1999;118(2-4):154-8. doi:10.1159/000024054

174. Bresciani M, Laliberte F, Laliberte MF, Gramiccioni C, Bonini S. Nerve growth factor localization in the nasal mucosa of patients with persistent allergic rhinitis. *Allergy*. Jan 2009;64(1):112-7. doi:10.1111/j.1398-9995.2008.01831.x

175. O'Hanlon S, Facer P, Simpson KD, Sandhu G, Saleh HA, Anand P. Neuronal markers in allergic rhinitis: expression and correlation with sensory testing. *Laryngoscope*. Sep 2007;117(9):1519-27. doi:10.1097/MLG.0b013e3180ca7846

176. Abbott-Banner K, Poll C, Verkuyl JM. Targeting TRP channels in airway disorders. *Curr Top Med Chem*. 2013;13(3):310-21. doi:10.2174/1568026611313030008

177. Ba G, Tang R, Sun X, Li Z, Lin H, Zhang W. Therapeutic effects of SKF-96365 on murine allergic rhinitis induced by OVA. *Int J Immunopathol Pharmacol*. Jan-Dec 2021;35:20587384211015054. doi:10.1177/20587384211015054

178. Backaert W, Steelant B, Hellings PW, Talavera K, Van Gerven L. A TRiP Through the Roles of Transient Receptor Potential Cation Channels in Type 2 Upper Airway Inflammation. *Curr Allergy Asthma Rep*. Mar 18 2021;21(3):20. doi:10.1007/s11882-020-00981-x

179. Nam JH, Kim WK. The Role of TRP Channels in Allergic Inflammation and its Clinical Relevance. *Curr Med Chem*. 2020;27(9):1446-1468. doi:10.2174/0929867326666181126113015

180. Vareille M, Kieninger E, Edwards MR, Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. *Clin Microbiol Rev*. Jan 2011;24(1):210-29. doi:10.1128/CMR.00014-10

181. Wang DY, Li Y, Yan Y, Li C, Shi L. Upper airway stem cells: understanding the nose and role for future cell therapy. *Curr Allergy Asthma Rep*. Jan 2015;15(1):490. doi:10.1007/s11882-014-0490-0

182. Akira S. Pathogen recognition by innate immunity and its signaling. *Proc Jpn Acad Ser B Phys Biol Sci*. 2009;85(4):143-56. doi:10.2183/pjab.85.143

183. Chen CR, Kachramanoglou C, Li D, Andrews P, Choi D. Anatomy and cellular constituents of the human olfactory mucosa: a review. *J Neurol Surg B Skull Base*. Oct 2014;75(5):293-300. doi:10.1055/s-0033-1361837

184. Bustamante-Marin XM, Ostrowski LE. Cilia and Mucociliary Clearance. *Cold Spring Harb Perspect Biol*. Apr 3 2017;9(4)doi:10.1101/cshperspect.a028241

185. Scherzad A, Hagen R, Hackenberg S. Current Understanding of Nasal Epithelial Cell Mis-Differentiation. *J Inflamm Res*. 2019;12:309-317. doi:10.2147/JIR.S180853

186. Hamelmann E. Development of allergic airway inflammation in early life - interaction of early viral infections and allergic sensitization. *Allergol Select*. 2018;2(1):132-137. doi:10.5414/ALX01635E

187. Shin SH, Ye MK, Lee DW, Chae MH, Han BD. Nasal Epithelial Cells Activated with Alternaria and House Dust Mite Induce Not Only Th2 but Also Th1 Immune Responses. *Int J Mol Sci*. Apr 13 2020;21(8)doi:10.3390/ijms21082693

188. Bergougnan C, Dittlein DC, Hummer E, et al. Physical and immunological barrier of human primary nasal epithelial cells from non-allergic and allergic donors. *World Allergy Organ J*. Mar 2020;13(3):100109. doi:10.1016/j.waojou.2020.100109

189. Orban NT, Jacobson MR, Nouri-Aria KT, Durham SR, Eifan AO. Repetitive nasal allergen challenge in allergic rhinitis: Priming and Th2-type inflammation but no evidence of remodelling. *Clin Exp Allergy*. Feb 2021;51(2):329-338. doi:10.1111/cea.13775

190. Watts AM, West NP, Cripps AW, Smith PK, Cox AJ. Distinct Gene Expression Patterns between Nasal Mucosal Cells and Blood Collected from Allergic Rhinitis Sufferers. *Int Arch Allergy Immunol*. 2018;177(1):29-34. doi:10.1159/000489609

191. Groneberg DA, Peiser C, Dinh QT, et al. Distribution of respiratory mucin proteins in human nasal mucosa. *Laryngoscope*. Mar 2003;113(3):520-4. doi:10.1097/00005537-200303000-00023

192. Lee SN, Kim SJ, Yoon SA, et al. CD44v3-Positive Intermediate Progenitor Cells Contribute to Airway Goblet Cell Hyperplasia. *Am J Respir Cell Mol Biol*. Feb 2021;64(2):247-259. doi:10.1165/rcmb.2020-0350OC

193. Siti Sarah CO, Md Shukri N, Mohd Ashari NS, Wong KK. Zonula occludens and nasal epithelial barrier integrity in allergic rhinitis. *PeerJ*. 2020;8:e9834. doi:10.7717/peerj.9834

194. Steelant B, Wawrzyniak P, Martens K, et al. Blocking histone deacetylase activity as a novel target for epithelial barrier defects in patients with allergic rhinitis. *J Allergy Clin Immunol*. Nov 2019;144(5):1242-1253 e7. doi:10.1016/j.jaci.2019.04.027

195. Zhou LB, Zheng YM, Liao WJ, et al. MUC1 deficiency promotes nasal epithelial barrier dysfunction in subjects with allergic rhinitis. *J Allergy Clin Immunol*. Dec 2019;144(6):1716-1719 e5. doi:10.1016/j.jaci.2019.07.042

196. Buckle FG, Cohen AB. Nasal mucosal hyperpermeability to macromolecules in atopic rhinitis and extrinsic asthma. *J Allergy Clin Immunol*. Apr 1975;55(4):213-21. doi:10.1016/0091-6749(75)90139-6

197. Zhang Y, Derycke L, Holtappels G, et al. Th2 cytokines orchestrate the secretion of MUC5AC and MUC5B in IL-5-positive chronic rhinosinusitis with nasal polyps. *Allergy*. Jan 2019;74(1):131-140. doi:10.1111/all.13489

198. Wang J, Wen L, Wang Y, Chen F. Therapeutic Effect of Histone Deacetylase Inhibitor, Sodium Butyrate, on Allergic Rhinitis In Vivo. *DNA Cell Biol*. Apr 2016;35(4):203-8. doi:10.1089/dna.2015.3037

199. Runswick S, Mitchell T, Davies P, Robinson C, Garrod DR. Pollen proteolytic enzymes degrade tight junctions. *Respirology*. Nov 2007;12(6):834-42. doi:10.1111/j.1440-1843.2007.01175.x

200. Henriquez OA, Den Beste K, Hoddeson EK, Parkos CA, Nusrat A, Wise SK. House dust mite allergen Der p 1 effects on sinonasal epithelial tight junctions. *Int Forum Allergy Rhinol*. Aug 2013;3(8):630-5. doi:10.1002/alr.21168

201. Steelant B, Seys SF, Van Gerven L, et al. Histamine and T helper cytokine-driven epithelial barrier dysfunction in allergic rhinitis. *J Allergy Clin Immunol*. Mar 2018;141(3):951-963 e8. doi:10.1016/j.jaci.2017.08.039

202. Ohwada K, Konno T, Kohno T, et al. Effects of HMGB1 on Tricellular Tight Junctions via TGF-beta Signaling in Human Nasal Epithelial Cells. *Int J Mol Sci*. Aug 4 2021;22(16)doi:10.3390/ijms22168390

203. Fukuoka A, Matsushita K, Morikawa T, Takano H, Yoshimoto T. Diesel exhaust particles exacerbate allergic rhinitis in mice by disrupting the nasal epithelial barrier. *Clin Exp Allergy*. Jan 2016;46(1):142-52. doi:10.1111/cea.12597

204. Kamekura R, Kojima T, Koizumi J, et al. Thymic stromal lymphopoietin enhances tight-junction barrier function of human nasal epithelial cells. *Cell Tissue Res*. Nov 2009;338(2):283-93. doi:10.1007/s00441-009-0855-1

205. Hupin C, Gohy S, Bouzin C, Lecocq M, Polette M, Pilette C. Features of mesenchymal transition in the airway epithelium from chronic rhinosinusitis. *Allergy*. Nov 2014;69(11):1540-9. doi:10.1111/all.12503

206. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. Nov 2021;21(11):739-751. doi:10.1038/s41577-021-00538-7

207. Wawrzyniak P, Wawrzyniak M, Wanke K, et al. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients. *J Allergy Clin Immunol*. Jan 2017;139(1):93-103. doi:10.1016/j.jaci.2016.03.050

208. Nur Husna SM, Siti Sarah CO, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Reduced occludin and claudin-7 expression is associated with urban locations and exposure to second-hand smoke in allergic rhinitis patients. *Sci Rep*. Jan 13 2021;11(1):1245. doi:10.1038/s41598-020-79208-y

209. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. Aug 2010;10(4):482-96. doi:10.1016/j.coph.2010.04.001

210. Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol Metab*. Feb 2010;95(2):471-8. doi:10.1210/jc.2009-1773

211. Kongsbak M, Levring TB, Geisler C, von Essen MR. The vitamin d receptor and T cell function. *Front Immunol*. 2013;4:148. doi:10.3389/fimmu.2013.00148

212. Tian HQ, Cheng L. The role of vitamin D in allergic rhinitis. *Asia Pac Allergy*. Apr 2017;7(2):65-73. doi:10.5415/apallergy.2017.7.2.65

213. Hamzaoui A, Berraies A, Hamdi B, Kaabachi W, Ammar J, Hamzaoui K. Vitamin D reduces the differentiation and expansion of Th17 cells in young asthmatic children. *Immunobiology*. Nov 2014;219(11):873-9. doi:10.1016/j.imbio.2014.07.009

214. Zhang H, Shih DQ, Zhang X. Mechanisms underlying effects of 1,25-Dihydroxyvitamin D3 on the Th17 cells. *Eur J Microbiol Immunol (Bp)*. Dec 2013;3(4):237-40. doi:10.1556/EuJMI.3.2013.4.1

215. Urry Z, Chambers ES, Xystrakis E, et al. The role of 1alpha,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct Foxp3+ and IL-10+ CD4+ T cells. *Eur J Immunol*. Oct 2012;42(10):2697-708. doi:10.1002/eji.201242370

216. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med*. Nov 2017;5(11):881-890. doi:10.1016/S2213-2600(17)30306-5

217. Riverin BD, Maguire JL, Li P. Vitamin D Supplementation for Childhood Asthma: A Systematic Review and Meta-Analysis. *PLoS One*. 2015;10(8):e0136841. doi:10.1371/journal.pone.0136841

218. Wee JH, Cho SW, Kim JW, Rhee CS. Non-association between low vitamin d levels and aeroallergen-positivity evaluated using multiple allergen simultaneous test in Korean adults. *Allergy Asthma Clin Immunol*. Feb 27 2021;17(1):23. doi:10.1186/s13223-021-00525-6

219. Bener A, Ehlayel MS, Bener HZ, Hamid Q. The impact of Vitamin D deficiency on asthma, allergic rhinitis and wheezing in children: An emerging public health problem. *J Family Community Med*. Sep 2014;21(3):154-61. doi:10.4103/2230-8229.142967

220. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. Sep 2016;27(6):580-90. doi:10.1111/pai.12599

221. Bakhshaee M, Sharifian M, Esmatinia F, Rasoulian B, Mohebbi M. Therapeutic effect of vitamin D supplementation on allergic rhinitis. *Eur Arch Otorhinolaryngol*. Oct 2019;276(10):2797-2801. doi:10.1007/s00405-019-05546-x

222. Jerzynska J, Stelmach W, Rychlik B, et al. Clinical and immunological effects of vitamin D supplementation during the pollen season in children with allergic rhinitis. *Arch Med Sci*. Jan 2018;14(1):122-131. doi:10.5114/aoms.2016.61978

223. Takeno S, Yoshimura H, Kubota K, Taruya T, Ishino T, Hirakawa K. Comparison of nasal nitric oxide levels between the inferior turbinate surface and the middle meatus in patients with symptomatic allergic rhinitis. *Allergol Int*. Sep 2014;63(3):475-83. doi:10.2332/allergolint.14-OA-0689

224. Takeno S, Osada R, Furukido K, Chen JH, Yajin K. Increased nitric oxide production in nasal epithelial cells from allergic patients--RT-PCR analysis and direct imaging by a fluorescence indicator: DAF-2 DA. *Clin Exp Allergy*. Jun 2001;31(6):881-8. doi:10.1046/j.1365-2222.2001.01093.x

225. Yuksel H, Kirmaz C, Yilmaz O, et al. Nasal mucosal expression of nitric oxide synthases in patients with allergic rhinitis and its relation to asthma. *Ann Allergy Asthma Immunol*. Jan 2008;100(1):12-6. doi:10.1016/S1081-1206(10)60398-5

226. Hou J, Lou H, Wang Y, et al. Nasal ventilation is an important factor in evaluating the diagnostic value of nasal nitric oxide in allergic rhinitis. *Int Forum Allergy Rhinol*. Jun 2018;8(6):686-694. doi:10.1002/alr.22087

227. Ren L, Zhang W, Zhang Y, Zhang L. Nasal Nitric Oxide Is Correlated With Nasal Patency and Nasal Symptoms. *Allergy Asthma Immunol Res*. May 2019;11(3):367-380. doi:10.4168/aair.2019.11.3.367

228. Liu C, Zheng K, Liu X, et al. Use of Nasal Nitric Oxide in the Diagnosis of Allergic Rhinitis and Nonallergic Rhinitis in Patients with and without Sinus Inflammation. *J Allergy Clin Immunol Pract*. May 2020;8(5):1574-1581 e4. doi:10.1016/j.jaip.2019.12.017

229. Maniscalco M, Sofia M, Pelaia G. Nitric oxide in upper airways inflammatory diseases. *Inflamm Res*. Feb 2007;56(2):58-69. doi:10.1007/s00011-006-6111-1

230. Barnes PJ, Dweik RA, Gelb AF, et al. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest*. Sep 2010;138(3):682-92. doi:10.1378/chest.09-2090

231. Maniscalco M, Bianco A, Mazzarella G, Motta A. Recent Advances on Nitric Oxide in the Upper Airways. *Curr Med Chem*. 2016;23(24):2736-2745. doi:10.2174/0929867323666160627115335

232. Alam MS, Akaike T, Okamoto S, et al. Role of nitric oxide in host defense in murine salmonellosis as a function of its antibacterial and antiapoptotic activities. *Infect Immun*. Jun 2002;70(6):3130-42. doi:10.1128/IAI.70.6.3130-3142.2002

233. Poljakovic M, Persson K. Urinary tract infection in iNOS-deficient mice with focus on bacterial sensitivity to nitric oxide. *Am J Physiol Renal Physiol*. Jan 2003;284(1):F22-31. doi:10.1152/ajprenal.00101.2002

234. Rajaram K, Nelson DE. Chlamydia muridarum infection of macrophages elicits bactericidal nitric oxide production via reactive oxygen species and cathepsin B. *Infect Immun*. Aug 2015;83(8):3164-75. doi:10.1128/IAI.00382-15

235. Yadav R, Samuni Y, Abramson A, et al. Pro-oxidative synergic bactericidal effect of NO: kinetics and inhibition by nitroxides. *Free Radic Biol Med*. Feb 2014;67:248-54. doi:10.1016/j.freeradbiomed.2013.10.012

236. Workman AD, Carey RM, Kohanski MA, et al. Relative susceptibility of airway organisms to antimicrobial effects of nitric oxide. *Int Forum Allergy Rhinol*. Aug 2017;7(8):770-776. doi:10.1002/alr.21966

237. Carey RM, Chen B, Adappa ND, et al. Human upper airway epithelium produces nitric oxide in response to Staphylococcus epidermidis. *Int Forum Allergy Rhinol*. Dec 2016;6(12):1238-1244. doi:10.1002/alr.21837

238. Freund JR, Mansfield CJ, Doghramji LJ, et al. Activation of airway epithelial bitter taste receptors by Pseudomonas aeruginosa quinolones modulates calcium, cyclic-AMP, and nitric oxide signaling. *J Biol Chem*. Jun 22 2018;293(25):9824-9840. doi:10.1074/jbc.RA117.001005

239. Antosova M, Bencova A, Mokra D, Plevkova J, Pepucha L, Buday T. Exhaled and Nasal Nitric Oxide - Impact for Allergic Rhinitis. *Physiol Res*. Mar 27 2020;69(Suppl 1):S123-S130. doi:10.33549/physiolres.934393

240. Rolim WR, Pieretti JC, Reno DLS, et al. Antimicrobial Activity and Cytotoxicity to Tumor Cells of Nitric Oxide Donor and Silver Nanoparticles Containing PVA/PEG Films for Topical Applications. *ACS Appl Mater Interfaces*. Feb 13 2019;11(6):6589-6604. doi:10.1021/acsami.8b19021

241. Akaberi D, Krambrich J, Ling J, et al. Mitigation of the replication of SARS-CoV-2 by nitric oxide in vitro. *Redox Biol*. Oct 2020;37:101734. doi:10.1016/j.redox.2020.101734

242. Pieretti JC, Rubilar O, Weller RB, Tortella GR, Seabra AB. Nitric oxide (NO) and nanoparticles - Potential small tools for the war against COVID-19 and other human coronavirus infections. *Virus Res*. Jan 2 2021;291:198202. doi:10.1016/j.virusres.2020.198202

243. Li D, Shirakami G, Zhan X, Johns RA. Regulation of ciliary beat frequency by the nitric oxide-cyclic guanosine monophosphate signaling pathway in rat airway epithelial cells. *Am J Respir Cell Mol Biol*. Aug 2000;23(2):175-81. doi:10.1165/ajrcmb.23.2.4022

244. Hariri BM, Payne SJ, Chen B, et al. In vitro effects of anthocyanidins on sinonasal epithelial nitric oxide production and bacterial physiology. *Am J Rhinol Allergy*. Jul 2016;30(4):261-8. doi:10.2500/ajra.2016.30.4331

245. Fowler CJ, Olivier KN, Leung JM, et al. Abnormal nasal nitric oxide production, ciliary beat frequency, and Toll-like receptor response in pulmonary nontuberculous mycobacterial disease epithelium. *Am J Respir Crit Care Med*. Jun 15 2013;187(12):1374-81. doi:10.1164/rccm.201212-2197OC

246. Jiao J, Wang H, Lou W, et al. Regulation of ciliary beat frequency by the nitric oxide signaling pathway in mouse nasal and tracheal epithelial cells. *Exp Cell Res*. Oct 15 2011;317(17):2548-53. doi:10.1016/j.yexcr.2011.07.007

247. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity*. Jul 2003;19(1):59-70. doi:10.1016/s1074-7613(03)00171-7

248. Cobb JP, Hotchkiss RS, Swanson PE, et al. Inducible nitric oxide synthase (iNOS) gene deficiency increases the mortality of sepsis in mice. *Surgery*. Aug 1999;126(2):438-42.

249. MacMicking JD, North RJ, LaCourse R, Mudgett JS, Shah SK, Nathan CF. Identification of nitric oxide synthase as a protective locus against tuberculosis. *Proc Natl Acad Sci U S A*. May 13 1997;94(10):5243-8. doi:10.1073/pnas.94.10.5243

250. Mishra BB, Lovewell RR, Olive AJ, et al. Nitric oxide prevents a pathogen-permissive granulocytic inflammation during tuberculosis. *Nat Microbiol*. May 15 2017;2:17072. doi:10.1038/nmicrobiol.2017.72

251. Bajwa G, DeBerardinis RJ, Shao B, Hall B, Farrar JD, Gill MA. Cutting Edge: Critical Role of Glycolysis in Human Plasmacytoid Dendritic Cell Antiviral Responses. *J Immunol*. Mar 1 2016;196(5):2004-9. doi:10.4049/jimmunol.1501557

252. Kopincova J, Calkovska A. Meconium-induced inflammation and surfactant inactivation: specifics of molecular mechanisms. *Pediatr Res*. Apr 2016;79(4):514-21. doi:10.1038/pr.2015.265

253. Heffler E, Carpagnano GE, Favero E, et al. Fractional Exhaled Nitric Oxide (FENO) in the management of asthma: a position paper of the Italian Respiratory Society (SIP/IRS) and Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC). *Multidiscip Respir Med*. Jan 28 2020;15(1):36. doi:10.4081/mrm.2020.36

254. Soares MP, Teixeira L, Moita LF. Disease tolerance and immunity in host protection against infection. *Nat Rev Immunol*. Feb 2017;17(2):83-96. doi:10.1038/nri.2016.136

255. Garcia-Ortiz A, Serrador JM. Nitric Oxide Signaling in T Cell-Mediated Immunity. *Trends Mol Med*. Apr 2018;24(4):412-427. doi:10.1016/j.molmed.2018.02.002

256. Akdis CA, Arkwright PD, Bruggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy*. Jul 2020;75(7):1582-1605. doi:10.1111/all.14318

257. Monga N, Sethi GS, Kondepudi KK, Naura AS. Lipid mediators and asthma: Scope of therapeutics. *Biochem Pharmacol*. Sep 2020;179:113925. doi:10.1016/j.bcp.2020.113925

258. Huang F, Yin JN, Wang HB, Liu SY, Li YN. Association of imbalance of effector T cells and regulatory cells with the severity of asthma and allergic rhinitis in children. *Allergy Asthma Proc*. Nov 1 2017;38(6):70-77. doi:10.2500/aap.2017.38.4076

259. Amiel E, Everts B, Fritz D, et al. Mechanistic target of rapamycin inhibition extends cellular lifespan in dendritic cells by preserving mitochondrial function. *J Immunol*. Sep 15 2014;193(6):2821-30. doi:10.4049/jimmunol.1302498

260. Everts B, Amiel E, van der Windt GJ, et al. Commitment to glycolysis sustains survival of NO-producing inflammatory dendritic cells. *Blood*. Aug 16 2012;120(7):1422-31. doi:10.1182/blood-2012-03-419747

261. Lawless SJ, Kedia-Mehta N, Walls JF, et al. Glucose represses dendritic cell-induced T cell responses. *Nat Commun*. May 30 2017;8:15620. doi:10.1038/ncomms15620

262. Linke M, Fritsch SD, Sukhbaatar N, Hengstschlager M, Weichhart T. mTORC1 and mTORC2 as regulators of cell metabolism in immunity. *FEBS Lett*. Oct 2017;591(19):3089-3103. doi:10.1002/1873-3468.12711

263. Chen C, Pore N, Behrooz A, Ismail-Beigi F, Maity A. Regulation of glut1 mRNA by hypoxia-inducible factor-1. Interaction between H-ras and hypoxia. *J Biol Chem*. Mar 23 2001;276(12):9519-25. doi:10.1074/jbc.M010144200

264. Xu L, Huang Y, Yang J, et al. Dendritic cell-derived nitric oxide is involved in IL-4-induced suppression of experimental allergic encephalomyelitis (EAE) in Lewis rats. *Clin Exp Immunol*. Oct 1999;118(1):115-21. doi:10.1046/j.1365-2249.1999.01029.x

265. Nathan C. Nitric oxide as a secretory product of mammalian cells. *FASEB J*. Sep 1992;6(12):3051-64.

266. Bogdan C. Nitric oxide and the immune response. *Nat Immunol*. Oct 2001;2(10):907-16. doi:10.1038/ni1001-907

267. Nathan C. Specificity of a third kind: reactive oxygen and nitrogen intermediates in cell signaling. *J Clin Invest*. Mar 2003;111(6):769-78. doi:10.1172/JCI18174

268. Bogdan C. Regulation of lymphocytes by nitric oxide. *Methods Mol Biol*. 2011;677:375-93. doi:10.1007/978-1-60761-869-0_24

269. Wink DA, Hines HB, Cheng RY, et al. Nitric oxide and redox mechanisms in the immune response. *J Leukoc Biol*. Jun 2011;89(6):873-91. doi:10.1189/jlb.1010550

270. Ibiza S, Serrador JM. The role of nitric oxide in the regulation of adaptive immune responses. *Immunologia*. 2008;27:103-117.

271. Bogdan C. Nitric oxide synthase in innate and adaptive immunity: an update. *Trends Immunol*. Mar 2015;36(3):161-78. doi:10.1016/j.it.2015.01.003

272. Bailey JD, Diotallevi M, Nicol T, et al. Nitric Oxide Modulates Metabolic Remodeling in Inflammatory Macrophages through TCA Cycle Regulation and Itaconate Accumulation. *Cell Rep*. Jul 2 2019;28(1):218-230 e7. doi:10.1016/j.celrep.2019.06.018

273. Lee M, Rey K, Besler K, Wang C, Choy J. Immunobiology of Nitric Oxide and Regulation of Inducible Nitric Oxide Synthase. *Results Probl Cell Differ*. 2017;62:181-207. doi:10.1007/978-3-319-54090-0_8

274. Pavord ID, Afzalnia S, Menzies-Gow A, Heaney LG. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. *Clin Exp Allergy*. Feb 2017;47(2):148-160. doi:10.1111/cea.12881

275. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. Nov 2 2019;394(10209):1638-1650. doi:10.1016/S0140-6736(19)31881-1

276. Nesi RT, Barroso MV, Souza Muniz V, et al. Pharmacological modulation of reactive oxygen species (ROS) improves the airway hyperresponsiveness by shifting the Th1 response in allergic inflammation induced by ovalbumin. *Free Radic Res*. Jul-Aug 2017;51(7-8):708-722. doi:10.1080/10715762.2017.1364377

277. Bove PF, van der Vliet A. Nitric oxide and reactive nitrogen species in airway epithelial signaling and inflammation. *Free Radic Biol Med*. Aug 15 2006;41(4):515-27. doi:10.1016/j.freeradbiomed.2006.05.011

278. Sparkman L, Boggaram V. Nitric oxide increases IL-8 gene transcription and mRNA stability to enhance IL-8 gene expression in lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. Oct 2004;287(4):L764-73. doi:10.1152/ajplung.00165.2004

279. Gottipati KR, Bandari SK, Nonnenmann MW, et al. Transcriptional mechanisms and protein kinase signaling mediate organic dust induction of IL-8 expression in lung epithelial and THP-1 cells. *Am J Physiol Lung Cell Mol Physiol*. Jan 1 2015;308(1):L11-21. doi:10.1152/ajplung.00215.2014

280. Vocca L, Di Sano C, Uasuf CG, et al. IL-33/ST2 axis controls Th2/IL-31 and Th17 immune response in allergic airway diseases. *Immunobiology*. Aug 2015;220(8):954-63. doi:10.1016/j.imbio.2015.02.005

281. Uchida M, Anderson EL, Squillace DL, et al. Oxidative stress serves as a key checkpoint for IL-33 release by airway epithelium. *Allergy*. Oct 2017;72(10):1521-1531. doi:10.1111/all.13158

282. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. *Nutr Rev*. Aug 2012;70 Suppl 1:S38-44. doi:10.1111/j.1753-4887.2012.00493.x

283. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. Mar 4 2010;464(7285):59-65. doi:10.1038/nature08821

284. International Human Genome Sequencing C. Finishing the euchromatic sequence of the human genome. *Nature*. Oct 21 2004;431(7011):931-45. doi:10.1038/nature03001

285. Fierer N, Hamady M, Lauber CL, Knight R. The influence of sex, handedness, and washing on the diversity of hand surface bacteria. *Proc Natl Acad Sci U S A*. Nov 18 2008;105(46):17994-9. doi:10.1073/pnas.0807920105

286. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature*. Jan 22 2009;457(7228):480-4. doi:10.1038/nature07540

287. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy*. Jun 2014;44(6):842-50. doi:10.1111/cea.12253

288. Sjogren YM, Jenmalm MC, Bottcher MF, Bjorksten B, Sverremark-Ekstrom E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clin Exp Allergy*. Apr 2009;39(4):518-26. doi:10.1111/j.1365-2222.2008.03156.x

289. Melli LC, do Carmo-Rodrigues MS, Araujo-Filho HB, Sole D, de Morais MB. Intestinal microbiota and allergic diseases: A systematic review. *Allergol Immunopathol (Madr)*. Mar-Apr 2016;44(2):177-88. doi:10.1016/j.aller.2015.01.013

290. Fujimura KE, Sitarik AR, Havstad S, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. Oct 2016;22(10):1187-1191. doi:10.1038/nm.4176

291. Ipci K, Altintoprak N, Muluk NB, Senturk M, Cingi C. The possible mechanisms of the human microbiome in allergic diseases. *Eur Arch Otorhinolaryngol*. Feb 2017;274(2):617-626. doi:10.1007/s00405-016-4058-6

292. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol*. Sep 2011;128(3):646-52 e1-5. doi:10.1016/j.jaci.2011.04.060

293. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

294. Watts AM, West NP, Zhang P, Smith PK, Cripps AW, Cox AJ. The Gut Microbiome of Adults with Allergic Rhinitis Is Characterised by Reduced Diversity and an Altered Abundance of Key Microbial Taxa Compared to Controls. *Int Arch Allergy Immunol*. 2021;182(2):94-105. doi:10.1159/000510536

295. Zhou MS, Zhang B, Gao ZL, et al. Altered diversity and composition of gut microbiota in patients with allergic rhinitis. *Microb Pathog*. Dec 2021;161(Pt A):105272. doi:10.1016/j.micpath.2021.105272

296. Hua X, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. *EBioMedicine*. Jan 2016;3:172-179. doi:10.1016/j.ebiom.2015.11.038

297. Choi CH, Poroyko V, Watanabe S, et al. Seasonal allergic rhinitis affects sinonasal microbiota. *Am J Rhinol Allergy*. Jul-Aug 2014;28(4):281-6. doi:10.2500/ajra.2014.28.4050

298. Gan W, Yang F, Meng J, Liu F, Liu S, Xian J. Comparing the nasal bacterial microbiome diversity of allergic rhinitis, chronic rhinosinusitis and control subjects. *Eur Arch Otorhinolaryngol*. Mar 2021;278(3):711-718. doi:10.1007/s00405-020-06311-1

299. Bender ME, Read TD, Edwards TS, et al. A Comparison of the Bacterial Nasal Microbiome in Allergic Rhinitis Patients Before and After Immunotherapy. *Laryngoscope*. Dec 2020;130(12):E882-E888. doi:10.1002/lary.28599

300. Hu B, Kuang Y, Jing Y, Li Y, Zhao H, Ouyang H. Pediatric allergic rhinitis with functional gastrointestinal disease: Associations with the intestinal microbiota and gastrointestinal peptides and therapeutic effects of interventions. *Hum Exp Toxicol*. Nov 2021;40(11):2012-2021. doi:10.1177/09603271211017325

301. Morin A, McKennan CG, Pedersen CT, et al. Epigenetic landscape links upper airway microbiota in infancy with allergic rhinitis at 6 years of age. *J Allergy Clin Immunol*. Dec 2020;146(6):1358-1366. doi:10.1016/j.jaci.2020.07.005

302. Zhu L, Xu F, Wan W, et al. Gut microbial characteristics of adult patients with allergy rhinitis. *Microb Cell Fact*. Sep 1 2020;19(1):171. doi:10.1186/s12934-020-01430-0

303. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. *J Asthma Allergy*. 2016;9:93-100. doi:10.2147/JAA.S81541

304. Genuneit J, Seibold AM, Apfelbacher CJ, et al. Overview of systematic reviews in allergy epidemiology. *Allergy*. Jun 2017;72(6):849-856. doi:10.1111/all.13123

305. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy*. May 2020;75(5):1023-1042. doi:10.1111/all.14221

306. Shamji MH, Palmer E, Layhadi JA, Moraes TJ, Eiwegger T. Biological treatment in allergic disease. *Allergy*. Sep 2021;76(9):2934-2937. doi:10.1111/all.14954

307. Kanda A, Kobayashi Y, Asako M, Tomoda K, Kawauchi H, Iwai H. Regulation of Interaction between the Upper and Lower Airways in United Airway Disease. *Med Sci (Basel)*. Feb 11 2019;7(2)doi:10.3390/medsci7020027

308. Akdis CA, Bachert C, Cingi C, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. Jun 2013;131(6):1479-90. doi:10.1016/j.jaci.2013.02.036

309. Asano K, Ueki S, Tamari M, Imoto Y, Fujieda S, Taniguchi M. Adult-onset eosinophilic airway diseases. *Allergy*. Dec 2020;75(12):3087-3099. doi:10.1111/all.14620

310. Backaert W, Steelant B, Jorissen M, et al. Self-reported nasal hyperreactivity is common in all chronic upper airway inflammatory phenotypes and not related to general well-being. *Allergy*. Dec 2021;76(12):3806-3809. doi:10.1111/all.15060

311. Feijen J, Seys SF, Steelant B, et al. Prevalence and triggers of self-reported nasal hyperreactivity in adults with asthma. *World Allergy Organ J*. Jun 2020;13(6):100132. doi:10.1016/j.waojou.2020.100132

312. Doulaptsi M, Steelant B, Prokopakis E, et al. Prevalence and impact of nasal hyperreactivity in chronic rhinosinusitis. *Allergy*. Jul 2020;75(7):1768-1771. doi:10.1111/all.14199

313. Agache I, Sugita K, Morita H, Akdis M, Akdis CA. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. *Curr Allergy Asthma Rep*. Jun 2015;15(6):29. doi:10.1007/s11882-015-0529-x

314. Avdeeva KS, Fokkens WJ, Reitsma S. Towards a new epidemiological definition of chronic rhinitis: prevalence of nasal complaints in the general population. *Rhinology*. Jun 1 2021;59(3):258-266. doi:10.4193/Rhin20.637

315. Viiu B, Christer J, Fredrik S, et al. Asthma in combination with rhinitis and eczema is associated with a higher degree of type-2 inflammation and symptom burden than asthma alone. *Allergy*. Dec 2021;76(12):3827-3829. doi:10.1111/all.15082

316. Camp J, Cane JL, Bafadhel M. Shall We Focus on the Eosinophil to Guide Treatment with Systemic Corticosteroids during Acute Exacerbations of COPD?: PRO. *Med Sci (Basel)*. Sep 11 2018;6(3)doi:10.3390/medsci6030074

317. Hox V, Lourijsen E, Jordens A, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy*. 2020;10:1. doi:10.1186/s13601-019-0303-6

318. Hox V, Lourijsen E, Jordens A, et al. Correction to: Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy*. 2020;10:38. doi:10.1186/s13601-020-00343-w

319. Agache I, Song Y, Alonso-Coello P, et al. Efficacy and safety of treatment with biologicals for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAACI guidelines. *Allergy*. Aug 2021;76(8):2337-2353. doi:10.1111/all.14809

320. Hellings PW, Verhoeven E, Fokkens WJ. State-of-the-art overview on biological treatment for CRSwNP. *Rhinology*. Apr 1 2021;59(2):151-163. doi:10.4193/Rhin20.570

321. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. May 2016;137(5):1449-1456 e4. doi:10.1016/j.jaci.2015.12.1324

322. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: Relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. *Allergy*. Mar 2022;77(3):812-826. doi:10.1111/all.15074

323. Steelant B, Seys SF, Boeckxstaens G, Akdis CA, Ceuppens JL, Hellings PW. Restoring airway epithelial barrier dysfunction: a new therapeutic challenge in allergic airway disease. *Rhinology*. Sep 2016;54(3):195-205. doi:10.4193/Rhino15.376

324. Scadding GK, Scadding GW. Innate and Adaptive Immunity: ILC2 and Th2 Cells in Upper and Lower Airway Allergic Diseases. *J Allergy Clin Immunol Pract*. May 2021;9(5):1851-1857. doi:10.1016/j.jaip.2021.02.013

325. van der Ploeg EK, Golebski K, van Nimwegen M, et al. Steroid-resistant human inflammatory ILC2s are marked by CD45RO and elevated in type 2 respiratory diseases. *Sci Immunol*. Jan 29 2021;6(55)doi:10.1126/sciimmunol.abd3489

326. Braunstahl GJ, Fokkens W. Nasal involvement in allergic asthma. *Allergy*. Dec 2003;58(12):1235-43. doi:10.1046/j.0105-4538.2003.00354.x

327. Izuhara Y, Matsumoto H, Nagasaki T, et al. Mouth breathing, another risk factor for asthma: the Nagahama Study. *Allergy*. Jul 2016;71(7):1031-6. doi:10.1111/all.12885

328. Braunstahl GJ. United airways concept: what does it teach us about systemic inflammation in airways disease? *Proc Am Thorac Soc*. Dec 2009;6(8):652-4. doi:10.1513/pats.200906-052DP

329. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol*. Feb 1992;89(2):611-8. doi:10.1016/0091-6749(92)90329-z

330. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med*. Jun 2000;161(6):2051-7. doi:10.1164/ajrccm.161.6.9906121

331. Braunstahl GJ, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med*. Sep 1 2001;164(5):858-65. doi:10.1164/ajrccm.164.5.2006082

332. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol*. Mar 2001;107(3):469-76. doi:10.1067/mai.2001.113046

333. Allakhverdi Z, Comeau MR, Smith DE, et al. CD34+ hemopoietic progenitor cells are potent effectors of allergic inflammation. *J Allergy Clin Immunol*. Feb 2009;123(2):472-8. doi:10.1016/j.jaci.2008.10.022

334. Sergejeva S, Malmhall C, Lotvall J, Pullerits T. Increased number of CD34+ cells in nasal mucosa of allergic rhinitis patients: inhibition by a local corticosteroid. *Clin Exp Allergy*. Jan 2005;35(1):34-8. doi:10.1111/j.1365-2222.2004.02038.x

335. Lans R, Fokkens WJ, Adriaensen G, Hoven DR, Drubbel JJ, Reitsma S. Real-life observational cohort verifies high efficacy of dupilumab for chronic rhinosinusitis with nasal polyps. *Allergy*. Feb 2022;77(2):670-674. doi:10.1111/all.15134

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]

REFERENCES

1. ISAAC Steering Committee. ISAAC - The International Study of Asthma and Allergies in Childhood. Accessed November 2021, http://isaac.auckland.ac.nz

2. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. Apr 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

3. World Health Organization. International Statistical Classigfication of Diseases and Related Health Problems (ICD). Accessed November 2021, https://www.who.int/standards/classifications/classification-of-diseases

4. Alqahtani JM. Atopy and allergic diseases among Saudi young adults: A cross-sectional study. *J Int Med Res*. Jan 2020;48(1):300060519899760. doi:10.1177/0300060519899760

5. Oliveira TB, Persigo ALK, Ferrazza CC, Ferreira ENN, Veiga ABG. Prevalence of asthma, allergic rhinitis and pollinosis in a city of Brazil: A monitoring study. *Allergol Immunopathol (Madr)*. Nov - Dec 2020;48(6):537-544. doi:10.1016/j.aller.2020.03.010

6. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

7. Nam JS, Hwang CS, Hong MP, Kim KS. Prevalence and clinical characteristics of allergic rhinitis in the elderly Korean population. *Eur Arch Otorhinolaryngol*. Dec 2020;277(12):3367-3373. doi:10.1007/s00405-020-06256-5

8. Mortz CG, Andersen KE, Poulsen LK, Kjaer HF, Broesby-Olsen S, Bindslev-Jensen C. Atopic diseases and type I sensitization from adolescence to adulthood in an unselected population (TOACS) with focus on predictors for allergic rhinitis. *Allergy*. Feb 2019;74(2):308-317. doi:10.1111/all.13630

9. Wang XY, Ma TT, Wang XY, et al. Prevalence of pollen-induced allergic rhinitis with high pollen exposure in grasslands of northern China. *Allergy*. Jun 2018;73(6):1232-1243. doi:10.1111/all.13388

10. Schmitt J, Stadler E, Kuster D, Wustenberg EG. Medical care and treatment of allergic rhinitis: a population-based cohort study based on routine healthcare utilization data. *Allergy*. Jun 2016;71(6):850-8. doi:10.1111/all.12838

11. Sorensen M, Wickman M, Sollid JU, Furberg AS, Klingenberg C. Allergic disease and Staphylococcus aureus carriage in adolescents in the Arctic region of Norway. *Pediatr Allergy Immunol*. Nov 2016;27(7):728-735. doi:10.1111/pai.12595

12. Winther A, Dennison E, Ahmed LA, et al. The Tromso Study: Fit Futures: a study of Norwegian adolescents' lifestyle and bone health. *Arch Osteoporos*. 2014;9:185. doi:10.1007/s11657-014-0185-0

13. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. *Int J Epidemiol*. Aug 2012;41(4):961-7. doi:10.1093/ije/dyr049

14. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. *Front Immunol*. 2020;11:1907. doi:10.3389/fimmu.2020.01907

15. Park S, Jung PK, Choi M, et al. Association between occupational clusters and allergic rhinitis in the Korean population: analysis of the Korean National Health and Nutrition Examination Survey data. *J Occup Health*. Jul 25 2018;60(4):312-319. doi:10.1539/joh.2017-0234-OA

16. Cardell LO, Olsson P, Andersson M, et al. TOTALL: high cost of allergic rhinitis-a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med*. Feb 4 2016;26:15082. doi:10.1038/npjpcrm.2015.82

17. Idani E, Raji H, Madadizadeh F, Cheraghian B, Haddadzadeh Shoshtari M, Dastoorpoor M. Prevalence of asthma and other allergic conditions in adults in Khuzestan, southwest Iran, 2018. *BMC Public Health*. Mar 13 2019;19(1):303. doi:10.1186/s12889-019-6491-0

18. Reijula J, Latvala J, Makela M, Siitonen S, Saario M, Haahtela T. Long-term trends of asthma, allergic rhinitis and atopic eczema in young Finnish men: a retrospective analysis, 1926-2017. *Eur Respir J*. Dec 2020;56(6)doi:10.1183/13993003.02144-2019

19. Maio S, Baldacci S, Carrozzi L, et al. Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. *Respir Med*. Jan 2016;110:58-65. doi:10.1016/j.rmed.2015.11.006

20. Janson C, Johannessen A, Franklin K, et al. Change in the prevalence asthma, rhinitis and respiratory symptom over a 20 year period: associations to year of birth, life style and sleep related symptoms. *BMC Pulm Med*. Sep 12 2018;18(1):152. doi:10.1186/s12890-018-0690-9

21. Sucharew H, Ryan PH, Bernstein D, et al. Exposure to traffic exhaust and night cough during early childhood: the CCAAPS birth cohort. *Pediatr Allergy Immunol*. Mar 2010;21(2 Pt 1):253-9. doi:10.1111/j.1399-3038.2009.00952.x

22. Herr M, Clarisse B, Nikasinovic L, et al. Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort. *Allergy*. Feb 2011;66(2):214-21. doi:10.1111/j.1398-9995.2010.02467.x

23. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol*. Nov 2000;106(5):832-9. doi:10.1067/mai.2000.110098

24. Westman M, Stjarne P, Asarnoj A, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol*. Feb 2012;129(2):403-8. doi:10.1016/j.jaci.2011.09.036

25. Ait-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. Jan 2009;64(1):123-48. doi:10.1111/j.1398-9995.2008.01884.x

26. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D, Group IPIS. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. Mar 2008;19(2):110-24. doi:10.1111/j.1399-3038.2007.00601.x

27. Mallol J, Crane J, von Mutius E, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. *Allergol Immunopathol (Madr)*. Mar-Apr 2013;41(2):73-85. doi:10.1016/j.aller.2012.03.001

28. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol*. Nov 1997;8(4):161-76. doi:10.1111/j.1399-3038.1997.tb00156.x

29. Soto-Martinez ME, Yock-Corrales A, Camacho-Badilla K, et al. The current prevalence of asthma, allergic rhinitis, and eczema related symptoms in school-aged children in Costa Rica. *J Asthma*. Apr 2019;56(4):360-368. doi:10.1080/02770903.2018.1455860

30. Morikawa E, Sasaki M, Yoshida K, Adachi Y, Odajima H, Akasawa A. Nationwide survey of the prevalence of wheeze, rhino-conjunctivitis, and eczema among Japanese children in 2015. *Allergol Int*. Jan 2020;69(1):98-103. doi:10.1016/j.alit.2019.08.010

31. Ibrahim NM, Almarzouqi FI, Al Melaih FA, Farouk H, Alsayed M, AlJassim FM. Prevalence of asthma and allergies among children in the United Arab Emirates: A cross-sectional study. *World Allergy Organ J*. Oct 2021;14(10):100588. doi:10.1016/j.waojou.2021.100588

32. Ozoh OB, Aderibigbe SA, Ayuk AC, et al. The prevalence of asthma and allergic rhinitis in Nigeria: A nationwide survey among children, adolescents and adults. *PLoS One*. 2019;14(9):e0222281. doi:10.1371/journal.pone.0222281

33. de Oliveira TB, Moscon JG, Ferreira E, da Veiga ABG. Prevalence of symptoms of asthma and allergic rhinitis in children in Southern Brazil: a ten-year monitoring study. *J Asthma*. Apr 2020;57(4):373-380. doi:10.1080/02770903.2019.1573253

34. Ochoa-Aviles C, Morillo D, Rodriguez A, et al. Prevalence and risk factors for asthma, rhinitis, eczema, and atopy among preschool children in an Andean city. *PLoS One*. 2020;15(7):e0234633. doi:10.1371/journal.pone.0234633

35. Tong H, Gao L, Deng Y, et al. Prevalence of Allergic Rhinitis and Associated Risk Factors in 6 to 12 Years Schoolchildren From Wuhan in Central China: A Cross-sectional Study. *Am J Rhinol Allergy*. Sep 2020;34(5):632-641. doi:10.1177/1945892420920499

36. Zhang HL, Wang BY, Luo Y, et al. Association of pet-keeping in home with self-reported asthma and asthma-related symptoms in 11611 school children from China. *J Asthma*. Dec 2021;58(12):1555-1564. doi:10.1080/02770903.2020.1818772

37. Pols DH, Wartna JB, Moed H, van Alphen EI, Bohnen AM, Bindels PJ. Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review. *Scand J Prim Health Care*. Jun 2016;34(2):143-50. doi:10.3109/02813432.2016.1160629

38. Van Wonderen KE, Van Der Mark LB, Mohrs J, Bindels PJ, Van Aalderen WM, Ter Riet G. Different definitions in childhood asthma: how dependable is the dependent variable? *Eur Respir J*. Jul 2010;36(1):48-56. doi:10.1183/09031936.00154409

39. Pols DHJ, Nielen MMJ, Korevaar JC, Bindels PJE, Bohnen AM. Reliably estimating prevalences of atopic children: an epidemiological study in an extensive and representative primary care database. *NPJ Prim Care Respir Med*. Apr 13 2017;27(1):23. doi:10.1038/s41533-017-0025-y

40. Kurukulaaratchy RJ, Karmaus W, Raza A, Matthews S, Roberts G, Arshad SH. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. *Clin Exp Allergy*. Jun 2011;41(6):851-9. doi:10.1111/j.1365-2222.2011.03765.x

41. de Jong NW, Elbert NJ, Mensink-Bout SM, et al. Parental and child factors associated with inhalant and food allergy in a population-based prospective cohort study: the Generation R Study. *Eur J Pediatr*. Oct 2019;178(10):1507-1517. doi:10.1007/s00431-019-03441-5

42. Strachan DP, Rutter CE, Asher MI, et al. Worldwide time trends in prevalence of symptoms of rhinoconjunctivitis in children: Global Asthma Network Phase I. *Pediatr Allergy Immunol*. Jan 2022;33(1):e13656. doi:10.1111/pai.13656

43. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. Nov 2004;24(5):758-64. doi:10.1183/09031936.04.00013904

44. Bousquet PJ, Leynaert B, Neukirch F, et al. Geographical distribution of atopic rhinitis in the European Community Respiratory Health Survey I. *Allergy*. Oct 2008;63(10):1301-9. doi:10.1111/j.1398-9995.2008.01824.x

45. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J*. Apr 1996;9(4):687-95. doi:10.1183/09031936.96.09040687

46. Weinmayr G, Forastiere F, Weiland SK, et al. International variation in prevalence of rhinitis and its relationship with sensitisation to perennial and seasonal allergens. *Eur Respir J*. Nov 2008;32(5):1250-61. doi:10.1183/09031936.00157807

47. Wang XD, Zheng M, Lou HF, et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy*. Aug 2016;71(8):1170-80. doi:10.1111/all.12874

48. Anderegg WRL, Abatzoglou JT, Anderegg LDL, Bielory L, Kinney PL, Ziska L. Anthropogenic climate change is worsening North American pollen seasons. *Proc Natl Acad Sci U S A*. Feb 16 2021;118(7)doi:10.1073/pnas.2013284118

49. Lake IR, Jones NR, Agnew M, et al. Climate Change and Future Pollen Allergy in Europe. *Environ Health Perspect*. Mar 2017;125(3):385-391. doi:10.1289/EHP173

50. Erbas B, Lowe AJ, Lodge CJ, et al. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. *Clin Exp Allergy*. Mar 2013;43(3):337-43. doi:10.1111/cea.12071

51. Toth I, Peternel R, Gajnik D, Vojnikovic B. Micro-regional hypersensitivity variations to inhalant allergens in the city of Zagreb and Zagreb County. *Coll Antropol*. Sep 2011;35 Suppl 2:31-7.

52. Kim J, Han Y, Seo SC, et al. Association of carbon monoxide levels with allergic diseases in children. *Allergy Asthma Proc*. Jan-Feb 2016;37(1):e1-7. doi:10.2500/aap.2016.37.3918

53. Li CW, Chen DD, Zhong JT, et al. Epidemiological characterization and risk factors of allergic rhinitis in the general population in Guangzhou City in china. *PLoS One*. 2014;9(12):e114950. doi:10.1371/journal.pone.0114950

54. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and Risk Factors of Chronic Rhinosinusitus, Allergic Rhinitis, and Nasal Septal Deviation: Results of the Korean National Health and Nutrition Survey 2008-2012. *JAMA Otolaryngol Head Neck Surg*. Feb 2016;142(2):162-7. doi:10.1001/jamaoto.2015.3142

55. Song WJ, Sohn KH, Kang MG, et al. Urban-rural differences in the prevalence of allergen sensitization and self-reported rhinitis in the elderly population. *Ann Allergy Asthma Immunol*. Jun 2015;114(6):455-61. doi:10.1016/j.anai.2015.03.008

56. Zheng M, Wang X, Wang M, et al. Clinical characteristics of allergic rhinitis patients in 13 metropolitan cities of China. *Allergy*. Feb 2021;76(2):577-581. doi:10.1111/all.14561

57. Beggs PJ, Katelaris CH, Medek D, et al. Differences in grass pollen allergen exposure across Australia. *Aust N Z J Public Health*. Feb 2015;39(1):51-5. doi:10.1111/1753-6405.12325

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**)

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	>97% European ancestry	1) rs1438673 2) rs2101521	1) 3.7E-19 2) 6.0E-17 3) 9.9E-	1) *WDR36* 2) *TLR1-TLR6 - TLR10* 3) *IL1RL2* -	1) Cellular processes and T cell activation 2) Pathogen recognition and activation of innate immunity	3

			for self-reported allergy)		3) rs10189629	15	*IL1RL1*	3) Pro-inflammatory effects, T helper cell function	
Ferreira et al[4]	2014	Meta-analysis of four cohorts/ datasets	16,513 hay fever cases 17,256 controls	European ancestry	1) rs4833095 2) rs2155219 3 rs10197862	1) 4E-12 2) 7E-10 3) 2E-09	1) *TLR1* 2) *LRRC32* or *C11orf30* 3) *IL1RL1*	1) Pathogen recognition and activation of innate immunity 2) See above 3) Pro-inflammatory effects, T helper cell function	3
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	Known loci: 1) 1.00 × 10–30 2) 1.74 × 10–30 3) 4.38 × 10–27 4) 3.15 × 10–26 5) 6.53 × 10–24 Novel loci: 1) 3.78 × 1	Known loci: 1) *HLA-DQB1, HLA-DQA1* 2) *IL1RL1* 3) *TLR1, TLR10* 4) *CAMK4, WDR36* 5) *LRRC32, C11orf30* Novel loci: 1) *CAPSL, IL7R* 2) *CDK2AP1, C12orf65* 3) *CXCR5, DDX6* 4) *AL590714.*	Known loci: 1) Antigen presentation 2) See above 3) See above 4) See above 5) See above Novel loci: 1) CAPSL: Calcium ion binding involved in adipogenesis, IL7R: Receptor for IL-7 (and TSLP); immunoregulation 2) CDK2AP1: cell-cycle kinase inhibitor 3) CXCR5: Involved in	3

					SNPs in novel loci (20 in total): 1) rs7717955 2) rs63406760 3) rs28361986 4) rs2070902 5) rs1504215	0–32 2) 2.54 × 10–24 3) 2.32 × 10–23 4) 6.19 × 10–19 5) 1.54 × 10–18	*1, FCER1G* 5) *BACH2, GJA10*	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 animals during first year of life	-Dogs: protective factor for AR (OR 0.72; 95% CI 0.53-0.97) -Exposure to cats and farm animals non-significant
Al-Tamprouri et al[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 samples (at 1 year) -Prenatal (at 3rd trimester of pregnancy) and perinatal (at 1 year) dog exposure and	-Cat: no association with AR at 13 years old (OR prenatal 1.2; 95% CI 0.44-3.82); (OR perinatal 1.33; 95% CI 0.53-3.42); (OR Fel d 1 1.10; 95% CI 1.2-4.96) -Dog: no association with AR at 13 years old (OR prenatal 0.95; 95% CI 0.21-4.3); (OR perinatal 0.86; 95% CI 0.19-3.89); (OR Can f 1 1.0: 95% CI 0.87-1.16)

					Can f 1 in dust samples (at 1 year)	
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 to current) exposure to indoor mold/dampness	Risk factors for rhinitis-like current symptoms: prenatal (OR 1.5; 95% CI 1.2-1.9); postnatal (OR 2.1; 95% CI 1.6-2.8)
Lin et al[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 ≥0.2 m^2 or a combined area of visible mold and water damage on the same surface ≥0.2 m^2) during early infancy (average 7.5 months) -Low mold exposure (mold in one room <0.2 m^2 or a combined area of visible mold and water damage on the same surface <0.2 m^2) during early infancy (average 7.5 months)	No association with AR at low (OR 1.2; 95% CI 0.6-2.5) or high levels (OR 3.2; 95% CI 0.7-14.8)

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,	10,313 children (4 years or younger); 3112	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

			subgroup analysis (GRADE)	children (5-14 years old		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 milk restricted diet -83 daily ingestion of one egg and 11 oz milk	Maternal diet very low in egg and milk during last 3 months of pregnancy	No association with the development of AR at 18 months
Falth-Magnusson & 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	38,389 children (7 years old)	Maternal diet to include ≥1 serving tree nuts/week or to have ≥1	-Maternal tree nut ingestion associated with reduced risk for

			cohort		serving of peanuts/pistachios/week from mid-pregnancy to delivery	self-reported AR at age 7 (OR 0.80; 95% CI 0.64-1.01) -Maternal ingestion of peanuts/pistachios had no association with self-reported AR at age 7
Virtanen et al[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	Development of AR from age 1 to 4	DEP exposure at age 1 associated with allergen sensitization at ages 2 and 3, though not

				(<66th percentile)		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 males with or without family stress: -High exposure -Low exposure	Diagnosis or parent-reported symptoms of AR at age 2-4 years	Early exposure to PM_{10} and NO_2 among young boys with family stress may increase risk of AR
Singh et al[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,	Measurements of pulmonary functions and allergic sensitization in children 6-14	Positive association between distance to and the length of main road with the prevalence of AR

				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%)	years old	
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	Association between smoking-associated SNPs and disease outcomes (hay fever, asthma,	-Current smokers had lower risk of hay fever and allergic sensitization than never smokers -Current smokers had lower risks of hay fever and allergic

				-Ever smokers	and allergic sensitization)	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 AR.

Harm: Pet keeping in childhood could have a negative effect, especially in Asians.

Cost: Various.

Benefits-harm assessment: Difficulty distinguishing between benefits and harm.

Value judgment: There is conflicting evidence that childhood pet exposure prevents the developme nt of AR.

Policy level: Option.

Intervention: Recommendation to expose or avoid pets for the prevention of AR in children cannot b e provided 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 birth until 5 years of age	Association of sensitization and wheezing at 1 year with fecal microbiota at age 3 months and 1 year	Suggests that reduced colonization of *Faecalibacterium*, *Lachnospira*, *Veillonella* and *Rothia* during the first 3 months of life may increase the risk of atopic asthma
Strachan et al[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 controls) followed until 7 years of age	Association of sensitization, asthma, and AR with fecal diversity in infancy	-Low microbial diversity associated with asthma later in childhood -No association with sensitization or rhinitis
Sjogren et al[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

REFERENCES

1. Westman M, Kull I, Lind T, et al. The link between parental allergy and offspring allergic and nonallergic rhinitis. *Allergy*. Dec 2013;68(12):1571-8. doi:10.1111/all.12267

2. Thomsen SF, Ulrik CS, Kyvik KO, et al. Genetic and environmental contributions to hay fever among young adult twins. *Respir Med*. Dec 2006;100(12):2177-82. doi:10.1016/j.rmed.2006.03.013

3. Rasanen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA. Hay fever--a Finnish nationwide study of adolescent twins and their parents. *Allergy*. Sep 1998;53(9):885-90. doi:10.1111/j.1398-9995.1998.tb03996.x

4. Ferreira MA, Matheson MC, Tang CS, et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. *J Allergy Clin Immunol*. Jun 2014;133(6):1564-71. doi:10.1016/j.jaci.2013.10.030

5. Hinds DA, McMahon G, Kiefer AK, et al. A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci. *Nat Genet*. Aug 2013;45(8):907-11. doi:10.1038/ng.2686

6. Ramasamy A, Curjuric I, Coin LJ, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. *J Allergy Clin Immunol*. Nov 2011;128(5):996-1005. doi:10.1016/j.jaci.2011.08.030

7. Johansson A, Rask-Andersen M, Karlsson T, Ek WE. Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Hum Mol Genet*. Dec 1 2019;28(23):4022-4041. doi:10.1093/hmg/ddz175

8. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet*. Aug 2018;50(8):1072-1080. doi:10.1038/s41588-018-0157-1

9. Ferreira MA, Matheson MC, Duffy DL, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. *Lancet*. Sep 10 2011;378(9795):1006-14. doi:10.1016/S0140-6736(11)60874-X

10. Weidinger S, Willis-Owen SA, Kamatani Y, et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. *Hum Mol Genet*. Dec 1 2013;22(23):4841-56. doi:10.1093/hmg/ddt317

11. Marenholz I, Esparza-Gordillo J, Ruschendorf F, et al. Meta-analysis identifies seven susceptibility loci involved in the atopic march. *Nat Commun*. Nov 6 2015;6:8804. doi:10.1038/ncomms9804

12. Stockis J, Colau D, Coulie PG, Lucas S. Membrane protein GARP is a receptor for latent TGF-beta on the surface of activated human Treg. *Eur J Immunol*. Dec 2009;39(12):3315-22. doi:10.1002/eji.200939684

13. Bonnelykke K, Matheson MC, Pers TH, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. *Nat Genet*. Aug 2013;45(8):902-906. doi:10.1038/ng.2694

14. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. Dec 2017;49(12):1752-1757. doi:10.1038/ng.3985

15. Ferreira MAR, Vonk JM, Baurecht H, et al. Eleven loci with new reproducible genetic associations with allergic disease risk. *J Allergy Clin Immunol*. Feb 2019;143(2):691-699. doi:10.1016/j.jaci.2018.03.012

16. Backman JD, Li AH, Marcketta A, et al. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature*. Nov 2021;599(7886):628-634. doi:10.1038/s41586-021-04103-z

17. Davila I, Mullol J, Ferrer M, et al. Genetic aspects of allergic rhinitis. *J Investig Allergol Clin Immunol*. 2009;19 Suppl 1:25-31.

18. Andiappan AK, Nilsson D, Hallden C, et al. Investigating highly replicated asthma genes as candidate genes for allergic rhinitis. *BMC Med Genet*. May 10 2013;14:51. doi:10.1186/1471-2350-14-51

19. Nilsson D, Andiappan AK, Hallden C, et al. Toll-like receptor gene polymorphisms are associated with allergic rhinitis: a case control study. *BMC Med Genet*. Aug 2 2012;13:66. doi:10.1186/1471-2350-13-66

20. Kang I, Oh YK, Lee SH, Jung HM, Chae SC, Lee JH. Identification of polymorphisms in the Toll-like receptor gene and the association with allergic rhinitis. *Eur Arch Otorhinolaryngol*. Mar 2010;267(3):385-9. doi:10.1007/s00405-009-1100-y

21. Kormann MS, Ferstl R, Depner M, et al. Rare TLR2 mutations reduce TLR2 receptor function and can increase atopy risk. *Allergy*. Apr 2009;64(4):636-42. doi:10.1111/j.1398-9995.2008.01891.x

22. Moller-Larsen S, Nyegaard M, Haagerup A, Vestbo J, Kruse TA, Borglum AD. Association analysis identifies TLR7 and TLR8 as novel risk genes in asthma and related disorders. *Thorax*. Dec 2008;63(12):1064-9. doi:10.1136/thx.2007.094128

23. Sun Q, Liu Y, Zhang S, et al. Thymic stromal lymphopoietin polymorphisms and allergic rhinitis risk: a systematic review and meta-analysis with 6351 cases and 11472 controls. *Int J Clin Exp Med*. 2015;8(9):15752-8.

24. Nilsson D, Andiappan AK, Hallden C, et al. Poor reproducibility of allergic rhinitis SNP associations. *PLoS One*. 2013;8(1):e53975. doi:10.1371/journal.pone.0053975

25. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol*. Mar 2008;8(3):169-82. doi:10.1038/nri2257

26. London SJ, Melen E. Genomic interactions with exposure to inhaled pollutants. *J Allergy Clin Immunol*. Jun 2019;143(6):2011-2013 e1. doi:10.1016/j.jaci.2019.04.008

27. Gruzieva O, Xu CJ, Breton CV, et al. Epigenome-Wide Meta-Analysis of Methylation in Children Related to Prenatal NO2 Air Pollution Exposure. *Environ Health Perspect*. Jan 2017;125(1):104-110. doi:10.1289/EHP36

28. Merid SK, Novoloaca A, Sharp GC, et al. Epigenome-wide meta-analysis of blood DNA methylation in newborns and children identifies numerous loci related to gestational age. *Genome Med*. Mar 2 2020;12(1):25. doi:10.1186/s13073-020-0716-9

29. Li JY, Zhang Y, Lin XP, et al. Association between DNA hypomethylation at IL13 gene and allergic rhinitis in house dust mite-sensitized subjects. *Clin Exp Allergy*. Feb 2016;46(2):298-307. doi:10.1111/cea.12647

30. Nestor CE, Barrenas F, Wang H, et al. DNA methylation changes separate allergic patients from healthy controls and may reflect altered CD4+ T-cell population structure. *PLoS Genet*. Jan 2014;10(1):e1004059. doi:10.1371/journal.pgen.1004059

31. Sarnowski C, Laprise C, Malerba G, et al. DNA methylation within melatonin receptor 1A (MTNR1A) mediates paternally transmitted genetic variant effect on asthma plus rhinitis. *J Allergy Clin Immunol*. Sep 2016;138(3):748-753. doi:10.1016/j.jaci.2015.12.1341

32. Liang L, Willis-Owen SAG, Laprise C, et al. An epigenome-wide association study of total serum immunoglobulin E concentration. *Nature*. Apr 30 2015;520(7549):670-674. doi:10.1038/nature14125

33. Everson TM, Lyons G, Zhang H, et al. DNA methylation loci associated with atopy and high serum IgE: a genome-wide application of recursive Random Forest feature selection. *Genome Med*. Aug 21 2015;7:89. doi:10.1186/s13073-015-0213-8

34. Qi C, Jiang Y, Yang IV, et al. Nasal DNA methylation profiling of asthma and rhinitis. *J Allergy Clin Immunol*. Jun 2020;145(6):1655-1663. doi:10.1016/j.jaci.2019.12.911

35. Xu CJ, Gruzieva O, Qi C, et al. Shared DNA methylation signatures in childhood allergy: The MeDALL study. *J Allergy Clin Immunol*. Mar 2021;147(3):1031-1040. doi:10.1016/j.jaci.2020.11.044

36. Andiappan AK, Wang de Y, Anantharaman R, et al. Genome-wide association study for atopy and allergic rhinitis in a Singapore Chinese population. *PLoS One*. 2011;6(5):e19719. doi:10.1371/journal.pone.0019719

37. Bunyavanich S, Schadt EE, Himes BE, et al. Integrated genome-wide association, coexpression network, and expression single nucleotide polymorphism analysis identifies novel pathway in allergic rhinitis. *BMC Med Genomics*. Aug 2 2014;7:48. doi:10.1186/1755-8794-7-48

38. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. Oct 2021;53(10):1415-1424. doi:10.1038/s41588-021-00931-x

39. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

40. Toelle BG, Ng KK, Crisafulli D, et al. Eight-year outcomes of the Childhood Asthma Prevention Study. *J Allergy Clin Immunol*. Aug 2010;126(2):388-9, 389 e1-3. doi:10.1016/j.jaci.2010.04.031

41. Marks GB, Mihrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol*. Jul 2006;118(1):53-61. doi:10.1016/j.jaci.2006.04.004

42. Gehring U, de Jongste JC, Kerkhof M, et al. The 8-year follow-up of the PIAMA intervention study assessing the effect of mite-impermeable mattress covers. *Allergy*. Feb 2012;67(2):248-56. doi:10.1111/j.1398-9995.2011.02739.x

43. Gabet S, Ranciere F, Just J, et al. Asthma and allergic rhinitis risk depends on house dust mite specific IgE levels in PARIS birth cohort children. *World Allergy Organ J*. Sep 2019;12(9):100057. doi:10.1016/j.waojou.2019.100057

44. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol*. Feb 2007;119(2):307-13. doi:10.1016/j.jaci.2006.12.621

45. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol*. Jul 2005;116(1):49-55. doi:10.1016/j.jaci.2005.03.029

46. Calderon MA, Linneberg A, Kleine-Tebbe J, et al. Respiratory allergy caused by house dust mites: What do we really know? *J Allergy Clin Immunol*. Jul 2015;136(1):38-48. doi:10.1016/j.jaci.2014.10.012

47. Wahn U, Lau S, Bergmann R, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol*. Jun 1997;99(6 Pt 1):763-9. doi:10.1016/s0091-6749(97)80009-7

48. Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. *J Allergy Clin Immunol*. Jul 2008;122(1):114-8, 118 e1-5. doi:10.1016/j.jaci.2008.05.010

49. Schram-Bijkerk D, Doekes G, Boeve M, et al. Nonlinear relations between house dust mite allergen levels and mite sensitization in farm and nonfarm children. *Allergy*. May 2006;61(5):640-7. doi:10.1111/j.1398-9995.2006.01079.x

50. Torrent M, Sunyer J, Munoz L, et al. Early-life domestic aeroallergen exposure and IgE sensitization at age 4 years. *J Allergy Clin Immunol*. Sep 2006;118(3):742-8. doi:10.1016/j.jaci.2006.04.059

51. Cullinan P, MacNeill SJ, Harris JM, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax*. Oct 2004;59(10):855-61. doi:10.1136/thx.2003.019877

52. Lau S, Falkenhorst G, Weber A, et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol*. Nov 1989;84(5 Pt 1):718-25. doi:10.1016/0091-6749(89)90300-x

53. Kuehr J, Frischer T, Meinert R, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol*. Jul 1994;94(1):44-52. doi:10.1016/0091-6749(94)90070-1

54. Lodge CJ, Lowe AJ, Gurrin LC, et al. House dust mite sensitization in toddlers predicts current wheeze at age 12 years. *J Allergy Clin Immunol*. Oct 2011;128(4):782-788 e9. doi:10.1016/j.jaci.2011.06.038

55. Schoos AM, Chawes BL, Jelding-Dannemand E, Elfman LB, Bisgaard H. Early indoor aeroallergen exposure is not associated with development of sensitization or allergic rhinitis in high-risk children. *Allergy*. May 2016;71(5):684-91. doi:10.1111/all.12853

56. Illi S, Weber J, Zutavern A, et al. Perinatal influences on the development of asthma and atopy in childhood. *Ann Allergy Asthma Immunol*. Feb 2014;112(2):132-139 e1. doi:10.1016/j.anai.2013.11.019

57. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. *Allergy*. Apr 2007;62(4):385-93. doi:10.1111/j.1398-9995.2006.01294.x

58. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol*. Nov 2000;106(5):832-9. doi:10.1067/mai.2000.110098

59. Erbas B, Lowe AJ, Lodge CJ, et al. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. *Clin Exp Allergy*. Mar 2013;43(3):337-43. doi:10.1111/cea.12071

60. Kihlstrom A, Lilja G, Pershagen G, Hedlin G. Exposure to birch pollen in infancy and development of atopic disease in childhood. *J Allergy Clin Immunol*. Jul 2002;110(1):78-84. doi:10.1067/mai.2002.125829

61. Scadding GK, Smith PK, Blaiss M, et al. Allergic Rhinitis in Childhood and the New EUFOREA Algorithm. *Front Allergy*. 2021;2:706589. doi:10.3389/falgy.2021.706589

62. Lipiec A, Sybilski A, Komorowski J, et al. Sensitisation to airborne allergens as a risk factor for allergic rhinitis and asthma in the Polish population. *Postepy Dermatol Alergol*. Oct 2020;37(5):751-759. doi:10.5114/ada.2019.84231

63. Hatzler L, Panetta V, Lau S, et al. Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. *J Allergy Clin Immunol*. Oct 2012;130(4):894-901 e5. doi:10.1016/j.jaci.2012.05.053

64. Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol*. Aug 2015;26(5):431-7. doi:10.1111/pai.12410

65. Grabenhenrich LB, Keil T, Reich A, et al. Prediction and prevention of allergic rhinitis: A birth cohort study of 20 years. *J Allergy Clin Immunol*. Oct 2015;136(4):932-40 e12. doi:10.1016/j.jaci.2015.03.040

66. Lee KS, Kim K, Choi YJ, et al. Increased sensitization rates to tree pollens in allergic children and adolescents and a change in the pollen season in the metropolitan area of Seoul, Korea. *Pediatr Allergy Immunol*. Jul 2021;32(5):872-879. doi:10.1111/pai.13472

67. Westman M, Aberg K, Apostolovic D, et al. Sensitization to grass pollen allergen molecules in a birth cohort-natural Phl p 4 as an early indicator of grass pollen allergy. *J Allergy Clin Immunol*. Apr 2020;145(4):1174-1181 e6. doi:10.1016/j.jaci.2020.01.006

68. Westman M, Lupinek C, Bousquet J, et al. Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *J Allergy Clin Immunol*. May 2015;135(5):1199-206 e1-11. doi:10.1016/j.jaci.2014.10.042

69. Gao X, Yin M, Yang P, et al. Effect of Exposure to Cats and Dogs on the Risk of Asthma and Allergic Rhinitis: A Systematic Review and Meta-analysis. *Am J Rhinol Allergy*. Sep 2020;34(5):703-714. doi:10.1177/1945892420932487

70. Ojwang V, Nwaru BI, Takkinen HM, et al. Early exposure to cats, dogs and farm animals and the risk of childhood asthma and allergy. *Pediatr Allergy Immunol*. Apr 2020;31(3):265-272. doi:10.1111/pai.13186

71. Al-Tamprouri C, Malin B, Bill H, Lennart B, Anna S. Cat and dog ownership during/after the first year of life and risk for sensitization and reported allergy symptoms at age 13. *Immun Inflamm Dis*. Dec 2019;7(4):250-257. doi:10.1002/iid3.267

72. Sultesz M, Horvath A, Molnar D, et al. Prevalence of allergic rhinitis, related comorbidities and risk factors in schoolchildren. *Allergy Asthma Clin Immunol*. Nov 11 2020;16(1):98. doi:10.1186/s13223-020-00495-1

73. Ho CL, Wu WF. Risk factor analysis of allergic rhinitis in 6-8 year-old children in Taipei. *PLoS One*. 2021;16(4):e0249572.

74. Alm B, Goksor E, Thengilsdottir H, et al. Early protective and risk factors for allergic rhinitis at age 4(1/2) yr. *Pediatr Allergy Immunol*. Jun 2011;22(4):398-404. doi:10.1111/j.1399-3038.2011.01153.x

75. Dunlop J, Matsui E, Sharma HP. Allergic Rhinitis: Environmental Determinants. *Immunol Allergy Clin North Am*. May 2016;36(2):367-77. doi:10.1016/j.iac.2015.12.012

76. Sandini U, Kukkonen AK, Poussa T, Sandini L, Savilahti E, Kuitunen M. Protective and risk factors for allergic diseases in high-risk children at the ages of two and five years. *Int Arch Allergy Immunol*. 2011;156(3):339-48. doi:10.1159/000323907

77. Fasce L, Tosca MA, Silvestri M, Olcese R, Pistorio A, Rossi GA. "Early" cat ownership and the risk of sensitization and allergic rhinitis in Ligurian children with respiratory symptoms. *Ann Allergy Asthma Immunol*. May 2005;94(5):561-5. doi:10.1016/S1081-1206(10)61134-9

78. Dimich-Ward H, Chow Y, Chung J, Trask C. Contact with livestock--a protective effect against allergies and asthma? *Clin Exp Allergy*. Sep 2006;36(9):1122-9. doi:10.1111/j.1365-2222.2006.02556.x

79. Majkowska-Wojciechowska B, Pelka J, Korzon L, et al. Prevalence of allergy, patterns of allergic sensitization and allergy risk factors in rural and urban children. *Allergy*. Sep 2007;62(9):1044-50. doi:10.1111/j.1398-9995.2007.01457.x

80. Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study--an international population-based cohort study. *J Allergy Clin Immunol*. Oct 2011;128(4):816-823 e5. doi:10.1016/j.jaci.2011.05.039

81. Perkin MR, Bader T, Rudnicka AR, Strachan DP, Owen CG. Inter-Relationship between Rhinitis and Conjunctivitis in Allergic Rhinoconjunctivitis and Associated Risk Factors in Rural UK Children. *PLoS One*. 2015;10(11):e0143651. doi:10.1371/journal.pone.0143651

82. Vargas C, Bustos P, Diaz PV, Amigo H, Rona RJ. Childhood environment and atopic conditions, with emphasis on asthma in a Chilean agricultural area. *J Asthma*. Jan-Feb 2008;45(1):73-8. doi:10.1080/02770900701752540

83. Lampi J, Canoy D, Jarvis D, et al. Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland. *Clin Exp Allergy*. Jul 2011;41(7):987-93. doi:10.1111/j.1365-2222.2011.03777.x

84. Perzanowski MS, Chew GL, Divjan A, et al. Cat ownership is a risk factor for the development of anti-cat IgE but not current wheeze at age 5 years in an inner-city cohort. *J Allergy Clin Immunol*. Apr 2008;121(4):1047-52. doi:10.1016/j.jaci.2008.02.005

85. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJ. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy*. Apr 2001;56(4):307-12. doi:10.1034/j.1398-9995.2001.00881.x

86. Tamay Z, Akcay A, Ones U, Guler N, Kilic G, Zencir M. Prevalence and risk factors for allergic rhinitis in primary school children. *Int J Pediatr Otorhinolaryngol*. Mar 2007;71(3):463-71. doi:10.1016/j.ijporl.2006.11.013

87. Batlles-Garrido J, Torres-Borrego J, Rubi-Ruiz T, et al. Prevalence and factors linked to allergic rhinitis in 10 and 11-year-old children in Almeria. Isaac Phase II, Spain. *Allergol Immunopathol (Madr)*. May-Jun 2010;38(3):135-41. doi:10.1016/j.aller.2009.09.005

88. Lombardi E, Simoni M, La Grutta S, et al. Effects of pet exposure in the first year of life on respiratory and allergic symptoms in 7-yr-old children. The SIDRIA-2 study. *Pediatr Allergy Immunol*. Mar 2010;21(2 Pt 1):268-76. doi:10.1111/j.1399-3038.2009.00910.x

89. Ibargoyen-Roteta N, Aguinaga-Ontoso I, Fernandez-Benitez M, et al. Role of the home environment in rhinoconjunctivitis and eczema in schoolchildren in Pamplona, Spain. *J Investig Allergol Clin Immunol*. 2007;17(3):137-44.

90. Kurosaka F, Terada T, Tanaka A, et al. Risk factors for wheezing, eczema and rhinoconjunctivitis in the previous 12 months among six-year-old children in Himeji City, Japan: food allergy, older siblings, day-care attendance and parental allergy history. *Allergol Int*. Sep 2011;60(3):317-30. doi:10.2332/allergolint.10-OA-0246

91. Brunekreef B, Von Mutius E, Wong G, et al. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. *Epidemiology*. Sep 2012;23(5):742-50. doi:10.1097/EDE.0b013e318261f040

92. Tamay Z, Akcay A, Ergin A, Guler N. Prevalence of allergic rhinitis and risk factors in 6- to 7-yearold children in Istanbul, Turkey. *Turk J Pediatr*. Jan-Feb 2014;56(1):31-40.

93. Yang SI, Lee E, Jung YH, et al. Effect of antibiotic use and mold exposure in infancy on allergic rhinitis in susceptible adolescents. *Ann Allergy Asthma Immunol*. Aug 2014;113(2):160-165 e1. doi:10.1016/j.anai.2014.05.019

94. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy*. May 1999;29(5):611-7. doi:10.1046/j.1365-2222.1999.00534.x

95. Leynaert B, Neukirch C, Jarvis D, et al. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? *Am J Respir Crit Care Med*. Nov 15 2001;164(10 Pt 1):1829-34. doi:10.1164/ajrccm.164.10.2103137

96. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NA, van Vliet P. Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy*. Mar 2002;32(3):361-6. doi:10.1046/j.1365-2222.2002.01254.x

97. Waser M, von Mutius E, Riedler J, et al. Exposure to pets, and the association with hay fever, asthma, and atopic sensitization in rural children. *Allergy*. Feb 2005;60(2):177-84. doi:10.1111/j.1398-9995.2004.00645.x

98. Sultesz M, Katona G, Hirschberg A, Galffy G. Prevalence and risk factors for allergic rhinitis in primary schoolchildren in Budapest. *Int J Pediatr Otorhinolaryngol*. May 2010;74(5):503-9. doi:10.1016/j.ijporl.2010.02.008

99. Kim WK, Kwon JW, Seo JH, et al. Interaction between IL13 genotype and environmental factors in the risk for allergic rhinitis in Korean children. *J Allergy Clin Immunol*. Aug 2012;130(2):421-6 e5. doi:10.1016/j.jaci.2012.04.052

100. Lam A, Wong GW, Poon CM, Lee SS. A GIS-based assessment of environmental influences on allergy development in children. *Asia Pac J Public Health*. Nov 2014;26(6):575-87. doi:10.1177/1010539511428488

101. Torfi Y, Bitarafan N, Rajabi M. Impact of socioeconomic and environmental factors on atopic eczema and allergic rhinitis: a cross sectional study. *EXCLI J*. 2015;14:1040-8. doi:10.17179/excli2015-519

102. Kellberger J, Dressel H, Vogelberg C, et al. Prediction of the incidence and persistence of allergic rhinitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol*. Feb 2012;129(2):397-402, 402 e1-3. doi:10.1016/j.jaci.2011.08.016

103. Lodrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One*. 2012;7(8):e43214. doi:10.1371/journal.pone.0043214

104. Chen CM, Morgenstern V, Bischof W, et al. Dog ownership and contact during childhood and later allergy development. *Eur Respir J*. May 2008;31(5):963-73. doi:10.1183/09031936.00092807

105. Chen CM, Rzehak P, Zutavern A, et al. Longitudinal study on cat allergen exposure and the development of allergy in young children. *J Allergy Clin Immunol*. May 2007;119(5):1148-55. doi:10.1016/j.jaci.2007.02.017

106. Tischer CG, Hohmann C, Thiering E, et al. Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy*. Dec 2011;66(12):1570-9. doi:10.1111/j.1398-9995.2011.02712.x

107. Behbod B, Sordillo JE, Hoffman EB, et al. Asthma and allergy development: contrasting influences of yeasts and other fungal exposures. *Clin Exp Allergy*. Jan 2015;45(1):154-63. doi:10.1111/cea.12401

108. Ellie AS, Sun Y, Hou J, Wang P, Zhang Q, Sundell J. Prevalence of Childhood Asthma and Allergies and Their Associations with Perinatal Exposure to Home Environmental Factors: A Cross-Sectional Study in Tianjin, China. *Int J Environ Res Public Health*. Apr 14 2021;18(8)doi:10.3390/ijerph18084131

109. Caillaud D, Leynaert B, Keirsbulck M, Nadif R, mould Awg. Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies. *Eur Respir Rev*. Jun 30 2018;27(148)doi:10.1183/16000617.0137-2017

110. Nevalainen A, Taubel M, Hyvarinen A. Indoor fungi: companions and contaminants. *Indoor Air*. Apr 2015;25(2):125-56. doi:10.1111/ina.12182

111. Deng Q, Lu C, Ou C, Chen L, Yuan H. Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. *Chemosphere*. Jun 2016;152:459-67. doi:10.1016/j.chemosphere.2016.03.032

112. Lin Z, Norback D, Wang T, et al. The first 2-year home environment in relation to the new onset and remission of asthmatic and allergic symptoms in 4246 preschool children. *Sci Total Environ*. May 15 2016;553:204-210. doi:10.1016/j.scitotenv.2016.02.040

113. Kuyucu S, Saraclar Y, Tuncer A, et al. Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr Allergy Immunol*. Jun 2006;17(4):269-77. doi:10.1111/j.1399-3038.2006.00407.x

114. Bornehag CG, Sundell J, Hagerhed-Engman L, et al. 'Dampness' at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study. *Indoor Air*. 2005;15 Suppl 10:48-55. doi:10.1111/j.1600-0668.2005.00306.x

115. Thacher JD, Gruzieva O, Pershagen G, et al. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy*. Jun 2017;72(6):967-974. doi:10.1111/all.13102

116. Biagini JM, LeMasters GK, Ryan PH, et al. Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol*. Jun 2006;17(4):278-84. doi:10.1111/j.1399-3038.2006.00386.x

117. Testa D, M DIB, Nunziata M, et al. Allergic rhinitis and asthma assessment of risk factors in pediatric patients: A systematic review. *Int J Pediatr Otorhinolaryngol*. Feb 2020;129:109759. doi:10.1016/j.ijporl.2019.109759

118. Hardjojo A, Shek LP, van Bever HP, Lee BW. Rhinitis in children less than 6 years of age: current knowledge and challenges. *Asia Pac Allergy*. Oct 2011;1(3):115-22. doi:10.5415/apallergy.2011.1.3.115

119. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. *JAMA*. Sep 20 2016;316(11):1181-1192. doi:10.1001/jama.2016.12623

120. du Toit G, Sayre PH, Roberts G, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort. *J Allergy Clin Immunol*. Apr 2018;141(4):1343-1353. doi:10.1016/j.jaci.2017.09.034

121. Fong WCG, Chan A, Zhang H, et al. Childhood food allergy and food allergen sensitisation are associated with adult airways disease: A birth cohort study. *Pediatr Allergy Immunol*. Nov 2021;32(8):1764-1772. doi:10.1111/pai.13592

122. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy*. Jun 2009;39(6):875-82. doi:10.1111/j.1365-2222.2009.03234.x

123. Oien T, Schjelvaag A, Storro O, Johnsen R, Simpson MR. Fish Consumption at One Year of Age Reduces the Risk of Eczema, Asthma and Wheeze at Six Years of Age. *Nutrients*. Aug 21 2019;11(9)doi:10.3390/nu11091969

124. Markevych I, Standl M, Lehmann I, von Berg A, Heinrich J. Food diversity during the first year of life and allergic diseases until 15 years. *J Allergy Clin Immunol*. Dec 2017;140(6):1751-1754 e4. doi:10.1016/j.jaci.2017.08.011

125. Maslova E, Granstrom C, Hansen S, et al. Peanut and tree nut consumption during pregnancy and allergic disease in children-should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. *J Allergy Clin Immunol*. Sep 2012;130(3):724-32. doi:10.1016/j.jaci.2012.05.014

126. Maslova E, Strom M, Oken E, et al. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. *Br J Nutr*. Oct 2013;110(7):1313-25. doi:10.1017/S000711451300038X

127. Willers SM, Wijga AH, Brunekreef B, et al. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med*. Jul 15 2008;178(2):124-31. doi:10.1164/rccm.200710-1544OC

128. Nwaru BI, Takkinen HM, Kaila M, et al. Food diversity in infancy and the risk of childhood asthma and allergies. *J Allergy Clin Immunol*. Apr 2014;133(4):1084-91. doi:10.1016/j.jaci.2013.12.1069

129. Roduit C, Frei R, Depner M, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol*. Apr 2014;133(4):1056-64. doi:10.1016/j.jaci.2013.12.1044

130. Nwaru BI, Takkinen HM, Niemela O, et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. *J Allergy Clin Immunol*. Jan 2013;131(1):78-86. doi:10.1016/j.jaci.2012.10.028

131. Virtanen SM, Kaila M, Pekkanen J, et al. Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis. *Br J Nutr*. Jan 2010;103(2):266-73. doi:10.1017/S0007114509991541

132. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol*. Jun 1995;95(6):1179-90. doi:10.1016/s0091-6749(95)70074-9

133. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age--in-vivo results. *Clin Exp Allergy*. Jul 1989;19(4):473-9. doi:10.1111/j.1365-2222.1989.tb02416.x

134. Falth-Magnusson K, Kjellman NI. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy--a randomized study. *J Allergy Clin Immunol*. Dec 1987;80(6):868-75. doi:10.1016/s0091-6749(87)80279-8

135. Willers SM, Devereux G, Craig LC, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax*. Sep 2007;62(9):773-9. doi:10.1136/thx.2006.074187

136. Alduraywish SA, Lodge CJ, Campbell B, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. *Allergy*. Jan 2016;71(1):77-89. doi:10.1111/all.12784

137. Brockow I, Zutavern A, Hoffmann U, et al. Early allergic sensitizations and their relevance to atopic diseases in children aged 6 years: results of the GINI study. *J Investig Allergol Clin Immunol*. 2009;19(3):180-7.

138. Garden FL, Simpson JM, Marks GB, Investigators C. Atopy phenotypes in the Childhood Asthma Prevention Study (CAPS) cohort and the relationship with allergic disease: clinical mechanisms in allergic disease. *Clin Exp Allergy*. Jun 2013;43(6):633-41. doi:10.1111/cea.12095

139. Kulig M, Bergmann R, Tacke U, Wahn U, Guggenmoos-Holzmann I. Long-lasting sensitization to food during the first two years precedes allergic airway disease. The MAS Study Group, Germany. *Pediatr Allergy Immunol*. May 1998;9(2):61-7. doi:10.1111/j.1399-3038.1998.tb00305.x

140. Chiu CY, Huang YL, Tsai MH, et al. Sensitization to food and inhalant allergens in relation to atopic diseases in early childhood: a birth cohort study. *PLoS One*. 2014;9(7):e102809. doi:10.1371/journal.pone.0102809

141. Kjaer HF, Eller E, Andersen KE, Host A, Bindslev-Jensen C. The association between early sensitization patterns and subsequent allergic disease. The DARC birth cohort study. *Pediatr Allergy Immunol*. Dec 2009;20(8):726-34. doi:10.1111/j.1399-3038.2009.00862.x

142. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics*. Jan 2008;121(1):e44-52. doi:10.1542/peds.2006-3553

143. Ekelund L, Gloppen I, Oien T, Simpson MR. Duration of breastfeeding, age at introduction of complementary foods and allergy-related diseases: a prospective cohort study. *Int Breastfeed J*. Jan 6 2021;16(1):5. doi:10.1186/s13006-020-00352-2

144. Venter C, Agostoni C, Arshad SH, et al. Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology. *Pediatr Allergy Immunol*. Nov 2020;31(8):889-912. doi:10.1111/pai.13303

145. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. *J Allergy Clin Immunol Pract*. Jan 2013;1(1):29-36. doi:10.1016/j.jaip.2012.09.003

146. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on N, American Academy of Pediatrics Section on A, Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. Jan 2008;121(1):183-91. doi:10.1542/peds.2007-3022

147. Domejean S, Zhan L, DenBesten PK, Stamper J, Boyce WT, Featherstone JD. Horizontal transmission of mutans streptococci in children. *J Dent Res*. Jan 2010;89(1):51-5. doi:10.1177/0022034509353400

148. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev*. Sep 12 2012;(9):CD000133. doi:10.1002/14651858.CD000133.pub3

149. Air pollution. Accessed November 18, 2021, https://www.who.int/health-topics/air-pollution

150. Gorr MW, Falvo MJ, Wold LE. Air Pollution and Other Environmental Modulators of Cardiac Function. *Compr Physiol*. Sep 12 2017;7(4):1479-1495. doi:10.1002/cphy.c170017

151. Li J, Sun S, Tang R, et al. Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:3079-3091. doi:10.2147/COPD.S122282

152. Carlsten C, Blomberg A, Pui M, et al. Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: a controlled human exposure study. *Thorax*. Jan 2016;71(1):35-44. doi:10.1136/thoraxjnl-2015-207399

153. Hernandez M, Brickey WJ, Alexis NE, et al. Airway cells from atopic asthmatic patients exposed to ozone display an enhanced innate immune gene profile. *J Allergy Clin Immunol*. Jan 2012;129(1):259-61 e1-2. doi:10.1016/j.jaci.2011.11.007

154. Anderson HR, Ruggles R, Pandey KD, et al. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). *Occup Environ Med*. May 2010;67(5):293-300. doi:10.1136/oem.2009.048785

155. Chiang TY, Yuan TH, Shie RH, Chen CF, Chan CC. Increased incidence of allergic rhinitis, bronchitis and asthma, in children living near a petrochemical complex with SO2 pollution. *Environ Int*. Nov 2016;96:1-7. doi:10.1016/j.envint.2016.08.009

156. Singh S, Sharma BB, Salvi S, et al. Allergic rhinitis, rhinoconjunctivitis, and eczema: prevalence and associated factors in children. *Clin Respir J*. Feb 2018;12(2):547-556. doi:10.1111/crj.12561

157. Jung DY, Leem JH, Kim HC, et al. Effect of Traffic-Related Air Pollution on Allergic Disease: Results of the Children's Health and Environmental Research. *Allergy Asthma Immunol Res*. Jul 2015;7(4):359-66. doi:10.4168/aair.2015.7.4.359

158. Shirinde J, Wichmann J, Voyi K. Allergic rhinitis, rhinoconjunctivitis and hayfever symptoms among children are associated with frequency of truck traffic near residences: a cross sectional study. *Environ Health*. Oct 26 2015;14:84. doi:10.1186/s12940-015-0072-1

159. Kim J, Han Y, Seo SC, et al. Association of carbon monoxide levels with allergic diseases in children. *Allergy Asthma Proc*. Jan-Feb 2016;37(1):e1-7. doi:10.2500/aap.2016.37.3918

160. Kim BJ, Kwon JW, Seo JH, et al. Association of ozone exposure with asthma, allergic rhinitis, and allergic sensitization. *Ann Allergy Asthma Immunol*. Sep 2011;107(3):214-9 e1. doi:10.1016/j.anai.2011.05.025

161. Codispoti CD, LeMasters GK, Levin L, et al. Traffic pollution is associated with early childhood aeroallergen sensitization. *Ann Allergy Asthma Immunol*. Feb 2015;114(2):126-33. doi:10.1016/j.anai.2014.10.020

162. Gehring U, Wijga AH, Hoek G, et al. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. *Lancet Respir Med*. Dec 2015;3(12):933-42. doi:10.1016/S2213-2600(15)00426-9

163. Li S, Wu W, Wang G, et al. Association between exposure to air pollution and risk of allergic rhinitis: A systematic review and meta-analysis. *Environ Res*. Apr 1 2022;205:112472. doi:10.1016/j.envres.2021.112472

164. Burte E, Leynaert B, Marcon A, et al. Long-term air pollution exposure is associated with increased severity of rhinitis in 2 European cohorts. *J Allergy Clin Immunol*. Mar 2020;145(3):834-842 e6. doi:10.1016/j.jaci.2019.11.040

165. Teng B, Zhang X, Yi C, et al. The Association between Ambient Air Pollution and Allergic Rhinitis: Further Epidemiological Evidence from Changchun, Northeastern China. *Int J Environ Res Public Health*. Feb 23 2017;14(3)doi:10.3390/ijerph14030226

166. To T, Zhu J, Stieb D, et al. Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema. *Eur Respir J*. Feb 2020;55(2)doi:10.1183/13993003.00913-2019

167. Zou QY, Shen Y, Ke X, Hong SL, Kang HY. Exposure to air pollution and risk of prevalence of childhood allergic rhinitis: A meta-analysis. *Int J Pediatr Otorhinolaryngol*. Sep 2018;112:82-90. doi:10.1016/j.ijporl.2018.06.039

168. Lin L, Li T, Sun M, et al. Effect of particulate matter exposure on the prevalence of allergic rhinitis in children: A systematic review and meta-analysis. *Chemosphere*. Apr 2021;268:128841. doi:10.1016/j.chemosphere.2020.128841

169. Hao S, Yuan F, Pang P, Yang B, Jiang X, Yan A. Early childhood traffic-related air pollution and risk of allergic rhinitis at 2-4 years of age modification by family stress and male gender: a case-control study in Shenyang, China. *Environ Health Prev Med*. Apr 17 2021;26(1):48. doi:10.1186/s12199-021-00969-7

170. Mookherjee N, Piyadasa H, Ryu MH, et al. Inhaled diesel exhaust alters the allergen-induced bronchial secretome in humans. *Eur Respir J*. Jan 2018;51(1)doi:10.1183/13993003.01385-2017

171. Clifford RL, Jones MJ, MacIsaac JL, et al. Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. *J Allergy Clin Immunol*. Jan 2017;139(1):112-121. doi:10.1016/j.jaci.2016.03.046

172. Wooding DJ, Ryu MH, Huls A, et al. Particle Depletion Does Not Remediate Acute Effects of Traffic-related Air Pollution and Allergen. A Randomized, Double-Blind Crossover Study. *Am J Respir Crit Care Med*. Sep 1 2019;200(5):565-574. doi:10.1164/rccm.201809-1657OC

173. Ellis AK, Murrieta-Aguttes M, Furey S, Picard P, Carlsten C. Effect of fexofenadine hydrochloride on allergic rhinitis aggravated by air pollutants. *ERJ Open Res*. Apr 2021;7(2)doi:10.1183/23120541.00806-2020

174. Bousquet J, Anto JM, Annesi-Maesano I, et al. POLLAR: Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. *Clin Transl Allergy*. 2018;8:36. doi:10.1186/s13601-018-0221-z

175. Naclerio R, Ansotegui IJ, Bousquet J, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: Impact of air pollution on patients with AR: Current knowledge and future strategies. *World Allergy Organ J*. Mar 2020;13(3):100106. doi:10.1016/j.waojou.2020.100106

176. Chung HY, Hsieh CJ, Tseng CC, Yiin LM. Association between the First Occurrence of Allergic Rhinitis in Preschool Children and Air Pollution in Taiwan. *Int J Environ Res Public Health*. Feb 27 2016;13(3)doi:10.3390/ijerph13030268

177. Liu W, Huang C, Hu Y, et al. Associations of gestational and early life exposures to ambient air pollution with childhood respiratory diseases in Shanghai, China: A retrospective cohort study. *Environ Int*. Jul-Aug 2016;92-93:284-93. doi:10.1016/j.envint.2016.04.019

178. Wang IJ, Tung TH, Tang CS, Zhao ZH. Allergens, air pollutants, and childhood allergic diseases. *Int J Hyg Environ Health*. Jan 2016;219(1):66-71. doi:10.1016/j.ijheh.2015.09.001

179. Kim HH, Lee CS, Yu SD, et al. Near-Road Exposure and Impact of Air Pollution on Allergic Diseases in Elementary School Children: A Cross-Sectional Study. *Yonsei Med J*. May 2016;57(3):698-713. doi:10.3349/ymj.2016.57.3.698

180. Hur K, Liang J, Lin SY. The role of secondhand smoke in sinusitis: a systematic review. *Int Forum Allergy Rhinol*. Jan 2014;4(1):22-8. doi:10.1002/alr.21232

181. Saulyte J, Regueira C, Montes-Martinez A, Khudyakov P, Takkouche B. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. *PLoS Med*. Mar 2014;11(3):e1001611. doi:10.1371/journal.pmed.1001611

182. Keil T, Lau S, Roll S, et al. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy*. Mar 2009;64(3):445-51. doi:10.1111/j.1398-9995.2008.01867.x

183. Lin SY, Reh DD, Clipp S, Irani L, Navas-Acien A. Allergic rhinitis and secondhand tobacco smoke: a population-based study. *Am J Rhinol Allergy*. Mar-Apr 2011;25(2):e66-71. doi:10.2500/ajra.2011.25.3580

184. Bendtsen P, Gronbaek M, Kjaer SK, Munk C, Linneberg A, Tolstrup JS. Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. *Clin Exp Allergy*. Jul 2008;38(7):1179-85. doi:10.1111/j.1365-2222.2008.02945.x

185. Gangl K, Reininger R, Bernhard D, et al. Cigarette smoke facilitates allergen penetration across respiratory epithelium. *Allergy*. Mar 2009;64(3):398-405. doi:10.1111/j.1398-9995.2008.01861.x

186. Ueha R, Ueha S, Kondo K, Nishijima H, Yamasoba T. Effects of Cigarette Smoke on the Nasal Respiratory and Olfactory Mucosa in Allergic Rhinitis Mice. *Front Neurosci*. 2020;14:126. doi:10.3389/fnins.2020.00126

187. Mishra NC, Rir-Sima-Ah J, Langley RJ, et al. Nicotine primarily suppresses lung Th2 but not goblet cell and muscle cell responses to allergens. *J Immunol*. Jun 1 2008;180(11):7655-63. doi:10.4049/jimmunol.180.11.7655

188. Skaaby T, Taylor AE, Jacobsen RK, et al. Investigating the causal effect of smoking on hay fever and asthma: a Mendelian randomization meta-analysis in the CARTA consortium. *Sci Rep*. May 22 2017;7(1):2224. doi:10.1038/s41598-017-01977-w

189. Zhou Y, Chen J, Dong Y, et al. Maternal tobacco exposure during pregnancy and allergic rhinitis in offspring: A systematic review and meta-analysis. *Medicine (Baltimore)*. Aug 27 2021;100(34):e26986. doi:10.1097/MD.0000000000026986

190. Thacher JD, Gehring U, Gruzieva O, et al. Maternal Smoking during Pregnancy and Early Childhood and Development of Asthma and Rhinoconjunctivitis - a MeDALL Project. *Environ Health Perspect*. Apr 12 2018;126(4):047005. doi:10.1289/EHP2738

191. Abramson MJ, Schindler C, Schikowski T, et al. Rhinitis in Swiss adults is associated with asthma and early life factors, but not second hand tobacco smoke or obesity. *Allergol Int*. Apr 2016;65(2):192-198. doi:10.1016/j.alit.2015.11.004

192. Ciprandi G, Silvestri M, Pistorio A, Tosca MA, Cirillo I. Clustering analysis in outpatients with allergic rhinitis in clinical practice. *Allergy*. Mar 2019;74(3):607-610. doi:10.1111/all.13645

193. Chung SJ, Kim BK, Oh JH, et al. Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey. *Allergy*. Jul 2020;75(7):1640-1648. doi:10.1111/all.14212

194. Waite KJ. Blackley and the development of hay fever as a disease of civilization in the nineteenth century. *Med Hist*. Apr 1995;39(2):186-96. doi:10.1017/s0025727300059834

195. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax*. Aug 2000;55 Suppl 1:S2-10. doi:10.1136/thorax.55.suppl_1.s2

196. Wee JH, Park MW, Min C, Park IS, Park B, Choi HG. The association between high hygiene scores and allergic rhinitis in Korean adolescents. *Int Forum Allergy Rhinol*. Aug 2020;10(8):1024-1030. doi:10.1002/alr.22569

197. Ait-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. Jan 2009;64(1):123-48. doi:10.1111/j.1398-9995.2008.01884.x

198. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D, Group IPIS. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. Mar 2008;19(2):110-24. doi:10.1111/j.1399-3038.2007.00601.x

199. Mallol J, Crane J, von Mutius E, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. *Allergol Immunopathol (Madr)*. Mar-Apr 2013;41(2):73-85. doi:10.1016/j.aller.2012.03.001

200. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol*. Nov 1997;8(4):161-76. doi:10.1111/j.1399-3038.1997.tb00156.x

201. Chen JT, Krieger N, Van Den Eeden SK, Quesenberry CP. Different slopes for different folks: socioeconomic and racial/ethnic disparities in asthma and hay fever among 173,859 U.S. men and women. *Environ Health Perspect*. Apr 2002;110 Suppl 2:211-6. doi:10.1289/ehp.02110s2211

202. Li F, Zhou Y, Li S, et al. Prevalence and risk factors of childhood allergic diseases in eight metropolitan cities in China: a multicenter study. *BMC Public Health*. Jun 6 2011;11:437. doi:10.1186/1471-2458-11-437

203. Hammer-Helmich L, Linneberg A, Thomsen SF, Glumer C. Association between parental socioeconomic position and prevalence of asthma, atopic eczema and hay fever in children. *Scand J Public Health*. Mar 2014;42(2):120-7. doi:10.1177/1403494813505727

204. Mercer MJ, Joubert G, Ehrlich RI, et al. Socioeconomic status and prevalence of allergic rhinitis and atopic eczema symptoms in young adolescents. *Pediatr Allergy Immunol*. Jun 2004;15(3):234-41. doi:10.1111/j.1399-3038.2004.00125.x

205. Talay F, Kurt B, Tug T, Kurt OK, Goksugur N, Yasar Z. The prevalence of asthma and allergic diseases among adults 30-49 years of age in Bolu, Western Black Sea Region of Turkey. *Clin Ter*. 2014;165(1):e59-63. doi:10.7471/CT.2014.1673

206. Lewis SA, Weiss ST, Platts-Mills TA, Syring M, Gold DR. Association of specific allergen sensitization with socioeconomic factors and allergic disease in a population of Boston women. *J Allergy Clin Immunol*. Apr 2001;107(4):615-22. doi:10.1067/mai.2001.113523

207. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy*. May 2005;35(5):612-8. doi:10.1111/j.1365-2222.2005.02243.x

208. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and Risk Factors of Chronic Rhinosinusitus, Allergic Rhinitis, and Nasal Septal Deviation: Results of the Korean National Health and Nutrition Survey 2008-2012. *JAMA Otolaryngol Head Neck Surg*. Feb 2016;142(2):162-7. doi:10.1001/jamaoto.2015.3142

209. Lee KS, Rha YH, Oh IH, Choi YS, Choi SH. Socioeconomic and sociodemographic factors related to allergic diseases in Korean adolescents based on the Seventh Korea Youth Risk Behavior Web-based Survey: a cross-sectional study. *BMC Pediatr*. Jan 27 2016;16:19. doi:10.1186/s12887-016-0549-2

210. Braback L, Hjern A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort study over three decades. *Eur Respir J*. Dec 2005;26(6):1064-8. doi:10.1183/09031936.05.00022105

211. Penaranda A, Garcia E, Barragan AM, et al. Factors associated with Allergic Rhinitis in Colombian subpopulations aged 1 to 17 and 18 to 59. *Rhinology*. Mar 2016;54(1):56-67. doi:10.4193/Rhino14.234

212. Bergmann RL, Edenharter G, Bergmann KE, Lau S, Wahn U. Socioeconomic status is a risk factor for allergy in parents but not in their children. *Clin Exp Allergy*. Dec 2000;30(12):1740-5. doi:10.1046/j.1365-2222.2000.00927.x

213. Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. *Respir Med*. Oct 1998;92(10):1237-44. doi:10.1016/s0954-6111(98)90427-9

214. Goh DY, Chew FT, Quek SC, Lee BW. Prevalence and severity of asthma, rhinitis, and eczema in Singapore schoolchildren. *Arch Dis Child*. Feb 1996;74(2):131-5. doi:10.1136/adc.74.2.131

215. Bion V, Lockett GA, Soto-Ramirez N, et al. Evaluating the efficacy of breastfeeding guidelines on long-term outcomes for allergic disease. *Allergy*. May 2016;71(5):661-70. doi:10.1111/all.12833

216. Muraro A, Halken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy*. May 2014;69(5):590-601. doi:10.1111/all.12398

217. Hoppu U, Kalliomaki M, Laiho K, Isolauri E. Breast milk--immunomodulatory signals against allergic diseases. *Allergy*. 2001;56 Suppl 67:23-6. doi:10.1034/j.1398-9995.2001.00908.x

218. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol*. Jun 2005;115(6):1238-48. doi:10.1016/j.jaci.2005.01.069

219. Hoang MP, Samuthpongtorn J, Seresirikachorn K, Snidvongs K. Prolonged breastfeeding and protective effects against the development of allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. Apr 1 2022;60(2):82-91. doi:10.4193/Rhin21.274

220. Gungor D, Nadaud P, LaPergola CC, et al. Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. *Am J Clin Nutr*. Mar 1 2019;109(Suppl_7):772S-799S. doi:10.1093/ajcn/nqy283

221. Codispoti CD, Levin L, LeMasters GK, et al. Breast-feeding, aeroallergen sensitization, and environmental exposures during infancy are determinants of childhood allergic rhinitis. *J Allergy Clin Immunol*. May 2010;125(5):1054-1060 e1. doi:10.1016/j.jaci.2010.02.004

222. Huang C, Liu W, Cai J, et al. Breastfeeding and timing of first dietary introduction in relation to childhood asthma, allergies, and airway diseases: A cross-sectional study. *J Asthma*. Jun 2017;54(5):488-497. doi:10.1080/02770903.2016.1231203

223. Han DH, Shin JM, An S, et al. Long-term Breastfeeding in the Prevention of Allergic Rhinitis: Allergic Rhinitis Cohort Study for Kids (ARCO-Kids Study). *Clin Exp Otorhinolaryngol*. Aug 2019;12(3):301-307. doi:10.21053/ceo.2018.01781

224. Ek WE, Karlsson T, Hernandes CA, Rask-Andersen M, Johansson A. Breast-feeding and risk of asthma, hay fever, and eczema. *J Allergy Clin Immunol*. Mar 2018;141(3):1157-1159 e9. doi:10.1016/j.jaci.2017.10.022

225. Heinrich J. Modulation of allergy risk by breast feeding. *Curr Opin Clin Nutr Metab Care*. May 2017;20(3):217-221. doi:10.1097/MCO.0000000000000366

226. Nuzzi G, Di Cicco ME, Peroni DG. Breastfeeding and Allergic Diseases: What's New? *Children (Basel)*. Apr 24 2021;8(5)doi:10.3390/children8050330

227. Lodge CJ, Tan DJ, Lau MX, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr*. Dec 2015;104(467):38-53. doi:10.1111/apa.13132

228. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. Sep 2010;126(3):466-76. doi:10.1016/j.jaci.2010.06.047

229. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2015;152(1 Suppl):S1-43. doi:10.1177/0194599814561600

230. Lodge CJ, Lowe AJ, Gurrin LC, et al. Pets at birth do not increase allergic disease in at-risk children. *Clin Exp Allergy*. Sep 2012;42(9):1377-85. doi:10.1111/j.1365-2222.2012.04032.x

231. Takkouche B, Gonzalez-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy*. Jul 2008;63(7):857-64. doi:10.1111/j.1398-9995.2008.01732.x

232. Lodge CJ, Allen KJ, Lowe AJ, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. *Clin Dev Immunol*. 2012;2012:176484. doi:10.1155/2012/176484

233. Luo S, Sun Y, Hou J, et al. Pet keeping in childhood and asthma and allergy among children in Tianjin area, China. *PLoS One*. 2018;13(5):e0197274. doi:10.1371/journal.pone.0197274

234. Chen CM, Heinrich J. Re: Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy*. Mar 2009;64(3):494-5. doi:10.1111/j.1398-9995.2008.01930.x

235. Holt PG, Sly PD. Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes. *Clin Exp Allergy*. Jun 2009;39(6):807-11. doi:10.1111/j.1365-2222.2009.03258.x

236. Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ. Exposure to cats: update on risks for sensitization and allergic diseases. *Curr Allergy Asthma Rep*. Oct 2012;12(5):413-23. doi:10.1007/s11882-012-0288-x

237. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. Nov 18 1989;299(6710):1259-60. doi:10.1136/bmj.299.6710.1259

238. von Hertzen L, Hanski I, Haahtela T. Natural immunity. Biodiversity loss and inflammatory diseases are two global megatrends that might be related. *EMBO Rep*. Oct 28 2011;12(11):1089-93. doi:10.1038/embor.2011.195

239. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol*. Sep 2011;128(3):646-52 e1-5. doi:10.1016/j.jaci.2011.04.060

240. Morin A, McKennan CG, Pedersen CT, et al. Epigenetic landscape links upper airway microbiota in infancy with allergic rhinitis at 6 years of age. *J Allergy Clin Immunol*. Dec 2020;146(6):1358-1366. doi:10.1016/j.jaci.2020.07.005

241. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health*. Mar 2002;56(3):209-17. doi:10.1136/jech.56.3.209

242. Strachan DP, Ait-Khaled N, Foliaki S, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin Exp Allergy*. Jan 2015;45(1):126-36. doi:10.1111/cea.12349

243. Campbell BE, Lodge CJ, Lowe AJ, Burgess JA, Matheson MC, Dharmage SC. Exposure to 'farming' and objective markers of atopy: a systematic review and meta-analysis. *Clin Exp Allergy*. Apr 2015;45(4):744-57. doi:10.1111/cea.12429

244. House JS, Wyss AB, Hoppin JA, et al. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. *J Allergy Clin Immunol*. Jul 2017;140(1):249-256 e14. doi:10.1016/j.jaci.2016.09.036

245. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy*. Feb 2000;30(2):194-200. doi:10.1046/j.1365-2222.2000.00799.x

246. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy*. Feb 2000;30(2):187-93. doi:10.1046/j.1365-2222.2000.00801.x

247. Riedler J, Braun-Fahrlander C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet*. Oct 6 2001;358(9288):1129-33. doi:10.1016/S0140-6736(01)06252-3

248. Barnes M, Cullinan P, Athanasaki P, et al. Crete: does farming explain urban and rural differences in atopy? *Clin Exp Allergy*. Dec 2001;31(12):1822-8. doi:10.1046/j.1365-2222.2001.01240.x

249. Downs SH, Marks GB, Mitakakis TZ, Leuppi JD, Car NG, Peat JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy*. Apr 2001;31(4):570-5. doi:10.1046/j.1365-2222.2001.01070.x

250. Wickens K, Lane JM, Fitzharris P, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy*. Dec 2002;57(12):1171-9. doi:10.1034/j.1398-9995.2002.t01-1-23644.x

251. Remes ST, Pekkanen J, Soininen L, Kajosaari M, Husman T, Koivikko A. Does heredity modify the association between farming and allergy in children? *Acta Paediatr*. 2002;91(11):1163-9. doi:10.1111/j.1651-2227.2002.tb00122.x

252. Remes ST, Iivanainen K, Koskela H, Pekkanen J. Which factors explain the lower prevalence of atopy amongst farmers' children? *Clin Exp Allergy*. Apr 2003;33(4):427-34. doi:10.1046/j.1365-2222.2003.01566.x

253. Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet*. Sep 1999;354 Suppl 2:SII12-5. doi:10.1016/s0140-6736(99)90437-3

254. Simpson A, Martinez FD. The role of lipopolysaccharide in the development of atopy in humans. *Clin Exp Allergy*. Feb 2010;40(2):209-23. doi:10.1111/j.1365-2222.2009.03391.x

255. Tischer C, Gehring U, Chen CM, et al. Respiratory health in children, and indoor exposure to (1,3)-beta-D-glucan, EPS mould components and endotoxin. *Eur Respir J*. May 2011;37(5):1050-9. doi:10.1183/09031936.00091210

256. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy*. Jun 2014;44(6):842-50. doi:10.1111/cea.12253

257. Arrieta MC, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med*. Sep 30 2015;7(307):307ra152. doi:10.1126/scitranslmed.aab2271

258. Fujimura KE, Sitarik AR, Havstad S, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. Oct 2016;22(10):1187-1191. doi:10.1038/nm.4176

259. Hua X, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. *EBioMedicine*. Jan 2016;3:172-179. doi:10.1016/j.ebiom.2015.11.038

260. Hanski I, von Hertzen L, Fyhrquist N, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. *Proc Natl Acad Sci U S A*. May 22 2012;109(21):8334-9. doi:10.1073/pnas.1205624109

261. Fyhrquist N, Ruokolainen L, Suomalainen A, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. *J Allergy Clin Immunol*. Dec 2014;134(6):1301-1309 e11. doi:10.1016/j.jaci.2014.07.059

262. Sjogren YM, Jenmalm MC, Bottcher MF, Bjorksten B, Sverremark-Ekstrom E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clin Exp Allergy*. Apr 2009;39(4):518-26. doi:10.1111/j.1365-2222.2008.03156.x

263. Stsepetova J, Sepp E, Julge K, Vaughan E, Mikelsaar M, de Vos WM. Molecularly assessed shifts of Bifidobacterium ssp. and less diverse microbial communities are characteristic of 5-year-old allergic children. *FEMS Immunol Med Microbiol*. Nov 2007;51(2):260-9. doi:10.1111/j.1574-695X.2007.00306.x

264. Cuello-Garcia CA, Brozek JL, Fiocchi A, et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. Oct 2015;136(4):952-61. doi:10.1016/j.jaci.2015.04.031

265. Holster IL, Vila AM, Caudri D, et al. The impact of Helicobacter pylori on atopic disorders in childhood. *Helicobacter*. Jun 2012;17(3):232-7. doi:10.1111/j.1523-5378.2012.00934.x

266. Akiner U, Yener HM, Gozen ED, Kuzu SB, Canakcioglu S. Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role? *Eur Arch Otorhinolaryngol*. Jan 2020;277(1):141-145. doi:10.1007/s00405-019-05659-3

267. Lionetti E, Leonardi S, Lanzafame A, et al. Helicobacter pylori infection and atopic diseases: is there a relationship? A systematic review and meta-analysis. *World J Gastroenterol*. Dec 14 2014;20(46):17635-47. doi:10.3748/wjg.v20.i46.17635

268. Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy*. May 2017;47(5):665-674. doi:10.1111/cea.12895

269. Valkonen M, Wouters IM, Taubel M, et al. Bacterial Exposures and Associations with Atopy and Asthma in Children. *PLoS One*. 2015;10(6):e0131594. doi:10.1371/journal.pone.0131594

270. Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. Feb 24 2011;364(8):701-9. doi:10.1056/NEJMoa1007302

271. von Hertzen L, Laatikainen T, Pitkanen T, et al. Microbial content of drinking water in Finnish and Russian Karelia - implications for atopy prevalence. *Allergy*. Mar 2007;62(3):288-92. doi:10.1111/j.1398-9995.2006.01281.x

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 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.

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): -Likely AR from stratified sample, n=515 -Cluster sample, n=814	VAS	-AR in 15.8-19.4% -AR impacts QOL, sleep, emotions, and memory
Bousquet et al[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	-Nasal congestion more strongly correlated to outcomes

					Sleep, PANAS-X	-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):	RQLQ	-QOL significantly affected by AR

				-SLIT, n=19 -Placebo, n=15		-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): -Enzyme potentiated desensitization, n=90 -Placebo, n=93	RQLQ, problem-free days	Enzyme potentiated desensitization does not improve QOL or symptom scores compared to placebo
Gerth van Wijk et al[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	Perennial AR treated with desloratadine-	Acoustic	Desloratadine-montelukast improves nasal obstruction

			cohort	montelukast, n=40	rhinometry, RQLQ	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	OSA and rhinitis,	ESS, symptoms scores, CPAP	-Control of rhinitis (with varying regimens

			cohort	n=43	compliance	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	ESS, stress, score, fatigue score,	AR in OSA increases stress and fatigue,

				-OSA without rhinitis, n=75	coping score, RQLQ	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,	Questionnaire	AR risk factor for snoring

				n=437		
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	Questionnaire on nocturnal	AR increases risk of nocturnal enuresis

				rhinitis, n=327,061	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 American urban	Clinical evaluation and follow-up	Poor AR and asthma control related to high frequency of sleep problems and poor sleep

				children, n=195		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]

REFERENCES

1. Chen R, Zheng D, Zhang Y, Sima G. Efficacy and safety of twice-daily olopatadine-mometasone combination nasal spray (GSP301) in the treatment of allergic rhinitis: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. Apr 2022;279(4):1691-1699. doi:10.1007/s00405-021-07085-w

2. Zhang K, Li AR, Miglani A, Nguyen SA, Schlosser RJ. Effect of Medical Therapy in Allergic Rhinitis: A Systematic Review and Meta-Analysis. *Am J Rhinol Allergy*. Mar 2022;36(2):269-280. doi:10.1177/19458924211041438

3. Li AR, Zhang K, Reddy PD, et al. Systematic review of measures of disease severity in rhinitis. *Int Forum Allergy Rhinol*. Sep 2021;11(9):1367-1377. doi:10.1002/alr.22794

4. Calderon MA, Casale TB, Demoly P. Validation of Patient-Reported Outcomes for Clinical Trials in Allergic Rhinitis: A Systematic Review. *J Allergy Clin Immunol Pract*. May - Jun 2019;7(5):1450-1461 e6. doi:10.1016/j.jaip.2019.01.015

5. Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. Burden of allergic respiratory disease: a systematic review. *Clin Mol Allergy*. 2016;14:12. doi:10.1186/s12948-016-0049-9

6. Hahn-Pedersen J, Boxall N, Maier W, Linneberg A, Serup-Hansen N. Systematic Literature Review Assessing Data on the Burden of Allergic Rhinitis from a Cost and Quality of Life Perspective. *Value Health*. Nov 2014;17(7):A602. doi:10.1016/j.jval.2014.08.2087

7. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. Jan 1991;21(1):77-83. doi:10.1111/j.1365-2222.1991.tb00807.x

8. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. Jan 1994;32(1):40-66. doi:10.1097/00005650-199401000-00004

9. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. Mar 1996;34(3):220-33. doi:10.1097/00005650-199603000-00003

10. Husain Q, Hoehle L, Phillips K, Caradonna DS, Gray ST, Sedaghat AR. The 22-Item Sinonasal Outcome Test as a Tool for the Assessment of Quality of Life and Symptom Control in Allergic Rhinitis. *Am J Rhinol Allergy*. Mar 2020;34(2):209-216. doi:10.1177/1945892419884789

11. Passali FM, Passali GC, Passali D, Ciprandi G. Smell impairment in patients with allergic rhinitis. *Int Forum Allergy Rhinol*. Jun 2021;11(6):1031-1032. doi:10.1002/alr.22786

12. Yamada T, Yamamoto H, Kubo S, et al. Efficacy of mometasone furoate nasal spray for nasal symptoms, quality of life, rhinitis-disturbed sleep, and nasal nitric oxide in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Mar-Apr 2012;33(2):e9-16. doi:10.2500/aap.2012.33.3509

13. Bousquet J, Zuberbier T, Canonica GW, Fokkens WJ, Gopalan G, Shekar T. Randomized controlled trial of desloratadine for persistent allergic rhinitis: correlations between symptom improvement and quality of life. *Allergy Asthma Proc*. May-Jun 2013;34(3):274-82. doi:10.2500/aap.2013.34.3668

14. Holmberg K, Tonnel AB, Dreyfus I, et al. Desloratadine relieves nasal congestion and improves quality-of-life in persistent allergic rhinitis. *Allergy*. Nov 2009;64(11):1663-70. doi:10.1111/j.1398-9995.2009.02096.x

15. Walter Canonica G, Bousquet J, Van Hammee G, et al. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respir Med*. Oct 2006;100(10):1706-15. doi:10.1016/j.rmed.2006.03.039

16. Bachert C, Bousquet J, Canonica GW, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol*. Oct 2004;114(4):838-44. doi:10.1016/j.jaci.2004.05.070

17. Pedregal-Mallo D, Pacheco E, Rodrigo JP, Llorente JL, Alvarez-Marcos C. Impact of immunotherapy on quality of life in patients with house dust mite allergic rhinitis. *Allergy*. Jul 2020;75(7):1783-1785. doi:10.1111/all.14215

18. Hoiby AS, Strand V, Robinson DS, Sager A, Rak S. Efficacy, safety, and immunological effects of a 2-year immunotherapy with Depigoid birch pollen extract: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. Jul 2010;40(7):1062-70. doi:10.1111/j.1365-2222.2010.03521.x

19. Di Rienzo V, Pucci S, D'Alo S, et al. Effects of high-dose sublingual immunotherapy on quality of life in patients with cypress-induced rhinitis: a placebo-controlled study. *Clin Exp Allergy Reviews*. 2006;6(3):67-70.

20. Colas C, Monzon S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of Salsola kali (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol*. Apr 2006;117(4):810-6. doi:10.1016/j.jaci.2005.11.039

21. Juel-Berg N, Darling P, Bolvig J, et al. Intranasal corticosteroids compared with oral antihistamines in allergic rhinitis: A systematic review and meta-analysis. *Am J Rhinol Allergy*. Jan 9 2017;31(1):19-28. doi:10.2500/ajra.2016.30.4397

22. Tatar EC, Surenoglu UA, Ozdek A, Saylam G, Korkmaz H. The effect of combined medical treatment on quality of life in persistent allergic rhinitis. *Indian J Otolaryngol Head Neck Surg*. Aug 2013;65(Suppl 2):333-7. doi:10.1007/s12070-012-0486-9

23. Fasola S, Montalbano L, Ferrante G, et al. RAPP-children: A new tool for assessing quality of life in patients with asthma and rhinitis. *Clin Exp Allergy*. Jun 2020;50(6):662-671. doi:10.1111/cea.13599

24. Bosnic-Anticevich S, Smith P, Abramson M, et al. Impact of allergic rhinitis on the day-to-day lives of children: insights from an Australian cross-sectional study. *BMJ Open*. Nov 24 2020;10(11):e038870. doi:10.1136/bmjopen-2020-038870

25. Hwang TY, Kim SK, Kim SH, Kim M. A cross sectional survey on health-related quality of life among parents of children with allergic symptoms using the EQ-5D-5L. *J Asthma*. Nov 2019;56(11):1239-1245. doi:10.1080/02770903.2019.1571086

26. Valls-Mateus M, Marino-Sanchez F, Ruiz-Echevarria K, et al. Nasal obstructive disorders impair health-related quality of life in adolescents with persistent allergic rhinitis: A real-life study. *Pediatr Allergy Immunol*. Aug 2017;28(5):438-445. doi:10.1111/pai.12724

27. Sikorska-Szaflik H, Sozanska B. Quality of life in allergic rhinitis - children's and their parents' perspective in polish urban and rural population. *Health Qual Life Outcomes*. Mar 10 2020;18(1):64. doi:10.1186/s12955-020-01315-1

28. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. *Qual Life Res*. Jul 1998;7(5):399-407. doi:10.1023/a:1008853819715

29. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol*. Feb 1998;101(2 Pt 1):163-70. doi:10.1016/s0091-6749(98)70380-x

30. Segall N, Prenner B, Lumry W, Caracta CF, Tantry SK. Long-term safety and efficacy of olopatadine-mometasone combination nasal spray in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Sep 1 2019;40(5):301-310. doi:10.2500/aap.2019.40.4233

31. Majani G, Baiardini I, Giardini A, et al. Health-related quality of life assessment in young adults with seasonal allergic rhinitis. *Allergy*. Apr 2001;56(4):313-7. doi:10.1034/j.1398-9995.2001.00852.x

32. Aruthra R, Kumar M. To study the impact of allergic rhinitis on quality of life in a tertiary care hospital. *Intern J Cur Res Rev*. 2021;13(2):118-120.

33. Zhu R, Wang J, Wu Y, et al. The Allergic Rhinitis Control Test Questionnaire Is Valuable in Guiding Step-Down Pharmacotherapy Treatment of Allergic Rhinitis. *J Allergy Clin Immunol Pract*. Jan 2019;7(1):272-278. doi:10.1016/j.jaip.2018.05.028

34. Bousquet J, Arnavielhe S, Bedbrook A, et al. The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: The MASK study. *Allergy*. Feb 2018;73(2):505-510. doi:10.1111/all.13307

35. Hoehle LP, Speth MM, Phillips KM, et al. Association between symptoms of allergic rhinitis with decreased general health-related quality of life. *Am J Rhinol Allergy*. Jul 1 2017;31(4):235-239. doi:10.2500/ajra.2017.31.4444

36. Filanowicz M, Szynkiewicz E, Cegla B, Bartuzi Z. Analysis of the quality of life of patients with asthma and allergic rhinitis after immunotherapy. *Postepy Dermatol Alergol*. Apr 2016;33(2):134-41. doi:10.5114/pdia.2015.48061

37. Jaruvongvanich V, Mongkolpathumrat P, Chantaphakul H, Klaewsongkram J. Extranasal symptoms of allergic rhinitis are difficult to treat and affect quality of life. *Allergol Int*. Apr 2016;65(2):199-203. doi:10.1016/j.alit.2015.11.006

38. Song Y, Wang M, Xie J, et al. Prevalence of allergic rhinitis among elementary and middle school students in Changsha city and its impact on quality of life. *J Laryngol Otol*. Nov 2015;129(11):1108-14. doi:10.1017/S0022215115002492

39. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. *Int Arch Allergy Immunol*. 2013;160(4):393-400. doi:10.1159/000342991

40. Katelaris CH, Sacks R, Theron PN. Allergic rhinoconjunctivitis in the Australian population: burden of disease and attitudes to intranasal corticosteroid treatment. *Am J Rhinol Allergy*. Nov-Dec 2013;27(6):506-9. doi:10.2500/ajra.2013.27.3965

41. de la Hoz Caballer B, Rodriguez M, Fraj J, Cerecedo I, Antolin-Amerigo D, Colas C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evAluate work Productivity in allergic Rhinitis compared with other common dIseases (CAPRI) study. *Am J Rhinol Allergy*. Sep-Oct 2012;26(5):390-4. doi:10.2500/ajra.2012.26.3799

42. Meltzer EO, Gross GN, Katial R, Storms WW. Allergic rhinitis substantially impacts patient quality of life: findings from the Nasal Allergy Survey Assessing Limitations. *J Fam Pract*. Feb 2012;61(2 Suppl):S5-10.

43. Stull DE, Schaefer M, Crespi S, Sandor DW. Relative strength of relationships of nasal congestion and ocular symptoms with sleep, mood and productivity. *Curr Med Res Opin*. Jul 2009;25(7):1785-92. doi:10.1185/03007990903021968

44. Witt CM, Reinhold T, Jena S, Brinkhaus B, Willich SN. Cost-effectiveness of acupuncture in women and men with allergic rhinitis: a randomized controlled study in usual care. *Am J Epidemiol*. Mar 1 2009;169(5):562-71. doi:10.1093/aje/kwn370

45. Brinkhaus B, Witt CM, Jena S, Liecker B, Wegscheider K, Willich SN. Acupuncture in patients with allergic rhinitis: a pragmatic randomized trial. *Ann Allergy Asthma Immunol*. Nov 2008;101(5):535-43. doi:10.1016/S1081-1206(10)60294-3

46. Petersen KD, Kronborg C, Gyrd-Hansen D, Dahl R, Larsen JN, Lowenstein H. Quality of life in rhinoconjunctivitis assessed with generic and disease-specific questionnaires. *Allergy*. Mar 2008;63(3):284-91. doi:10.1111/j.1398-9995.2007.01583.x

47. Ciprandi G, Klersy C, Cirillo I, Marseglia GL. Quality of life in allergic rhinitis: relationship with clinical, immunological, and functional aspects. *Clin Exp Allergy*. Oct 2007;37(10):1528-35. doi:10.1111/j.1365-2222.2007.02809.x

48. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ*. Aug 2 2003;327(7409):251-4. doi:10.1136/bmj.327.7409.251

49. Gerth Van Wijk R, Terreehorst IT, Mulder PG, Garrelds IM, Blom HM, Popering S. Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study. *Clin Exp Allergy*. Dec 2000;30(12):1792-8. doi:10.1046/j.1365-2222.2000.00920.x

50. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med*. Oct 2000;162(4 Pt 1):1391-6. doi:10.1164/ajrccm.162.4.9912033

51. Cuesta-Herranz J, Laguna JJ, Mielgo R, et al. Quality of life improvement with allergen immunotherapy treatment in patients with rhinoconjunctivitis in real life conditions. Results of an observational prospective study (ICARA). *Eur Ann Allergy Clin Immunol*. Sep 16 2019;51(5)doi:10.23822/EurAnnACI.1764-1489.104

52. Gillman GS, Staltari GV, Chang YF, Mattos JL. A Prospective Study of Outcomes of Septoplasty with Turbinate Reductions in Patients with Allergic Rhinitis. *Otolaryngol Head Neck Surg*. Jun 2019;160(6):1118-1123. doi:10.1177/0194599819838761

53. Baiardini I, Fasola S, Montalbano L, et al. RHINASTHMA-Children: A new quality of life tool for patients with respiratory allergy. *Pediatr Allergy Immunol*. Feb 2017;28(1):102-105. doi:10.1111/pai.12667

54. Novakova SM, Staevska MT, Novakova PI, et al. Quality of life improvement after a three-year course of sublingual immunotherapy in patients with house dust mite and grass pollen induced allergic rhinitis: results from real-life. *Health Qual Life Outcomes*. Sep 29 2017;15(1):189. doi:10.1186/s12955-017-0764-z

55. Schwanke T, Carragee E, Bremberg M, Reisacher WR. Quality-of-life outcomes in patients who underwent subcutaneous immunotherapy and sublingual immunotherapy in a real-world clinical setting. *Am J Rhinol Allergy*. Sep 1 2017;31(5):310-316. doi:10.2500/ajra.2017.31.4465

56. Bukstein D, Parikh R, Eid S, Ferro T, Morello JP. Beclomethasone Dipropionate Nasal Aerosol in Patients with Perennial Allergic Rhinitis (BALANCE) study: 6-month results. *Allergy Asthma Proc*. Mar-Apr 2016;37(2):121-30. doi:10.2500/aap.2016.37.3939

57. Cingi C, Oghan F, Eskiizmir G, Yaz A, Ural A, Erdogmus N. Desloratadine-montelukast combination improves quality of life and decreases nasal obstruction in patients with perennial allergic rhinitis. *Int Forum Allergy Rhinol*. Oct 2013;3(10):801-6. doi:10.1002/alr.21185

58. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy*. Aug 2013;43(8):881-8. doi:10.1111/cea.12121

59. Ciprandi G, Cadario G, Valle C, et al. Sublingual immunotherapy in polysensitized patients: effect on quality of life. *J Investig Allergol Clin Immunol*. 2010;20(4):274-9.

60. Cadario G, Ciprandi G, Di Cara G, et al. Comparison between continuous or intermittent schedules of sublingual immunotherapy for house dust mites: effects on compliance, patients satisfaction, quality of life and safety. *Int J Immunopathol Pharmacol*. Apr-Jun 2008;21(2):471-3. doi:10.1177/039463200802100229

61. Laforest L, Bousquet J, Neukirch F, et al. Influence of sociodemographic factors on quality of life during pollen season in seasonal allergic rhinitis patients. *Ann Allergy Asthma Immunol*. Jul 2005;95(1):26-32. doi:10.1016/S1081-1206(10)61184-2

62. Zheng M, Wang X, Ge S, et al. Allergic and Non-Allergic Rhinitis Are Common in Obstructive Sleep Apnea but Not Associated With Disease Severity. *J Clin Sleep Med*. Aug 15 2017;13(8):959-966. doi:10.5664/jcsm.6694

63. Liu J, Wu Y, Wu P, Xu Z, Ni X. Analysis of the impact of allergic rhinitis on the children with sleep disordered breathing. *Int J Pediatr Otorhinolaryngol*. Nov 2020;138:110380. doi:10.1016/j.ijporl.2020.110380

64. Shanqun L, Shenyuan L, Zhou J, Bai C. The role of montelukast and intranasal budesonide on OSAHS and allergic rhinitis. *Allergy*. 2009;64:591.

65. Gurevich F, Glass C, Davies M, et al. The effect of intranasal steroid budesonide on the congestion-related sleep disturbance and daytime somnolence in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Jul-Aug 2005;26(4):268-74.

66. Hughes K, Glass C, Ripchinski M, et al. Efficacy of the topical nasal steroid budesonide on improving sleep and daytime somnolence in patients with perennial allergic rhinitis. *Allergy*. May 2003;58(5):380-5. doi:10.1034/j.1398-9995.2003.00093.x

67. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol*. May 1998;101(5):633-7. doi:10.1016/s0091-6749(98)70171-x

68. Mansfield LE, Posey CR. Daytime sleepiness and cognitive performance improve in seasonal allergic rhinitis treated with intranasal fluticasone propionate. *Allergy Asthma Proc*. Mar-Apr 2007;28(2):226-9. doi:10.2500/aap.2007.28.2950

69. Bilgilisoy Filiz M, Filiz S, Baran RT, et al. Restless legs syndrome in children with allergic rhinitis: A comparative study on frequency, severity and sleep quality. *Turk J Phys Med Rehabil*. Sep 2018;64(3):198-204. doi:10.5606/tftrd.2018.2265

70. Kim DK, Han DH. Impact of allergic rhinitis on quality of life after adenotonsillectomy for pediatric sleep-disordered breathing. *Int Forum Allergy Rhinol*. Aug 2015;5(8):741-6. doi:10.1002/alr.21529

71. Lai PH, Yang PS, Lai WY, Lin CL, Hsu CY, Wei CC. Allergic rhinitis and the associated risk of nocturnal enuresis in children: a population-based cohort study. *Int Forum Allergy Rhinol*. Nov 2018;8(11):1260-1266. doi:10.1002/alr.22219

72. Krouse HJ, Davis JE, Krouse JH. Immune mediators in allergic rhinitis and sleep. *Otolaryngol Head Neck Surg*. Jun 2002;126(6):607-13. doi:10.1067/mhn.2002.125300

73. McNicholas WT, Tarlo S, Cole P, et al. Obstructive apneas during sleep in patients with seasonal allergic rhinitis. *Am Rev Respir Dis*. Oct 1982;126(4):625-8. doi:10.1164/arrd.1982.126.4.625

74. Acar M, Cingi C, Sakallioglu O, San T, Fatih Yimenicioglu M, Bal C. The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis. *Am J Rhinol Allergy*. Jul-Aug 2013;27(4):e113-6. doi:10.2500/ajra.2013.27.3921

75. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. *J Allergy Clin Immunol*. Feb 1997;99(2):S757-62. doi:10.1016/s0091-6749(97)70124-6

76. Lavigne F, Petrof BJ, Johnson JR, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clin Exp Allergy*. Oct 2013;43(10):1124-33. doi:10.1111/cea.12158

77. Lavie P, Gertner R, Zomer J, Podoshin L. Breathing disorders in sleep associated with "microarousals' in patients with allergic rhinitis. *Acta Otolaryngol*. Nov-Dec 1981;92(5-6):529-33. doi:10.3109/00016488109133292

78. Berson SR, Klimczak J, Prezio EA, Hu S, Abraham M. Clinical associations between allergies and rapid eye movement sleep disturbances. *Int Forum Allergy Rhinol*. Jul 2018;8(7):817-824. doi:10.1002/alr.22099

79. Liu J, Zhang X, Zhao Y, Wang Y. The association between allergic rhinitis and sleep: A systematic review and meta-analysis of observational studies. *PLoS One*. 2020;15(2):e0228533. doi:10.1371/journal.pone.0228533

80. Berson SR, Klimczak JA, Prezio EA, Abraham MT. House Dust Mite Related Allergic Rhinitis and REM Sleep Disturbances. *Am J Otolaryngol*. Nov - Dec 2020;41(6):102709. doi:10.1016/j.amjoto.2020.102709

81. Pace A, Iannella G, Rossetti V, et al. Diagnosis of Obstructive Sleep Apnea in Patients with Allergic and Non-Allergic Rhinitis. *Medicina (Kaunas)*. Sep 8 2020;56(9)doi:10.3390/medicina56090454

82. Meng J, Xuan J, Qiao X, et al. Assessment of sleep impairment in persistent allergic rhinitis patients using polysomnography. *Int Arch Allergy Immunol*. 2011;155(1):57-62. doi:10.1159/000317244

83. Bozkurt B, Serife Ugur K, Karamanli H, Kucuker F, Ozol D. Polysomnographic findings in persistent allergic rhinitis. *Sleep Breath*. May 2017;21(2):255-261. doi:10.1007/s11325-016-1390-4

84. Thompson A, Sardana N, Craig TJ. Sleep impairment and daytime sleepiness in patients with allergic rhinitis: the role of congestion and inflammation. *Ann Allergy Asthma Immunol*. Dec 2013;111(6):446-51. doi:10.1016/j.anai.2013.05.020

85. Rimmer J, Downie S, Bartlett DJ, Gralton J, Salome C. Sleep disturbance in persistent allergic rhinitis measured using actigraphy. *Ann Allergy Asthma Immunol*. Sep 2009;103(3):190-4. doi:10.1016/S1081-1206(10)60180-9

86. Camhi SL, Morgan WJ, Pernisco N, Quan SF. Factors affecting sleep disturbances in children and adolescents. *Sleep Med*. Apr 1 2000;1(2):117-123. doi:10.1016/s1389-9457(99)00005-2

87. Parikh NG, Junaid I, Sheinkopf L, Randhawa I, Santiago SM, Klaustermeyer WB. Clinical control in the dual diagnosis of obstructive sleep apnea syndrome and rhinitis: a prospective analysis. *Am J Rhinol Allergy*. Jan-Feb 2014;28(1):e52-5. doi:10.2500/ajra.2014.28.3977

88. Fried J, Yuen E, Zhang K, et al. Impact of Treatment for Nasal Cavity Disorders on Sleep Quality: Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Apr 2022;166(4):633-642. doi:10.1177/01945998211029527

89. Munoz-Cano R, Ribo P, Araujo G, Giralt E, Sanchez-Lopez J, Valero A. Severity of allergic rhinitis impacts sleep and anxiety: results from a large Spanish cohort. *Clin Transl Allergy*. 2018;8:23. doi:10.1186/s13601-018-0212-0

90. Colas C, Galera H, Anibarro B, et al. Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). *Clin Exp Allergy*. Jul 2012;42(7):1080-7. doi:10.1111/j.1365-2222.2011.03935.x

91. Romano M, James S, Farrington E, Perry R, Elliott L. The impact of perennial allergic rhinitis with/without allergic asthma on sleep, work and activity level. *Allergy Asthma Clin Immunol*. 2019;15:81. doi:10.1186/s13223-019-0391-9

92. Roxbury CR, Qiu M, Shargorodsky J, Lin SY. Association between allergic rhinitis and poor sleep parameters in U.S. adults. *Int Forum Allergy Rhinol*. Oct 2018;8(10):1098-1106. doi:10.1002/alr.22174

93. Leger D, Bonnefoy B, Pigearias B, de La Giclais B, Chartier A. Poor sleep is highly associated with house dust mite allergic rhinitis in adults and children. *Allergy Asthma Clin Immunol*. 2017;13:36. doi:10.1186/s13223-017-0208-7

94. Gadi G, Wali S, Koshak E, et al. The prevalence of allergic rhinitis and atopic markers in obstructive sleep apnea. *J Epidemiol Glob Health*. Mar 2017;7(1):37-44. doi:10.1016/j.jegh.2016.06.001

95. Park CE, Shin SY, Lee KH, Cho JS, Kim SW. The effect of allergic rhinitis on the degree of stress, fatigue and quality of life in OSA patients. *Eur Arch Otorhinolaryngol*. Sep 2012;269(9):2061-4. doi:10.1007/s00405-011-1888-0

96. Udaka T, Suzuki H, Fujimura T, et al. Chronic nasal obstruction causes daytime sleepiness and decreased quality of life even in the absence of snoring. *Am J Rhinol*. Sep-Oct 2007;21(5):564-9. doi:10.2500/ajr.2007.21.3087

97. Leger D, Annesi-Maesano I, Carat F, et al. Allergic rhinitis and its consequences on quality of sleep: An unexplored area. *Arch Intern Med*. Sep 18 2006;166(16):1744-8. doi:10.1001/archinte.166.16.1744

98. Canova CR, Downs SH, Knoblauch A, Andersson M, Tamm M, Leuppi JD. Increased prevalence of perennial allergic rhinitis in patients with obstructive sleep apnea. *Respiration*. Mar-Apr 2004;71(2):138-43. doi:10.1159/000076674

99. Mintz M, Garcia J, Diener P, Liao Y, Dupclay L, Georges G. Triamcinolone acetonide aqueous nasal spray improves nocturnal rhinitis-related quality of life in patients treated in a primary care setting: the Quality of Sleep in Allergic Rhinitis study. *Ann Allergy Asthma Immunol*. Feb 2004;92(2):255-61. doi:10.1016/S1081-1206(10)61557-8

100. Stuck BA, Czajkowski J, Hagner AE, et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol*. Apr 2004;113(4):663-8. doi:10.1016/j.jaci.2003.12.589

101. Janson C, De Backer W, Gislason T, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J*. Oct 1996;9(10):2132-8. doi:10.1183/09031936.96.09102132

102. Lin SY, Melvin TA, Boss EF, Ishman SL. The association between allergic rhinitis and sleep-disordered breathing in children: a systematic review. *Int Forum Allergy Rhinol*. Jun 2013;3(6):504-9. doi:10.1002/alr.21123

103. Lee K, Choi IH, Hong Y, Lee H, Lee SH, Kim TH. Association between allergic rhinitis-related factors and sleep duration in adolescents: Korea National Health and Nutrition Examination Survey V (2010-2012). *Int J Pediatr Otorhinolaryngol*. Mar 2021;142:110613. doi:10.1016/j.ijporl.2021.110613

104. Giraldo-Cadavid LF, Perdomo-Sanchez K, Cordoba-Gravini JL, et al. Allergic Rhinitis and OSA in Children Residing at a High Altitude. *Chest*. Feb 2020;157(2):384-393. doi:10.1016/j.chest.2019.09.018

105. Perikleous E, Steiropoulos P, Nena E, et al. Association of Asthma and Allergic Rhinitis With Sleep-Disordered Breathing in Childhood. *Front Pediatr*. 2018;6:250. doi:10.3389/fped.2018.00250

106. Di Francesco RC, Alvarez J. Allergic rhinitis affects the duration of rapid eye movement sleep in children with sleep-disordered breathing without sleep apnea. *Int Forum Allergy Rhinol*. May 2016;6(5):465-71. doi:10.1002/alr.21689

107. Chimenz R, Manti S, Fede C, et al. Primary Nocturnal Enuresis in Children with Allergic Rhinitis and Severe Adenotonsillar Hypertrophy: A Single Center Pilot Study. *J Biol Regul Homeost Agents*. Apr-Jun 2015;29(2 Suppl 1):73-9.

108. Koinis-Mitchell D, Kopel SJ, Boergers J, et al. Asthma, allergic rhinitis, and sleep problems in urban children. *J Clin Sleep Med*. Jan 15 2015;11(2):101-10. doi:10.5664/jcsm.4450

109. Poachanukoon O, Kitcharoensakkul M. Snoring and sleep problems in children with and without allergic rhinitis: a case control study. *J Med Assoc Thai*. Mar 2015;98 Suppl 2:S138-44.

110. Kwon JA, Lee M, Yoo KB, Park EC. Does the duration and time of sleep increase the risk of allergic rhinitis? Results of the 6-year nationwide Korea youth risk behavior web-based survey. *PLoS One*. 2013;8(8):e72507. doi:10.1371/journal.pone.0072507

111. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. Sep 1 2010;182(5):676-83. doi:10.1164/rccm.200912-1930OC

112. Li AM, Au CT, So HK, Lau J, Ng PC, Wing YK. Prevalence and risk factors of habitual snoring in primary school children. *Chest*. Sep 2010;138(3):519-27. doi:10.1378/chest.09-1926

113. Vichyanond P, Suratannon C, Lertbunnaphong P, Jirapongsananuruk O, Visitsunthorn N. Clinical characteristics of children with non-allergic rhinitis vs with allergic rhinitis. *Asian Pac J Allergy Immunol*. Dec 2010;28(4):270-4.

114. Barone JG, Hanson C, DaJusta DG, Gioia K, England SJ, Schneider D. Nocturnal enuresis and overweight are associated with obstructive sleep apnea. *Pediatrics*. Jul 2009;124(1):e53-9. doi:10.1542/peds.2008-2805

115. Sogut A, Yilmaz O, Dinc G, Yuksel H. Prevalence of habitual snoring and symptoms of sleep-disordered breathing in adolescents. *Int J Pediatr Otorhinolaryngol*. Dec 2009;73(12):1769-73. doi:10.1016/j.ijporl.2009.09.026

116. Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkaranta A. All snoring is not adenoids in young children. *Int J Pediatr Otorhinolaryngol*. Jun 2008;72(6):879-84. doi:10.1016/j.ijporl.2008.02.018

117. Kalra M, Lemasters G, Bernstein D, et al. Atopy as a risk factor for habitual snoring at age 1 year. *Chest*. Apr 2006;129(4):942-6. doi:10.1378/chest.129.4.942

118. Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am J Respir Crit Care Med*. Aug 1 2005;172(3):364-70. doi:10.1164/rccm.200408-1064OC

119. Ng DK, Kwok KL, Cheung JM, et al. Prevalence of sleep problems in Hong Kong primary school children: a community-based telephone survey. *Chest*. Sep 2005;128(3):1315-23. doi:10.1378/chest.128.3.1315

120. Sogut A, Altin R, Uzun L, et al. Prevalence of obstructive sleep apnea syndrome and associated symptoms in 3--11-year-old Turkish children. *Pediatr Pulmonol*. Mar 2005;39(3):251-6. doi:10.1002/ppul.20179

121. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol*. Sep 2004;38(3):210-6. doi:10.1002/ppul.20075

122. Kidon MI, See Y, Goh A, Chay OM, Balakrishnan A. Aeroallergen sensitization in pediatric allergic rhinitis in Singapore: is air-conditioning a factor in the tropics? *Pediatr Allergy Immunol*. Aug 2004;15(4):340-3. doi:10.1111/j.1399-3038.2004.00152.x

123. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol*. Feb 2004;92(2):240-4. doi:10.1016/S1081-1206(10)61554-2

124. Anuntaseree W, Rookkapan K, Kuasirikul S, Thongsuksai P. Snoring and obstructive sleep apnea in Thai school-age children: prevalence and predisposing factors. *Pediatr Pulmonol*. Sep 2001;32(3):222-7. doi:10.1002/ppul.1112

125. McColley SA, Carroll JL, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. *Chest*. Jan 1997;111(1):170-3. doi:10.1378/chest.111.1.170

126. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. Oct 2017;140(4):950-958. doi:10.1016/j.jaci.2017.03.050

127. Katelaris CH, Lee BW, Potter PC, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. *Clin Exp Allergy*. Feb 2012;42(2):186-207. doi:10.1111/j.1365-2222.2011.03891.x

128. Dierick BJH, van der Molen T, Flokstra-de Blok BMJ, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. *Expert Rev Pharmacoecon Outcomes Res*. Oct 2020;20(5):437-453. doi:10.1080/14737167.2020.1819793

129. Kritikos V, Price D, Papi A, et al. The Burden of Self-Reported Rhinitis and Associated Risk for Exacerbations with Moderate-Severe Asthma in Primary Care Patients. *J Asthma Allergy*. 2020;13:415-428. doi:10.2147/JAA.S266204

130. Strozek J, Samolinski BK, Klak A, et al. The indirect costs of allergic diseases. *Int J Occup Med Environ Health*. Jun 14 2019;32(3):281-290. doi:10.13075/ijomeh.1896.01275

131. Al-Digheari A, Mahboub B, Tarraf H, et al. The clinical burden of allergic rhinitis in five Middle Eastern countries: results of the SNAPSHOT program. *Allergy Asthma Clin Immunol*. 2018;14:63. doi:10.1186/s13223-018-0298-x

132. Goetzel RZ, Long SR, Ozminkowski RJ, Hawkins K, Wang S, Lynch W. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med*. Apr 2004;46(4):398-412. doi:10.1097/01.jom.0000121151.40413.bd

133. Workman AD, Dattilo L, Rathi VK, Bhattacharyya N. Contemporary Incremental Healthcare Costs for Allergic Rhinitis in the United States. *Laryngoscope*. Sep 2 2021;doi:10.1002/lary.29846

134. Roland LT, Wise SK, Wang H, Zhang P, Mehta C, Levy JM. The cost of rhinitis in the United States: a national insurance claims analysis. *Int Forum Allergy Rhinol*. May 2021;11(5):946-948. doi:10.1002/alr.22748

135. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. *Ann Allergy Asthma Immunol*. Feb 2011;106(2 Suppl):S12-6. doi:10.1016/j.anai.2010.10.014

136. Law AW, Reed SD, Sundy JS, Schulman KA. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. *J Allergy Clin Immunol*. Feb 2003;111(2):296-300. doi:10.1067/mai.2003.68

137. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics*. 2004;22(6):345-61. doi:10.2165/00019053-200422060-00002

138. Avdeeva KS, Reitsma S, Fokkens WJ. Direct and indirect costs of allergic and non-allergic rhinitis in the Netherlands. *Allergy*. Nov 2020;75(11):2993-2996. doi:10.1111/all.14457

139. Bousquet J, Schroder-Bernhardi D, Bachert C, et al. Heterogeneity of the pharmacologic treatment of allergic rhinitis in Europe based on MIDAS and OTCims platforms. *Clin Exp Allergy*. Aug 2021;51(8):1033-1045. doi:10.1111/cea.13884

140. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2015;152(1 Suppl):S1-43. doi:10.1177/0194599814561600

141. Smith P, Price D, Harvey R, et al. Medication-related costs of rhinitis in Australia: a NostraData cross-sectional study of pharmacy purchases. *J Asthma Allergy*. 2017;10:153-161. doi:10.2147/JAA.S128431

142. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. Jan 2020;145(1):70-80 e3. doi:10.1016/j.jaci.2019.06.049

143. Price D, Scadding G, Ryan D, et al. The hidden burden of adult allergic rhinitis: UK healthcare resource utilisation survey. *Clin Transl Allergy*. 2015;5:39. doi:10.1186/s13601-015-0083-6

144. Cardell LO, Olsson P, Andersson M, et al. TOTALL: high cost of allergic rhinitis-a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med*. Feb 4 2016;26:15082. doi:10.1038/npjpcrm.2015.82

145. Belhassen M, Demoly P, Bloch-Morot E, et al. Costs of perennial allergic rhinitis and allergic asthma increase with severity and poor disease control. *Allergy*. Jun 2017;72(6):948-958. doi:10.1111/all.13098

146. Celik G, Mungan D, Abadoglu O, Pinar NM, Misirligil Z. Direct cost assessments in subjects with seasonal allergic rhinitis living in Ankara, Turkey. *Allergy Asthma Proc*. Mar-Apr 2004;25(2):107-13.

147. Yoo KH, Ahn HR, Park JK, et al. Burden of Respiratory Disease in Korea: An Observational Study on Allergic Rhinitis, Asthma, COPD, and Rhinosinusitis. *Allergy Asthma Immunol Res*. Nov 2016;8(6):527-34. doi:10.4168/aair.2016.8.6.527

148. Kim SY, Yoon SJ, Jo MW, Kim EJ, Kim HJ, Oh IH. Economic burden of allergic rhinitis in Korea. *Am J Rhinol Allergy*. Sep-Oct 2010;24(5):e110-3. doi:10.2500/ajra.2010.24.3513

149. Ghoshal AG, Ravindran GD, Gangwal P, et al. The burden of segregated respiratory diseases in India and the quality of care in these patients: Results from the Asia-Pacific Burden of Respiratory Diseases study. *Lung India*. Nov-Dec 2016;33(6):611-619. doi:10.4103/0970-2113.192878

150. Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc*. Jan-Feb 2007;28(1):3-9. doi:10.2500/aap.2007.28.2934

151. Crystal-Peters J, Crown WH, Goetzel RZ, Schutt DC. The cost of productivity losses associated with allergic rhinitis. *Am J Manag Care*. Mar 2000;6(3):373-8.

152. Fineman SM. The burden of allergic rhinitis: beyond dollars and cents. *Ann Allergy Asthma Immunol*. Apr 2002;88(4 Suppl 1):2-7. doi:10.1016/s1081-1206(10)62022-4

153. Colas C, Brosa M, Anton E, et al. Estimate of the total costs of allergic rhinitis in specialized care based on real-world data: the FERIN Study. *Allergy*. Jun 2017;72(6):959-966. doi:10.1111/all.13099

154. Canonica GW, Klimek L, Acaster S, et al. Burden of allergic rhinitis and impact of MP-AzeFlu from the patient perspective: pan European patient survey. *Curr Med Res Opin*. Jul 2021;37(7):1259-1272. doi:10.1080/03007995.2021.1911973

155. Vandenplas O, Vinnikov D, Blanc PD, et al. Impact of Rhinitis on Work Productivity: A Systematic Review. *J Allergy Clin Immunol Pract*. Jul - Aug 2018;6(4):1274-1286 e9. doi:10.1016/j.jaip.2017.09.002

156. Lamb CE, Ratner PH, Johnson CE, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin*. Jun 2006;22(6):1203-10. doi:10.1185/030079906X112552

157. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold--high cost to society. *Allergy*. Jun 1 2010;65(6):776-83. doi:10.1111/j.1398-9995.2009.02269.x

158. Roger A, Arcala Campillo E, Torres MC, et al. Reduced work/academic performance and quality of life in patients with allergic rhinitis and impact of allergen immunotherapy. *Allergy Asthma Clin Immunol*. 2016;12:40. doi:10.1186/s13223-016-0146-9

159. Jauregui I, Mullol J, Davila I, et al. Allergic rhinitis and school performance. *J Investig Allergol Clin Immunol*. 2009;19 Suppl 1:32-9.

160. Schoenwetter WF, Dupclay L, Jr., Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin*. Mar 2004;20(3):305-17. doi:10.1185/030079903125003053

161. Mir E, Panjabi C, Shah A. Impact of allergic rhinitis in school going children. *Asia Pac Allergy*. Apr 2012;2(2):93-100. doi:10.5415/apallergy.2012.2.2.93

162. Trikojat K, Buske-Kirschbaum A, Plessow F, Schmitt J, Fischer R. Memory and multitasking performance during acute allergic inflammation in seasonal allergic rhinitis. *Clin Exp Allergy*. Apr 2017;47(4):479-487. doi:10.1111/cea.12893

163. Wang J, Xiao D, Chen H, Hu J. Cumulative evidence for association of rhinitis and depression. *Allergy Asthma Clin Immunol*. Oct 24 2021;17(1):111. doi:10.1186/s13223-021-00615-5

164. Klimek L, Bachert C, Pfaar O, et al. ARIA guideline 2019: treatment of allergic rhinitis in the German health system. *Allergol Select*. 2019;3(1):22-50. doi:10.5414/ALX02120E

165. Cingi C, Bayar Muluk N, Scadding GK. Will every child have allergic rhinitis soon? *Int J Pediatr Otorhinolaryngol*. Mar 2019;118:53-58. doi:10.1016/j.ijporl.2018.12.019

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 -SPT	Physical examination alone yields unreliable and 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	Allergic phenotype of CRSwNP has worse symptomatic and radiologic disease burden

					-Allergy testing	
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	On SPT with cat antigen, a wheal size of $\geq$3 mm had a sensitivity of 100% and specificity of 74.1%; improved

					NPT	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	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

				challenge performed for 5 allergens		(+) 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 -Standardized grass pollen, tree pollen, cat, HDM tested	IDST, RAST, clinical history	-Ideal cutoff for positive IDST is wheal diameter 0.7 times the size of histamine control -IDST has 83% predictive value 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(+) -Group III: SPT(-), IDST(-)	Nasal allergen provocation for *Alternaria* compared to skin tests	IDST after SPT increased the sensitivity from 42% to 58%
Nelson et al[66]	1996	4	Prospective case-control	70 subjects: -Group I: SAR, SPT(-),	Nasal challenge with Timothy grass	(+) IDST after (-) SPT did not indicate the

				IDST(+) -Group II: SAR, SPT(+) -Group III: SAR, SPT(-), IDST(+) -Group IV: no rhinitis	compared to skin tests	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 dose of herbal preparation	-Fexofenadine significantly reduced SPT wheal size vs placebo -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	No effect of 7 days methylprednisolone on intradermal wheal size

					48/80	
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	-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

				terfenadine x2 days		
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, chlorpheniramine or sodium cromoglycate	Inhibition of allergen and histamine induced wheals	Ketotifen, clemastine, and chlorpheniramine but not 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)	tIgE levels in AR versus controls	-Mean log tIgE in cases: 5.65 (IgE 814.36 IU/ml), and in controls: 4.43 (tIgE

				-42 controls		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	Discrimination of AR (defined as symptoms with	-tIgE of 98.7 IU/ml strong predictor of AR: AUC 0.79 (0.74-0.83), 75.2%

				33 (8-76) years, from otolaryngology department	positive sIgE)	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 from tertiary clinic, mean age 31.8 years, 205 with AR, asthma equally present in both groups	tIgE levels between AR and NAR	-tIgE: AR 261 (359), NAR 126 (172), p<0.01 -Differences in complaints and seasonality between AR and NAR
Satwani et al[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 -Cat exposure model	Compared the predictive values of SPT, ID and RAST in diagnosis of cat allergy	-SPT and RAST values had excellent efficiency in cat allergy diagnosis -ID added little to the diagnostic evaluation -Sensitivity and specificity of RAST were 69% and 100%, respectively
Tschopp et al[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	1967	3	Prospective	31 allergic	Acoustic rhinometry of	Good correlation between

al[148]			cohort	patients	minimal nasal cavity cross-sectional area	provocation tests and in-vitro tests for allergy
Bignardi et al[153]	2019	4	Retrospective 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	Retrospective cohort	2635 patients who underwent SPT and sIgE	sIgE measured by Phadia CAP compared to SPT	-Moderate agreement between SPT and sIgE (75.8%) -Sensitivity of CAP higher than SPT wheal size (72.8%) -Specificity of CAP higher than SPT wheal size (78.2%) -SPT mean wheal size and sIgE levels correlated for all allergens except *T. putrescentiae*
Seidman et al[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	NPT, nasal sIgE, serum sIgE, SPT	Nasal sIgE does not predict response to NPT in patients with NAR

				-Control, n=18		
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:	Nasal sIgE	-AR with higher nasal sIgE to HDM than NAR, no difference between adults

				-NAR children, n=12 -AR children, n=15 -NAR adults, n=9 -AR adults, n=15		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:	Nasal sIgE, tIgE, histologic immunolocalization	Nasal sIgE to fungi and other antigens found in mucosa of subjects with

				-AFRS, n=11 -CRSsNP, n=8 -Control, n=9		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	Nasal sIgE to grass and HDM	sIgE to grass and HDM found in seasonal and perennial AR subjects, respectively

				-Perennial AR, n=10 -Control, n=10		
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 -Control, n=1	Nasal IgE heavy chain	Somatic hypermutation, clonal expansion, and class switching occurs within the nasal mucosa of AR patients
Sensi et al[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 with dual SLIT (n=20) or placebo (n=10)	Clinical outcomes and laboratory markers, including BAT	-BAT based on CD203c positivity -HDM SLIT decreased basophil activation in treatment group at 24 months 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	Basophil activation after 2 and 4 months of therapy	-BAT based on CD203c positivity -No significant changes in basophil activation between

				months		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)	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

				and regular treatment (n=20)		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	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%,

				atopy (negative SPT)		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	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

				group of 23 children with HDM negative SPT but positive to other allergens, non-allergic controls		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

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

POLLEN	Specific components	Percent	Cross-reactivity components

		sensitization[130]	
Ragweed	Amb a 1 (Peptate Lyase)* Amb a 4 (defensin-like) Amb a 6 (LTP) Amb a 8 (profilin) Amb a 9 (polcalcin) Amb a 10 (polcacin) Amb a 11 (cysteine protease)	100% 20-40% 20% 35-50% 10-15% 10-15% 66%	Amb-1 and Art v 6 Amb v 8 (profilins) Amb v 9 (polcalcins)
Mugwort	Art v 1 (Defensin)* Art v 3 (LTP)* Art v 4 (profilin) Art v 5 (polcalcin) Art v 6 (peptate lyase)	95% 22-70% 35% 10-28% 26%	Art v 3 (LTPs) Art v 4 (profilins) Art v 5 (polcalcins) Art v 6 and Amb 1
Parietaria, wall pellitory	Par j 1 (LTP) Par j 2 (LTP)* Par j 3 (profilin) Par j 4 (polcalcin)	95% 80% ? 6%	Par j 2 (LTP) Par j 3 (profilins) Par j 4 (polcalcins)
Russian thistle or saltwort	Sal k 1 (Pectinesterase)* Sal k 4 (profilin) Sal k 5 (Ole-1 like)	70% 46% 30-60%	Sal k 4 (profillins)
Goosefoot	Che a 1 (trypsin inhibitor) Che a 2 (profilin) Che a 3 (polcalcin)	70% 55% 46%	Chea a 2 (profilins)
Timothy	Phl p 1 (expansin)* Ph l p 2 (?) Phl p 3 (?) Phl p 4 (berberine bridge enzymes)* Phl p 5 (ribonuclease)*	95% 55% 60% 70% 50-95%	Phl p 4 (berberines) Phl p 7 (polcalcins) Phl p 11 (trypsin inhibibitors) Phl p 12 (profilin) Phl p 5 & Phl p 2 & Phl p 6

	Phl p 6 (?)* Ph l p 7 (polcalcin)* Ph l p 11 (Ole-1 like) Ph l p 12 (profilin)* Ph l p 13 (polygalacturonase)	44-75% 10% 32-43% 15% 50%	
Bermuda grass	Cyn d 1 (expansin)* Cyn d 4 (berberine bridge enzyme)	100% 100%	Cyn d 1 and Phl p 1
Alder	Aln g 1 (PR-10) Aln g 4 (polcalcin)	100% 18%	Aln g 1 (PR 10)
Birch	Bet v 1 (PR-10)* Bet v 2 (profillin)* Bet v 3 (polcalcin)* Bet v 4 (polcalcin) Bet v 6 (isoflavone reductase) Bet v 7 (cyclophilin)	95% 22% 10% 5% 32% 21%	Bet v 1 (PR10) Bet v 2 (profilins) Bet v 4 (polcalcins)
Olive	Ole e 1 (trypsin inhibitors)* Ole e 2 (profilin) Ole e 3 (polcalcin) Ole e 4 (?) 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)	90% 50% ? 80% 35% 15% 47% ? 68% 90% ? 4-33%	Ole e 2 (profilins) Ole e3 (polcalcins)
Japanese cedar	Cry j 1 (pectate lyases)	98%	Japanese cedar, Mountain cedar and

	Cry j 2 (polygalacturonase)	82%	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	-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	After CRD, AIT prescription or composition was changed in 42%

				Betulaceae pollen	then remodeled considering CRD	
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 IgE protocol (nOle e 1, rPhl p 1-5b, rPhl p 12, rPhl p 7, and rPru p 3)	Choice of immunotherapy was changed in more than 50% of patients
Nolte et al[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 al[266]	2019	4	Retrospective case series	Patients with HDM allergy treated with AIT in a double-blind placebo-controlled clinical study	-Post hoc analysis of serum IgE and IgG reactivity against a comprehensive panel of HDM allergens -Respiratory symptoms during controlled HDM exposure in the Vienna Challenge Chamber	-Der p 1, Der p 2, and Der p 23 were the most frequently recognized *D. pteronyssinus* allergens -AIT performed with HDM extracts inducing IgG antibodies mainly to Der p 1 and Der p 2 was beneficial for patients sensitized exclusively to Der p 1 and/or Der p 2 but not those sensitized to other HDM allergens
diCoste et al[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	-Costs for SPT-based diagnosis lower than the costs for allergen molecule-based sIgE -Allergen molecule-based

					-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	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	-SPT -Micro-array-based panel of allergens (ISAC) -Indication of AIT and	-Agreement in AIT indication before and after ISAC results found in only 46% of patients -Very low agreement

				without concomitant food allergy	use of allergens following EAACI recommendations, based on clinical history and SPT results before and after obtaining the ISAC results	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	2021	5	Review	Studies on CRD for pet	Not applicable	CRD has a role in developing patient-tailored

al[249]				components published between 1997 and mid-2020		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	2020	2	RCT	Patients with cat allergy:	-TNSS	-EEC showed higher magnitude in TNSS and

et al[362]				-24 patients: NPT then EEC -12 patients: EEC then NPT -28-day delay between test modalities	-PNIF -Expression of cytokine and chemokine genes	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	Comparison of NC cell counts	Higher number of eosinophils (p=0.005) and mast cells (p=0.001) in polysensitized patients

				-Polysensitized, n=48		
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:	Allergen-induced CD4+-, CD4+ CD25+-, IL-10-, TGF-β-positive	-No histologic differences at baseline -After pollen season: AIT group

				-AIT, n=12 -Placebo, n=7	cells in nasal biopsies pre- and post-pollen season	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: -Omalizumab, n=19 -Placebo, n=11	Anti-CD4, CD8, anti-eosinophil peroxidase, anti-human neutrophil lipocalin, IgE and FcεRI in nasal biopsies	Eosinophil peroxidase-positive staining cells significantly increased in the placebo-treated group but not in the actively treated group
Pullerits et al[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-	ARM, RM	Comparing ARM to AAR, cut-off to end NPT represented by reduction of 19-21% in nasal volume in the first 5cm

				18 years old, n=40		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	-Laboratory evaluation (eosinophil, IgE)	-Elevated FeNO in allergic asthma and asthma+AR vs AR and healthy controls

				-Asthma+AR, n=38 -AR, n=43 -Healthy controls, n=28	-SPT -Spirometry -FeNO	-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 -AR with one exacerbation in last month -Allergic asthma without rhinitis -Allergic asthma with rhinitis -All groups, n=15	-Allergy sensitization -FeNO -Spirometry	-All groups had statistically higher FeNO vs controls -FeNO higher in patients with active AR, allergic asthma 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	-Spirometry	-Elevated FeNO in children with asthma, atopy, recent wheeze

				at age 11, n=155	-FeNO -Eosinophils -SPT	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 -Laboratory evaluation (eosinophils, IgE)	-nNO significantly higher in AR -FeNO significantly higher in AR
Moody et	2006	4	Case-	-Perennial AR	-Validated symptom	-nNO levels were not elevated in subjects with

al[496]			control	-Non-atopic subjects	questionnaire -FeNO -nNO	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 Quality of Life Questionnaire	Rhinoconjunctivitis	28	Yes	No	0-168	Reflective assessment of previous week's symptoms; often used in clinical trials
RhinAsthma (RhinAsthma children also available)	Rhinitis, asthma	30	Yes	No	120	Able to differentiate patients with rhinitis from those with both rhinitis and asthma
VAS: Visual Analog Scale	Rhinitis	1 or more	Yes	No	0-10 cm	Tool may be used to evaluate multiple symptomatology
RCAT: Rhinitis Control Assessment Test	AR, NAR	6	Yes	No	6-30[b]	Self-assessment of rhinitis symptom control
ARCT: Allergic Rhinitis Control Test	AR	5	Yes	Yes	5-25[b]	Self-assessment of ongoing AR symptoms control
CARAT-10: Control of Allergic Rhinitis and Asthma Test; CARATKids available for children	AR, NAR, asthma	10	Yes	Yes	0-30[b]	Used to compare groups in clinical trials
ACS: Allergy Control Score	Rhinitis, AC, asthma	10+ meds	Yes	Yes	0-60	Combined tool used for clinical trials and daily clinical practice
RC-ACS: Rhinoconjunctivitis Allergy Control Score	Rhinitis, AC	7+ meds	Yes	Yes	0-42	Similar to ACS but without asthma related questions
RAP: Respiratory Allergy Prediction	AR, asthma	9+ meds	Yes	Yes	0-9	Used to determine the need for referral and additional testing
SFAR: Symptom Score for Allergic	AR	8	Yes	No	0-16	Weighted score used to detect prevalence of

Rhinitis						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

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	Multiple differences in trial scoring methods/design, making

					investigating SLIT efficacy for seasonal AR	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-	-Significant correlation between VAS-global and VAS-work

					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	RHINASTHMA	-RHINASTHMA differentiates patients with rhinitis from those with rhinitis+asthma -In stable condition, RHINASTHMA showed good reliability

				-49 asthma+ARC		

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

REFERENCES

1. Small P, Frenkiel A, Becker A, Boisvert P, Bouchard J. The Canadian Rhinitis Working Group: Rhinitis - a practical and comprehensive approach to assessment and therapt. *J Otolaryngol*. 2007;36(1):S5-S27.

2. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2015;152(1 Suppl):S1-43. doi:10.1177/0194599814561600

3. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. Aug 2008;122(2 Suppl):S1-84. doi:10.1016/j.jaci.2008.06.003

4. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. Nov 2001;108(5 Suppl):S147-334. doi:10.1067/mai.2001.118891

5. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy*. Jul 2017;47(7):856-889. doi:10.1111/cea.12953

6. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy*. 2007;62 Suppl 85:9-16. doi:10.1111/j.1398-9995.2007.01548.x

7. Bousquet J, Devillier P, Anto JM, et al. Daily allergic multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study. *Allergy*. Aug 2018;73(8):1622-1631. doi:10.1111/all.13448

8. Ng ML, Warlow RS, Chrishanthan N, Ellis C, Walls R. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (I). *Clin Exp Allergy*. Sep 2000;30(9):1314-31. doi:10.1046/j.1365-2222.2000.00853.x

9. Scadding GK, Hellings PW, Bachert C, et al. Allergic respiratory disease care in the COVID-19 era: A EUFOREA statement. *World Allergy Organ J*. May 2020;13(5):100124. doi:10.1016/j.waojou.2020.100124

10. Costa DJ, Amouyal M, Lambert P, et al. How representative are clinical study patients with allergic rhinitis in primary care? *J Allergy Clin Immunol*. Apr 2011;127(4):920-6 e1. doi:10.1016/j.jaci.2010.10.058

11. Raza SN, Yousuf K, Small P, Frenkiel S. Diagnosing allergic rhinitis: effectiveness of the physical examination in comparison to conventional skin testing. *J Otolaryngol Head Neck Surg*. Oct 2011;40(5):407-12.

12. Shaker MS, Oppenheimer J, Grayson M, et al. COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic. *J Allergy Clin Immunol Pract*. May 2020;8(5):1477-1488 e5. doi:10.1016/j.jaip.2020.03.012

13. Ziade GK, Karami RA, Fakhri GB, et al. Reliability assessment of the endoscopic examination in patients with allergic rhinitis. *Allergy Rhinol (Providence)*. Jan 1 2016;7(3):135-138. doi:10.2500/ar.2016.7.0176

14. Jareoncharsri P, Thitadilok V, Bunnag C, Ungkanont K, Voraprayoon S, Tansuriyawong P. Nasal endoscopic findings in patients with perennial allergic rhinitis. *Asian Pac J Allergy Immunol*. Dec 1999;17(4):261-7.

15. Eren E, Aktas A, Arslanoglu S, et al. Diagnosis of allergic rhinitis: inter-rater reliability and predictive value of nasal endoscopic examination: a prospective observational study. *Clin Otolaryngol*. Dec 2013;38(6):481-6. doi:10.1111/coa.12171

16. Ameli F, Tosca MA, Licari A, Gallo F, Ciprandi G. Can an otorhinolaryngological visit induce the suspect of allergic rhinitis in children? *Eur Ann Allergy Clin Immunol*. Nov 2019;51(6):273-282. doi:10.23822/EurAnnACI.1764-1489.105

17. Ameli F, Brocchetti F, Tosca MA, Signori A, Ciprandi G. Nasal endoscopy in children with suspected allergic rhinitis. *Laryngoscope*. Oct 2011;121(10):2055-9. doi:10.1002/lary.22156

18. White LJ, Rotella MR, DelGaudio JM. Polypoid changes of the middle turbinate as an indicator of atopic disease. *Int Forum Allergy Rhinol*. May 2014;4(5):376-80. doi:10.1002/alr.21290

19. Hamizan AW, Christensen JM, Ebenzer J, et al. Middle turbinate edema as a diagnostic marker of inhalant allergy. *Int Forum Allergy Rhinol*. Jan 2017;7(1):37-42. doi:10.1002/alr.21835

20. Brunner JP, Jawad BA, McCoul ED. Polypoid Change of the Middle Turbinate and Paranasal Sinus Polyposis Are Distinct Entities. *Otolaryngol Head Neck Surg*. Sep 2017;157(3):519-523. doi:10.1177/0194599817711887

21. DelGaudio JM, Loftus PA, Hamizan AW, Harvey RJ, Wise SK. Central compartment atopic disease. *Am J Rhinol Allergy*. Jul 1 2017;31(4):228-234. doi:10.2500/ajra.2017.31.4443

22. DelGaudio JM, Levy JM, Wise SK. Central compartment involvement in aspirin-exacerbated respiratory disease: the role of allergy and previous sinus surgery. *Int Forum Allergy Rhinol*. Sep 2019;9(9):1017-1022. doi:10.1002/alr.22367

23. Hamizan AW, Loftus PA, Alvarado R, et al. Allergic phenotype of chronic rhinosinusitis based on radiologic pattern of disease. *Laryngoscope*. Sep 2018;128(9):2015-2021. doi:10.1002/lary.27180

24. Marcus S, Schertzer J, Roland LT, Wise SK, Levy JM, DelGaudio JM. Central compartment atopic disease: prevalence of allergy and asthma compared with other subtypes of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. Feb 2020;10(2):183-189. doi:10.1002/alr.22454

25. Roland LT, Marcus S, Schertzer JS, Wise SK, Levy JM, DelGaudio JM. Computed Tomography Findings Can Help Identify Different Chronic Rhinosinusitis With Nasal Polyp Phenotypes. *Am J Rhinol Allergy*. Sep 2020;34(5):679-685. doi:10.1177/1945892420923926

26. Lee K, Kim TH, Lee SH, Kang CH, Je BK, Oh S. Predictive Value of Radiologic Central Compartment Atopic Disease for Identifying Allergy and Asthma in Pediatric Patients. *Ear Nose Throat J*. Mar 9 2021:145561321997546. doi:10.1177/0145561321997546

27. Abdullah B, Vengathajalam S, Md Daud MK, Wan Mohammad Z, Hamizan A, Husain S. The Clinical and Radiological Characterizations of the Allergic Phenotype of Chronic Rhinosinusitis with Nasal Polyps. *J Asthma Allergy*. 2020;13:523-531. doi:10.2147/JAA.S275536

28. Kaymakci M, Erel F, Bulbul E, Yazici H, Acar M, Yanik B. Maxillary Sinus Aeration in Allergic Rhinitis. *J Craniofac Surg*. Jun 2015;26(4):e288-90. doi:10.1097/SCS.0000000000001558

29. Hizli O, Kayabasi S, Ozkan D. Is Nasal Septal Body Size Associated With Inferior Turbinate Hypertrophy and Allergic Rhinitis? *J Craniofac Surg*. May/Jun 2020;31(3):778-781. doi:10.1097/SCS.0000000000006107

30. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. Aug 4 2012;380(9840):499-505. doi:10.1016/S0140-6736(12)60815-0

31. Meulepas JM, Ronckers CM, Smets A, et al. Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands. *J Natl Cancer Inst*. Mar 1 2019;111(3):256-263. doi:10.1093/jnci/djy104

32. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ*. May 21 2013;346:f2360. doi:10.1136/bmj.f2360

33. Sharhan SSA, Lee EJ, Hwang CS, et al. Radiological comparison of inferior turbinate hypertrophy between allergic and non-allergic rhinitis: does allergy really augment turbinate hypertrophy? *Eur Arch Otorhinolaryngol*. Apr 2018;275(4):923-929. doi:10.1007/s00405-018-4893-8

34. Brown HM, Su S, Thantrey N. Prick testing for allergens standardized by using a precision needle. *Clin Allergy*. Jan 1981;11(1):95-8. doi:10.1111/j.1365-2222.1981.tb01571.x

35. Ates A, Kinikli G, Turgay M, Aydogan N, Duman M. The results of skin prick testing in patients with allergic rhinitis: a comparison between a multiple lancet device and a single lancet. *Asian Pac J Allergy Immunol*. Jun-Sep 2004;22(2-3):109-14.

36. Phagoo SB, Wilson NM, Silverman M. Skin prick testing using allergen-coated lancets: a comparison between a multiple lancet device and a single lancet applied with varying pressures. *Clin Exp Allergy*. Sep 1991;21(5):589-93. doi:10.1111/j.1365-2222.1991.tb00851.x

37. Rhodius R, Wickens K, Cheng S, Crane J. A comparison of two skin test methodologies and allergens from two different manufacturers. *Ann Allergy Asthma Immunol*. Apr 2002;88(4):374-9. doi:10.1016/S1081-1206(10)62367-8

38. Anon JB. Introduction to in vivo allergy testing. *Otolaryngol Head Neck Surg*. Sep 1993;109(3 Pt 2):593-600.

39. Kim BJ, Mun SK. Objective measurements using the skin prick test in allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. Nov 2010;136(11):1104-6. doi:10.1001/archoto.2010.185

40. Piette V, Bourret E, Bousquet J, Demoly P. Prick tests to aeroallergens: is it possible simply to wipe the device between tests? *Allergy*. Oct 2002;57(10):940-2. doi:10.1034/j.1398-9995.2002.23536.x

41. Sander I, Fleischer C, Meurer U, Bruning T, Raulf-Heimsoth M. Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy. *Allergy*. Oct 2009;64(10):1486-1492. doi:10.1111/j.1398-9995.2009.02040.x

42. Curin M, Reininger R, Swoboda I, Focke M, Valenta R, Spitzauer S. Skin prick test extracts for dog allergy diagnosis show considerable variations regarding the content of major and minor dog allergens. *Int Arch Allergy Immunol*. 2011;154(3):258-63. doi:10.1159/000321113

43. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy*. Jan 2012;67(1):18-24. doi:10.1111/j.1398-9995.2011.02728.x

44. Canonica GW, Ansotegui IJ, Pawankar R, et al. A WAO - ARIA - GA(2)LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J*. Oct 3 2013;6(1):17. doi:10.1186/1939-4551-6-17

45. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. Mar 2008;100(3 Suppl 3):S1-148. doi:10.1016/s1081-1206(10)60305-5

46. Oppenheimer J, Nelson HS. Skin testing: a survey of allergists. *Ann Allergy Asthma Immunol*. Jan 2006;96(1):19-23. doi:10.1016/S1081-1206(10)61034-4

47. Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA*. May 12 2010;303(18):1848-56. doi:10.1001/jama.2010.582

48. Tschopp JM, Sistek D, Schindler C, et al. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from

8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. *Allergy*. Jun 1998;53(6):608-13. doi:10.1111/j.1398-9995.1998.tb03937.x

49. Corren J, Shapiro G, Reimann J, et al. Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy. *J Allergy Clin Immunol*. Feb 2008;121(2):506-11. doi:10.1016/j.jaci.2007.11.026

50. Ansotegui IJ, Melioli G, Canonica GW, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. *World Allergy Organ J*. Feb 2020;13(2):100080. doi:10.1016/j.waojou.2019.100080

51. Nevis IF, Binkley K, Kabali C. Diagnostic accuracy of skin-prick testing for allergic rhinitis: a systematic review and meta-analysis. *Allergy Asthma Clin Immunol*. 2016;12:20. doi:10.1186/s13223-016-0126-0

52. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. *J Allergy Clin Immunol*. May 1999;103(5 Pt 1):773-9. doi:10.1016/s0091-6749(99)70419-7

53. Gungor A, Houser SM, Aquino BF, et al. A comparison of skin endpoint titration and skin-prick testing in the diagnosis of allergic rhinitis. *Ear Nose Throat J*. Jan 2004;83(1):54-60.

54. Krouse JH, Shah AG, Kerswill K. Skin testing in predicting response to nasal provocation with alternaria. *Laryngoscope*. Aug 2004;114(8):1389-93. doi:10.1097/00005537-200408000-00013

55. Krouse JH, Sadrazodi K, Kerswill K. Sensitivity and specificity of prick and intradermal testing in predicting response to nasal provocation with timothy grass antigen. *Otolaryngol Head Neck Surg*. Sep 2004;131(3):215-9. doi:10.1016/j.otohns.2004.03.024

56. Zarei M, Remer CF, Kaplan MS, et al. Optimal skin prick wheal size for diagnosis of cat allergy. *Ann Allergy Asthma Immunol*. Jun 2004;92(6):604-10. doi:10.1016/S1081-1206(10)61425-1

57. Pumhirun P, Jane-Trakoonroj S, Wasuwat P. Comparison of in vitro assay for specific IgE and skin prick test with intradermal test in patients with allergic rhinitis. *Asian Pac J Allergy Immunol*. Sep 2000;18(3):157-60.

58. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test - European standards. *Clin Transl Allergy*. Feb 1 2013;3(1):3. doi:10.1186/2045-7022-3-3

59. Escudero AI, Sanchez-Guerrero IM, Mora AM, et al. Cost-effectiveness of various methods of diagnosing hypersensitivity to Alternaria. *Allergol Immunopathol (Madr)*. Jul-Aug 1993;21(4):153-7.

60. Trevino RJ, Veling MC. The importance of quantifying skin reactivity in treating allergic rhinitis with immunotherapy. *Ear Nose Throat J*. May 2000;79(5):362-4, 366.

61. Peltier J, Ryan MW. Comparison of intradermal dilutional testing, skin prick testing, and modified quantitative testing for common allergens. *Otolaryngol Head Neck Surg*. Aug 2007;137(2):246-9. doi:10.1016/j.otohns.2007.05.002

62. Calabria CW, Hagan L. The role of intradermal skin testing in inhalant allergy. *Ann Allergy Asthma Immunol*. Oct 2008;101(4):337-47; quiz 347, 418. doi:10.1016/S1081-1206(10)60307-9

63. Niemeijer NR, Fluks AF, de Monchy JG. Optimization of skin testing. II. Evaluation of concentration and cutoff values, as compared with RAST and clinical history, in a multicenter study. *Allergy*. Oct 1993;48(7):498-503. doi:10.1111/j.1398-9995.1993.tb01105.x

64. Health Quality O. Skin Testing for Allergic Rhinitis: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2016;16(10):1-45.

65. Larrabee YC, Reisacher W. Intradermal testing after negative skin prick testing for patients with high suspicion of allergy. *Int Forum Allergy Rhinol*. Jun 2015;5(6):547-50. doi:10.1002/alr.21512

66. Nelson HS, Oppenheimer J, Buchmeier A, Kordash TR, Freshwater LL. An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass. *J Allergy Clin Immunol*. Jun 1996;97(6):1193-201. doi:10.1016/s0091-6749(96)70184-7

67. Schwindt CD, Hutcheson PS, Leu SY, Dykewicz MS. Role of intradermal skin tests in the evaluation of clinically relevant respiratory allergy assessed using patient history and nasal challenges. *Ann Allergy Asthma Immunol*. Jun 2005;94(6):627-33. doi:10.1016/S1081-1206(10)61319-1

68. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol*. Apr 1987;79(4):660-77. doi:10.1016/s0091-6749(87)80164-1

69. Sharma HP, Wood RA, Bravo AR, Matsui EC. A comparison of skin prick tests, intradermal skin tests, and specific IgE in the diagnosis of mouse allergy. *J Allergy Clin Immunol*. Apr 2008;121(4):933-9. doi:10.1016/j.jaci.2008.01.023

70. Simons JP, Rubinstein EN, Kogut VJ, Melfi PJ, Ferguson BJ. Comparison of Multi-Test II skin prick testing to intradermal dilutional testing. *Otolaryngol Head Neck Surg*. May 2004;130(5):536-44. doi:10.1016/j.otohns.2004.02.005

71. Niemeijer NR, Goedewaagen B, Kauffman HF, de Monchy JG. Optimization of skin testing. I. Choosing allergen concentrations and cutoff values by factorial design. *Allergy*. Oct 1993;48(7):491-7. doi:10.1111/j.1398-9995.1993.tb01104.x

72. Hurst DS, McDaniel AB. Clinical Relevance and Advantages of Intradermal Test Results in 371 Patients with Allergic Rhinitis, Asthma and/or Otitis Media with Effusion. *Cells*. Nov 18 2021;10(11)doi:10.3390/cells10113224

73. Erel F, Sarioglu N, Kose M, et al. Intradermal Skin Testing in Allergic Rhinitis and Asthma with Negative Skin Prick Tests. *Iran J Allergy Asthma Immunol*. Jun 2017;16(3):193-197.

74. Peltier J, Ryan MW. Comparison of intradermal dilutional testing with the Multi-Test II applicator in testing for mold allergy. *Otolaryngol Head Neck Surg*. Feb 2006;134(2):240-4. doi:10.1016/j.otohns.2005.10.051

75. Seshul M, Pillsbury H, 3rd, Eby T. Use of intradermal dilutional testing and skin prick testing: clinical relevance and cost efficiency. *Laryngoscope*. Sep 2006;116(9):1530-8. doi:10.1097/01.mlg.0000234916.43285.f8

76. Purohit A, Laffer S, Metz-Favre C, et al. Poor association between allergen-specific serum immunoglobulin E levels, skin sensitivity and basophil degranulation: a study with recombinant birch pollen allergen Bet v 1 and an immunoglobulin E detection system measuring immunoglobulin E capable of binding to Fc epsilon RI. *Clin Exp Allergy*. Feb 2005;35(2):186-92. doi:10.1111/j.1365-2222.2005.02156.x

77. Brown WG, Halonen MJ, Kaltenborn WT, Barbee RA. The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. *J Allergy Clin Immunol*. May 1979;63(5):328-35. doi:10.1016/0091-6749(79)90127-1

78. Reddy PM, Nagaya H, Pascual HC, et al. Reappraisal of intracutaneous tests in the diagnosis of reaginic allergy. *J Allergy Clin Immunol*. Jan 1978;61(1):36-41. doi:10.1016/0091-6749(78)90471-2

79. Fornadley JA. Skin testing for inhalant allergy. *Int Forum Allergy Rhinol*. Sep 2014;4 Suppl 2:S41-5. doi:10.1002/alr.21393

80. Krouse JH, Krouse HJ. Modulation of immune mediators with MQT-based immunotherapy. *Otolaryngol Head Neck Surg*. May 2006;134(5):746-50. doi:10.1016/j.otohns.2006.01.007

81. Tantilipikorn P, Danpornprasert P, Ngaotepprutaram P, Assanasen P, Bunnag C, Thinkhamrop B. The correlation between intradermal testing and serum specific IgE to house dust mite in negative skin prick test allergic rhinitis adult patients. *Asian Pac J Allergy Immunol*. Dec 2015;33(4):308-11. doi:10.12932/AP0579.33.4.2015

82. Lewis AF, Franzese C, Stringer SP. Diagnostic evaluation of inhalant allergies: a cost-effectiveness analysis. *Am J Rhinol*. May-Jun 2008;22(3):246-52. doi:10.2500/ajr.2008.22.3163

83. Long WF, Taylor RJ, Wagner CJ, Leavengood DC, Nelson HS. Skin test suppression by antihistamines and the development of subsensitivity. *J Allergy Clin Immunol*. Jul 1985;76(1):113-7. doi:10.1016/0091-6749(85)90813-9

84. Phillips MJ, Meyrick Thomas RH, Moodley I, Davies RJ. A comparison of the in vivo effects of ketotifen, clemastine, chlorpheniramine and sodium cromoglycate on histamine and allergen induced weals in human skin. *Br J Clin Pharmacol*. Mar 1983;15(3):277-86. doi:10.1111/j.1365-2125.1983.tb01500.x

85. Simons FE, Simons KJ. Clinical pharmacology of new histamine H1 receptor antagonists. *Clin Pharmacokinet*. May 1999;36(5):329-52. doi:10.2165/00003088-199936050-00003

86. Cook TJ, MacQueen DM, Wittig HJ, Thornby JI, Lantos RL, Virtue CM. Degree and duration of skin test suppression and side effects with antihistamines. A double blind controlled study with five antihistamines. *J Allergy Clin Immunol*. Feb 1973;51(2):71-7. doi:10.1016/s0091-6749(73)80002-8

87. Almind M, Dirksen A, Nielsen NH, Svendsen UG. Duration of the inhibitory activity on histamine-induced skin weals of sedative and non-sedative antihistamines. *Allergy*. Nov 1988;43(8):593-6. doi:10.1111/j.1398-9995.1988.tb00932.x

88. Pearlman DS, Grossman J, Meltzer EO. Histamine skin test reactivity following single and multiple doses of azelastine nasal spray in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2003;91(3):258-62. doi:10.1016/S1081-1206(10)63527-2

89. Miller J, Nelson HS. Suppression of immediate skin tests by ranitidine. *J Allergy Clin Immunol*. Dec 1989;84(6 Pt 1):895-9. doi:10.1016/0091-6749(89)90386-2

90. Kupczyk M, Kuprys I, Bochenska-Marciniak M, Gorski P, Kuna P. Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. *Allergy Asthma Proc*. Nov-Dec 2007;28(6):711-5. doi:10.2500/aap.2007.28.3064

91. Harvey RP, Schocket AL. The effect of H1 and H2 blockade on cutaneous histamine response in man. *J Allergy Clin Immunol*. 1990;65(2):136-139.

92. Rao KS, Menon PK, Hilman BC, Sebastian CS, Bairnsfather L. Duration of the suppressive effect of tricyclic antidepressants on histamine-induced wheal-and-flare reactions in human skin. *J Allergy Clin Immunol*. Nov 1988;82(5 Pt 1):752-7. doi:10.1016/0091-6749(88)90075-9

93. Isik SR, Celikel S, Karakaya G, Ulug B, Kalyoncu AF. The effects of antidepressants on the results of skin prick tests used in the diagnosis of allergic diseases. *Int Arch Allergy Immunol*. 2011;154(1):63-8. doi:10.1159/000319210

94. Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol*. May 2003;131(1):46-52. doi:10.1159/000070434

95. Hill SL, 3rd, Krouse JH. The effects of montelukast on intradermal wheal and flare. *Otolaryngol Head Neck Surg*. Sep 2003;129(3):199-203. doi:10.1016/S0194-5998(03)00607-7

96. Simons FE, Johnston L, Gu X, Simons KJ. Suppression of the early and late cutaneous allergic responses using fexofenadine and montelukast. *Ann Allergy Asthma Immunol*. Jan 2001;86(1):44-50. doi:10.1016/S1081-1206(10)62354-X

97. Cuhadaroglu C, Erelel M, Kiyan E, Ece T, Erkan F. Role of Zafirlukast on skin prick test. *Allergol Immunopathol (Madr)*. Mar-Apr 2001;29(2):66-8. doi:10.1016/s0301-0546(01)79020-9

98. Des Roches A, Paradis L, Bougeard YH, Godard P, Bousquet J, Chanez P. Long-term oral corticosteroid therapy does not alter the results of immediate-type allergy skin prick tests. *J Allergy Clin Immunol*. Sep 1996;98(3):522-7. doi:10.1016/s0091-6749(96)70085-4

99. Slott RI, Zweiman B. A controlled study of the effect of corticosteroids on immediate skin test reactivity. *J Allergy Clin Immunol*. Oct 1974;54(4):229-34. doi:10.1016/0091-6749(74)90065-7

100. Olson R, Karpink MH, Shelanski S, Atkins PC, Zweiman B. Skin reactivity to codeine and histamine during prolonged corticosteroid therapy. *J Allergy Clin Immunol*. Aug 1990;86(2):153-9. doi:10.1016/s0091-6749(05)80060-0

101. Geng B, Thakor A, Clayton E, Finkas L, Riedl MA. Factors associated with negative histamine control for penicillin allergy skin testing in the inpatient setting. *Ann Allergy Asthma Immunol*. Jul 2015;115(1):33-8. doi:10.1016/j.anai.2015.04.012

102. Narasimha SK, Srinivas CR, Mathew AC. Effect of topical corticosteroid application frequency on histamine-induced wheals. *Int J Dermatol*. May 2005;44(5):425-7. doi:10.1111/j.1365-4632.2005.02482.x

103. Andersson M, Pipkorn U. Inhibition of the dermal immediate allergic reaction through prolonged treatment with topical glucocorticosteroids. *J Allergy Clin Immunol*. Feb 1987;79(2):345-9. doi:10.1016/0091-6749(87)90153-9

104. Pipkorn U, Hammarlund A, Enerback L. Prolonged treatment with topical glucocorticoids results in an inhibition of the allergen-induced weal-and-flare response and a reduction in skin mast cell numbers and histamine content. *Clin Exp Allergy*. Jan 1989;19(1):19-25. doi:10.1111/j.1365-2222.1989.tb02338.x

105. Gradman J, Wolthers OD. Suppressive effects of topical mometasone furoate and tacrolimus on skin prick testing in children. *Pediatr Dermatol*. Mar-Apr 2008;25(2):269-70. doi:10.1111/j.1525-1470.2008.00651.x

106. Shah KM, Rank MA, Dave SA, Oslie CL, Butterfield JH. Predicting which medication classes interfere with allergy skin testing. *Allergy Asthma Proc*. Nov-Dec 2010;31(6):477-82. doi:10.2500/aap.2010.31.3382

107. Duenas-Laita A, Ruiz-Munoz P, Armentia A, Pinacho F, Martin-Armentia B. Successful treatment of chronic drug-resistant urticaria with alprazolam. *J Allergy Clin Immunol*. Feb 2009;123(2):504-5. doi:10.1016/j.jaci.2008.12.005

108. Spergel JM, Nurse N, Taylor P, ParneixSpake A. Effect of topical pimecrolimus on epicutaneous skin testing. *J Allergy Clin Immunol*. Sep 2004;114(3):695-7. doi:10.1016/j.jaci.2004.05.067

109. More DR, Napoli DC, Hagan LL. Herbal supplements and skin testing: the lack of effect of commonly used herbal supplements on histamine skin prick testing. *Allergy*. Jun 2003;58(6):492-4. doi:10.1034/j.1398-9995.2003.00140.x

110. Simons FE, Simons KJ. Peripheral H1-blockade effect of fexofenadine. *Ann Allergy Asthma Immunol*. Dec 1997;79(6):530-2. doi:10.1016/S1081-1206(10)63061-X

111. Komarow HD, Arceo S, Young M, Nelson C, Metcalfe DD. Dissociation between history and challenge in patients with physical urticaria. *J Allergy Clin Immunol Pract*. Nov-Dec 2014;2(6):786-90. doi:10.1016/j.jaip.2014.07.008

112. Ando M, Shima M. Serum interleukins 12 and 18 and immunoglobulin E concentrations and allergic symptoms in Japanese schoolchildren. *J Investig Allergol Clin Immunol*. 2007;17(1):14-9.

113. Marinho S, Simpson A, Soderstrom L, Woodcock A, Ahlstedt S, Custovic A. Quantification of atopy and the probability of rhinitis in preschool children: a population-based birth cohort study. *Allergy*. Dec 2007;62(12):1379-86. doi:10.1111/j.1398-9995.2007.01502.x

114. Salo PM, Calatroni A, Gergen PJ, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. May 2011;127(5):1226-35 e7. doi:10.1016/j.jaci.2010.12.1106

115. Jacobs TS, Forno E, Brehm JM, et al. Underdiagnosis of allergic rhinitis in underserved children. *J Allergy Clin Immunol*. Sep 2014;134(3):737-739 e6. doi:10.1016/j.jaci.2014.03.028

116. Tu YL, Chang SW, Tsai HJ, et al. Total serum IgE in a population-based study of Asian children in Taiwan: reference value and significance in the diagnosis of allergy. *PLoS One*. 2013;8(11):e80996. doi:10.1371/journal.pone.0080996

117. Park SC, Kim JH, Lee KH, Hong SC, Lee HS, Kang JW. Association of serum eosinophilia and total immunoglobulin E concentration with the risk of allergic symptoms and allergic sensitization, respectively: A 2-year follow-up study. *Int J Pediatr Otorhinolaryngol*. Jul 2016;86:167-71. doi:10.1016/j.ijporl.2016.05.005

118. Kalpaklioglu AF, Kavut AB. Allergic and nonallergic rhinitis: can we find the differences/similarities between the two pictures? *J Asthma*. Jun 2009;46(5):481-5. doi:10.1080/02770900902849897

119. Jung YG, Kim KH, Kim HY, Dhong HJ, Chung SK. Predictive capabilities of serum eosinophil cationic protein, percentage of eosinophils and total immunoglobulin E in allergic rhinitis without bronchial asthma. *J Int Med Res*. 2011;39(6):2209-16. doi:10.1177/147323001103900617

120. Li Y, Wu R, Tian Y, Bao T, Tian Z. The correlation of serum eosinophil cationic protein level with eosinophil count, and total IgE level in Korean adult allergic rhinitis patients. *Asian Pac J Allergy Immunol*. Dec 2016;34(1):33-37. doi:10.12932/AP0746

121. Sharma M, Khaitan T, Raman S, Jain R, Kabiraj A. Determination of Serum IgE and Eosinophils as a Diagnostic Indicator in Allergic Rhinitis. *Indian J Otolaryngol Head Neck Surg*. Nov 2019;71(Suppl 3):1957-1961. doi:10.1007/s12070-018-1383-7

122. Qamar S, Awan N, Cheema KM, Raza N, Ashraf S, Rehman A. Comparative Analysis of Nasal Smear Eosinophilia and Serum IgE Levels for the Diagnosis of Allergic Rhinitis. *J Coll Physicians Surg Pak*. Dec 2020;30(12):1297-1300. doi:10.29271/jcpsp.2020.12.1297

123. Karli R, Balbaloglu E, Uzun L, Cinar F, Ugur MB. Correlation of symptoms with total IgE and specific IgE levels in patients presenting with allergic rhinitis. *Ther Adv Respir Dis*. Apr 2013;7(2):75-9. doi:10.1177/1753465812468500

124. Chung D, Park KT, Yarlagadda B, Davis EM, Platt M. The significance of serum total immunoglobulin E for in vitro diagnosis of allergic rhinitis. *Int Forum Allergy Rhinol*. Jan 2014;4(1):56-60. doi:10.1002/alr.21240

125. Satwani H, Rehman A, Ashraf S, Hassan A. Is serum total IgE levels a good predictor of allergies in children? *J Pak Med Assoc*. Oct 2009;59(10):698-702.

126. Demirjian M, Rumbyrt JS, Gowda VC, Klaustermeyer WB. Serum IgE and eosinophil count in allergic rhinitis--analysis using a modified Bayes' theorem. *Allergol Immunopathol (Madr)*. Sep-Oct 2012;40(5):281-7. doi:10.1016/j.aller.2011.05.016

127. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. Aug 2017;72(8):1156-1173. doi:10.1111/all.13138

128. Goodman RE, Chapman MD, Slater JE. The Allergen: Sources, Extracts, and Molecules for Diagnosis of Allergic Disease. *J Allergy Clin Immunol Pract*. Sep 2020;8(8):2506-2514. doi:10.1016/j.jaip.2020.06.043

129. Hamilton RG. Clinical laboratory assessment of immediate-type hypersensitivity. *J Allergy Clin Immunol*. Feb 2010;125(2 Suppl 2):S284-96. doi:10.1016/j.jaci.2009.09.055

130. Steering Committee A, Review Panel M. A WAO - ARIA - GA(2)LEN consensus document on molecular-based allergy diagnosis (PAMD@): Update 2020. *World Allergy Organ J*. Feb 2020;13(2):100091. doi:10.1016/j.waojou.2019.100091

131. Westwood M, Ramaekers B, Lang S, et al. ImmunoCAP(R) ISAC and Microtest for multiplex allergen testing in people with difficult to manage allergic disease: a systematic review and cost analysis. *Health Technol Assess*. Sep 2016;20(67):1-178. doi:10.3310/hta20670

132. Cox L. Overview of serological-specific IgE antibody testing in children. *Curr Allergy Asthma Rep*. Dec 2011;11(6):447-53. doi:10.1007/s11882-011-0226-3

133. Emanuel IA. In vitro testing for allergy diagnosis. *Otolaryngol Clin North Am*. Oct 2003;36(5):879-93. doi:10.1016/s0030-6665(03)00051-3

134. Incorvaia C, Al-Ahmad M, Ansotegui IJ, et al. Personalized medicine for allergy treatment: Allergen immunotherapy still a unique and unmatched model. *Allergy*. Apr 2021;76(4):1041-1052. doi:10.1111/all.14575

135. Corsico AG, De Amici M, Ronzoni V, et al. Allergen-specific immunoglobulin E and allergic rhinitis severity. *Allergy Rhinol (Providence)*. Mar 1 2017;8(1):1-4. doi:10.2500/ar.2017.8.0187

136. Ciprandi G, De Amici M, Giunta V, Marseglia GL. Comparison of serum specific IgE and skin prick test in polysensitized patients. *Int J Immunopathol Pharmacol*. Oct-Dec 2010;23(4):1293-5. doi:10.1177/039463201002300438

137. Chen ST, Sun HL, Lu KH, Lue KH, Chou MC. Correlation of immunoglobulin E, eosinophil cationic protein, and eosinophil count with the severity of childhood perennial allergic rhinitis. *J Microbiol Immunol Infect*. Jun 2006;39(3):212-8.

138. Ciprandi G, Comite P, Ferrero F, Fontana V, Bruzzone M, Mussap M. Serum allergen-specific IgE, allergic rhinitis severity, and age. *Rhinology*. Sep 2016;54(3):231-8. doi:10.4193/Rhino15.300

139. Ciprandi G, Comite P, Ferrero F, et al. Birch allergy and oral allergy syndrome: The practical relevance of serum immunoglobulin E to Bet v 1. *Allergy Asthma Proc*. Jan-Feb 2016;37(1):43-9. doi:10.2500/aap.2016.37.3914

140. Howarth P, Malling HJ, Molimard M, Devillier P. Analysis of allergen immunotherapy studies shows increased clinical efficacy in highly symptomatic patients. *Allergy*. Mar 2012;67(3):321-7. doi:10.1111/j.1398-9995.2011.02759.x

141. Kowalski ML, Ansotegui I, Aberer W, et al. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. *World Allergy Organ J*. 2016;9(1):33. doi:10.1186/s40413-016-0122-3

142. Brown CE, Jones CJ, Stuttaford L, Robertson A, Rashid RS, Smith HE. A qualitative study of the allergy testing experiences, views and preferences of adult patients. *Clin Transl Allergy*. 2016;6(1):34. doi:10.1186/s13601-016-0125-8

143. Williams PB, Barnes JH, Szeinbach SL, Sullivan TJ. Analytic precision and accuracy of commercial immunoassays for specific IgE: establishing a standard. *J Allergy Clin Immunol*. Jun 2000;105(6 Pt 1):1221-30. doi:10.1067/mai.2000.105219

144. Wood RA, Segall N, Ahlstedt S, Williams PB. Accuracy of IgE antibody laboratory results. *Ann Allergy Asthma Immunol*. Jul 2007;99(1):34-41. doi:10.1016/S1081-1206(10)60618-7

145. Wang J, Godbold JH, Sampson HA. Correlation of serum allergy (IgE) tests performed by different assay systems. *J Allergy Clin Immunol*. May 2008;121(5):1219-24. doi:10.1016/j.jaci.2007.12.1150

146. Ownby DR, Bailey J. Comparison of MAST with radioallergosorbent and skin tests for diagnosis of allergy in children. *Am J Dis Child*. Jan 1986;140(1):45-8. doi:10.1001/archpedi.1986.02140150047031

147. Ferguson AC, Murray AB. Predictive value of skin prick tests and radioallergosorbent tests for clinical allergy to dogs and cats. *CMAJ*. Jun 15 1986;134(12):1365-8.

148. Wide L, Bennich H, Johansson SG. Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet*. Nov 25 1967;2(7526):1105-7. doi:10.1016/s0140-6736(67)90615-0

149. Tian M, Zhou Y, Zhang W, Cui Y. Der p 1 and Der p 2 specific immunoglobulin E measurement for diagnosis of Dermatophagoides pteronyssinus allergy: A systematic review and meta-analysis. *Allergy Asthma Proc*. Sep 1 2017;38(5):333-342. doi:10.2500/aap.2017.38.4073

150. Knight V, Wolf ML, Trikha A, Curran-Everett D, Hiserote M, Harbeck RJ. A comparison of specific IgE and skin prick test results to common environmental allergens using the HYTEC 288. *J Immunol Methods*. Nov 2018;462:9-12. doi:10.1016/j.jim.2018.07.005

151. van Hage M, Schmid-Grendelmeier P, Skevaki C, et al. Performance evaluation of ImmunoCAP(R) ISAC 112: a multi-site study. *Clin Chem Lab Med*. Mar 1 2017;55(4):571-577. doi:10.1515/cclm-2016-0586

152. Chinoy B, Yee E, Bahna SL. Skin testing versus radioallergosorbent testing for indoor allergens. *Clin Mol Allergy*. Apr 15 2005;3(1):4. doi:10.1186/1476-7961-3-4

153. Bignardi D, Comite P, Mori I, et al. Allergen-specific IgE: comparison between skin prick test and serum assay in real life. *Allergol Select*. 2019;3(1):9-14. doi:10.5414/ALX01891E

154. Nam YH, Lee SK. Comparison between skin prick test and serum immunoglobulin E by CAP system to inhalant allergens. *Ann Allergy Asthma Immunol*. May 2017;118(5):608-613. doi:10.1016/j.anai.2017.03.005

155. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. Oct 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

156. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol*. Jun 1979;122(6):2218-25.

157. Durham SR, Gould HJ, Thienes CP, et al. Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. *Eur J Immunol*. Nov 1997;27(11):2899-906. doi:10.1002/eji.1830271123

158. KleinJan A, Godthelp T, van Toornenenbergen AW, Fokkens WJ. Allergen binding to specific IgE in the nasal mucosa of allergic patients. *J Allergy Clin Immunol*. Apr 1997;99(4):515-21. doi:10.1016/s0091-6749(97)70079-4

159. Coker HA, Durham SR, Gould HJ. Local somatic hypermutation and class switch recombination in the nasal mucosa of allergic rhinitis patients. *J Immunol*. Nov 15 2003;171(10):5602-10. doi:10.4049/jimmunol.171.10.5602

160. Takhar P, Smurthwaite L, Coker HA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol*. Apr 15 2005;174(8):5024-32. doi:10.4049/jimmunol.174.8.5024

161. KleinJan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J*. Mar 2000;15(3):491-7. doi:10.1034/j.1399-3003.2000.15.11.x

162. Naclerio RM, Creticos PS, Norman PS, Lichtenstein LM. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis*. Nov 1986;134(5):1102. doi:10.1164/arrd.1986.134.5.1102

163. Ahn JY, Hong SJ, Choi BS. Clinical Evaluation of Techniques for Measuring Nasal-Specific Immunoglobulin E in Pediatric Patients. *J Korean Med Sci*. Dec 2017;32(12):2005-2008. doi:10.3346/jkms.2017.32.12.2005

164. Campo P, Del Carmen Plaza-Seron M, Eguiluz-Gracia I, et al. Direct intranasal application of the solid phase of ImmunoCAP(R) increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum Allergy Rhinol*. Jan 2018;8(1):15-19. doi:10.1002/alr.22039

165. Huggins KG, Brostoff J. Local production of specific IgE antibodies in allergic-rhinitis patients with negative skin tests. *Lancet*. Jul 26 1975;2(7926):148-50. doi:10.1016/s0140-6736(75)90056-2

166. Ota Y, Ikemiyagi Y, Sato T, et al. Measuring local immunoglobulin E in the inferior turbinate nasal mucosa in patients with allergic rhinitis. *Allergol Int*. Oct 2016;65(4):396-399. doi:10.1016/j.alit.2016.03.009

167. Hamizan A, Alvarado R, Rimmer J, et al. Nasal mucosal brushing as a diagnostic method for allergic rhinitis. *Allergy Asthma Proc*. May 1 2019;40(3):167-172. doi:10.2500/aap.2019.40.4209

168. Reisacher WR. Mucosal brush biopsy testing of the inferior turbinate to detect local, antigen-specific immunoglobulin E. *Int Forum Allergy Rhinol*. Jan-Feb 2012;2(1):69-74. doi:10.1002/alr.20103

169. Hamizan AW, Rimmer J, Alvarado R, et al. Turbinate-Specific IgE in Normal and Rhinitic Patients. *Am J Rhinol Allergy*. Mar 2019;33(2):178-183. doi:10.1177/1945892418825224

170. Saricilar EC, Hamizan A, Alvarado R, et al. Optimizing Protein Harvest From Nasal Brushings for Determining Local Allergy Responses. *Am J Rhinol Allergy*. Jul 2018;32(4):244-251. doi:10.1177/1945892418777668

171. Fuiano N, Fusilli S, Incorvaia C. A role for measurement of nasal IgE antibodies in diagnosis of Alternaria-induced rhinitis in children. *Allergol Immunopathol (Madr)*. Mar-Apr 2012;40(2):71-4. doi:10.1016/j.aller.2011.03.010

172. Krajewska-Wojtys A, Jarzab J, Gawlik R, Bozek A. Local allergic rhinitis to pollens is underdiagnosed in young patients. *Am J Rhinol Allergy*. Nov 1 2016;30(6):198-201. doi:10.2500/ajra.2016.30.4369

173. Lopez S, Rondon C, Torres MJ, et al. Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus in local allergic rhinitis. *Clin Exp Allergy*. Jul 2010;40(7):1007-14. doi:10.1111/j.1365-2222.2010.03492.x

174. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy*. Oct 2003;33(10):1374-9. doi:10.1046/j.1365-2222.2003.01737.x

175. Rondon C, Dona I, Lopez S, et al. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy*. Oct 2008;63(10):1352-8. doi:10.1111/j.1398-9995.2008.01695.x

176. Rondon C, Fernandez J, Lopez S, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol*. Nov 2009;124(5):1005-11 e1. doi:10.1016/j.jaci.2009.07.018

177. Rondon C, Romero JJ, Lopez S, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol*. Apr 2007;119(4):899-905. doi:10.1016/j.jaci.2007.01.006

178. Zicari AM, Occasi F, Di Fraia M, et al. Local allergic rhinitis in children: Novel diagnostic features and potential biomarkers. *Am J Rhinol Allergy*. Sep 2016;30(5):329-34. doi:10.2500/ajra.2016.30.4352

179. Rondon C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. Jun 2012;129(6):1460-7. doi:10.1016/j.jaci.2012.02.032

180. Gelardi M, Guglielmi AV, Iannuzzi L, et al. Local allergic rhinitis: entopy or spontaneous response? *World Allergy Organ J*. 2016;9(1):39. doi:10.1186/s40413-016-0126-z

181. Santamaria L, Calle A, Tejada-Giraldo Biol M, Calvo V, Sanchez J, Cardona R. Nasal specific IgE to Der p is not an acceptable screening test to predict the outcome of the nasal challenge test in patients with non-allergic rhinitis. *World Allergy Organ J*. Sep 2020;13(9):100461. doi:10.1016/j.waojou.2020.100461

182. Eckrich J, Hinkel J, Fischl A, et al. Nasal IgE in subjects with allergic and non-allergic rhinitis. *World Allergy Organ J*. Jun 2020;13(6):100129. doi:10.1016/j.waojou.2020.100129

183. Kim JH, Yoon MG, Seo DH, et al. Detection of Allergen Specific Antibodies From Nasal Secretion of Allergic Rhinitis Patients. *Allergy Asthma Immunol Res*. Jul 2016;8(4):329-37. doi:10.4168/aair.2016.8.4.329

184. Hamizan AW, Rimmer J, Husain S, et al. Local specific Immunoglobulin E among patients with nonallergic rhinitis: a systematic review. *Rhinology*. Feb 1 2019;57(1):10-20. doi:10.4193/Rhin18.074

185. Hamizan AW, Rimmer J, Alvarado R, et al. Positive allergen reaction in allergic and nonallergic rhinitis: a systematic review. *Int Forum Allergy Rhinol*. Sep 2017;7(9):868-877. doi:10.1002/alr.21988

186. Eguiluz-Gracia I, Ariza A, Testera-Montes A, Rondon C, Campo P. Allergen Immunotherapy for Local Respiratory Allergy. *Curr Allergy Asthma Rep*. May 19 2020;20(7):23. doi:10.1007/s11882-020-00920-w

187. Schiavi L, Brindisi G, De Castro G, et al. Nasal reactivity evaluation in children with allergic rhinitis receiving grass pollen sublingual immunotherapy. *Allergy Asthma Proc*. Sep 1 2020;41(5):357-362. doi:10.2500/aap.2020.41.200063

188. Lee KS, Yu J, Shim D, et al. Local Immune Responses in Children and Adults with Allergic and Nonallergic Rhinitis. *PLoS One*. 2016;11(6):e0156979. doi:10.1371/journal.pone.0156979

189. Bozek A, Ignasiak B, Kasperska-Zajac A, Scierski W, Grzanka A, Jarzab J. Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol*. Mar 2015;114(3):199-202. doi:10.1016/j.anai.2014.12.013

190. Sakaida H, Masuda S, Takeuchi K. Measurement of Japanese cedar pollen-specific IgE in nasal secretions. *Allergol Int*. Sep 2014;63(3):467-73. doi:10.2332/allergolint.13-OA-0668

191. Powe DG, Groot Kormelink T, Sisson M, et al. Evidence for the involvement of free light chain immunoglobulins in allergic and nonallergic rhinitis. *J Allergy Clin Immunol*. Jan 2010;125(1):139-45 e1-3. doi:10.1016/j.jaci.2009.07.025

192. Ahn CN, Wise SK, Lathers DM, Mulligan RM, Harvey RJ, Schlosser RJ. Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. *Otolaryngol Head Neck Surg*. Jul 2009;141(1):97-103. doi:10.1016/j.otohns.2009.03.002

193. Castelli S, Arasi S, Tripodi S, et al. IgE antibody repertoire in nasal secretions of children and adults with seasonal allergic rhinitis: A molecular analysis. *Pediatr Allergy Immunol*. Apr 2020;31(3):273-280. doi:10.1111/pai.13148

194. Becker S, Rasp J, Eder K, Berghaus A, Kramer MF, Groger M. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Otorhinolaryngol*. Jun 2016;273(6):1469-75. doi:10.1007/s00405-015-3769-4

195. Sensi LG, Piacentini GL, Nobile E, et al. Changes in nasal specific IgE to mites after periods of allergen exposure-avoidance: a comparison with serum levels. *Clin Exp Allergy*. Apr 1994;24(4):377-82. doi:10.1111/j.1365-2222.1994.tb00250.x

196. Tversky JR, Chelladurai Y, McGready J, Hamilton RG. Performance and Pain Tolerability of Current Diagnostic Allergy Skin Prick Test Devices. *J Allergy Clin Immunol Pract*. Nov-Dec 2015;3(6):888-93. doi:10.1016/j.jaip.2015.07.022

197. Nelson HS, Lahr J, Buchmeier A, McCormick D. Evaluation of devices for skin prick testing. *J Allergy Clin Immunol*. Feb 1998;101(2 Pt 1):153-6. doi:10.1016/S0091-6749(98)70409-9

198. Andersen HH, Lundgaard AC, Petersen AS, et al. The Lancet Weight Determines Wheal Diameter in Response to Skin Prick Testing with Histamine. *PLoS One*. 2016;11(5):e0156211. doi:10.1371/journal.pone.0156211

199. Carr WW, Martin B, Howard RS, et al. Comparison of test devices for skin prick testing. *J Allergy Clin Immunol*. Aug 2005;116(2):341-6. doi:10.1016/j.jaci.2005.03.035

200. Seibert SM, King TS, Kline D, Mende C, Craig T. Reliability of skin test results when read at different time points. *Allergy Asthma Proc*. May-Jun 2011;32(3):203-5. doi:10.2500/aap.2011.32.3436

201. van der Veen MJ, Mulder M, Witteman AM, et al. False-positive skin prick test responses to commercially available dog dander extracts caused by contamination with house dust mite (Dermatophagoides pteronyssinus) allergens. *J Allergy Clin Immunol*. Dec 1996;98(6 Pt 1):1028-34. doi:10.1016/s0091-6749(96)80187-4

202. McCann WA, Ownby DR. The reproducibility of the allergy skin test scoring and interpretation by board-certified/board-eligible allergists. *Ann Allergy Asthma Immunol*. Oct 2002;89(4):368-71. doi:10.1016/S1081-1206(10)62037-6

203. Choi IS, Koh YI, Koh JS, Lee MG. Sensitivity of the skin prick test and specificity of the serum-specific IgE test for airway responsiveness to house dust mites in asthma. *J Asthma*. Apr 2005;42(3):197-202.

204. Jung YG, Cho HJ, Park GY, et al. Comparison of the skin-prick test and Phadia ImmunoCAP as tools to diagnose house-dust mite allergy. *Am J Rhinol Allergy*. May-Jun 2010;24(3):226-9. doi:10.2500/ajra.2010.24.3459

205. Pastorello EA, Incorvaia C, Ortolani C, et al. Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens. *J Allergy Clin Immunol*. Nov 1995;96(5 Pt 1):580-7. doi:10.1016/s0091-6749(95)70255-5

206. Haxel BR, Huppertz T, Boessert P, Bast F, Fruth K. Correlation of skin test results and specific immunoglobulin E blood levels with nasal provocation testing for house-dust mite allergies. *Am J Rhinol Allergy*. Jan-Feb 2016;30(1):60-4. doi:10.2500/ajra.2016.30.4262

207. Gendo K, Larson EB. Evidence-based diagnostic strategies for evaluating suspected allergic rhinitis. *Ann Intern Med*. Feb 17 2004;140(4):278-89. doi:10.7326/0003-4819-140-4-200402170-00010

208. de Vos G, Nazari R, Ferastraoaru D, et al. Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years. *Ann Allergy Asthma Immunol*. Jun 2013;110(6):438-43. doi:10.1016/j.anai.2013.03.006

209. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy*. Nov 2015;70(11):1393-405. doi:10.1111/all.12698

210. Gonzalez-Munoz M, Villota J, Moneo I. Analysis of basophil activation by flow cytometry in pediatric house dust mite allergy. *Pediatr Allergy Immunol*. Jun 2008;19(4):342-7. doi:10.1111/j.1399-3038.2007.00656.x

211. Ozdemir SK, Guloglu D, Sin BA, Elhan AH, Ikinciogullari A, Misirligil Z. Reliability of basophil activation test using CD203c expression in diagnosis of pollen allergy. *Am J Rhinol Allergy*. Nov-Dec 2011;25(6):e225-31. doi:10.2500/ajra.2011.25.3723

212. Ogulur I, Kiykim A, Baris S, Ozen A, Yuce EG, Karakoc-Aydiner E. Basophil activation test for inhalant allergens in pediatric patients with allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Jun 2017;97:197-201. doi:10.1016/j.ijporl.2017.04.006

213. Zidarn M, Robic M, Krivec A, et al. Clinical and immunological differences between asymptomatic HDM-sensitized and HDM-allergic rhinitis patients. *Clin Exp Allergy*. Jun 2019;49(6):808-818. doi:10.1111/cea.13361

214. Mahmood F, Hetland G, Nentwich I, Mirlashari MR, Ghiasvand R, Nissen-Meyer LSH. Agaricus blazei-Based Mushroom Extract Supplementation to Birch Allergic Blood Donors: A Randomized Clinical Trial. *Nutrients*. Oct 2 2019;11(10)doi:10.3390/nu11102339

215. Saporta M, Kamei S, Persi L, Bousquet J, Arnoux B. Basophil activation during pollen season in patients monosensitized to grass pollens. *Allergy*. May 2001;56(5):442-5. doi:10.1034/j.1398-9995.2001.056005442.x

216. Qiao Y, Chen J. Investigating the inflammatory cascade effect of basophil activation in children with allergic rhinitis or asthma, via the IgE-FcepsilonRI-NF-kappaB signaling pathway. *Adv Clin Exp Med*. Jul 2021;30(7):673-679. doi:10.17219/acem/135756

217. Nagao M, Hiraguchi Y, Hosoki K, et al. Allergen-induced basophil CD203c expression as a biomarker for rush immunotherapy in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol*. 2008;146 Suppl 1:47-53. doi:10.1159/000126061

218. Van Overtvelt L, Baron-Bodo V, Horiot S, et al. Changes in basophil activation during grass-pollen sublingual immunotherapy do not correlate with clinical efficacy. *Allergy*. Dec 2011;66(12):1530-7. doi:10.1111/j.1398-9995.2011.02696.x

219. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol*. Jul 2012;130(1):215-24 e7. doi:10.1016/j.jaci.2012.04.021

220. Caruso M, Cibella F, Emma R, et al. Basophil biomarkers as useful predictors for sublingual immunotherapy in allergic rhinitis. *Int Immunopharmacol*. Jul 2018;60:50-58. doi:10.1016/j.intimp.2018.04.034

221. Kepil Ozdemir S, Sin BA, Guloglu D, Ikinciogullari A, Gencturk Z, Misirligil Z. Short-term preseasonal immunotherapy: is early clinical efficacy related to the basophil response? *Int Arch Allergy Immunol*. 2014;164(3):237-45. doi:10.1159/000365628

222. Zidarn M, Kosnik M, Silar M, Bajrovic N, Korosec P. Sustained effect of grass pollen subcutaneous immunotherapy on suppression of allergen-specific basophil response; a real-life, nonrandomized controlled study. *Allergy*. May 2015;70(5):547-55. doi:10.1111/all.12581

223. Schmid JM, Wurtzen PA, Siddhuraj P, et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. *Allergy*. May 2021;76(5):1528-1538. doi:10.1111/all.14264

224. Kim SH, Kim SH, Chung SJ, et al. Changes in basophil activation during immunotherapy with house dust mite and mugwort in patients with allergic rhinitis. *Asia Pac Allergy*. Jan 2018;8(1):e6. doi:10.5415/apallergy.2018.8.e6

225. Feng M, Zeng X, Su Q, et al. Allergen Immunotherapy-Induced Immunoglobulin G4 Reduces Basophil Activation in House Dust Mite-Allergic Asthma Patients. *Front Cell Dev Biol*. 2020;8:30. doi:10.3389/fcell.2020.00030

226. Soyyigit S, Guloglu D, Ikinciogullari A, et al. Immunologic alterations and efficacy of subcutaneous immunotherapy with Dermatophagoides pteronyssinus in monosensitized and polysensitized patients. *Ann Allergy Asthma Immunol*. Mar 2016;116(3):244-251 e2. doi:10.1016/j.anai.2016.01.002

227. Aasbjerg K, Backer V, Lund G, et al. Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. *Clin Exp Allergy*. Mar 2014;44(3):417-28. doi:10.1111/cea.12241

228. Ma S, Qiao Y. [Changes of basophil activation before and after treatment in children with allergic rhinitis and its clinical significance]. *Revue Francaise D'Allergologie*. 2021;61(6):393-397.

229. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol*. May 2016;27 Suppl 23:1-250. doi:10.1111/pai.12563

230. Sastre-Ibanez M, Sastre J. Molecular allergy diagnosis for the clinical characterization of asthma. *Expert Rev Mol Diagn*. Jun 2015;15(6):789-99. doi:10.1586/14737159.2015.1036745

231. Barber D, Diaz-Perales A, Escribese MM, et al. Molecular allergology and its impact in specific allergy diagnosis and therapy. *Allergy*. Dec 2021;76(12):3642-3658. doi:10.1111/all.14969

232. Sastre J, Sastre-Ibanez M. Molecular diagnosis and immunotherapy. *Curr Opin Allergy Clin Immunol*. Dec 2016;16(6):565-570. doi:10.1097/ACI.0000000000000318

233. Sastre J. Molecular diagnosis and immunotherapy. *Curr Opin Allergy Clin Immunol*. Dec 2013;13(6):646-50. doi:10.1097/ACI.0b013e328364f4c6

234. Saltabayeva U, Garib V, Morenko M, et al. Greater Real-Life Diagnostic Efficacy of Allergen Molecule-Based Diagnosis for Prescription of Immunotherapy in an Area with Multiple Pollen Exposure. *Int Arch Allergy Immunol*. 2017;173(2):93-98. doi:10.1159/000477442

235. Scala E, Abeni D, Pomponi D, et al. Ole e 1, Ole e 7, and Ole e 9: Identifying distinct clinical subsets of olive tree-allergic patients. *J Allergy Clin Immunol*. Feb 2016;137(2):629-631 e3. doi:10.1016/j.jaci.2015.07.009

236. Sastre J, Rodriguez F, Campo P, Laffond E, Marin A, Alonso MD. Adverse reactions to immunotherapy are associated with different patterns of sensitization to grass allergens. *Allergy*. May 2015;70(5):598-600. doi:10.1111/all.12575

237. Posa D, Perna S, Resch Y, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol*. Feb 2017;139(2):541-549 e8. doi:10.1016/j.jaci.2016.08.014

238. Custovic A, Sonntag HJ, Buchan IE, Belgrave D, Simpson A, Prosperi MCF. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol*. Dec 2015;136(6):1645-1652 e8. doi:10.1016/j.jaci.2015.03.041

239. Bronnert M, Mancini J, Birnbaum J, et al. Component-resolved diagnosis with commercially available D. pteronyssinus Der p 1, Der p 2 and Der p 10: relevant markers for house dust mite allergy. *Clin Exp Allergy*. Sep 2012;42(9):1406-15). doi:10.1111/j.1365-2222.2012.04035.x

240. Celi G, Brusca I, Scala E, et al. House dust mite allergy in Italy-Diagnostic and clinical relevance of Der p 23 (and of minor allergens): A real-life, multicenter study. *Allergy*. Sep 2019;74(9):1787-1789. doi:10.1111/all.13776

241. Barber D, Arias J, Boquete M, et al. Analysis of mite allergic patients in a diverse territory by improved diagnostic tools. *Clin Exp Allergy*. Jul 2012;42(7):1129-38. doi:10.1111/j.1365-2222.2012.03993.x

242. Carvalho Kdos A, de Melo-Neto OP, Magalhaes FB, et al. Blomia tropicalis Blo t 5 and Blo t 21 recombinant allergens might confer higher specificity to serodiagnostic assays than whole mite extract. *BMC Immunol*. Feb 27 2013;14:11. doi:10.1186/1471-2172-14-11

243. Ayuso R, Reese G, Leong-Kee S, Plante M, Lehrer SB. Molecular basis of arthropod cross-reactivity: IgE-binding cross-reactive epitopes of shrimp, house dust mite and cockroach tropomyosins. *Int Arch Allergy Immunol*. Sep 2002;129(1):38-48. doi:10.1159/000065172

244. Gamez C, Sanchez-Garcia S, Ibanez MD, et al. Tropomyosin IgE-positive results are a good predictor of shrimp allergy. *Allergy*. Oct 2011;66(10):1375-83. doi:10.1111/j.1398-9995.2011.02663.x

245. Rodriguez-Dominguez A, Berings M, Rohrbach A, et al. Molecular profiling of allergen-specific antibody responses may enhance success of specific immunotherapy. *J Allergy Clin Immunol*. Nov 2020;146(5):1097-1108. doi:10.1016/j.jaci.2020.03.029

246. Saarelainen S, Taivainen A, Rytkonen-Nissinen M, et al. Assessment of recombinant dog allergens Can f 1 and Can f 2 for the diagnosis of dog allergy. *Clin Exp Allergy*. Oct 2004;34(10):1576-82. doi:10.1111/j.1365-2222.2004.02071.x

247. Mattsson L, Lundgren T, Everberg H, Larsson H, Lidholm J. Prostatic kallikrein: a new major dog allergen. *J Allergy Clin Immunol*. Feb 2009;123(2):362-8. doi:10.1016/j.jaci.2008.11.021

248. Uriarte SA, Sastre J. Clinical relevance of molecular diagnosis in pet allergy. *Allergy*. Jul 2016;71(7):1066-8. doi:10.1111/all.12917

249. Schoos AM, Nwaru BI, Borres MP. Component-resolved diagnostics in pet allergy: Current perspectives and future directions. *J Allergy Clin Immunol*. Apr 2021;147(4):1164-1173. doi:10.1016/j.jaci.2020.12.640

250. Wintersand A, Asplund K, Binnmyr J, et al. Allergens in dog extracts: Implication for diagnosis and treatment. *Allergy*. Aug 2019;74(8):1472-1479. doi:10.1111/all.13785

251. Eder K, Becker S, San Nicolo M, Berghaus A, Groger M. Usefulness of component resolved analysis of cat allergy in routine clinical practice. *Allergy Asthma Clin Immunol*. 2016;12:58. doi:10.1186/s13223-016-0163-8

252. Smith W, Butler AJ, Hazell LA, et al. Fel d 4, a cat lipocalin allergen. *Clin Exp Allergy*. Nov 2004;34(11):1732-8. doi:10.1111/j.1365-2222.2004.02090.x

253. Saarelainen S, Rytkonen-Nissinen M, Rouvinen J, et al. Animal-derived lipocalin allergens exhibit immunoglobulin E cross-reactivity. *Clin Exp Allergy*. Feb 2008;38(2):374-81. doi:10.1111/j.1365-2222.2007.02895.x

254. Arruda LK, Vailes LD, Ferriani VP, Santos AB, Pomes A, Chapman MD. Cockroach allergens and asthma. *J Allergy Clin Immunol*. Mar 2001;107(3):419-28. doi:10.1067/mai.2001.112854

255. Postigo I, Gutierrez-Rodriguez A, Fernandez J, Guisantes JA, Sunen E, Martinez J. Diagnostic value of Alt a 1, fungal enolase and manganese-dependent superoxide dismutase in the component-resolved diagnosis of allergy to Pleosporaceae. *Clin Exp Allergy*. Mar 2011;41(3):443-51. doi:10.1111/j.1365-2222.2010.03671.x

256. Kespohl S, Raulf M. Mould allergens: Where do we stand with molecular allergy diagnostics?: Part 13 of the series Molecular Allergology. *Allergo J Int*. 2014;23(4):120-125. doi:10.1007/s40629-014-0014-4

257. Barber D, Moreno C, Ledesma A, et al. Degree of olive pollen exposure and sensitization patterns. Clinical implications. *J Investig Allergol Clin Immunol*. 2007;17 Suppl 1:11-6.

258. Sastre J. Molecular diagnosis in allergy. *Clin Exp Allergy*. Oct 2010;40(10):1442-60. doi:10.1111/j.1365-2222.2010.03585.x

259. Martinez-Canavate Burgos A, Torres-Borrego J, Molina Teran AB, et al. Molecular sensitization patterns and influence of molecular diagnosis in immunotherapy prescription in children sensitized to both grass and olive pollen. *Pediatr Allergy Immunol*. Jun 2018;29(4):369-374. doi:10.1111/pai.12866

260. Moreno C, Justicia JL, Quiralte J, et al. Olive, grass or both? Molecular diagnosis for the allergen immunotherapy selection in polysensitized pollinic patients. *Allergy*. Oct 2014;69(10):1357-63. doi:10.1111/all.12474

261. Stringari G, Tripodi S, Caffarelli C, et al. The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol*. Jul 2014;134(1):75-81. doi:10.1016/j.jaci.2014.01.042

262. Letran A, Espinazo M, Moreno F. Measurement of IgE to pollen allergen components is helpful in selecting patients for immunotherapy. *Ann Allergy Asthma Immunol*. Oct 2013;111(4):295-7. doi:10.1016/j.anai.2013.07.005

263. Nolte M, Barber D, Maloney J, et al. Timothy specific IgE levels are associated with efficacy and safety of timothy grass sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol*. Dec 2015;115(6):509-515 e2. doi:10.1016/j.anai.2015.09.018

264. Rodinkova VV, Yuriev SD, Kryvopustova MV, Mokin VB, Kryzhanovskyi YM, Kurchenko AI. Molecular Profile Sensitization to House Dust Mites as an Important Aspect for Predicting the

Efficiency of Allergen Immunotherapy. *Front Immunol*. 2022;13:848616. doi:10.3389/fimmu.2022.848616

265. Arroabarren E, Echechipia S, Galbete A, Lizaso MT, Olaguibel JM, Tabar AI. Association Between Component-Resolved Diagnosis of House Dust Mite Allergy and Efficacy and Safety of Specific Immunotherapy. *J Investig Allergol Clin Immunol*. Apr 2019;29(2):164-167. doi:10.18176/jiaci.0359

266. Chen KW, Zieglmayer P, Zieglmayer R, et al. Selection of house dust mite-allergic patients by molecular diagnosis may enhance success of specific immunotherapy. *J Allergy Clin Immunol*. Mar 2019;143(3):1248-1252 e12. doi:10.1016/j.jaci.2018.10.048

267. di Coste A, Occasi F, De Castro G, et al. Predictivity of clinical efficacy of sublingual immunotherapy (SLIT) based on sensitisation pattern to molecular allergens in children with allergic rhinoconjunctivitis. *Allergol Immunopathol (Madr)*. Sep - Oct 2017;45(5):452-456. doi:10.1016/j.aller.2017.01.001

268. Darsow U, Brockow K, Pfab F, et al. Allergens. Heterogeneity of molecular sensitization profiles in grass pollen allergy--implications for immunotherapy? *Clin Exp Allergy*. 2014;44(5):778-86. doi:10.1111/cea.12303

269. Sastre J, Landivar ME, Ruiz-Garcia M, Andregnette-Rosigno MV, Mahillo I. How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area. *Allergy*. May 2012;67(5):709-11. doi:10.1111/j.1398-9995.2012.02808.x

270. Tripodi S, Frediani T, Lucarelli S, et al. Molecular profiles of IgE to Phleum pratense in children with grass pollen allergy: implications for specific immunotherapy. *J Allergy Clin Immunol*. Mar 2012;129(3):834-839 e8. doi:10.1016/j.jaci.2011.10.045

271. Duffort O, Palomares O, Lombardero M, et al. Variability of Ole e 9 allergen in olive pollen extracts: relevance of minor allergens in immunotherapy treatments. *Int Arch Allergy Immunol*. 2006;140(2):131-8. doi:10.1159/000092532

272. Pfaar O, Calderon MA, Andrews CP, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future - an EAACI Position Paper. *Allergy*. Jul 2017;72(7):1035-1042. doi:10.1111/all.13133

273. Werfel T, Heratizadeh A, Niebuhr M, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol*. Jul 2015;136(1):96-103 e9. doi:10.1016/j.jaci.2015.04.015

274. Badorrek P, Dick M, Emmert L, et al. Pollen starch granules in bronchial inflammation. *Ann Allergy Asthma Immunol*. Sep 2012;109(3):208-214 e6. doi:10.1016/j.anai.2012.06.019

275. Ellis AK, Murrieta-Aguttes M, Furey S, Picard P, Carlsten C. Effect of fexofenadine hydrochloride on allergic rhinitis aggravated by air pollutants. *ERJ Open Res*. Apr 2021;7(2)doi:10.1183/23120541.00806-2020

276. Ahuja SK, Manoharan MS, Harper NL, et al. Preservation of epithelial cell barrier function and muted inflammation in resistance to allergic rhinoconjunctivitis from house dust mite challenge. *J Allergy Clin Immunol*. Mar 2017;139(3):844-854. doi:10.1016/j.jaci.2016.08.019

277. Smith AM, Ramirez RM, Harper N, et al. Large-scale provocation studies identify maladaptive responses to ubiquitous aeroallergens as a correlate of severe allergic rhinoconjunctivitis and asthma. *Allergy*. Jun 2022;77(6):1797-1814. doi:10.1111/all.15124

278. Smith AM, Harper N, Meunier JA, et al. Repetitive aeroallergen challenges elucidate maladaptive epithelial and inflammatory traits that underpin allergic airway diseases. *J Allergy Clin Immunol*. Aug 2021;148(2):533-549. doi:10.1016/j.jaci.2021.01.008

279. Ellis AK, Steacy LM, Hobsbawn B, Conway CE, Walker TJ. Clinical validation of controlled grass pollen challenge in the Environmental Exposure Unit (EEU). *Allergy Asthma Clin Immunol*. 2015;11(1):5. doi:10.1186/s13223-015-0071-3

280. Ellis AK, Soliman M, Steacy LM, Adams DE, Hobsbawn B, Walker TJ. Clinical validation of controlled exposure to birch pollen in the Environmental Exposure Unit (EEU). *Allergy Asthma Clin Immunol*. 2016;12:53. doi:10.1186/s13223-016-0156-7

281. Enomoto T, Ide T, Ogino S. Construction of an environmental exposure unit and investigation of the effects of cetirizine hydrochloride on symptoms of cedar pollinosis in Japan. *J Investig Allergol Clin Immunol*. 2007;17(3):173-81.

282. Hashiguchi K, Tang H, Fujita T, et al. Validation study of the OHIO Chamber in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol*. 2009;149(2):141-9. doi:10.1159/000189197

283. Jacobs RL, Ramirez DA, Andrews CP. Validation of the biogenics research chamber for Juniperus ashei (mountain cedar) pollen. *Ann Allergy Asthma Immunol*. Aug 2011;107(2):133-8. doi:10.1016/j.anai.2011.04.009

284. Krug N, Hohlfeld JM, Larbig M, et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy*. Dec 2003;33(12):1667-74. doi:10.1111/j.1365-2222.2003.01810.x

285. Lueer K, Biller H, Casper A, et al. Safety, efficacy and repeatability of a novel house dust mite allergen challenge technique in the Fraunhofer allergen challenge chamber. *Allergy*. Dec 2016;71(12):1693-1700. doi:10.1111/all.12947

286. Ronborg SM, Mosbech H, Poulsen LK. Exposure chamber for allergen challenge. A placebo-controlled, double-blind trial in house-dust-mite asthma. *Allergy*. Aug 1997;52(8):821-8. doi:10.1111/j.1398-9995.1997.tb02153.x

287. Zuberbier T, Abelson MB, Akdis CA, et al. Validation of the Global Allergy and Asthma European Network (GA(2)LEN) chamber for trials in allergy: Innovation of a mobile allergen exposure chamber. *J Allergy Clin Immunol*. Apr 2017;139(4):1158-1166. doi:10.1016/j.jaci.2016.08.025

288. Hohlfeld JM, Holland-Letz T, Larbig M, et al. Diagnostic value of outcome measures following allergen exposure in an environmental challenge chamber compared with natural conditions. *Clin Exp Allergy*. Jul 2010;40(7):998-1006. doi:10.1111/j.1365-2222.2010.03498.x

289. Boelke G, Berger U, Bergmann KC, et al. Peak nasal inspiratory flow as outcome for provocation studies in allergen exposure chambers: a GA(2)LEN study. *Clin Transl Allergy*. 2017;7:33. doi:10.1186/s13601-017-0169-4

290. Gherasim A, Fauquert JL, Domis N, Siomboing X, de Blay F. Birch allergen challenges in allergic conjunctivitis using standard conjunctival allergen challenge and environmental exposure chamber. *Clin Transl Allergy*. Aug 2021;11(6):e12053. doi:10.1002/clt2.12053

291. Jacobs RL, Ramirez DA, Rather CG, et al. Redness response phenotypes of allergic conjunctivitis in an allergen challenge chamber. *Ann Allergy Asthma Immunol*. Jan 2017;118(1):86-93 e2. doi:10.1016/j.anai.2016.10.023

292. Badorrek P, Muller M, Koch W, Hohlfeld JM, Krug N. Specificity and reproducibility of nasal biomarkers in patients with allergic rhinitis after allergen challenge chamber exposure. *Ann Allergy Asthma Immunol*. Mar 2017;118(3):290-297. doi:10.1016/j.anai.2017.01.018

293. North ML, Jones MJ, MacIsaac JL, et al. Blood and nasal epigenetics correlate with allergic rhinitis symptom development in the environmental exposure unit. *Allergy*. Jan 2018;73(1):196-205. doi:10.1111/all.13263

294. Krug N, Gupta A, Badorrek P, et al. Efficacy of the oral chemoattractant receptor homologous molecule on TH2 cells antagonist BI 671800 in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol*. Feb 2014;133(2):414-9. doi:10.1016/j.jaci.2013.10.013

295. Horak FF, Jager S, Nirnberger G, et al. Dose-related control of allergic rhinitis symptoms by a H1-receptor antagonist. Finding the proper doses [correction of dosis] of dimethindene maleate in patients with allergic rhinitis. *Int Arch Allergy Immunol*. 1994;103(3):298-302. doi:10.1159/000236643

296. Horak F, Jager S, Nirnberger G, et al. Pharmacodynamic dose finding of dimetindene in a sustained release formulation. *Arzneimittelforschung*. Nov 1993;43(11):1193-5.

297. Day JH, Briscoe MP, Ratz JD, Ellis AK, Yao R, Danzig M. Onset of action of loratadine/montelukast in seasonal allergic rhinitis subjects exposed to ragweed pollen in the Environmental Exposure Unit. *Allergy Asthma Proc*. May-Jun 2009;30(3):270-6. doi:10.2500/aap.2009.30.3234

298. Horak F, Zieglmayer P, Zieglmayer R, Lemell P. Onset of action of loratadine/montelukast in seasonal allergic rhinitis patients exposed to grass pollen. *Arzneimittelforschung*. 2010;60(5):249-55. doi:10.1055/s-0031-1296281

299. Berkowitz RB, Woodworth GG, Lutz C, et al. Onset of action, efficacy, and safety of fexofenadine 60 mg/pseudoephedrine 120 mg versus placebo in the Atlanta allergen exposure unit. *Ann Allergy Asthma Immunol*. Jul 2002;89(1):38-45. doi:10.1016/S1081-1206(10)61909-6

300. Day JH, Briscoe MP, Rafeiro E, Ratz JD. Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure Unit (EEU). *Int J Clin Pract*. Feb 2004;58(2):109-18. doi:10.1111/j.1368-5031.2004.0117.x

301. Horak F, Zieglmayer UP, Zieglmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin*. Jan 2006;22(1):151-7. doi:10.1185/030079906X80305

302. Bousquet J, Meltzer EO, Couroux P, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. *J Allergy Clin Immunol Pract*. Sep - Oct 2018;6(5):1726-1732 e6. doi:10.1016/j.jaip.2018.01.031

303. Tenn MW, Steacy LM, Ng CC, Ellis AK. Onset of action for loratadine tablets for the symptomatic control of seasonal allergic rhinitis in adults challenged with ragweed pollen in the Environmental Exposure Unit: a post hoc analysis of total symptom score. *Allergy Asthma Clin Immunol*. 2018;14:5. doi:10.1186/s13223-017-0227-4

304. Day JH, Briscoe MP, Rafeiro E, Hewlett D, Jr., Chapman D, Kramer B. Randomized double-blind comparison of cetirizine and fexofenadine after pollen challenge in the Environmental Exposure Unit: duration of effect in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. Jan-Feb 2004;25(1):59-68.

305. Murdoch RD, Bareille P, Ignar D, et al. Once-daily dosing of levocabastine has comparable efficacy to twice-daily dosing in the treatment of allergic rhinitis assessed in an allergen challenge chamber. *Int J Clin Pharmacol Ther*. Oct 2015;53(10):811-8. doi:10.5414/CP202389

306. Horak F, Zieglmayer PU, Zieglmayer R, Kavina A, Lemell P. Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. *Br J Clin Pharmacol*. Jul 2005;60(1):24-31. doi:10.1111/j.1365-2125.2005.02377.x

307. Krug N, Hohlfeld JM, Geldmacher H, et al. Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. *Allergy*. Mar 2005;60(3):354-9. doi:10.1111/j.1398-9995.2005.00703.x

308. Salapatek AM, Patel P, Gopalan G, Varghese ST. Mometasone furoate nasal spray provides early, continuing relief of nasal congestion and improves nasal patency in allergic patients. *Am J Rhinol Allergy*. Nov-Dec 2010;24(6):433-8. doi:10.2500/ajra.2010.24.3548

309. Zieglmayer P, Zieglmayer R, Bareille P, Rousell V, Salmon E, Horak F. Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber. *Curr Med Res Opin*. Jun 2008;24(6):1833-40. doi:10.1185/03007990802155792

310. Ng CC, Romaikin D, Steacy LM, et al. Comparative nasal airflow with loratadine-pseudoephedrine and fluticasone nasal spray for allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2021;127(3):342-348 e2. doi:10.1016/j.anai.2021.05.001

311. Zieglmayer P, Schmutz R, Lemell P, et al. Fast effectiveness of a solubilized low-dose budesonide nasal spray in allergic rhinitis. *Clin Exp Allergy*. Sep 2020;50(9):1065-1077. doi:10.1111/cea.13691

312. Badorrek P, Dick M, Schauerte A, et al. A combination of cetirizine and pseudoephedrine has therapeutic benefits when compared to single drug treatment in allergic rhinitis. *Int J Clin Pharmacol Ther*. Feb 2009;47(2):71-7. doi:10.5414/cpp47071

313. Barchuk WT, Salapatek AM, Ge T, D'Angelo P, Liu X. A proof-of-concept study of the effect of a novel H3-receptor antagonist in allergen-induced nasal congestion. *J Allergy Clin Immunol*. Oct 2013;132(4):838-46 e1-6. doi:10.1016/j.jaci.2013.05.001

314. Horak F, Toth J, Marks B, et al. Efficacy and safety relative to placebo of an oral formulation of cetirizine and sustained-release pseudoephedrine in the management of nasal congestion. *Allergy*. Sep 1998;53(9):849-56. doi:10.1111/j.1398-9995.1998.tb03990.x

315. Yonekura S, Okamoto Y, Yamamoto H, et al. Randomized double-blind study of prophylactic treatment with an antihistamine for seasonal allergic rhinitis. *Int Arch Allergy Immunol*. 2013;162(1):71-8. doi:10.1159/000350926

316. Jordakieva G, Kundi M, Lemell P, et al. Cetirizine inhibits gender-specific blood cell dynamics upon allergen contact in allergic rhinitis. *Clin Immunol*. Jun 2020;215:108422. doi:10.1016/j.clim.2020.108422

317. Yonekura S, Okamoto Y, Sakurai D, et al. Efficacy of Desloratadine and Levocetirizine in Patients with Cedar Pollen-Induced Allergic Rhinitis: A Randomized, Double-Blind Study. *Int Arch Allergy Immunol*. 2019;180(4):274-283. doi:10.1159/000503065

318. Hashiguchi K, Wakabayashi KI, Togawa M, Saito A, Okubo K. Therapeutic effect of bilastine in Japanese cedar pollinosis using an artificial exposure chamber (OHIO Chamber). *Allergol Int*. Jan 2017;66(1):123-131. doi:10.1016/j.alit.2016.06.009

319. Bareille P, Murdoch RD, Denyer J, et al. The effects of a TRPV1 antagonist, SB-705498, in the treatment of seasonal allergic rhinitis. *Int J Clin Pharmacol Ther*. Jul 2013;51(7):576-84. doi:10.5414/CP201890

320. Corren J, Wood RA, Patel D, et al. Effects of omalizumab on changes in pulmonary function induced by controlled cat room challenge. *J Allergy Clin Immunol*. Feb 2011;127(2):398-405. doi:10.1016/j.jaci.2010.09.043

321. Horak F. VTX-1463, a novel TLR8 agonist for the treatment of allergic rhinitis. *Expert Opin Investig Drugs*. Jul 2011;20(7):981-6. doi:10.1517/13543784.2011.583237

322. Horak F, Zieglmayer P, Zieglmayer R, et al. The CRTH2 antagonist OC000459 reduces nasal and ocular symptoms in allergic subjects exposed to grass pollen, a randomised, placebo-controlled, double-blind trial. *Allergy*. Dec 2012;67(12):1572-9. doi:10.1111/all.12042

323. Gomes PJ, Abelson MB, Stein L, Viirre E, Villafranca JE, Lasser EC. Iodixanol nasal solution reduces allergic rhinoconjunctivitis signs and symptoms in Allergen BioCube((R)): a randomized clinical trial. *J Asthma Allergy*. 2019;12:71-81. doi:10.2147/JAA.S150251

324. Struss N, Badorrek P, Mattern C, Mattern U, Hohlfeld JM. The Effect of a Thixotropic Nasal Gel on Nasal Symptoms and Inflammatory Biomarkers in Seasonal Allergic Rhinitis. *Int Arch Allergy Immunol*. 2020;181(5):385-394. doi:10.1159/000506129

325. Salapatek AM, Werkhauser N, Ismail B, Mosges R, Raskopf E, Bilstein A. Effects of ectoine containing nasal spray and eye drops on symptoms of seasonal allergic rhinoconjunctivitis. *Clin Transl Allergy*. Mar 2021;11(1):e12006. doi:10.1002/clt2.12006

326. Xiao JZ, Kondo S, Yanagisawa N, et al. Clinical efficacy of probiotic Bifidobacterium longum for the treatment of symptoms of Japanese cedar pollen allergy in subjects evaluated in an environmental exposure unit. *Allergol Int*. Mar 2007;56(1):67-75. doi:10.2332/allergolint.O-06-455

327. Bergmann KC, Krause L, Hiller J, et al. First evaluation of a symbiotic food supplement in an allergen exposure chamber in birch pollen allergic patients. *World Allergy Organ J*. Jan 2021;14(1):100494. doi:10.1016/j.waojou.2020.100494

328. Ellis AK, Frankish CW, Armstrong K, et al. Persistence of the clinical effect of grass allergen peptide immunotherapy after the second and third grass pollen seasons. *J Allergy Clin Immunol*. Feb 2020;145(2):610-618 e9. doi:10.1016/j.jaci.2019.09.010

329. Wagenmann M, Worm M, Akboga Y, Karjalainen M, Hohlfeld JM. Randomized immunotherapy trial in dual-allergic patients using "active allergen placebo" as control. *Allergy*. Aug 2019;74(8):1480-1489. doi:10.1111/all.13842

330. Couroux P, Ipsen H, Stage BS, et al. A birch sublingual allergy immunotherapy tablet reduces rhinoconjunctivitis symptoms when exposed to birch and oak and induces IgG4 to allergens from all trees in the birch homologous group. *Allergy*. Feb 2019;74(2):361-369. doi:10.1111/all.13606

331. Ellis AK, Tenn MW, Steacy LM, et al. Lack of effect of Timothy grass pollen sublingual immunotherapy tablet on birch pollen-induced allergic rhinoconjunctivitis in an environmental exposure unit. *Ann Allergy Asthma Immunol*. May 2018;120(5):495-503 e2. doi:10.1016/j.anai.2018.02.003

332. Pfaar O, Hohlfeld JM, Al-Kadah B, et al. Dose-response relationship of a new Timothy grass pollen allergoid in comparison with a 6-grass pollen allergoid. *Clin Exp Allergy*. Nov 2017;47(11):1445-1455. doi:10.1111/cea.12977

333. Ellis AK, Frankish CW, O'Hehir RE, et al. Treatment with grass allergen peptides improves symptoms of grass pollen-induced allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Aug 2017;140(2):486-496. doi:10.1016/j.jaci.2016.11.043

334. Zieglmayer P, Nolte H, Nelson HS, et al. Long-term effects of a house dust mite sublingual immunotherapy tablet in an environmental exposure chamber trial. *Ann Allergy Asthma Immunol*. Dec 2016;117(6):690-696 e1. doi:10.1016/j.anai.2016.10.015

335. Horak F, Zieglmayer P, Zieglmayer R, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol*. Sep 2009;124(3):471-7, 477 e1. doi:10.1016/j.jaci.2009.06.006

336. Meyer W, Narkus A, Salapatek AM, Hafner D. Double-blind, placebo-controlled, dose-ranging study of new recombinant hypoallergenic Bet v 1 in an environmental exposure chamber. *Allergy*. Jun 2013;68(6):724-31. doi:10.1111/all.12148

337. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. Jun 2015;135(6):1494-501 e6. doi:10.1016/j.jaci.2014.12.1911

338. Patel D, Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. Jan 2013;131(1):103-9 e1-7. doi:10.1016/j.jaci.2012.07.028

339. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. Jan 2014;133(1):121-9 e1-2. doi:10.1016/j.jaci.2013.05.032

340. Gherasim A, de Blay F. Does Air Filtration Work for Cat Allergen Exposure? *Curr Allergy Asthma Rep*. May 14 2020;20(6):18. doi:10.1007/s11882-020-00912-w

341. Gherasim A, Jacob A, Schoettel F, Domis N, de Blay F. Efficacy of air cleaners in asthmatics allergic to cat in ALYATEC((R)) environmental exposure chamber. *Clin Exp Allergy*. Feb 2020;50(2):160-169. doi:10.1111/cea.13511

342. Rogol AD, Tkachenko N, Badorrek P, Hohlfeld JM, Bryson N. Phase 1 pharmacokinetics and phase 3 efficacy of testosterone nasal gel in subjects with seasonal allergies. *Can Urol Assoc J*. Jul 2018;12(7):E349-E356. doi:10.5489/cuaj.4898

343. Khayath N, Doyen V, Gherasim A, et al. Validation of Strasbourg environmental exposure chamber (EEC) ALYATEC((R)) in mite allergic subjects with asthma. *J Asthma*. Feb 2020;57(2):140-148. doi:10.1080/02770903.2018.1563902

344. Zieglmayer P, Lemell P, Chen KW, et al. Clinical validation of a house dust mite environmental challenge chamber model. *J Allergy Clin Immunol*. Jul 2017;140(1):266-268 e5. doi:10.1016/j.jaci.2016.12.986

345. Koriyama M, Okamoto Y, Suzuki T, et al. Characteristics of Japanese cypress pollen-induced allergic rhinitis by environmental challenge chamber. *Allergol Int*. Jan 2022;71(1):144-146. doi:10.1016/j.alit.2021.08.013

346. Gomes PJ, Lane KJ, Angjeli E, Stein L, Abelson MB. Technical and clinical validation of an environmental exposure unit for ragweed. *J Asthma Allergy*. 2016;9:215-221. doi:10.2147/JAA.S123547

347. Pfaar O, Zieglmayer P. Allergen exposure chambers: implementation in clinical trials in allergen immunotherapy. *Clin Transl Allergy*. 2020;10:33. doi:10.1186/s13601-020-00336-9

348. Pfaar O, Agache I, de Blay F, et al. Perspectives in allergen immunotherapy: 2019 and beyond. *Allergy*. Dec 2019;74 Suppl 108:3-25. doi:10.1111/all.14077

349. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mosges R, Kleine-Tebbe J. Clinical trials in allergen immunotherapy: current concepts and future needs. *Allergy*. Sep 2018;73(9):1775-1783. doi:10.1111/all.13429

350. Pfaar O, Bergmann KC, Bonini S, et al. Technical standards in allergen exposure chambers worldwide - an EAACI Task Force Report. *Allergy*. Dec 2021;76(12):3589-3612. doi:10.1111/all.14957

351. Ellis AK, DeVeaux M, Steacy L, et al. Environmental exposure unit simulates natural seasonal birch pollen exposures while maximizing change in allergic symptoms. *Ann Allergy Asthma Immunol*. Oct 2021;127(4):488-495 e5. doi:10.1016/j.anai.2021.06.015

352. Agache I, Bilo M, Braunstahl GJ, et al. In vivo diagnosis of allergic diseases--allergen provocation tests. *Allergy*. Apr 2015;70(4):355-65. doi:10.1111/all.12586

353. Ramchandani R, Linton S, Hossenbaccus L, Ellis AK. Comparing the nasal allergen challenge and environmental exposure unit models of allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2021;127(2):163-164. doi:10.1016/j.anai.2021.04.012

354. Riechelmann H, Epple B, Gropper G. Comparison of conjunctival and nasal provocation test in allergic rhinitis to house dust mite. *Int Arch Allergy Immunol*. Jan 2003;130(1):51-9. doi:10.1159/000068369

355. Dordal MT, Lluch-Bernal M, Sanchez MC, et al. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol*. 2011;21(1):1-12; quiz follow 12.

356. Malm L, Gerth van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. *Rhinology*. Mar 2000;38(1):1-6.

357. Gosepath J, Amedee RG, Mann WJ. Nasal provocation testing as an international standard for evaluation of allergic and nonallergic rhinitis. *Laryngoscope*. Mar 2005;115(3):512-6. doi:10.1097/01.MLG.0000149682.56426.6B

358. Auge J, Vent J, Agache I, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy*. Aug 2018;73(8):1597-1608. doi:10.1111/all.13416

359. Casset A, Khayath N, de Blay F. How In Vitro Assays Contribute to Allergy Diagnosis. *Curr Allergy Asthma Rep*. Nov 2016;16(11):82. doi:10.1007/s11882-016-0659-9

360. Santos AF, Alpan O, Hoffmann HJ. Basophil activation test: Mechanisms and considerations for use in clinical trials and clinical practice. *Allergy*. Aug 2021;76(8):2420-2432. doi:10.1111/all.14747

361. Eguiluz-Gracia I, Testera-Montes A, Gonzalez M, et al. Safety and reproducibility of nasal allergen challenge. *Allergy*. Jun 2019;74(6):1125-1134. doi:10.1111/all.13728

362. Larson D, Patel P, Salapatek AM, et al. Nasal allergen challenge and environmental exposure chamber challenge: A randomized trial comparing clinical and biological responses to cat allergen. *J Allergy Clin Immunol*. Jun 2020;145(6):1585-1597. doi:10.1016/j.jaci.2020.02.024

363. Wanjun W, Qiurong H, Yanqing X, Mo X, Nili W, Jing L. Responsiveness of Nasal Provocation Testing-But Not Skin Test and Specific Immunoglobulin E Blood Level-Correlates With Severity of Allergic Rhinitis in Dermatophagoides Species-Sensitized Patients. *Am J Rhinol Allergy*. Jul 2018;32(4):236-243. doi:10.1177/1945892418779435

364. Joo SH, Hyun KJ, Kim YH. Korean Modification of the Nasal Provocation Test With House Dust Mite Antigen Following the EAACI Guidelines. *Clin Exp Otorhinolaryngol*. Nov 2021;14(4):382-389. doi:10.21053/ceo.2020.00563

365. Xiao H, Jia Q, Zhang H, Zhang L, Liu G, Meng J. The Importance of Nasal Provocation Testing in the Diagnosis of Dermatophagoides pteronyssinus-Induced Allergic Rhinitis. *Am J Rhinol Allergy*. Mar 2022;36(2):191-197. doi:10.1177/19458924211037913

366. Rhinitis ETFoO, Moscato G, Vandenplas O, et al. Occupational rhinitis. *Allergy*. Aug 2008;63(8):969-80. doi:10.1111/j.1398-9995.2008.01801.x

367. Ronsmans S, Steelant B, Backaert W, Nemery B, Van Gerven L. Diagnostic approach to occupational rhinitis: the role of nasal provocation tests. *Curr Opin Allergy Clin Immunol*. Apr 2020;20(2):122-130. doi:10.1097/ACI.0000000000000608

368. Campo P, Salas M, Blanca-Lopez N, Rondon C. Local Allergic Rhinitis. *Immunol Allergy Clin North Am*. May 2016;36(2):321-32. doi:10.1016/j.iac.2015.12.008

369. Rondon C, Campo P, Herrera R, et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. *J Allergy Clin Immunol*. Dec 2011;128(6):1192-7. doi:10.1016/j.jaci.2011.06.012

370. Duman H, Bostanci I, Ozmen S, Dogru M. The Relevance of Nasal Provocation Testing in Children with Nonallergic Rhinitis. *Int Arch Allergy Immunol*. 2016;170(2):115-21. doi:10.1159/000447635

371. Tantilipikorn P, Siriboonkoom P, Sookrung N, et al. Prevalence of local allergic rhinitis to Dermatophagoides pteronyssinus in chronic rhinitis with negative skin prick test. *Asian Pac J Allergy Immunol*. Jun 2021;39(2):111-116. doi:10.12932/AP-170918-0408

372. Moller C, Bjorksten B, Nilsson G, Dreborg S. The precision of the conjunctival provocation test. *Allergy*. Jan 1984;39(1):37-41. doi:10.1111/j.1398-9995.1984.tb01931.x

373. Bertel F, Mortemousque B, Sicard H, Andre C. [Conjunctival provocation test with Dermatophagoides pteronyssinus in the diagnosis of allergic conjunctivitis from house mites]. *J Fr Ophtalmol*. Jun 2001;24(6):581-9. Test de provocation conjonctival au Dermatophagoides pteronyssinus dans le diagnostic des conjonctivites allergiques aux acariens domestiques.

374. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, et al. Conjunctival allergen provocation test : guidelines for daily practice. *Allergy*. Jan 2017;72(1):43-54. doi:10.1111/all.12986

375. Schoos AM, Chawes BL, Bloch J, et al. Children Monosensitized to Can f 5 Show Different Reactions to Male and Female Dog Allergen Extract Provocation: A Randomized Controlled Trial. *J Allergy Clin Immunol Pract*. May 2020;8(5):1592-1597 e2. doi:10.1016/j.jaip.2019.12.012

376. Gelis S, Rueda M, Pascal M, et al. Usefulness of the Allergen Specific Nasal Provocation Test in the Diagnosis of Shellfish Allergy. *J Investig Allergol Clin Immunol*. Sep 6 2021:0. doi:10.18176/jiaci.0736

377. Krzych-Falta E, Furmanczyk K, Samolinski B. Specificity and sensitivity assessment of selected nasal provocation testing techniques. *Postepy Dermatol Alergol*. Dec 2016;33(6):464-468. doi:10.5114/pdia.2016.61339

378. de Blay F, Doyen V, Lutz C, et al. A new, faster, and safe nasal provocation test method for diagnosing mite allergic rhinitis. *Ann Allergy Asthma Immunol*. Nov 2015;115(5):385-390 e1. doi:10.1016/j.anai.2015.07.014

379. Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy*. Jul-Aug 2015;29(4):e100-4. doi:10.2500/ajra.2015.29.4214

380. Agarwal G, Hernandez D, Citardi MJ, Fakhri S, Luong A. End-organ testing for allergic rhinitis with fungi is poorly correlated with fungal sensitivity. *Otolaryngol Head Neck Surg*. Mar 2013;148(3):391-5. doi:10.1177/0194599812474224

381. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. NASAL cytology: practical aspects and clinical relevance. *Clin Exp Allergy*. Jun 2016;46(6):785-92. doi:10.1111/cea.12730

382. Waecker NJ, Jr., Shope TR, Weber PA, Buck ML, Domingo RC, Hooper DG. The Rhino-Probe nasal curette for detecting respiratory syncytial virus in children. *Pediatr Infect Dis J*. Apr 1993;12(4):326-9. doi:10.1097/00006454-199304000-00012

383. Gelardi M, Passalacqua G, Fiorella ML, Quaranta N. Assessment of biofilm by nasal cytology in different forms of rhinitis and its functional correlations. *Eur Ann Allergy Clin Immunol*. Feb 2013;45(1):25-9.

384. Canakcioglu S, Tahamiler R, Saritzali G, et al. Evaluation of nasal cytology in subjects with chronic rhinitis: a 7-year study. *Am J Otolaryngol*. Sep-Oct 2009;30(5):312-7. doi:10.1016/j.amjoto.2008.06.015

385. Di Lorenzo G, Pacor ML, Amodio E, et al. Differences and similarities between allergic and nonallergic rhinitis in a large sample of adult patients with rhinitis symptoms. *Int Arch Allergy Immunol*. 2011;155(3):263-70. doi:10.1159/000320050

386. Gelardi M, Ciprandi G, Incorvaia C, et al. Allergic rhinitis phenotypes based on mono-allergy or poly-allergy. *Inflamm Res*. Jun 2015;64(6):373-5. doi:10.1007/s00011-015-0826-9

387. Gelardi M, Incorvaia C, Passalacqua G, Quaranta N, Frati F. The classification of allergic rhinitis and its cytological correlate. *Allergy*. Dec 2011;66(12):1624-5. doi:10.1111/j.1398-9995.2011.02741.x

388. Gelardi M, Peroni DG, Incorvaia C, et al. Seasonal changes in nasal cytology in mite-allergic patients. *J Inflamm Res*. 2014;7:39-44. doi:10.2147/JIR.S54581

389. Ciofalo A, Cavaliere C, Incorvaia C, et al. Diagnostic performance of nasal cytology. *Eur Arch Otorhinolaryngol*. May 2022;279(5):2451-2455. doi:10.1007/s00405-021-07044-5

390. Cavaliere C, Masieri S, Greco A, Lambiase A, Segatto M. Nasal expression of the vascular endothelial growth factor and its receptors is reduced by mepolizumab in chronic rhinosinusitis with nasal polyposis. *Ann Allergy Asthma Immunol*. Apr 2021;126(4):442-443. doi:10.1016/j.anai.2021.01.010

391. Chen Y, Yang M, Deng J, Wang K, Shi J, Sun Y. Elevated Levels of Activated and Pathogenic Eosinophils Characterize Moderate-Severe House Dust Mite Allergic Rhinitis. *J Immunol Res*. 2020;2020:8085615. doi:10.1155/2020/8085615

392. Bentley AM, Jacobson MR, Cumberworth V, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol*. Apr 1992;89(4):877-83. doi:10.1016/0091-6749(92)90444-7

393. Spector SL, English G, Jones L. Clinical and nasal biopsy response to treatment of perennial rhinitis. *J Allergy Clin Immunol*. Aug 1980;66(2):129-37. doi:10.1016/0091-6749(80)90060-3

394. Powe DG, Huskisson RS, Carney AS, et al. Mucosal T-cell phenotypes in persistent atopic and nonatopic rhinitis show an association with mast cells. *Allergy*. Feb 2004;59(2):204-12. doi:10.1046/j.1398-9995.2003.00315.x

395. Lim MC, Taylor RM, Naclerio RM. The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage. *Am J Respir Crit Care Med*. Jan 1995;151(1):136-44. doi:10.1164/ajrccm.151.1.7812543

396. Howarth PH, Persson CG, Meltzer EO, Jacobson MR, Durham SR, Silkoff PE. Objective monitoring of nasal airway inflammation in rhinitis. *J Allergy Clin Immunol*. Mar 2005;115(3 Suppl 1):S414-41. doi:10.1016/j.jaci.2004.12.1134

397. De Corso E, Seccia V, Ottaviano G, et al. Clinical Evidence of Type 2 Inflammation in Non-allergic Rhinitis with Eosinophilia Syndrome: a Systematic Review. *Curr Allergy Asthma Rep*. Apr 2022;22(4):29-42. doi:10.1007/s11882-022-01027-0

398. Phothijindakul N, Chusakul S, Aeumjaturapat S, et al. Nasal Cytology as a Diagnostic Tool for Local Allergic Rhinitis. *Am J Rhinol Allergy*. Sep 2019;33(5):540-544. doi:10.1177/1945892419850926

399. Gelardi M. "Overlapped" rhinitis: a real trap for rhinoallergologists. *Eur Ann Allergy Clin Immunol*. Nov 2014;46(6):234-6.

400. McHugh T, Levin M, Snidvongs K, Banglawala SM, Sommer DD. Comorbidities associated with eosinophilic chronic rhinosinusitis: A systematic review and meta-analysis. *Clin Otolaryngol*. Jul 2020;45(4):574-583. doi:10.1111/coa.13536

401. Sivam A, Jeswani S, Reder L, et al. Olfactory cleft inflammation is present in seasonal allergic rhinitis and is reduced with intranasal steroids. *Am J Rhinol Allergy*. Jul-Aug 2010;24(4):286-90. doi:10.2500/ajra.2010.24.3478

402. Uller L, Emanuelsson CA, Andersson M, Erjefalt JS, Greiff L, Persson CG. Early phase resolution of mucosal eosinophilic inflammation in allergic rhinitis. *Respir Res*. May 9 2010;11:54. doi:10.1186/1465-9921-11-54

403. Asai K, Foley SC, Sumi Y, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy increases CD4+CD25+ T cells in the nasal mucosa of subjects with allergic rhinitis. *Allergol Int*. Dec 2008;57(4):377-81. doi:10.2332/allergolint.O-07-528

404. Rak S, Heinrich C, Scheynius A. Comparison of nasal immunohistology in patients with seasonal rhinoconjunctivitis treated with topical steroids or specific allergen immunotherapy. *Allergy*. May 2005;60(5):643-9. doi:10.1111/j.1398-9995.2005.00763.x

405. Plewako H, Arvidsson M, Petruson K, et al. The effect of omalizumab on nasal allergic inflammation. *J Allergy Clin Immunol*. Jul 2002;110(1):68-71. doi:10.1067/mai.2002.125488

406. Pullerits T, Linden A, Malmhall C, Lotvall J. Effect of seasonal allergen exposure on mucosal IL-16 and CD4+ cells in patients with allergic rhinitis. *Allergy*. Sep 2001;56(9):871-7.

407. Wilson DR, Nouri-Aria KT, Walker SM, et al. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. *J Allergy Clin Immunol*. Jun 2001;107(6):971-6. doi:10.1067/mai.2001.115483

408. Radulovic S, Jacobson MR, Durham SR, Nouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. *J Allergy Clin Immunol*. Jun 2008;121(6):1467-72, 1472 e1. doi:10.1016/j.jaci.2008.03.013

409. Till SJ, Jacobson MR, O'Brien F, et al. Recruitment of CD1a+ Langerhans cells to the nasal mucosa in seasonal allergic rhinitis and effects of topical corticosteroid therapy. *Allergy*. Feb 2001;56(2):126-31. doi:10.1034/j.1398-9995.2001.056002126.x

410. Vogt K, Bachmann-Harildstad G, Lintermann A, Nechyporenko A, Peters F, Wernecke KD. The new agreement of the international RIGA consensus conference on nasal airway function tests. *Rhinology*. Jun 1 2018;56(2):133-143. doi:10.4193/Rhin17.084

411. Vogt K, Wernecke KD, Behrbohm H, Gubisch W, Argale M. Four-phase rhinomanometry: a multicentric retrospective analysis of 36,563 clinical measurements. *Eur Arch Otorhinolaryngol*. May 2016;273(5):1185-98. doi:10.1007/s00405-015-3723-5

412. Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinology. *Rhinology*. Jul 25 2019;57(Suppl S28):1-41. doi:10.4193/Rhin19.410

413. Clement PA. Committee report on standardization of rhinomanometry. *Rhinology*. Sep 1984;22(3):151-5.

414. Ohki M, Naito K, Cole P. Dimensions and resistances of the human nose: racial differences. *Laryngoscope*. Mar 1991;101(3):276-8. doi:10.1288/00005537-199103000-00009

415. Jones AS, Lancer JM, Stevens JC, Beckingham E. Nasal resistance to airflow (its measurement, reproducibility and normal parameters). *J Laryngol Otol*. Aug 1987;101(8):800-8. doi:10.1017/s0022215100102762

416. Cole P. Stability of nasal airflow resistance. *Clin Otolaryngol Allied Sci*. Apr 1989;14(2):177-82. doi:10.1111/j.1365-2273.1989.tb00357.x

417. Shelton DM, Eiser NM. Evaluation of active anterior and posterior rhinomanometry in normal subjects. *Clin Otolaryngol Allied Sci*. Apr 1992;17(2):178-82. doi:10.1111/j.1365-2273.1992.tb01068.x

418. Chen IC, Lin YT, Hsu JH, Liu YC, Wu JR, Dai ZK. Nasal Airflow Measured by Rhinomanometry Correlates with FeNO in Children with Asthma. *PLoS One*. 2016;11(10):e0165440. doi:10.1371/journal.pone.0165440

419. Merkle J, Kohlhas L, Zadoyan G, Mosges R, Hellmich M. Rhinomanometric reference intervals for normal total nasal airflow resistance. *Rhinology*. Dec 2014;52(4):292-9. doi:10.4193/Rhino13.220

420. Suzina AH, Hamzah M, Samsudin AR. Active anterior rhinomanometry analysis in normal adult Malays. *J Laryngol Otol*. Aug 2003;117(8):605-8. doi:10.1258/002221503768199924

421. Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in daily practice. *Allergy*. Feb 2016;71(2):162-74. doi:10.1111/all.12778

422. Vogt K, Jalowayski AA, Althaus W, et al. 4-Phase-Rhinomanometry (4PR)--basics and practice 2010. *Rhinol Suppl*. 2010;21:1-50.

423. Andre RF, Vuyk HD, Ahmed A, Graamans K, Nolst Trenite GJ. Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. *Clin Otolaryngol*. Dec 2009;34(6):518-25. doi:10.1111/j.1749-4486.2009.02042.x

424. Mohan S, Fuller JC, Ford SF, Lindsay RW. Diagnostic and Therapeutic Management of Nasal Airway Obstruction: Advances in Diagnosis and Treatment. *JAMA Facial Plast Surg*. Sep 1 2018;20(5):409-418. doi:10.1001/jamafacial.2018.0279

425. Tarhan E, Coskun M, Cakmak O, Celik H, Cankurtaran M. Acoustic rhinometry in humans: accuracy of nasal passage area estimates, and ability to quantify paranasal sinus volume and ostium size. *J Appl Physiol (1985)*. Aug 2005;99(2):616-23. doi:10.1152/japplphysiol.00106.2005

426. Timperley D, Srubisky A, Stow N, Marcells GN, Harvey RJ. Minimal clinically important differences in nasal peak inspiratory flow. *Rhinology*. Mar 2011;49(1):37-40. doi:10.4193/Rhino10.097

427. Chin D, Marcells G, Malek J, et al. Nasal peak inspiratory flow (NPIF) as a diagnostic tool for differentiating decongestable from structural nasal obstruction. *Rhinology*. Jun 2014;52(2):116-21. doi:10.4193/Rhino13.126

428. Kirtsreesakul V, Leelapong J, Ruttanaphol S. Correlation Between Peak Nasal Flow Reversibility and Mucociliary Clearance in Allergic Rhinitis. *Laryngoscope*. Jun 2020;130(6):1372-1376. doi:10.1002/lary.28226

429. Mo S, Gupta SS, Stroud A, et al. Nasal Peak Inspiratory Flow in Healthy and Obstructed Patients: Systematic Review and Meta-Analysis. *Laryngoscope*. Feb 2021;131(2):260-267. doi:10.1002/lary.28682

430. Krzych-Falta E, Samolinski BK. Objectification of the nasal patency assessment techniques used in nasal allergen provocation testing. *Postepy Dermatol Alergol*. Oct 2020;37(5):635-640. doi:10.5114/ada.2019.81404

431. Ottaviano G, Ermolao A, Nardello E, et al. Breathing parameters associated to two different external nasal dilator strips in endurance athletes. *Auris Nasus Larynx*. Dec 2017;44(6):713-718. doi:10.1016/j.anl.2017.01.006

432. Kirtsreesakul V, Leelapong J, Ruttanaphol S. Nasal peak inspiratory and expiratory flow measurements for assessing nasal obstruction in allergic rhinitis. *Am J Rhinol Allergy*. Mar-Apr 2014;28(2):126-30. doi:10.2500/ajra.2014.28.4008

433. Wong DK, Saim L, Idrus RB, Saim A. Evaluating the incidence and severity of rhinitis using an peak nasal inspiratory flow meter and the SNOT-22 questionnaire. *J Med Assoc Thai*. 2021;104(5):701-708.

434. Canakcioglu S, Tahamiler R, Saritzali G, Isildak H, Alimoglu Y. Nasal patency by rhinomanometry in patients with sensation of nasal obstruction. *Am J Rhinol Allergy*. May-Jun 2009;23(3):300-2. doi:10.2500/ajra.2009.23.3312

435. Passali D, Mezzedimi C, Passali GC, Nuti D, Bellussi L. The role of rhinomanometry, acoustic rhinometry, and mucociliary transport time in the assessment of nasal patency. *Ear Nose Throat J*. May 2000;79(5):397-400.

436. Garcia GJM, Hariri BM, Patel RG, Rhee JS. The relationship between nasal resistance to airflow and the airspace minimal cross-sectional area. *J Biomech*. Jun 14 2016;49(9):1670-1678. doi:10.1016/j.jbiomech.2016.03.051

437. Aksoy C, Elsurer C, Artac H, Bozkurt MK. Evaluation of olfactory function in children with seasonal allergic rhinitis and its correlation with acoustic rhinometry. *Int J Pediatr Otorhinolaryngol*. Oct 2018;113:188-191. doi:10.1016/j.ijporl.2018.07.051

438. Barnes ML, Lipworth BJ. Removing nasal valve obstruction in peak nasal inspiratory flow measurement. *Ann Allergy Asthma Immunol*. Jul 2007;99(1):59-60. doi:10.1016/S1081-1206(10)60622-9

439. Burrow A, Eccles R, Jones AS. The effects of camphor, eucalyptus and menthol vapour on nasal resistance to airflow and nasal sensation. *Acta Otolaryngol*. Jul-Aug 1983;96(1-2):157-61. doi:10.3109/00016488309132886

440. Eccles R, Jones AS. The effect of menthol on nasal resistance to air flow. *J Laryngol Otol*. Aug 1983;97(8):705-9. doi:10.1017/s002221510009486x

441. Jones AS, Lancer JM, Shone G, Stevens JC. The effect of lignocaine on nasal resistance and nasal sensation of airflow. *Acta Otolaryngol*. Mar-Apr 1986;101(3-4):328-30. doi:10.3109/00016488609132846

442. Eccles R, Griffiths DH, Newton CG, Tolley NS. The effects of menthol isomers on nasal sensation of airflow. *Clin Otolaryngol Allied Sci*. Feb 1988;13(1):25-9. doi:10.1111/j.1365-2273.1988.tb00277.x

443. Naito K, Ohoka E, Kato R, Kondo Y, Iwata S. The effect of L-menthol stimulation of the major palatine nerve on nasal patency. *Auris Nasus Larynx*. 1991;18(3):221-6. doi:10.1016/s0385-8146(12)80260-4

444. Naito K, Komori M, Kondo Y, Takeuchi M, Iwata S. The effect of L-menthol stimulation of the major palatine nerve on subjective and objective nasal patency. *Auris Nasus Larynx*. Apr 1997;24(2):159-62. doi:10.1016/S0385-8146(96)00005-3

445. Jones AS, Crosher R, Wight RG, Lancer JM, Beckingham E. The effect of local anaesthesia of the nasal vestibule on nasal sensation of airflow and nasal resistance. *Clin Otolaryngol Allied Sci*. Dec 1987;12(6):461-4. doi:10.1111/j.1365-2273.1987.tb00233.x

446. Barnes ML, White PS, Gardiner Q. Re: Correlation between subjective and objective evaluation of the nasal airway. *Clin Otolaryngol*. Apr 2010;35(2):152-3; author reply 153. doi:10.1111/j.1749-4486.2010.02110.x

447. van Spronsen E, Ingels KJ, Jansen AH, Graamans K, Fokkens WJ. Evidence-based recommendations regarding the differential diagnosis and assessment of nasal congestion: using the new GRADE system. *Allergy*. Jul 2008;63(7):820-33. doi:10.1111/j.1398-9995.2008.01729.x

448. Ta NH, Gao J, Philpott C. A systematic review to examine the relationship between objective and patient-reported outcome measures in sinonasal disorders: recommendations for use in research and clinical practice. *Int Forum Allergy Rhinol*. May 2021;11(5):910-923. doi:10.1002/alr.22744

449. Vogt K, Hasse W, Jalowayski AA. New resistance patterns in rhinomanometry: clinical evaluation of 5000 measurements. presented at: European Rhinologic Society; 2002;

450. Iyer A, Athavale A. Nasal Airway Resistance and Latent Lower Airway Involvement in Allergic Rhinitis. *J Assoc Physicians India*. Mar 2020;68(3):43-47.

451. Pantin CT, Southworth T, Wetzel K, Singh D. Reproducibility of nasal allergen challenge responses in adults with allergic rhinitis. *Clin Pharmacol*. 2019;11:67-76. doi:10.2147/CPAA.S184404

452. Wong EH, Eccles R. Comparison of classic and 4-phase rhinomanometry methods, is there any difference? *Rhinology*. Dec 2014;52(4):360-5. doi:10.4193/Rhino13.187

453. Brindisi G, De Vittori V, De Nola R, et al. The Role of Nasal Nitric Oxide and Anterior Active Rhinomanometry in the Diagnosis of Allergic Rhinitis and Asthma: A Message for Pediatric Clinical Practice. *J Asthma Allergy*. 2021;14:265-274. doi:10.2147/JAA.S275692

454. Hou J, Lou H, Wang Y, et al. Nasal ventilation is an important factor in evaluating the diagnostic value of nasal nitric oxide in allergic rhinitis. *Int Forum Allergy Rhinol*. Jun 2018;8(6):686-694. doi:10.1002/alr.22087

455. Wandalsen GF, Mendes AI, Matsumoto F, Sole D. Acoustic Rhinometry in Nasal Provocation Tests in Children and Adolescents. *J Investig Allergol Clin Immunol*. 2016;26(3):156-60. doi:10.18176/jiaci.0036

456. Malizia V, Ferrante G, Cilluffo G, Fasola S, Montalbano L, La Grutta S. Rhinomanometry: point of care test (POCT) for allergic rhinitis in children? *Allergol Immunopathol (Madr)*. 2021;49(5):28-31. doi:10.15586/aei.v49i5.429

457. Valero A, Navarro AM, Del Cuvillo A, et al. Position paper on nasal obstruction: evaluation and treatment. *J Investig Allergol Clin Immunol*. 2018;28(2):67-90. doi:10.18176/jiaci.0232

458. Takeno S, Okabayashi Y, Kohno T, Yumii K, Hirakawa K. The role of nasal fractional exhaled nitric oxide as an objective parameter independent of nasal airflow resistance in the diagnosis of allergic rhinitis. *Auris Nasus Larynx*. Aug 2017;44(4):435-441. doi:10.1016/j.anl.2016.09.007

459. Demirbas D, Cingi C, Cakli H, Kaya E. Use of rhinomanometry in common rhinologic disorders. *Expert Rev Med Devices*. Nov 2011;8(6):769-77. doi:10.1586/erd.11.45

460. Eguiluz-Gracia I, Testera-Montes A, Salas M, et al. Comparison of diagnostic accuracy of acoustic rhinometry and symptoms score for nasal allergen challenge monitoring. *Allergy*. Jan 2021;76(1):371-375. doi:10.1111/all.14499

461. Isaac A, Major M, Witmans M, et al. Correlations between acoustic rhinometry, subjective symptoms, and endoscopic findings in symptomatic children with nasal obstruction. *JAMA Otolaryngol Head Neck Surg*. Jun 2015;141(6):550-5. doi:10.1001/jamaoto.2015.0468

462. Wandalsen GF, Mendes AI, Sole D. Correlation between nasal resistance and different acoustic rhinometry parameters in children and adolescents with and without allergic rhinitis. *Braz J Otorhinolaryngol*. Dec 2012;78(6):81-6. doi:10.5935/1808-8694.20120038

463. Ozturk F, Turktas I, Asal K, Ileri F, Munevver Pinar N. Effect of intranasal triamcinolone acetonide on bronchial hyper-responsiveness in children with seasonal allergic rhinitis and comparison of perceptional nasal obstruction with acoustic rhinometric assessment. *Int J Pediatr Otorhinolaryngol*. Aug 2004;68(8):1007-15. doi:10.1016/j.ijporl.2004.03.006

464. Sikorska-Szaflik H, Sozanska B. Peak nasal inspiratory flow in children with allergic rhinitis. Is it related to the quality of life? *Allergol Immunopathol (Madr)*. Mar - Apr 2020;48(2):187-193. doi:10.1016/j.aller.2019.08.002

465. Neighbour H, Soliman M, Steacy LM, et al. The Allergic Rhinitis Clinical Investigator Collaborative (AR-CIC): verification of nasal allergen challenge procedures in a study utilizing an investigational immunotherapy for cat allergy. *Clin Transl Allergy*. 2018;8:15. doi:10.1186/s13601-018-0198-7

466. Gupta N, Goel N, Kumar R. Correlation of exhaled nitric oxide, nasal nitric oxide and atopic status: A cross-sectional study in bronchial asthma and allergic rhinitis. *Lung India*. Oct 2014;31(4):342-7. doi:10.4103/0970-2113.142107

467. Kimberly B, Nejadnik B, Giraud GD, Holden WE. Nasal contribution to exhaled nitric oxide at rest and during breathholding in humans. *Am J Respir Crit Care Med*. Feb 1996;153(2):829-36. doi:10.1164/ajrccm.153.2.8564139

468. Lundberg JO, Farkas-Szallasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. *Nat Med*. Apr 1995;1(4):370-3. doi:10.1038/nm0495-370

469. Chatkin JM, Qian W, McClean PA, Zamel N, Haight J, Silkoff P. Nitric oxide accumulation in the nonventilated nasal cavity. *Arch Otolaryngol Head Neck Surg*. Jun 1999;125(6):682-5. doi:10.1001/archotol.125.6.682

470. American Thoracic S, European Respiratory S. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. Apr 15 2005;171(8):912-30. doi:10.1164/rccm.200406-710ST

471. Malmberg LP, Petays T, Haahtela T, et al. Exhaled nitric oxide in healthy nonatopic school-age children: determinants and height-adjusted reference values. *Pediatr Pulmonol*. Jul 2006;41(7):635-42. doi:10.1002/ppul.20417

472. Franklin PJ, Taplin R, Stick SM. A community study of exhaled nitric oxide in healthy children. *Am J Respir Crit Care Med*. Jan 1999;159(1):69-73. doi:10.1164/ajrccm.159.1.9804134

473. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax*. Dec 2003;58(12):1048-52. doi:10.1136/thorax.58.12.1048

474. Khatri SB, Iaccarino JM, Barochia A, et al. Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma: An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. Nov 15 2021;204(10):e97-e109. doi:10.1164/rccm.202109-2093ST

475. van Asch CJ, Balemans WA, Rovers MM, Schilder AG, van der Ent CK. Atopic disease and exhaled nitric oxide in an unselected population of young adults. *Ann Allergy Asthma Immunol*. Jan 2008;100(1):59-65. doi:10.1016/S1081-1206(10)60406-1

476. Dweik RA, Sorkness RL, Wenzel S, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. *Am J Respir Crit Care Med*. May 15 2010;181(10):1033-41. doi:10.1164/rccm.200905-0695OC

477. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. Feb 15 2010;181(4):315-23. doi:10.1164/rccm.200906-0896OC

478. Maniscalco M, Calabrese C, D'Amato M, et al. Association between exhaled nitric oxide and nasal polyposis in severe asthma. *Respir Med*. Jun 2019;152:20-24. doi:10.1016/j.rmed.2019.04.017

479. Lipworth B, Kuo CR, Chan R. 2020 Updated Asthma Guidelines: Clinical utility of fractional exhaled nitric oxide (Feno) in asthma management. *J Allergy Clin Immunol*. Dec 2020;146(6):1281-1282. doi:10.1016/j.jaci.2020.03.006

480. Bencova A, Rozborilova E, Antosova M. Bidirectional link between upper and lower airways in patients with allergic rhinitis. *Eur J Med Res*. Dec 7 2009;14 Suppl 4:18-20. doi:10.1186/2047-783x-14-s4-18

481. Hervas D, Rodriguez R, Garde J. Role of aeroallergen nasal challenge in asthmatic children. *Allergol Immunopathol (Madr)*. Jan-Feb 2011;39(1):17-22. doi:10.1016/j.aller.2010.03.003

482. Jang YY, Ahn JY. Evaluation of Fractional Exhaled Nitric Oxide in Pediatric Asthma and Allergic Rhinitis. *Children (Basel)*. Dec 23 2020;8(1)doi:10.3390/children8010003

483. Choi BS, Kim KW, Lee YJ, et al. Exhaled nitric oxide is associated with allergic inflammation in children. *J Korean Med Sci*. Oct 2011;26(10):1265-9. doi:10.3346/jkms.2011.26.10.1265

484. Lundberg JO, Nordvall SL, Weitzberg E, Kollberg H, Alving K. Exhaled nitric oxide in paediatric asthma and cystic fibrosis. *Arch Dis Child*. Oct 1996;75(4):323-6. doi:10.1136/adc.75.4.323

485. Byrnes CA, Dinarevic S, Shinebourne EA, Barnes PJ, Bush A. Exhaled nitric oxide measurements in normal and asthmatic children. *Pediatr Pulmonol*. Nov 1997;24(5):312-8. doi:10.1002/(sici)1099-0496(199711)24:5<312::aid-ppul2>3.0.co;2-k

486. Baraldi E, Azzolin NM, Carra S, Dario C, Marchesini L, Zacchello F. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. *Respir Med*. Mar 1998;92(3):558-61. doi:10.1016/s0954-6111(98)90308-0

487. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. Sep 1 2011;184(5):602-15. doi:10.1164/rccm.9120-11ST

488. Shapiro AJ, Dell SD, Gaston B, et al. Nasal Nitric Oxide Measurement in Primary Ciliary Dyskinesia. A Technical Paper on Standardized Testing Protocols. *Ann Am Thorac Soc*. Feb 2020;17(2):e1-e12. doi:10.1513/AnnalsATS.201904-347OT

489. Lee KJ, Cho SH, Lee SH, et al. Nasal and exhaled nitric oxide in allergic rhinitis. *Clin Exp Otorhinolaryngol*. Dec 2012;5(4):228-33. doi:10.3342/ceo.2012.5.4.228

490. Dotsch J, Demirakca S, Terbrack HG, Huls G, Rascher W, Kuhl PG. Airway nitric oxide in asthmatic children and patients with cystic fibrosis. *Eur Respir J*. Dec 1996;9(12):2537-40. doi:10.1183/09031936.96.09122537

491. Martin U, Bryden K, Devoy M, Howarth P. Increased levels of exhaled nitric oxide during nasal and oral breathing in subjects with seasonal rhinitis. *J Allergy Clin Immunol*. Mar 1996;97(3):768-72. doi:10.1016/s0091-6749(96)80154-0

492. Kalpaklioglu AF, Baccioglu A, Yalim SA. Can nasal nitric oxide be a biomarker to differentiate allergic and non-allergic rhinitis? *Egypt J Otolaryngol*. 2021;37(1):91.

493. Ambrosino P, Parrella P, Formisano R, et al. Clinical application of nasal nitric oxide measurement in allergic rhinitis: A systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. Oct 2020;125(4):447-459 e5. doi:10.1016/j.anai.2020.07.003

494. Wang B, Wu Z, Wang F, Yin Z, Shi L, Liu Y. Nasal nitric oxide testing for allergic rhinitis patients: Systematic review and meta-analysis. *Immun Inflamm Dis*. Sep 2021;9(3):635-648. doi:10.1002/iid3.439

495. Maniscalco M, Sofia M, Carratu L, Higenbottam T. Effect of nitric oxide inhibition on nasal airway resistance after nasal allergen challenge in allergic rhinitis. *Eur J Clin Invest*. May 2001;31(5):462-6. doi:10.1046/j.1365-2362.2001.00825.x

496. Moody A, Fergusson W, Wells A, Bartley J, Kolbe J. Nasal levels of nitric oxide as an outcome variable in allergic upper respiratory tract disease: Influence of atopy and hayfever on nNO. *Am J Rhinol*. Sep-Oct 2006;20(5):425-9. doi:10.2500/ajr.2006.20.2921

497. Henriksen AH, Sue-Chu M, Holmen TL, Langhammer A, Bjermer L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J*. Feb 1999;13(2):301-6. doi:10.1034/j.1399-3003.1999.13b14.x

498. Phillips PS, Sacks R, Marcells GN, Cohen NA, Harvey RJ. Nasal nitric oxide and sinonasal disease: a systematic review of published evidence. *Otolaryngol Head Neck Surg*. Feb 2011;144(2):159-69. doi:10.1177/0194599810392667

499. Hervas D, Milan JM, Garde J. Differences in exhaled nitric oxide in atopic children. *Allergol Immunopathol (Madr)*. Nov-Dec 2008;36(6):331-5. doi:10.1016/s0301-0546(08)75865-8

500. Mucci T, Govindaraj S, Tversky J. Allergic rhinitis. *Mt Sinai J Med*. Sep-Oct 2011;78(5):634-44. doi:10.1002/msj.20287

501. Tversky J, McGlashan D. Short wave infrared (SWIR) camera as a novel approach to allergy skin testing. *J Allergy Clin Immunol*. 2017;139(2):AB156.

502. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. *Perspect Clin Res*. Oct 2011;2(4):137-44. doi:10.4103/2229-3485.86879

503. Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. *JAMA*. Feb 14 2017;317(6):615-625. doi:10.1001/jama.2016.21040

504. Zieglmayer P, Focke-Tejkl M, Schmutz R, et al. Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy. *EBioMedicine*. Sep 2016;11:43-57. doi:10.1016/j.ebiom.2016.08.022

505. Mosbech H, Canonica GW, Backer V, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol*. Feb 2015;114(2):134-40. doi:10.1016/j.anai.2014.11.015

506. Casale TB. Anti-immunoglobulin E (omalizumab) therapy in seasonal allergic rhinitis. *Am J Respir Crit Care Med*. Oct 15 2001;164(8 Pt 2):S18-21. doi:10.1164/ajrccm.164.supplement_1.2103023

507. Calderon MA, Bernstein DI, Blaiss M, Andersen JS, Nolte H. A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. *Clin Exp Allergy*. Oct 2014;44(10):1228-39. doi:10.1111/cea.12331

508. Devillier P, Bousquet PJ, Grassin-Delyle S, et al. Comparison of outcome measures in allergic rhinitis in children, adolescents and adults. *Pediatr Allergy Immunol*. Jun 2016;27(4):375-81. doi:10.1111/pai.12561

509. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. *J Allergy Clin Immunol*. Jul 2019;144(1):135-143 e6. doi:10.1016/j.jaci.2019.01.053

510. Glattacker M, Boeker M, Anger R, et al. Evaluation of a Mobile Phone App for Patients With Pollen-Related Allergic Rhinitis: Prospective Longitudinal Field Study. *JMIR Mhealth Uhealth*. Apr 17 2020;8(4):e15514. doi:10.2196/15514

511. Bousquet J, Bewick M, Arnavielhe S, et al. Work productivity in rhinitis using cell phones: The MASK pilot study. *Allergy*. Oct 2017;72(10):1475-1484. doi:10.1111/all.13177

512. Sousa-Pinto B, Eklund P, Pfaar O, et al. Validity, reliability, and responsiveness of daily monitoring visual analog scales in MASK-air(R). *Clin Transl Allergy*. Aug 2021;11(7):e12062. doi:10.1002/clt2.12062

513. Zhou AH, Patel VR, Baredes S, Eloy JA, Hsueh WD. Mobile Applications for Allergic Rhinitis. *Ann Otol Rhinol Laryngol*. Nov 2018;127(11):836-840. doi:10.1177/0003489418798385

514. Jacome C, Pereira R, Almeida R, et al. Validation of App and Phone Versions of the Control of Allergic Rhinitis and Asthma Test (CARAT). *J Investig Allergol Clin Immunol*. Jun 22 2021;31(3):270-273. doi:10.18176/jiaci.0640

515. Hafner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORE(TM)': a novel symptom-medication score for clinical trials. *Allergy*. May 2011;66(5):629-36. doi:10.1111/j.1398-9995.2010.02531.x

516. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. *Clin Exp Allergy*. Jun 2011;41(6):860-8. doi:10.1111/j.1365-2222.2011.03734.x

517. Demoly P, Calderon MA, Casale T, et al. Assessment of disease control in allergic rhinitis. *Clin Transl Allergy*. Feb 18 2013;3(1):7. doi:10.1186/2045-7022-3-7

518. Meltzer EO, Schatz M, Nathan R, Garris C, Stanford RH, Kosinski M. Reliability, validity, and responsiveness of the Rhinitis Control Assessment Test in patients with rhinitis. *J Allergy Clin Immunol*. Feb 2013;131(2):379-86. doi:10.1016/j.jaci.2012.10.022

519. Spector SL, Nicklas RA, Chapman JA, et al. Symptom severity assessment of allergic rhinitis: part 1. *Ann Allergy Asthma Immunol*. Aug 2003;91(2):105-14. doi:10.1016/s1081-1206(10)62160-6

520. Annesi-Maesano I, Didier A, Klossek M, Chanal I, Moreau D, Bousquet J. The score for allergic rhinitis (SFAR): a simple and valid assessment method in population studies. *Allergy*. Feb 2002;57(2):107-14. doi:10.1034/j.1398-9995.2002.1o3170.x

521. Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy*. Apr 2007;62(4):367-72. doi:10.1111/j.1398-9995.2006.01276.x

522. Devillier P, Chassany O, Vicaut E, et al. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. *Allergy*. Dec 2014;69(12):1689-95. doi:10.1111/all.12518

523. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy*. Aug 2010;65(8):1042-8. doi:10.1111/j.1398-9995.2009.02310.x

524. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy*. Aug 2013;43(8):881-8. doi:10.1111/cea.12121

525. Baiardini I, Pasquali M, Giardini A, et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy*. Apr 2003;58(4):289-94. doi:10.1034/j.1398-9995.2003.00079.x

526. Fasola S, Montalbano L, Ferrante G, et al. RAPP-children: A new tool for assessing quality of life in patients with asthma and rhinitis. *Clin Exp Allergy*. Jun 2020;50(6):662-671. doi:10.1111/cea.13599

527. Tosca MA, Del Barba P, Licari A, Ciprandi G, Asthma, Rhinitis Control Study G. The Measurement of Asthma and Allergic Rhinitis Control in Children and Adolescents. *Children (Basel)*. May 7 2020;7(5)doi:10.3390/children7050043

528. Baiardini I, Fasola S, Montalbano L, et al. RHINASTHMA-Children: A new quality of life tool for patients with respiratory allergy. *Pediatr Allergy Immunol*. Feb 2017;28(1):102-105. doi:10.1111/pai.12667

529. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. Feb 2016;137(2):444-451 e8. doi:10.1016/j.jaci.2015.06.036

530. Galimberti M, Passalacqua G, Incorvaia C, et al. Catching allergy by a simple questionnaire. *World Allergy Organ J*. 2015;8(1):16. doi:10.1186/s40413-015-0067-y

531. Klimek L, Bachert C, Lukat KF, Pfaar O, Meyer H, Narkus A. Allergy immunotherapy with a hypoallergenic recombinant birch pollen allergen rBet v 1-FV in a randomized controlled trial. *Clin Transl Allergy*. 2015;5:28. doi:10.1186/s13601-015-0071-x

532. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. *Arch Otolaryngol Head Neck Surg*. Nov 1997;123(11):1175-9. doi:10.1001/archotol.1997.01900110025004

533. Benninger MS, Benninger RM. The impact of allergic rhinitis on sexual activity, sleep, and fatigue. *Allergy Asthma Proc*. Jul-Aug 2009;30(4):358-65. doi:10.2500/aap.2009.30.3244

534. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. Jan 1991;21(1):77-83. doi:10.1111/j.1365-2222.1991.tb00807.x

535. Husain Q, Hoehle L, Phillips K, Caradonna DS, Gray ST, Sedaghat AR. The 22-Item Sinonasal Outcome Test as a Tool for the Assessment of Quality of Life and Symptom Control in Allergic Rhinitis. *Am J Rhinol Allergy*. Mar 2020;34(2):209-216. doi:10.1177/1945892419884789

536. Calderon MA, Casale TB, Demoly P. Validation of Patient-Reported Outcomes for Clinical Trials in Allergic Rhinitis: A Systematic Review. *J Allergy Clin Immunol Pract*. May - Jun 2019;7(5):1450-1461 e6. doi:10.1016/j.jaip.2019.01.015

537. Kupczyk M, Baiardini I, Molinengo G, et al. Cross-cultural adaptation and validation of the RhinAsthma Patient Perspective (RAPP) in the Polish population. *Postepy Dermatol Alergol*. Feb 2020;37(1):97-102. doi:10.5114/ada.2020.93387

538. Werner CU, Koch L, Linde K, et al. Prospective observational study validating the German version of the Control of Allergic Rhinitis and Asthma Test (CARAT10). *NPJ Prim Care Respir Med*. Dec 4 2018;28(1):45. doi:10.1038/s41533-018-0112-8

539. Emons JA, Flokstra BM, de Jong C, et al. Use of the Control of Allergic Rhinitis and Asthma Test (CARATkids) in children and adolescents: Validation in Dutch. *Pediatr Allergy Immunol*. Mar 2017;28(2):185-190. doi:10.1111/pai.12678

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	-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

				room only, n=20		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 impregnated bedding, n=20 -Adults with AR and placebo bedding, n=20	-HDM (Der p 1) concentration -Symptom scores -QOL scores -Use of reliever medication	-No difference in HDM levels between intervention and placebo bedding -Differences in secondary outcome measures between intervention and placebo not significant
Stillerman et al[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	-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

				bedding		
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	Enviracare HEPA filtration associated with improved particulate counts and symptom/medication

					treatment	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	2017	1	SR of RCTs	Home group	-Allergic and respiratory	Supported effectiveness of

al[19]				interventions: -Education-based methods -Physical methods -Combination of both Interventions, also included control measures for multiple allergens (HDM, CR, cat, dog)	symptoms (cough, daytime symptoms, wheeze, nighttime symptoms) -Lung function -Medication use -Urgent care use for respiratory symptoms	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,	No direct clinical endpoints	-Professional extermination treatments reduced

				sodium hypochlorite -Control homes: no cleaning, extermination, or bleach solution		CR numbers and reduced median allergen levels by 80-90% -Cleaning solution did not add any improvements -Unclear if this level of reduction is sufficient to have clinical benefits in CR-sensitized individuals
Gergen et al[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	-Cat allergen levels (airborne and settled dust) -Symptom scores -Medication	HEPA filters associated with reduced airborne, but not settled dust, cat allergen levels without effect on disease activity

				placebo	scores -Spirometry	
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 recommendations and EC	Avoidance recommendations may be impractical with high rates of sensitization, indirect 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	-Primary outcome: maximal asthma symptom days -Secondary outcomes: mouse antigen levels, spirometry	No significant difference in any outcome measure between the interventions

				management education alone	measurements	
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	Allergen sensitization, symptoms, and atopic diagnoses	Furry pet (cat, dog, rodent) ownership associated with a lower risk of sensitization to pollen

				questionnaire on pet ownership		
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	-Subjective and objective measures -TNSS	-Bilastine has similar efficacy to other second-generation oral antihistamines -Improved TNSS &

				-Cetirizine -Desloratadine	-RQLQ	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; ≥12 years old) treated with: -Desloratadine -Ebastine -Fexofenadine -Levocetirizine	-TSS -TNSS	Second-generation levocetirizine significantly improved symptom scores, especially in severe AR
Compalati et al[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:	-TSS -DNS -DES	Improvement in TSS, total 5 symptoms score, daytime nasal symptoms, and QOL

				-Levocetirizine -Loratadine		
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 -TNNSS -PNIF -Intermittent, persistent, seasonal, perennial AR	Desloratadine is well tolerated and efficacious for intermittent and persistent AR with reductions in congestion, TSS, TNSS, TNNSS, and improved QOL
Canonica et al[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:	Oral	---	Second-generation,

			ARIA, EAACI, Royal College of Paediatrics and Child Health	antihistamines		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: -PO cetirizine -PO ranitidine	-Nasal lavage fluid protein concentration -Nasal airway resistance	-Ranitidine improved nasal resistance more than cetirizine -Cetirizine decreased total protein and albumin more than ranitidine
Havas et al[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	-No difference in subjective scores -Increased secretion and sneeze count, no difference in

					-Nasal secretion weight	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	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and

					-CGTSQ-AR	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 -Placebo	TNSS	Both azelastine doses superior to 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	-RSS	Azelastine superior to placebo for improving

				-Placebo	-ESS	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 -Placebo spray + azelastine 0.5mg tablet BID	13-item symptom score	Azelastine spray showed limited benefit over placebo in patients already 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	-8-item symptom score	Azelastine superior to placebo and comparable to beclomethasone for

				BID -Placebo	-Nasal lavage -Response to methacholine challenge	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	Azelastine at least as effective as budesonide for

				-Budesonide 0.10mg spray BID	symptom score -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	SAR out of season (n=13): prednisone	Sneezes; levels of histamine,	Prednisone inhibited the late phase response to nasal

			challenge study	60mg PO daily for 2 days	TAME-esterase, kinins, PGD2, LTC4/D4, albumin in nasal lavages	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	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

				days		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	ESS; Functional Outcomes of Sleep Questionnaire; RQLQ; diary of nasal symptoms, sleep problems, daytime	Budesonide significantly improved daytime fatigue, somnolence, and quality of sleep vs placebo

				x8 weeks	fatigue	
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	1990	2	DBRCT, parallel	-Ragweed-sensitive	-Sneezing, stuffy nose, rhinorrhea, measured	Nasal symptoms, QOL, and rescue medication

al[196]			group	adults, n=60 -Aqueous BDNS 200μg BID -Aqueous BDNS 100μg as needed, up to 400μg daily	by a daily diary -QOL questionnaires -Rescue medication use (terfenadine)	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 QOL, rescue medication use	-INCS spray significantly improved FEV_1, bronchial challenge, asthma symptom scores, morning/evening peak expiratory flow, and rescue medication use -No significant changes in asthma outcomes with addition of INCS spray to orally inhaled corticosteroids
Bielory et al[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	-TNSS -TOSS -Adverse events	-Adults: TNSS and TOSS scores favored double-dose INCS -Pediatric: TNSS, no

				-5 adult studies, n=1414 -2 studies with mixed populations, n=884 -Double- vs standard-dose INCS		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, nasal resistance, eye symptoms,	-INCS had greater relief than oral antihistamines in nasal blockage, discharge, sneezing, nasal itch, postnasal drip, total nasal symptoms -No significant differences between

					global ratings	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	2015	2	DBRCT	Patients with perennial AR (6-11 years old)	Change from baseline in 24-hour	-No decrease in serum cortisol from baseline in

al[242]				treated for 6 weeks: -BDP nasal aerosol 80μg/day, n = 67 -Placebo, n=32	serum cortisol	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 -BDPNS 168μg daily	Symptom control and safety	-Appropriate symptom control in both groups -Incidence of epistaxis was 12.7% with MFNS and 9.4% for BDPNS
Tripathy et al[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, parallel group	-Children (2-5 years old) with perennial AR treated for 6 or 12 weeks -Ciclesonide 200μg daily	-Cortisol levels -Systemic exposure of ciclesonide and its active metabolite, des-CIC, examined at end of 6-week study	-Changes in plasma or urine cortisol levels with ciclesonide were not significantly different from placebo -Serum concentrations of ciclesonide and des-CIC were below the lower limit of quantification in many samples
Rosenblut	2007	2	DBRCT, parallel	-Patients with perennial AR treated for 12	Adverse events, 24-hour urine cortisol,	-Incidence of adverse events similar to

et al[227]			group	months, n=806 -FFNS 110μg -Placebo	nasal and ophthalmic examinations, electrocardiograms, clinical laboratory tests	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): -Nebulized BDP (400μg BID) -Placebo *Treatment for 4 weeks after a 2-week run-in *Inhalation via nose and mouth	-Nasal and oral FeNO -PFTs -Nasal and oral pH and IL-5 -Nasal and bronchial symptom scores	-Nasal IL-5 significantly reduced & nasal pH significantly increased with BDP -Reduction in nasal obstruction, sneezing, rhinorrhea with BDP, no change with placebo, no significant difference between groups
Camargos et al[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	Symptom scores (nasal blockage, rhinorrhea, sneezing, nasal itching, eye itching)	Depot injection was significantly more effective than placebo and intranasal preparation

				of season		
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: -Methylprednisolone IM 80mg -Placebo	-Sneezing and nose blowing during the day -Reflective symptom scores at end of day	-Marked beneficial effect of active treatment on nasal blockage lasting >4 weeks, moderate effect on eye symptoms -Effect obtained irrespective of timing of therapy -Best to administer as soon as symptoms start during the season
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	Symptom scores (rhinorrhea, congestion, ocular symptoms) at 1, 2, 4 weeks -Cortisol and glucose blood	-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

				disodium phosphate-acetate (3mg-3mg) -Methylprednisolone acetate (4 mg)	levels (n=38)	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 hyposensitization or with no previous treatment received single injection: -Methylprednisone 80mg -Betamethasone phosphate-acetate (6mg-6mg) -Dexamethasone acetate-phosphate	Patient satisfaction (none, poor, fair, good, excellent) at 2 weeks	All treatments were beneficial with no difference between them

				disodium (16mg-4mg) -Dexamethasone acetate 16mg		
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	-RQLQ -Nocturnal RQLQ	-PSE and montelukast were nearly equally effective and improved QOL scores, PNIF,

				daily	-Total symptom score -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 sustained release daily -Desloratadine 5mg daily -PSE 240mg sustained release daily	-Total symptom score (excluding nasal congestion) -Nasal congestion score	-Desloratadine-PSE provided additional benefit over individual components alone -Monotherapies were equally effective and led to improved symptom scores 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	-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

				Study protocol: 5 doses of medication BID on the 2 days before challenge, 1 dose on the morning of challenge day		
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 infection or hay fever (n=21): -Intranasal oxymetazoline -Placebo	-Inferior turbinate total volume -Middle turbinate total volume	Up to and including 12 hours post-treatment, 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	-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

				-Placebo		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	-Symptoms -QOL	-Montelukast improved symptoms and QOL compared to placebo -Montelukast was inferior

				-Placebo		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	-Symptoms	Montelukast and

				-Pseudoephedrine	-QOL -PNIF	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	-Symptoms	-Montelukast was more effective than placebo at reducing eosinophil count,

				-Loratadine -Placebo	-QOL -Peripheral 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:	Nasal symptoms	DSCG was more efficacious than placebo

				-DSCG QID, n=14 -Placebo, n=7		
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	Nasal/ocular symptoms	Levocabastine was most efficacious

				sprays each nostril QID, n=18 -DSCG 20mg/ml, 2 sprays QID, n=19 -Placebo, n=20		
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	Nasal symptoms	Flunisolide was more efficacious than DSCG

				-Flunisolide spray 25µg BID, n=38		
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):	-Symptom score -Rescue	DSCG was more efficacious than placebo

				-DSCG 4%, 6 times daily -Placebo	medication use	
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):	Sneezing	IPB resulted in increase in nasal reactivity to histamine, increase in

				-IPB 80µg QID -Placebo		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	Study groups	Clinical endpoints	Conclusions

			design			
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 -No local or intranasal treatment	-Symptom score -Oral antihistamine use -Mucociliary clearance time	Symptoms, oral antihistamine use, mucociliary clearance times significantly better in hypertonic saline group
Lin et al[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	RQLQ	After 7 days, Dead Sea saline group had clinically and statistically significant overall improvement

				spray daily -Placebo nasal saline spray TID		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	-Total 5 symptom score	After 21 days, symptom scores significantly better in the buffered

				saline spray BID -Normal saline spray BID	-Nasal cytology -Pediatric RQLQ -Pittsburgh Sleep Quality Index	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 medications for control	-Saccharin clearance time -TNSS -QOL score (Rcq-36) -Oral antihistamine use	-Over 4 weeks, greater improvement in saccharin clearance time and symptoms with buffered hypertonic saline -No significant difference in QOL or antihistamine use
Li et al[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	2012	1	SRMA	Patients with AR:	-Nasal	-Up to 7 weeks, saline irrigations improve nasal

et al[434]				-Saline irrigations -No irrigations	symptom score -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 (n=82)	-TSS -PNIF	-Loratadine-PSE improved PNIF vs placebo tablet and vs fluticasone nasal spray -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	-TSS (without nasal congestion) -Nasal congestion	Desloratadine-PSE significantly reduced TSS and nasal congestion vs desloratadine-placebo and vs PSE

				(n=598)		
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	2003	2	RCT	-Clemastine-PSE-	Major symptom	Clemastine-PSE-acetaminophen significantly

al[452]				acetaminophen -PSE-acetaminophen -Placebo (n=298)	complex score	reduced major symptom 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	1998	2	RCT	-Loratadine-PSE Qday	Total nasal and non-nasal	Loratadine-PSE daily or BID was superior to placebo in

al[470]				-Loratadine-PSE BID -Placebo (n=469)	symptom scores	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 itching, ocular itching	Cetirizine-PSE significantly improved symptoms vs cetirizine or PSE alone
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	TSS	Loratadine-PSE more effective than loratadine, PSE, or placebo in reducing TSS

				(n=435)		

LOE=level of evidence; RCT=randomized controlled trial; PSE; pseudoephedrinel TSS=total symptom score; 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	-TNSS -Rhinoconjunctivitis scores -PNIF	Desloratadine-mometasone and montelukast-mometasone superior to mometasone alone or placebo for symptom scores and QOL

				(n=95)		
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 -Nasal fluticasone -Placebo (n=100)	-Symptoms -Eosinophil count -ECP in nasal lavage	-All treatment groups superior to placebo in improving symptoms, rhinorrhea, sneezing, nasal itching scores -Groups treated with fluticasone alone or as combination therapy superior to placebo or cetirizine-montelukast for TSS, nasal congestion on waking, daily nasal congestion -Combination of cetirizine-fluticasone showed no added benefit 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	-PNIF	Cetirizine-mometasone statistically equivalent to cetirizine alone for

				-Cetirizine-montelukast -Cetirizine (n=38)	-Symptom diary	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	Symptoms	-Both reduced symptoms -LTRA-levocetirizine

				-Montelukast-fexofenadine		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	-Symptoms -Turbinate	-No difference in symptoms in children treated with combination

				-Loratadine-placebo	hypertrophy	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	-Symptoms -QOL	-Combination therapy improved symptoms and

				-Loratadine -Placebo		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	TNSS	No difference between

				-Olopatadine-FP		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	Combination therapy had superior improvement

					-FeNO	
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 -Mometasone-oxymetazoline (1 spray pn Qday) nasal spray; -Mometasone nasal spray -Oxymetazoline (2 sprays pn BID) nasal spray -Placebo	TNSS	-Combination therapy significantly more effective in improving nasal congestion than mometasone alone, oxymetazoline alone, and placebo -No dose-dependent relationship seen with oxymetazoline in combination therapy
Matreja et al[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 -Conventional medication (2 RCTs)	-Nasal symptom scores -RQLQ -Rescue medication use	Favorable effects of acupuncture on symptom scores for perennial AR, but not for seasonal AR
Roberts et al[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	-Improvement in AR symptom -Clinical	No conclusion could be made due to several methodological shortcomings and risk of

				medicine -Moxibustion in mid-summer	efficacy rate	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-	No evidence of a therapeutic effect of intranasal capsaicin in AR[542,579,580]	Mucosal irritation, burning, lacrimation,

	fibers and myelinated A-δ fibers, acting as a blocking agent of neuropeptides [577-579]		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]	*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	Gastrointestinal complaints with oral intake, nasal dryness

	-Thymoquinone may inhibit Th2 cytokines and eosinophil infiltration in airways[590]	treatment and placebo[591]	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,	None reported

		rhinorrhea, nasal obstruction[612]	
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 +/- turbinoplasty, including those with AR	Septal perforation rates	No AR patient had a septal perforation
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 &	1983	5*	Retrospective	Heterogenous case series of patients undergoing	Evaluation of normal nasal	Patients with AR reached post-

Gutierrez[624]			case series	septorhinoplasty, including those with AR	passages	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 -Acoustic rhinometry -Rhinomanometry	Nasal RFA reduced IT mucous membrane volume and may decrease subjective symptoms and nasal blockage, with only minor discomfort and side effects
Ghosh et al[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	2014	2	Prospective	-RFA turbinoplasty with	Severity/frequency of nasal	Post-operative nasal obstruction

al[641]			randomized	lateral displacement -RFA turbinoplasty alone	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	-RFA turbinoplasty provided more reduction in nasal congestion -QOL scores improved in

					-QOL	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 -Submucosal turbinoplasty alone	Nasal obstruction, sneezing, nose blowing, mouth breathing, hyposmia	Rhinorrhea severity, detection threshold, and recognition threshold significantly lower after resection of the posterior 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	2017	3	Case-control	Microdebrider IT surgery with or without	-SNOT-22	-Nasal obstruction, SNOT-22, global nasal function,

et al[702]				septoplasty in: -AR -Non-allergic rhinitis	-Nasal obstruction -Global nasal function -Nasal airflow	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	-VAS -Anterior	-Both groups experienced significant improvement in nasal obstruction, sneezing,

				lateralization -IT submucous resection	rhinomanometry -Saccharin test	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	-Rhinomanometry -Acoustic rhinometry -Mucociliary	Submucosal resection with lateral displacement of the inferior turbinate had the greatest improvement in nasal respiratory function with the lowest

				displacement -Turbinectomy	transport time -Secretory IgA -Symptoms	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 polypectomy, sinus surgery, and septoplasty (when indicated): -No further treatment -Vidian neurectomy	-VAS: nasal symptoms -TNSS -PFT, methacholine challenge	-Vidian neurectomy group had greater improvement in VAS nasal obstruction & rhinorrhea, but not sneezing or itching -TNSS was significantly improved in vidian neurectomy group 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	AR patients chose to undergo one of the	-RQLQ	-Both the neurectomy and septoplasty/turbinectomy group experienced

			trial	following: -Bilateral endoscopic vidian neurectomy -Partial inferior turbinectomy and/or septoplasty -Conservative treatment	-VAS for QOL -Patient-reported improvement in symptoms	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 -Bilateral endoscopic vidian neurectomy	-RQLQ -VAS -TASS -AQLQ -Medication scores	-Neurectomy group experienced significant improvement in RQLQ, VAS, AQLQ, and medication scores vs medical management -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:	VAS: nasal obstruction, itching, sneezing, rhinorrhea	-Both groups experienced improvement -No comparison of results between groups

				-Cold instrumentation -Laser-ablation		-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	-Symptoms (sneezing, rhinorrhea, nasal obstruction, severity), as classified by Okuda's	-Significant improvement in all symptoms -Many cytokines (e.g., IL-

				turbinectomy combined with PNN neurectomy	criteria -Cytokine levels and histopathology	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 -Resection of peripheral branches of PNN **All patients also underwent submucous inferior turbinectomy	-Subjective symptoms (rhinorrhea, sneezing, nasal obstruction) -Medication use	-All symptoms and medication scores improved in both groups -PNN trunk resection showed significantly greater improvement in medication scores, sneezing symptoms & 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	rTNSS	-Significant improvement in TNSS,

				radiofrequency neurolysis of PNN, including those with AR		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	-rTNSS	-Significant improvements in all

				cryotherapy of PNN at middle and inferior meatus, including those with AR	-NOSE -SNOT-22 -VAS for rhinorrhea, congestion -mini-RQLQ -Physician-derived CGI-I -Endoscopic images	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
	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

Category	Adjuvant	Examples and comments
		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.
	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 -Dupilumab -Placebo	Symptom scores following nasal challenge	-Dupilumab did not provide additional symptom benefit to SCIT -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	Combined symptom and medication	SCIT group had improvement in symptom

				-Placebo	scores	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	2011	3	Placebo-controlled	-Grass pollen SCIT	-Symptoms	SCIT group had improvement in symptom

al[935]			study	-Placebo	-Medication use	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 -Skin test response -FEV_1	SCIT group had improvement in symptom and medication scores
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	-Symptoms -Nasal provocation	SCIT group had reduced symptom scores

				-Placebo	-sIgE and sIgG -Basophil histamine release	
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 -Adults and children -RCTs, observational cohorts, case series	-Combined symptom-medication score -SR rate -Cutaneous testing -Provocation challenges -sIgE and sIgG	-SR rate significantly higher for rush SCIT (27-100%) -Baseline FEV_1 <80% and high skin test reactivity are predictive of SR -Premedication reduced risk of SRs with rush SCIT
Akmanlar et al[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	-Similar efficacy between rush and conventional SCIT -Significantly higher side effect score was seen in the rush SCIT group -3 had mild SRs

					testing -Bronchial provocation -sIgE and sIgG4	-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	-Skin prick test -Allergen and	Improvement in skin prick test and bronchial challenges for treatment

				active arm after 1 year)	histamine 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	SR rate and severity	Per-patient incidence of SRs was 4-fold higher in rush SCIT patients

				-Adults and children		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	Conventional and cluster SCIT have similar efficacies and no significant difference in SRs

					-Adverse reactions	
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 conventional SCIT or placebo	Not applicable	-Similar efficacy and safety of cluster SCIT vs conventional SCIT -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,	-Combined symptom-medication score -SR rate	Similar risk of SRs for cluster SCIT vs conventional SCIT

				imported fire ant -RCTs, observation cohorts, case series	-Cutaneous testing -Provocation challenges -sIgE and sIgG	
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 -SRs	Treatment group showed improvement in all categories versus placebo, 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	2020	1	SRMA	-SLIT for HDM tablet	-Symptoms	-Improved symptom (p=0.0001) and

al[986]				vs placebo in children with perennial AR -16 RCTs	-Medication use -Adverse events	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	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

				placebo -SCIT vs placebo		
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	-Symptoms	Significant benefit of SLIT over

				poly-sensitized HDM AR	-Medication use	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 -Placebo-controlled	-TNSS -Random effect MA versus placebo	SEASONAL AR: TNSS reduction (95% CI; T = number of trials) -INCS 1.38 (1.18-1.58; T39) -INCS-INAH 1.34 (1.15-1.54; T4) -INAH 0.72 (0.56-0.89; T13) -Oral AH 0.62 (0.35-0.90; T18) -SLIT tablets 0.57 (0.41-0.73; T4) -LTRA 0.48 (0.36-0.60; T10) PERENNIAL AR: TNSS reduction

						(95% CI; T = number of trials) -INCS 0.82 (0.66-0.97; T14) -SLIT tablet 0.65 (0.42-0.88; T3) -Oral AH 0.27 (0.11-0.42; T3)
Chen et al[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	-TEAEs -Local and systemic	-Severe asthma-related TRAE in 6/120 SLIT and 2/60 placebo -No difference in TRAE in SLIT-

				patients with (24%) and without (76%) mild asthma	allergic reactions -Asthma related TRAEs	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]			
SLIT with ragweed pollen is effective for seasonal AR	A	Yes	Moderate effect	Strong recommendation**
	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	-May be performed with SPT results only -Substantially more antigen needed for

	dilutions -Need injection supplies	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 -High dose grass patches, n=33	-Symptoms -Medication use -SPT -CPT	-Symptoms improved only in highest dose group -No difference in medication use, SPT, or CPT -Local reactions common -Systemic reactions occurred in 8.3%
Agostinis et al[1082]	2010	2	DBRCT	Children, 12 weekly patches kept on for 24 hours:	-Symptoms -Antihistamine use	-No difference in skin wheal size at study end -Treatment group had less

				-Grass patches, n=15 -Placebo patches, n=15	-Skin test wheal size	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	-Total nasal symptom score -NPT -Serum IgG4/IgE level	-Improvement in symptoms -Reduction in nasal reactivity -Increased IgG4 level -Transient increase in IgE

				adsorbed, birch- or grass-pollen vaccine -Placebo	-Rescue medication use -Adverse events	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	-CSMS -Global seasonal assessment	ILIT produced immunological changes but no improvement in symptoms

				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	-RQLQ	
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 -54 subcutaneous injections over 3 years (cumulative dose of 4,031,540 SQU).	-Seasonal allergic symptoms by VAS -Adverse events -Safety of injections -Rescue medication use -SPT -Grass-specific IgE levels	ILIT enhanced safety and efficacy of immunotherapy and reduced treatment time from 3 years to 8 weeks

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]

REFERENCES

1. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. *Allergy*. Feb 2012;67(2):158-65. doi:10.1111/j.1398-9995.2011.02752.x

2. International Consensus Report on the diagnosis and management of rhinitis. International Rhinitis Management Working Group. *Allergy*. 1994;49(19 Suppl):1-34.

3. Mackay IS, Durham SR. ABC of allergies. Perennial rhinitis. *BMJ*. Mar 21 1998;316(7135):917-20. doi:10.1136/bmj.316.7135.917

4. Woodcock A, Custovic A. ABC of allergies. Avoiding exposure to indoor allergens. *BMJ*. Apr 4 1998;316(7137):1075-8. doi:10.1136/bmj.316.7137.1075

5. Krouse HJ. Environmental controls and avoidance measures. *Int Forum Allergy Rhinol*. Sep 2014;4 Suppl 2:S32-4. doi:10.1002/alr.21383

6. Ghazala L, Schmid F, Helbling A, Pichler WJ, Pichler CE. Efficacy of house dust mite and allergen impermeable encasisgs in patients with house dust mite allergy [German]. *Allergologie*. 2004;27:26-34.

7. Kniest FM, Wolfs BJ, Vos H, et al. Mechanisms and patient compliance of dust-mite avoidance regimens in dwellings of mite-allergic rhinitic patients. *Clin Exp Allergy*. Jul 1992;22(7):681-9. doi:10.1111/j.1365-2222.1992.tb00191.x

8. Moon JS, Choi SO. Environmental controls in reducing house dust mites and nasal symptoms in patients with allergic rhinitis. *Yonsei Med J*. Jun 1999;40(3):238-43. doi:10.3349/ymj.1999.40.3.238

9. Reisman RE, Mauriello PM, Davis GB, Georgitis JW, DeMasi JM. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma. *J Allergy Clin Immunol*. Jun 1990;85(6):1050-7. doi:10.1016/0091-6749(90)90050-e

10. Terreehorst I, Hak E, Oosting AJ, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med*. Jul 17 2003;349(3):237-46. doi:10.1056/NEJMoa023171

11. Berings M, Jult A, Vermeulen H, et al. Probiotics-impregnated bedding covers for house dust mite allergic rhinitis: A pilot randomized clinical trial. *Clin Exp Allergy*. Aug 2017;47(8):1092-1096. doi:10.1111/cea.12937

12. Jeon YH, Lee YJ, Sohn MH, Lee HR. Effects of Vacuuming Mattresses on Allergic Rhinitis Symptoms in Children. *Allergy Asthma Immunol Res*. Sep 2019;11(5):655-663. doi:10.4168/aair.2019.11.5.655

13. Antonicelli L, Bilo MB, Pucci S, Schou C, Bonifazi F. Efficacy of an air-cleaning device equipped with a high efficiency particulate air filter in house dust mite respiratory allergy. *Allergy*. Nov 1991;46(8):594-600. doi:10.1111/j.1398-9995.1991.tb00629.x

14. Geller-Bernstein C, Pibourdin JM, Dornelas A, Fondarai J. Efficacy of the acaricide: acardust for the prevention of asthma and rhinitis due to dust mite allergy, in children. *Allerg Immunol (Paris)*. May 1995;27(5):147-54.

15. Chen M, Wu Y, Yuan S, et al. Allergic Rhinitis Improvement in Asthmatic Children After Using Acaricidal Bait: A Randomized, Double-Blind, Cross-Placebo Study. *Front Pediatr*. 2021;9:709139. doi:10.3389/fped.2021.709139

16. Sheikh A, Hurwitz B, Nurmatov U, van Schayck CP. House dust mite avoidance measures for perennial allergic rhinitis. *Cochrane Database Syst Rev*. 2010;4

17. Stillerman A, Nachtsheim C, Li W, Albrecht M, Waldman J. Efficacy of a novel air filtration pillow for avoidance of perennial allergens in symptomatic adults. *Ann Allergy Asthma Immunol*. May 2010;104(5):440-9. doi:10.1016/j.anai.2010.03.006

18. Brehler R, Kniest F. Encasing study in mite-allergic patients: one-year, double-blind placebo and environment-controlled investigation. *Allergy Clin Immunol Inter*. 2006;18:15-19.

19. Le Cann P, Paulus H, Glorennec P, Le Bot B, Frain S, Gangneux JP. Home Environmental Interventions for the Prevention or Control of Allergic and Respiratory Diseases: What Really Works. *J Allergy Clin Immunol Pract*. Jan - Feb 2017;5(1):66-79. doi:10.1016/j.jaip.2016.07.011

20. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med*. May 8 1997;336(19):1356-63. doi:10.1056/NEJM199705083361904

21. Chew GL. Assessment of environmental cockroach allergen exposure. *Curr Allergy Asthma Rep*. Oct 2012;12(5):456-64. doi:10.1007/s11882-012-0287-y

22. Sever ML, Arbes SJ, Jr., Gore JC, et al. Cockroach allergen reduction by cockroach control alone in low-income urban homes: a randomized control trial. *J Allergy Clin Immunol*. Oct 2007;120(4):849-55. doi:10.1016/j.jaci.2007.07.003

23. McConnell R, Milam J, Richardson J, et al. Educational intervention to control cockroach allergen exposure in the homes of hispanic children in Los Angeles: results of the La Casa study. *Clin Exp Allergy*. Apr 2005;35(4):426-33. doi:10.1111/j.1365-2222.2005.02196.x

24. Arbes SJ, Jr., Sever M, Mehta J, et al. Abatement of cockroach allergens (Bla g 1 and Bla g 2) in low-income, urban housing: month 12 continuation results. *J Allergy Clin Immunol*. Jan 2004;113(1):109-14. doi:10.1016/j.jaci.2003.10.042

25. McConnell R, Jones C, Milam J, et al. Cockroach counts and house dust allergen concentrations after professional cockroach control and cleaning. *Ann Allergy Asthma Immunol*. Dec 2003;91(6):546-52. doi:10.1016/S1081-1206(10)61532-3

26. Wood RA, Eggleston PA, Rand C, Nixon WJ, Kanchanaraksa S. Cockroach allergen abatement with extermination and sodium hypochlorite cleaning in inner-city homes. *Ann Allergy Asthma Immunol*. Jul 2001;87(1):60-4. doi:10.1016/S1081-1206(10)62324-1

27. Gergen PJ, Mortimer KM, Eggleston PA, et al. Results of the National Cooperative Inner-City Asthma Study (NCICAS) environmental intervention to reduce cockroach allergen exposure in inner-city homes. *J Allergy Clin Immunol*. Mar 1999;103(3 Pt 1):501-6. doi:10.1016/s0091-6749(99)70477-x

28. Eggleston PA, Wood RA, Rand C, Nixon WJ, Chen PH, Lukk P. Removal of cockroach allergen from inner-city homes. *J Allergy Clin Immunol*. Oct 1999;104(4 Pt 1):842-6. doi:10.1016/s0091-6749(99)70296-4

29. Williams LW, Reinfried P, Brenner RJ. Cockroach extermination does not rapidly reduce allergen in settled dust. *J Allergy Clin Immunol*. Sep 1999;104(3 Pt 1):702-3. doi:10.1016/s0091-6749(99)70346-5

30. Wang C, Eiden AL, Cooper R, Zha C, Wang D, Hamilton RG. Abatement of cockroach allergens by effective cockroach management in apartments. *J Allergy Clin Immunol Pract*. Nov - Dec 2020;8(10):3608-3609. doi:10.1016/j.jaip.2020.06.040

31. Eggleston PA, Butz A, Rand C, et al. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Ann Allergy Asthma Immunol*. Dec 2005;95(6):518-24. doi:10.1016/S1081-1206(10)61012-5

32. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. Sep 9 2004;351(11):1068-80. doi:10.1056/NEJMoa032097

33. Sever ML, Salo PM, Haynes AK, Zeldin DC. Inner-city environments and mitigation of cockroach allergen. *Am J Prev Med*. Aug 2011;41(2 Suppl 1):S55-6. doi:10.1016/j.amepre.2011.05.007

34. Sanchez J, Diez S, Cardona R. Pet avoidance in allergy cases: Is it possible to implement it? *Biomedica*. Jul-Sep 2015;35(3):357-62. doi:10.7705/biomedica.v35i3.2634

35. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). *Allergy*. Sep 2005;60(9):1112-5. doi:10.1111/j.1398-9995.2005.00934.x

36. Portnoy J, Kennedy K, Sublett J, et al. Environmental assessment and exposure control: a practice parameter--furry animals. *Ann Allergy Asthma Immunol*. Apr 2012;108(4):223 e1-15. doi:10.1016/j.anai.2012.02.015

37. Arshad SH. Environmental control for secondary prevention of asthma. *Clin Exp Allergy*. Jan 2010;40(1):2-4. doi:10.1111/j.1365-2222.2009.03407.x

38. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma. 2007.

39. Bjornsdottir US, Jakobinudottir S, Runarsdottir V, Juliusson S. The effect of reducing levels of cat allergen (Fel d 1) on clinical symptoms in patients with cat allergy. *Ann Allergy Asthma Immunol*. Aug 2003;91(2):189-94. doi:10.1016/s1081-1206(10)62176-x

40. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med*. Jul 1998;158(1):115-20. doi:10.1164/ajrccm.158.1.9712110

41. Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1. *J Allergy Clin Immunol*. Sep 1997;100(3):307-12. doi:10.1016/s0091-6749(97)70242-2

42. Hodson T, Custovic A, Simpson A, Chapman M, Woodcock A, Green R. Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. *J Allergy Clin Immunol*. Apr 1999;103(4):581-5. doi:10.1016/s0091-6749(99)70227-7

43. Matsui EC, Simons E, Rand C, et al. Airborne mouse allergen in the homes of inner-city children with asthma. *J Allergy Clin Immunol*. Feb 2005;115(2):358-63. doi:10.1016/j.jaci.2004.11.007

44. Grant T, Phipatanakul W, Perzanowski M, et al. Reduction in mouse allergen exposure is associated with greater lung function growth. *J Allergy Clin Immunol*. Feb 2020;145(2):646-653 e1. doi:10.1016/j.jaci.2019.08.043

45. Pongracic JA, Visness CM, Gruchalla RS, Evans R, 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. *Ann Allergy Asthma Immunol*. Jul 2008;101(1):35-41. doi:10.1016/S1081-1206(10)60832-0

46. Phipatanakul W, Cronin B, Wood RA, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Ann Allergy Asthma Immunol*. Apr 2004;92(4):420-5. doi:10.1016/S1081-1206(10)61777-2

47. DiMango E, Serebrisky D, Narula S, et al. Individualized Household Allergen Intervention Lowers Allergen Level But Not Asthma Medication Use: A Randomized Controlled Trial. *J Allergy Clin Immunol Pract*. Jul-Aug 2016;4(4):671-679 e4. doi:10.1016/j.jaip.2016.01.016

48. Phipatanakul W, Matsui E, Portnoy J, et al. Environmental assessment and exposure reduction of rodents: a practice parameter. *Ann Allergy Asthma Immunol*. Dec 2012;109(6):375-87. doi:10.1016/j.anai.2012.09.019

49. Lodrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One*. 2012;7(8):e43214. doi:10.1371/journal.pone.0043214

50. Kellberger J, Dressel H, Vogelberg C, et al. Prediction of the incidence and persistence of allergic rhinitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol*. Feb 2012;129(2):397-402, 402 e1-3. doi:10.1016/j.jaci.2011.08.016

51. Jacobs TS, Forno E, Brehm JM, et al. Mouse allergen exposure and decreased risk of allergic rhinitis in school-aged children. *Ann Allergy Asthma Immunol*. Dec 2014;113(6):614-618 e2. doi:10.1016/j.anai.2014.09.007

52. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NA, van Vliet P. Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy*. Mar 2002;32(3):361-6. doi:10.1046/j.1365-2222.2002.01254.x

53. Sakaguchi M, Inouye S, Miyazawa H, Kamimura H, Kimura M, Yamazaki S. Evaluation of dust respirators for elimination of mouse aeroallergens. *Lab Anim Sci*. Jan 1989;39(1):63-6.

54. Bertelsen RJ, Carlsen KC, Granum B, et al. Do allergic families avoid keeping furry pets? *Indoor Air*. Jun 2010;20(3):187-95. doi:10.1111/j.1600-0668.2009.00640.x

55. Curtin-Brosnan J, Saams J, Breysse P, Diette G, Bradley H, Matsui E. Relationship between cat and mouse allergen levels in the homes of inner city children with asthma. *J Allergy Clin Immunol*. 2009;123:64.

56. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. Aug 2008;122(2 Suppl):S1-84. doi:10.1016/j.jaci.2008.06.003

57. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. Apr 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

58. Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol*. Dec 2017;119(6):489-511 e41. doi:10.1016/j.anai.2017.08.012

59. Reisacher WR. Allergy treatment: environmental control strategies. *Otolaryngol Clin North Am*. Jun 2011;44(3):711-25, x. doi:10.1016/j.otc.2011.03.019

60. Ferguson BJ. Environmental controls of allergies. *Otolaryngol Clin North Am*. Apr 2008;41(2):411-7, viii-ix. doi:10.1016/j.otc.2007.11.006

61. Bergmann KC, Berger M, Klimek L, et al. Nonpharmacological measures to prevent allergic symptoms in pollen allergy: A critical review. *Allergol Select*. 2021;5:349-360. doi:10.5414/ALX02294E

62. Li L, Zhang L, Mo JH, et al. Efficacy of indoor air purification in the treatment of Artemisia pollen-allergic rhinitis: A randomised, double-blind, clinical controlled trial. *Clin Otolaryngol*. May 2020;45(3):394-401. doi:10.1111/coa.13514

63. Green BJ, Levetin E, Horner WE, Codina R, Barnes CS, Filley WV. Landscape Plant Selection Criteria for the Allergic Patient. *J Allergy Clin Immunol Pract*. Nov - Dec 2018;6(6):1869-1876. doi:10.1016/j.jaip.2018.05.020

64. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy*. Feb 2000;55(2):116-34. doi:10.1034/j.1398-9995.2000.00526.x

65. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. Oct 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

66. Comert S, Karakaya G, Kalyoncu AF. Wraparound eyeglasses improve symptoms and quality of life in patients with seasonal allergic rhinoconjunctivitis. *Int Forum Allergy Rhinol*. Jul 2016;6(7):722-30. doi:10.1002/alr.21737

67. Kenney P, Hilberg O, Laursen AC, Peel RG, Sigsgaard T. Preventive effect of nasal filters on allergic rhinitis: A randomized, double-blind, placebo-controlled crossover park study. *J Allergy Clin Immunol*. Dec 2015;136(6):1566-1572 e5. doi:10.1016/j.jaci.2015.05.015

68. Chen X, Deng C, Mi J, et al. Barrier Protection Measures for the Management of Allergic Rhinitis: A Systematic Review and Meta-analysis. *Am J Rhinol Allergy*. Jul 2020;34(4):564-572. doi:10.1177/1945892420912370

69. Chen QY, Li L, Zhang L, et al. Efficacy of indoor air purification in treating Artemisia (mugwort) pollen allergic rhinitis: study protocol for a randomised controlled trial. *BMC Public Health*. Jul 6 2018;18(1):841. doi:10.1186/s12889-018-5678-0

70. Gautrin D, Desrosiers M, Castano R. Occupational rhinitis. *Curr Opin Allergy Clin Immunol*. Apr 2006;6(2):77-84. doi:10.1097/01.all.0000216848.87699.38

71. Moscato G, Vandenplas O, Van Wijk RG, et al. EAACI position paper on occupational rhinitis. *Respir Res*. Mar 3 2009;10:16. doi:10.1186/1465-9921-10-16

72. Hox V, Steelant B, Fokkens W, Nemery B, Hellings PW. Occupational upper airway disease: how work affects the nose. *Allergy*. Mar 2014;69(3):282-91. doi:10.1111/all.12347

73. Vandenplas O, Hox V, Bernstein D. Occupational Rhinitis. *J Allergy Clin Immunol Pract*. Nov - Dec 2020;8(10):3311-3321. doi:10.1016/j.jaip.2020.06.047

74. Castano R, Trudeau C, Castellanos L, Malo JL. Prospective outcome assessment of occupational rhinitis after removal from exposure. *J Occup Environ Med*. May 2013;55(5):579-85. doi:10.1097/JOM.0b013e318289ee17

75. Airaksinen LK, Luukkonen RA, Lindstrom I, Lauerma AI, Toskala EM. Long-term exposure and health-related quality of life among patients with occupational rhinitis. *J Occup Environ Med*. Nov 2009;51(11):1288-97. doi:10.1097/JOM.0b013e3181b9b242

76. Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. *J Allergy Clin Immunol*. Jan 2002;109(1):125-30. doi:10.1067/mai.2002.120760

77. Merget R, Schulte A, Gebler A, et al. Outcome of occupational asthma due to platinum salts after transferral to low-exposure areas. *Int Arch Occup Environ Health*. Jan 1999;72(1):33-9. doi:10.1007/s004200050331

78. Taivainen AI, Tukiainen HO, Terho EO, Husman KR. Powered dust respirator helmets in the prevention of occupational asthma among farmers. *Scand J Work Environ Health*. Dec 1998;24(6):503-7. doi:10.5271/sjweh.375

79. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs*. 2005;65(3):341-84. doi:10.2165/00003495-200565030-00004

80. Lieberman P. The basics of histamine biology. *Ann Allergy Asthma Immunol*. Feb 2011;106(2 Suppl):S2-5. doi:10.1016/j.anai.2010.08.005

81. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: Newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy Asthma Clin Immunol*. 2019;15:61. doi:10.1186/s13223-019-0375-9

82. Sanchez-Borges M, Ansotegui IJ. Second generation antihistamines: an update. *Curr Opin Allergy Clin Immunol*. Aug 2019;19(4):358-364. doi:10.1097/ACI.0000000000000556

83. Slavin RG. Treating rhinitis in the older population: special considerations. *Allergy Asthma Clin Immunol*. Dec 1 2009;5(1):9. doi:10.1186/1710-1492-5-9

84. Bousquet J, Bindslev-Jensen C, Canonica GW, et al. The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety and pharmacology of desloratadine. *Allergy*. 2004;59 Suppl 77:4-16. doi:10.1111/j.1398-9995.2004.00577.x

85. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2015;152(1 Suppl):S1-43. doi:10.1177/0194599814561600

86. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. Sep 2010;126(3):466-76. doi:10.1016/j.jaci.2010.06.047

87. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. Oct 2017;140(4):950-958. doi:10.1016/j.jaci.2017.03.050

88. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. Jan 2020;145(1):70-80 e3. doi:10.1016/j.jaci.2019.06.049

89. Kardas G, Panek M, Kuna P, Cieszynski J, Kardas P. Primary Non-Adherence to Antihistamines-Conclusions From E-Prescription Pilot Data in Poland. *Front Pharmacol*. 2020;11:783. doi:10.3389/fphar.2020.00783

90. Blaiss MS. Cost-effectiveness of H1-antihistamines. *Clin Allergy Immunol*. 2002;17:319-36.

91. Miligkos M, Dakoutrou M, Statha E, et al. Newer-generation antihistamines and the risk of adverse events in children: A systematic review. *Pediatr Allergy Immunol*. Oct 2021;32(7):1533-1558. doi:10.1111/pai.13522

92. Zhang K, Li AR, Miglani A, Nguyen SA, Schlosser RJ. Effect of Medical Therapy in Allergic Rhinitis: A Systematic Review and Meta-Analysis. *Am J Rhinol Allergy*. Mar 2022;36(2):269-280. doi:10.1177/19458924211041438

93. Sastre J. Ebastine in the Treatment of Allergic Rhinitis and Urticaria: 30 Years of Clinical Studies and Real-World Experience. *J Investig Allergol Clin Immunol*. 2020;30(3):156-168. doi:10.18176/jiaci.0401

94. Mullol J, Bousquet J, Bachert C, et al. Update on rupatadine in the management of allergic disorders. *Allergy*. Jan 2015;70 Suppl 100:1-24. doi:10.1111/all.12531

95. Ridolo E, Montagni M, Bonzano L, Incorvaia C, Canonica GW. Bilastine: new insight into antihistamine treatment. *Clin Mol Allergy*. 2015;13(1):1. doi:10.1186/s12948-015-0008-x

96. Compalati E, Canonica GW. Efficacy and safety of rupatadine for allergic rhino-conjunctivitis: a systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. *Curr Med Res Opin*. Nov 2013;29(11):1539-51. doi:10.1185/03007995.2013.822855

97. Mosges R, Konig V, Koberlein J. The effectiveness of modern antihistamines for treatment of allergic rhinitis - an IPD meta-analysis of 140,853 patients. *Allergol Int*. Jun 2013;62(2):215-22. doi:10.2332/allergolint.12-OA-0486

98. Compalati E, Baena-Cagnani R, Penagos M, et al. Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. *Int Arch Allergy Immunol*. 2011;156(1):1-15. doi:10.1159/000321896

99. Ferrer M. Pharmacokinetic evaluation of levocetirizine. *Expert Opin Drug Metab Toxicol*. Aug 2011;7(8):1035-47. doi:10.1517/17425255.2011.590131

100. Mosges R, Konig V, Koberlein J. The effectiveness of levocetirizine in comparison with loratadine in treatment of allergic rhinitis--a meta-analysis. *Allergol Int*. Dec 2011;60(4):541-6. doi:10.2332/allergolint.10-OA-0300

101. Bachert C. A review of the efficacy of desloratadine, fexofenadine, and levocetirizine in the treatment of nasal congestion in patients with allergic rhinitis. *Clin Ther*. May 2009;31(5):921-44. doi:10.1016/j.clinthera.2009.05.017

102. Katiyar S, Prakash S. Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis. *Prim Care Respir J*. Jun 2009;18(2):57-68. doi:10.3132/pcrj.2008.00043

103. Bachert C, van Cauwenberge P. Desloratadine treatment for intermittent and persistent allergic rhinitis: a review. *Clin Ther*. Sep 2007;29(9):1795-802. doi:10.1016/j.clinthera.2007.09.009

104. Canonica GW, Tarantini F, Compalati E, Penagos M. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy*. Apr 2007;62(4):359-66. doi:10.1111/j.1398-9995.2006.01277.x

105. Patou J, De Smedt H, van Cauwenberge P, Bachert C. Pathophysiology of nasal obstruction and meta-analysis of early and late effects of levocetirizine. *Clin Exp Allergy*. Aug 2006;36(8):972-81. doi:10.1111/j.1365-2222.2006.02544.x

106. Hore I, Georgalas C, Scadding G. Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis--a systematic review of randomized controlled trials. *Clin Exp Allergy*. Feb 2005;35(2):207-12. doi:10.1111/j.1365-2222.2005.02159.x

107. Passalacqua G, Canonica GW. A review of the evidence from comparative studies of levocetirizine and desloratadine for the symptoms of allergic rhinitis. *Clin Ther*. Jul 2005;27(7):979-92. doi:10.1016/j.clinthera.2005.07.011

108. Greisner WA, 3rd. Onset of action for the relief of allergic rhinitis symptoms with second-generation antihistamines. *Allergy Asthma Proc*. Mar-Apr 2004;25(2):81-3.

109. Limon L, Kockler DR. Desloratadine: a nonsedating antihistamine. *Ann Pharmacother*. Feb 2003;37(2):237-46; quiz 313-6. doi:10.1177/106002800303700216

110. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. *J Allergy Clin Immunol*. Jul 2019;144(1):135-143 e6. doi:10.1016/j.jaci.2019.01.053

111. Scadding GK. Optimal management of allergic rhinitis. *Arch Dis Child*. Jun 2015;100(6):576-82. doi:10.1136/archdischild-2014-306300

112. Penston J, Wormsley KG. Adverse reactions and interactions with H2-receptor antagonists. *Med Toxicol*. May-Jun 1986;1(3):192-216. doi:10.1007/BF03259837

113. Wood-Baker R, Lau L, Howarth PH. Histamine and the nasal vasculature: the influence of H1 and H2-histamine receptor antagonism. *Clin Otolaryngol Allied Sci*. Aug 1996;21(4):348-52. doi:10.1111/j.1365-2273.1996.tb01085.x

114. Taylor-Clark T, Sodha R, Warner B, Foreman J. Histamine receptors that influence blockage of the normal human nasal airway. *Br J Pharmacol*. Mar 2005;144(6):867-74. doi:10.1038/sj.bjp.0706118

115. Wang D, Clement P, Smitz J. Effect of H1 and H2 antagonists on nasal symptoms and mediator release in atopic patients after nasal allergen challenge during the pollen season. *Acta Otolaryngol*. Jan 1996;116(1):91-6. doi:10.3109/00016489609137720

116. Havas TE, Cole P, Parker L, Oprysk D, Ayiomamitis A. The effects of combined H1 and H2 histamine antagonists on alterations in nasal airflow resistance induced by topical histamine provocation. *J Allergy Clin Immunol*. Nov 1986;78(5 Pt 1):856-60. doi:10.1016/0091-6749(86)90230-7

117. Juliusson S, Bende M. Effect of systemically administered H1- and H2-receptor antagonists on nasal blood flow as measured with laser Doppler flowmetry in a provoked allergic reaction. *Rhinology*. Mar 1996;34(1):24-7.

118. Brooks CD, Butler D, Metzler C. Effect of H2 blockade in the challenged allergic nose. *J Allergy Clin Immunol*. Nov 1982;70(5):373-6. doi:10.1016/0091-6749(82)90027-6

119. Carpenter GB, Bunker-Soler AL, Nelson HS. Evaluation of combined H1- and H2-receptor blocking agents in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Apr 1983;71(4):412-7. doi:10.1016/0091-6749(83)90071-4

120. Carr WW, Ratner P, Munzel U, et al. Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis. *Allergy Asthma Proc*. Nov-Dec 2012;33(6):450-8. doi:10.2500/aap.2012.33.3626

121. Kalpaklioglu AF, Kavut AB. Comparison of azelastine versus triamcinolone nasal spray in allergic and nonallergic rhinitis. *Am J Rhinol Allergy*. Jan-Feb 2010;24(1):29-33. doi:10.2500/ajra.2010.24.3423

122. Kaliner MA, Storms W, Tilles S, et al. Comparison of olopatadine 0.6% nasal spray versus fluticasone propionate 50 microg in the treatment of seasonal allergic rhinitis. *Allergy Asthma Proc*. May-Jun 2009;30(3):255-62. doi:10.2500/aap.2009.30.3232

123. Patel P, D'Andrea C, Sacks HJ. Onset of action of azelastine nasal spray compared with mometasone nasal spray and placebo in subjects with seasonal allergic rhinitis evaluated in an environmental exposure chamber. *Am J Rhinol*. Jul-Aug 2007;21(4):499-503. doi:10.2500/ajr.2007.21.3058

124. Patel D, Garadi R, Brubaker M, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients: olopatadine hydrochloride versus mometasone furoate monohydrate. *Allergy Asthma Proc*. Sep-Oct 2007;28(5):592-9. doi:10.2500/aap2007.28.3033

125. Berger W, Hampel F, Jr., Bernstein J, Shah S, Sacks H, Meltzer EO. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2006;97(3):375-81. doi:10.1016/S1081-1206(10)60804-6

126. Horak F, Zieglmayer UP, Zieglmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin*. Jan 2006;22(1):151-7. doi:10.1185/030079906X80305

127. Corren J, Storms W, Bernstein J, et al. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther*. May 2005;27(5):543-53. doi:10.1016/j.clinthera.2005.04.012

128. LaForce CF, Corren J, Wheeler WJ, Berger WE, Rhinitis Study G. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. *Ann Allergy Asthma Immunol*. Aug 2004;93(2):154-9. doi:10.1016/S1081-1206(10)61468-8

129. Berger WE, White MV, Rhinitis Study G. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol*. Aug 2003;91(2):205-11. doi:10.1016/S1081-1206(10)62179-5

130. Berlin JM, Golden SJ, Teets S, Lehman EB, Lucas T, Craig TJ. Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis. *J Am Osteopath Assoc*. Jul 2000;100(7 Suppl):S8-13.

131. Berger WE, Fineman SM, Lieberman P, Miles RM. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. Rhinitis Study Groups. *Ann Allergy Asthma Immunol*. Jun 1999;82(6):535-41. doi:10.1016/s1081-1206(10)63161-4

132. Stern MA, Wade AG, Ridout SM, Cambell LM. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. *Ann Allergy Asthma Immunol*. Oct 1998;81(4):354-8. doi:10.1016/s1081-1206(10)63128-6

133. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. Jan 2012;67(1):91-8. doi:10.1111/j.1398-9995.2011.02709.x

134. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. *Ann Allergy Asthma Immunol*. Feb 1996;76(2):181-8. doi:10.1016/S1081-1206(10)63420-5

135. Charpin D, Godard P, Garay RP, Baehre M, Herman D, Michel FB. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. *Eur Arch Otorhinolaryngol*. 1995;252(8):455-8. doi:10.1007/BF02114749

136. Pelucchi A, Chiapparino A, Mastropasqua B, Marazzini L, Hernandez A, Foresi A. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. *J Allergy Clin Immunol*. Feb 1995;95(2):515-23. doi:10.1016/s0091-6749(95)70313-6

137. Gastpar H, Nolte D, Aurich R, et al. Comparative efficacy of azelastine nasal spray and terfenadine in seasonal and perennial rhinitis. *Allergy*. Mar 1994;49(3):152-8. doi:10.1111/j.1398-9995.1994.tb00818.x

138. Meltzer EO, Weiler JM, Dockhorn RJ, Widlitz MD, Freitag JJ. Azelastine nasal spray in the management of seasonal allergic rhinitis. *Ann Allergy*. Apr 1994;72(4):354-9.

139. Passali D, Piragine F. A comparison of azelastine nasal spray and cetirizine tablets in the treatment of allergic rhinitis. *J Int Med Res*. Jan-Feb 1994;22(1):17-23. doi:10.1177/030006059402200102

140. Davies RJ, Lund VJ, Harten-Ash VJ. The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis. *Rhinology*. Dec 1993;31(4):159-64.

141. Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. *Arzneimittelforschung*. Aug 1993;43(8):909-12.

142. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratidine tablets in the treatment of seasonal allergic rhinitis. *J Int Med Res*. Sep-Oct 1993;21(5):268-75. doi:10.1177/030006059302100505

143. Gastpar H, Aurich R, Petzold U, et al. Intranasal treatment of perennial allergic rhinitis. Comparison of azelastine nasal spray and budesonide nasal aerosol. *Arzneimittelforschung*. Apr 1993;43(4):475-9.

144. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. *Int Forum Allergy Rhinol*. Jul-Aug 2011;1(4):275-9. doi:10.1002/alr.20065

145. Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. *Allergy Asthma Proc*. May-Jun 2011;32(3):213-20. doi:10.2500/aap.2011.32.3448

146. Berger WE, Ratner PH, Casale TB, Meltzer EO, Wall GM. Safety and efficacy of olopatadine hydrochloride nasal spray 0.6% in pediatric subjects with allergic rhinitis. *Allergy Asthma Proc*. Nov-Dec 2009;30(6):612-23. doi:10.2500/aap.2009.30.3298

147. Bernstein JA, Prenner B, Ferguson BJ, Portnoy J, Wheeler WJ, Sacks HJ. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*. Sep-Oct 2009;23(5):512-7. doi:10.2500/ajra.2009.23.3396

148. Shah S, Berger W, Lumry W, La Force C, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. Nov-Dec 2009;30(6):628-33. doi:10.2500/aap.2009.30.3296

149. Shah SR, Nayak A, Ratner P, Roland P, Michael Wall G. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. *Clin Ther*. Jan 2009;31(1):99-107. doi:10.1016/j.clinthera.2009.01.016

150. van Bavel J, Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. Sep-Oct 2009;30(5):512-8. doi:10.2500/aap.2009.30.3284

151. Pipkorn P, Costantini C, Reynolds C, et al. The effects of the nasal antihistamines olopatadine and azelastine in nasal allergen provocation. *Ann Allergy Asthma Immunol*. Jul 2008;101(1):82-9. doi:10.1016/S1081-1206(10)60839-3

152. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. *Ann Allergy Asthma Immunol*. Sep 2007;99(3):267-72. doi:10.1016/S1081-1206(10)60663-1

153. Hampel FC, Jr., Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCl nasal spray 0.4% and olopatadine HCl nasal spray 0.6% compared with vehicle placebo. *Allergy Asthma Proc*. May-Jun 2006;27(3):202-7. doi:10.2500/aap.2006.27.2862

154. Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Dec 2005;95(6):600-6. doi:10.1016/S1081-1206(10)61025-3

155. Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. *Ann Allergy Asthma Immunol*. Nov 2005;95(5):474-9. doi:10.1016/S1081-1206(10)61174-X

156. Saengpanich S, Assanasen P, deTineo M, Haney L, Naclerio RM, Baroody FM. Effects of intranasal azelastine on the response to nasal allergen challenge. *Laryngoscope*. Jan 2002;112(1):47-52. doi:10.1097/00005537-200201000-00009

157. Golden S, Teets SJ, Lehman EB, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Jul 2000;85(1):53-7. doi:10.1016/S1081-1206(10)62434-9

158. Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. *Int J Pediatr Otorhinolaryngol*. Feb 14 1997;39(1):1-8. doi:10.1016/S0165-5876(96)01457-7

159. Newson-Smith G, Powell M, Baehre M, Garnham SP, MacMahon MT. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. *Eur Arch Otorhinolaryngol*. 1997;254(5):236-41. doi:10.1007/BF00874095

160. Weiler JM, Meltzer EO. Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Oct 1997;79(4):327-32. doi:10.1016/S1081-1206(10)63023-2

161. Ratner PH, Findlay SR, Hampel F, Jr., van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *J Allergy Clin Immunol*. Nov 1994;94(5):818-25. doi:10.1016/0091-6749(94)90148-1

162. Han D, Chen L, Cheng L, et al. A multicenter randomized double-blind 2-week comparison study of azelastine nasal spray 0.1% versus levocabastine nasal spray 0.05% in patients with moderate-to-severe allergic rhinitis. *ORL J Otorhinolaryngol Relat Spec*. 2011;73(5):260-5. doi:10.1159/000330269

163. Meltzer EO, Garadi R, Laforce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. *Allergy Asthma Proc*. Nov-Dec 2008;29(6):659-68. doi:10.2500/aap.2008.29.3181

164. Falser N, Wober W, Rahlfs VW, Baehre M. Comparative efficacy and safety of azelastine and levocabastine nasal sprays in patients with seasonal allergic rhinitis. *Arzneimittelforschung*. 2001;51(5):387-93. doi:10.1055/s-0031-1300052

165. Pipkorn U, Proud D, Lichtenstein LM, et al. Effect of short-term systemic glucocorticoid treatment on human nasal mediator release after antigen challenge. *J Clin Invest*. Oct 1987;80(4):957-61. doi:10.1172/JCI113188

166. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. *Am Rev Respir Dis*. Aug 1988;138(2):406-12. doi:10.1164/ajrccm/138.2.406

167. Bascom R, Pipkorn U, Proud D, et al. Major basic protein and eosinophil-derived neurotoxin concentrations in nasal-lavage fluid after antigen challenge: effect of systemic corticosteroids and relationship to eosinophil influx. *J Allergy Clin Immunol*. Sep 1989;84(3):338-46. doi:10.1016/0091-6749(89)90418-1

168. Schwartz E, Levin L, Leibowitz H, et al. Oral cortisone therapy in ragweed hay fever. *J Allergy*. Jan 1952;23(1):32-8. doi:10.1016/0021-8707(52)90071-3

169. Schiller IW, Lowell FC. Oral cortisone in the treatment of hay fever. *J Allergy*. Jul 1953;24(4):297-301. doi:10.1016/0021-8707(53)90172-5

170. Schwartz E. Oral hydrocortisone therapy in bronchial asthma and bay fever. *J Allergy*. Mar 1954;25(2):112-9. doi:10.1016/0021-8707(54)90149-5

171. Brooks CD, Karl KJ, Francom SF. Oral methylprednisolone acetate (Medrol Tablets) for seasonal rhinitis: examination of dose and symptom response. *J Clin Pharmacol*. Sep 1993;33(9):816-22. doi:10.1002/j.1552-4604.1993.tb01957.x

172. Snyman JR, Potter PC, Groenewald M, Levin J, Claricort Study G. Effect of betamethasone-loratadine combination therapy on severe exacerbations of allergic rhinitis : a randomised, controlled trial. *Clin Drug Investig*. 2004;24(5):265-74. doi:10.2165/00044011-200424050-00003

173. Kwaselow A, McLean J, Busse W, et al. A comparison of intranasal and oral flunisolide in the therapy of allergic rhinitis. Evidence for a topical effect. *Allergy*. Jul 1985;40(5):363-7. doi:10.1111/j.1398-9995.1985.tb00248.x

174. Karaki M, Akiyama K, Mori N. Efficacy of intranasal steroid spray (mometasone furoate) on treatment of patients with seasonal allergic rhinitis: comparison with oral corticosteroids. *Auris Nasus Larynx*. Jun 2013;40(3):277-81. doi:10.1016/j.anl.2012.09.004

175. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol*. Mar 1988;81(3):580-9.

176. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med*. Jun 11 1987;316(24):1506-10. doi:10.1056/NEJM198706113162403

177. Erin EM, Leaker BR, Zacharasiewicz AS, et al. Single dose topical corticosteroid inhibits IL-5 and IL-13 in nasal lavage following grass pollen challenge. *Allergy*. Dec 2005;60(12):1524-9. doi:10.1111/j.1398-9995.2005.00928.x

178. Meltzer EO, Jalowayski AA, Orgel HA, Harris AG. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. *J Allergy Clin Immunol*. Jul 1998;102(1):39-49. doi:10.1016/s0091-6749(98)70053-3

179. Xie Y, Ju X, Beaudin S, et al. Effect of intranasal corticosteroid treatment on allergen-induced changes in group 2 innate lymphoid cells in allergic rhinitis with mild asthma. *Allergy*. Sep 2021;76(9):2797-2808. doi:10.1111/all.14835

180. Baroody FM, Cruz AA, Lichtenstein LM, Kagey-Sobotka A, Proud D, Naclerio RM. Intranasal beclomethasone inhibits antigen-induced nasal hyperresponsiveness to histamine. *J Allergy Clin Immunol*. Sep 1992;90(3 Pt 1):373-6. doi:10.1016/s0091-6749(05)80017-x

181. Meyer P, Andersson M, Persson CG, Greiff L. Steroid-sensitive indices of airway inflammation in children with seasonal allergic rhinitis. *Pediatr Allergy Immunol*. Feb 2003;14(1):60-5. doi:10.1034/j.1399-3038.2003.02102.x

182. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy*. Oct 2008;63(10):1280-91. doi:10.1111/j.1398-9995.2008.01808.x

183. Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy*. Feb 2011;41(2):160-70. doi:10.1111/j.1365-2222.2010.03654.x

184. Urdaneta E, Tunceli K, Gates D. Effect of mometasone furoate nasal spray on moderate-to-severe nasal congestion in seasonal allergic rhinitis: A responder analysis. *Allergy Asthma Proc*. May 1 2019;40(3):173-179. doi:10.2500/aap.2019.40.4214

185. Herman H. Once-daily administration of intranasal corticosteroids for allergic rhinitis: a comparative review of efficacy, safety, patient preference, and cost. *Am J Rhinol*. Jan-Feb 2007;21(1):70-9. doi:10.2500/ajr.2007.21.2896

186. Rachelefsky G, Farrar JR. A control model to evaluate pharmacotherapy for allergic rhinitis in children. *JAMA Pediatr*. Apr 2013;167(4):380-6. doi:10.1001/jamapediatrics.2013.623

187. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol*. May 1998;101(5):633-7. doi:10.1016/s0091-6749(98)70171-x

188. Craig TJ, Mende C, Hughes K, Kakumanu S, Lehman EB, Chinchilli V. The effect of topical nasal fluticasone on objective sleep testing and the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Allergy Asthma Proc*. Jan-Feb 2003;24(1):53-8.

189. Hughes K, Glass C, Ripchinski M, et al. Efficacy of the topical nasal steroid budesonide on improving sleep and daytime somnolence in patients with perennial allergic rhinitis. *Allergy*. May 2003;58(5):380-5. doi:10.1034/j.1398-9995.2003.00093.x

190. Meltzer EO, Munafo DA, Chung W, Gopalan G, Varghese ST. Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep. *Ann Allergy Asthma Immunol*. Jul 2010;105(1):65-74. doi:10.1016/j.anai.2010.04.020

191. Yamada T, Yamamoto H, Kubo S, et al. Efficacy of mometasone furoate nasal spray for nasal symptoms, quality of life, rhinitis-disturbed sleep, and nasal nitric oxide in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Mar-Apr 2012;33(2):e9-16. doi:10.2500/aap.2012.33.3509

192. Day JH, Briscoe MP, Rafeiro E, Ellis AK, Pettersson E, Akerlund A. Onset of action of intranasal budesonide (Rhinocort aqua) in seasonal allergic rhinitis studied in a controlled exposure model. *J Allergy Clin Immunol*. Mar 2000;105(3):489-94. doi:10.1067/mai.2000.104550

193. Fokkens WJ, Cserhati E, dos Santos JM, et al. Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. *Ann Allergy Asthma Immunol*. Sep 2002;89(3):279-84. doi:10.1016/s1081-1206(10)61955-2

194. Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Jun 2007;119(6):1430-7. doi:10.1016/j.jaci.2007.02.022

195. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. Dec 1998;102(6 Pt 1):902-8. doi:10.1016/s0091-6749(98)70326-4

196. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Sep 1990;86(3 Pt 1):380-6. doi:10.1016/s0091-6749(05)80101-0

197. Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. *J Allergy Clin Immunol*. Jul 1993;92(1 Pt 1):66-72. doi:10.1016/0091-6749(93)90039-i

198. Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Apr 2000;105(4):732-8. doi:10.1067/mai.2000.105225

199. Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). *Ann Allergy Asthma Immunol*. Jul 2003;91(1):44-8. doi:10.1016/S1081-1206(10)62057-1

200. Thongngarm T, Wongsa C, Phinyo P, Assanasen P, Tantilipikorn P, Sompornrattanaphan M. As-Needed Versus Regular Use of Fluticasone Furoate Nasal Spray in Patients with Moderate to Severe, Persistent, Perennial Allergic Rhinitis: A Randomized Controlled Trial. *J Allergy Clin Immunol Pract*. Mar 2021;9(3):1365-1373 e6. doi:10.1016/j.jaip.2020.09.057

201. DeWester J, Philpot EE, Westlund RE, Cook CK, Rickard KA. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. *Allergy Asthma Proc*. Sep-Oct 2003;24(5):331-7.

202. Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. *Allergy*. May 2011;66(5):686-93. doi:10.1111/j.1398-9995.2010.02543.x

203. Ratner P, Van Bavel J, Mohar D, et al. Efficacy of daily intranasal fluticasone propionate on ocular symptoms associated with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Feb 2015;114(2):141-7. doi:10.1016/j.anai.2014.11.012

204. Bielory L, Gross GN, Letierce A, Melas-Melt L, Lucio L. Ocular symptoms improvement from intranasal triamcinolone compared with placebo and intranasal fluticasone propionate: A meta-analysis. *Ann Allergy Asthma Immunol*. Jun 2020;124(6):616-621 e3. doi:10.1016/j.anai.2020.01.012

205. Baroody FM, Shenaq D, DeTineo M, Wang J, Naclerio RM. Fluticasone furoate nasal spray reduces the nasal-ocular reflex: a mechanism for the efficacy of topical steroids in controlling allergic eye symptoms. *J Allergy Clin Immunol*. Jun 2009;123(6):1342-8. doi:10.1016/j.jaci.2009.03.015

206. Keith PK, Scadding GK. Are intranasal corticosteroids all equally consistent in managing ocular symptoms of seasonal allergic rhinitis? *Curr Med Res Opin*. Aug 2009;25(8):2021-41. doi:10.1185/03007990903094106

207. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev*. 2003;(4):CD003570. doi:10.1002/14651858.CD003570

208. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy*. 2013;68(5):569-79. doi:10.1111/all.12124

209. Yu CL, Huang WT, Wang CM. Treatment of allergic rhinitis reduces acute asthma exacerbation risk among asthmatic children aged 2-18 years. *J Microbiol Immunol Infect*. Dec 2019;52(6):991-999. doi:10.1016/j.jmii.2018.10.003

210. Khattiyawittayakun L, Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Effects of double-dose intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Jan 2019;9(1):72-78. doi:10.1002/alr.22204

211. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ*. Dec 12 1998;317(7173):1624-9. doi:10.1136/bmj.317.7173.1624

212. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. Nov 2002;89(5):479-84. doi:10.1016/S1081-1206(10)62085-6

213. Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol*. Jan 2010;104(1):13-29. doi:10.1016/j.anai.2009.11.020

214. Ng CC, Romaikin D, Steacy LM, et al. Comparative nasal airflow with loratadine-pseudoephedrine and fluticasone nasal spray for allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2021;127(3):342-348 e2. doi:10.1016/j.anai.2021.05.001

215. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med*. Mar 1 2004;116(5):338-44. doi:10.1016/j.amjmed.2003.10.030

216. Bhattachan S, Neupane Y, Pradhan B, Thapa N. Comparison of Outcomes Between Mometasone Furoate Intranasal Spray and Oral Montelukast in Patients with Allergic Rhinitis. *J Nepal Health Res Counc*. Sep 8 2020;18(2):268-270. doi:10.33314/jnhrc.v18i2.2509

217. Meltzer EO. Formulation considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol*. Jan 2007;98(1):12-21. doi:10.1016/S1081-1206(10)60854-X

218. May JR, Dolen WK. Evaluation of Intranasal Corticosteroid Sensory Attributes and Patient Preference for Fluticasone Furoate for the Treatment of Allergic Rhinitis. *Clin Ther*. Aug 2019;41(8):1589-1596. doi:10.1016/j.clinthera.2019.05.017

219. van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. Sep-Oct 2012;33(5):386-96. doi:10.2500/aap.2012.33.3593

220. Meltzer EO, Jacobs RL, LaForce CF, Kelley CL, Dunbar SA, Tantry SK. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. *Allergy Asthma Proc*. May-Jun 2012;33(3):249-57. doi:10.2500/aap.2012.33.3571

221. Ratner PH, Andrews C, Martin B, et al. A study of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis from mountain cedar pollen. *Allergy Asthma Proc*. Jan-Feb 2012;33(1):27-35. doi:10.2500/aap.2012.33.3490

222. LaForce C, van Bavel J, Meltzer EO, Wingertzahn MA. Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2009;103(2):166-73. doi:10.1016/S1081-1206(10)60171-8

223. Bukstein D, Parikh R, Eid S, Ferro T, Morello JP. Beclomethasone Dipropionate Nasal Aerosol in Patients with Perennial Allergic Rhinitis (BALANCE) study: 6-month results. *Allergy Asthma Proc*. Mar-Apr 2016;37(2):121-30. doi:10.2500/aap.2016.37.3939

224. Yang Q, Wang F, Li B, et al. The efficacy and safety of ciclesonide for the treatment of perennial allergic rhinitis: a systematic review and meta-analysis. *Braz J Otorhinolaryngol*. May - Jun 2019;85(3):371-378. doi:10.1016/j.bjorl.2018.10.008

225. Maspero JF, Rosenblut A, Finn A, Jr., Lim J, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. *Otolaryngol Head Neck Surg*. Jan 2008;138(1):30-7. doi:10.1016/j.otohns.2007.10.023

226. Meltzer EO, Tripathy I, Maspero JF, Wu W, Philpot E. Safety and tolerability of fluticasone furoate nasal spray once daily in paediatric patients aged 6-11 years with allergic rhinitis: subanalysis of three randomized, double-blind, placebo-controlled, multicentre studies. *Clin Drug Investig*. 2009;29(2):79-86. doi:10.2165/0044011-200929020-00002

227. Rosenblut A, Bardin PG, Muller B, et al. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy*. Sep 2007;62(9):1071-7. doi:10.1111/j.1398-9995.2007.01521.x

228. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. May 2009;73(5):651-7. doi:10.1016/j.ijporl.2008.12.025

229. Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. *Ann Allergy Asthma Immunol*. Dec 2007;99(6):473-9; quiz 480-1, 521. doi:10.1016/S1081-1206(10)60373-0

230. Verkerk MM, Bhatia D, Rimmer J, Earls P, Sacks R, Harvey RJ. Intranasal steroids and the myth of mucosal atrophy: a systematic review of original histological assessments. *Am J Rhinol Allergy*. Jan-Feb 2015;29(1):3-18. doi:10.2500/ajra.2015.29.4111

231. van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone diproprionate. *J Allergy Clin Immunol*. Jun 1993;91(6):1146-54. doi:10.1016/0091-6749(93)90317-9

232. Brannan MD, Herron JM, Reidenberg P, Affrime MB. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. *Clin Ther*. Jul-Aug 1995;17(4):637-47. doi:10.1016/0149-2918(95)80040-9

233. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol*. Aug 1998;102(2):191-7. doi:10.1016/s0091-6749(98)70085-5

234. Howland WC, 3rd, Dockhorn R, Gillman S, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. *J Allergy Clin Immunol*. Jul 1996;98(1):32-8. doi:10.1016/s0091-6749(96)70223-3

235. Nayak AS, Ellis MH, Gross GN, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. *J Allergy Clin Immunol*. Feb 1998;101(2 Pt 1):157-62. doi:10.1016/S0091-6749(98)70379-3

236. Galant SP, Melamed IR, Nayak AS, et al. Lack of effect of fluticasone propionate aqueous nasal spray on the hypothalamic-pituitary-adrenal axis in 2- and 3-year-old patients. *Pediatrics*. Jul 2003;112(1 Pt 1):96-100. doi:10.1542/peds.112.1.96

237. Kim K, Weiswasser M, Nave R, et al. Safety of once-daily ciclesonide nasal spray in cildren 2 to 5 years of age with perennial allergic rhinitis. *Ped Asthma Allergy Immunol*. 2007;20:229-242.

238. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Jul 2007;99(1):69-76. doi:10.1016/S1081-1206(10)60624-2

239. Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on adult and adolescent hypothalamic-pituitary-adrenal axis function with use of fluticasone furoate nasal spray. *Ann Allergy Asthma Immunol*. May 2008;100(5):490-6. doi:10.1016/S1081-1206(10)60476-0

240. Weinstein S, Qaqundah P, Georges G, Nayak A. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension. *Ann Allergy Asthma Immunol*. Apr 2009;102(4):339-47. doi:10.1016/S1081-1206(10)60340-7

241. Tripathy I, Levy A, Ratner P, Clements D, Wu W, Philpot E. HPA axis safety of fluticasone furoate nasal spray once daily in children with perennial allergic rhinitis. *Pediatr Allergy Immunol*. May 2009;20(3):287-94. doi:10.1111/j.1399-3038.2008.00775.x

242. Hampel FC, Jr., Nayak NA, Segall N, Small CJ, Li J, Tantry SK. No hypothalamic-pituitary-adrenal function effect with beclomethasone dipropionate nasal aerosol, based on 24-hour serum cortisol in pediatric allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2015;115(2):137-42. doi:10.1016/j.anai.2015.05.019

243. Sampieri G, Namavarian A, Lee JJW, Hamour AF, Lee JM. Hypothalamic-pituitary-adrenal axis suppression and intranasal corticosteroid use: A systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Jan 2022;12(1):11-27. doi:10.1002/alr.22863

244. Liu A, Manche EE. Bilateral posterior subcapsular cataracts associated with long-term intranasal steroid use. *J Cataract Refract Surg*. Aug 2011;37(8):1555-8. doi:10.1016/j.jcrs.2011.05.020

245. Ahmadi N, Snidvongs K, Kalish L, et al. Intranasal corticosteroids do not affect intraocular pressure or lens opacity: a systematic review of controlled trials. *Rhinology*. Dec 2015;53(4):290-302. doi:10.4193/Rhino15.020

246. Valenzuela CV, Liu JC, Vila PM, Simon L, Doering M, Lieu JEC. Intranasal Corticosteroids Do Not Lead to Ocular Changes: A Systematic Review and Meta-analysis. *Laryngoscope*. Jan 2019;129(1):6-12. doi:10.1002/lary.27209

247. Mener DJ, Shargorodsky J, Varadhan R, Lin SY. Topical intranasal corticosteroids and growth velocity in children: a meta-analysis. *Int Forum Allergy Rhinol*. Feb 2015;5(2):95-103. doi:10.1002/alr.21430

248. Periasamy N, Pujary K, Bhandarkar AM, Bhandarkar ND, Ramaswamy B. Budesonide vs Saline Nasal Irrigation in Allergic Rhinitis: A Randomized Placebo-Controlled Trial. *Otolaryngol Head Neck Surg*. Jun 2020;162(6):979-984. doi:10.1177/0194599820919363

249. Brown K, Lane J, Silva MP, DeTineo M, Naclerio RM, Baroody FM. A pilot study of the effects of intranasal budesonide delivered by NasoNeb(R) on patients with perennial allergic rhinitis. *Int Forum Allergy Rhinol*. Jan 2014;4(1):43-8. doi:10.1002/alr.21239

250. Profita M, Riccobono L, Bonanno A, et al. Effect of nebulized beclomethasone on airway inflammation and clinical status of children with allergic asthma and rhinitis: a randomized, double-blind, placebo-controlled study. *Int Arch Allergy Immunol*. 2013;161(1):53-64. doi:10.1159/000343137

251. Hehar SS, Mason JD, Stephen AB, et al. Twenty-four hour ambulatory nasal pH monitoring. *Clin Otolaryngol Allied Sci*. Feb 1999;24(1):24-5. doi:10.1046/j.1365-2273.1999.00190.x

252. Camargos P, Ibiapina C, Lasmar L, Cruz AA. Obtaining concomitant control of allergic rhinitis and asthma with a nasally inhaled corticosteroid. *Allergy*. Mar 2007;62(3):310-6. doi:10.1111/j.1398-9995.2007.01241.x

253. Shaikh WA. Exhaling a budesonide inhaler through the nose results in a significant reduction in dose requirement of budesonide nasal spray in patients having asthma with rhinitis. *J Investig Allergol Clin Immunol*. Jan-Feb 1999;9(1):45-9.

254. Daman Willems CE, Dinwiddie R, Grant DB, Rivers RP, Zahir M. Temporary inhibition of growth and adrenal suppression associated with the use of steroid nose drops. *Eur J Pediatr*. Sep 1994;153(9):632-4. doi:10.1007/BF02190681

255. Kimmerle R, Rolla AR. Iatrogenic Cushing's syndrome due to dexamethasone nasal drops. *Am J Med*. Oct 1985;79(4):535-7. doi:10.1016/0002-9343(85)90046-4

256. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol*. Jan 2001;51(1):103-5. doi:10.1046/j.1365-2125.2001.01325.x

257. Brown EB, Seidemen T, Siegelaub AB, Popovits C. Depo-methylprednisolone in the treatment of ragweed hay fever. *Ann Allergy*. 1960;18:1321-1330.

258. Borum P, Gronborg H, Mygind N. Seasonal allergic rhinitis and depot injection of a corticosteroid. Evaluation of the efficacy of medication early and late in the season based on detailed symptom recording. *Allergy*. Jan 1987;42(1):26-32. doi:10.1111/j.1398-9995.1987.tb02183.x

259. Axelsson A, Lindholm B. The effect of triamcinolone acetonide on allergic and vasomotor rhinitis. *Acta Otolaryngol*. Jan 1972;73(1):64-7. doi:10.3109/00016487209138195

260. Laursen LC, Faurschou P, Munch EP. Intramuscular betamethasone dipropionate vs. topical beclomethasone dipropionate and placebo in hay fever. *Allergy*. Aug 1988;43(6):420-4. doi:10.1111/j.1398-9995.1988.tb00912.x

261. Kronholm A. Injectable depot corticosteroid therapy in hay fever. *J Int Med Res*. 1979;7(4):314-7. doi:10.1177/030006057900700410

262. Ohlander BO, Hansson RE, Karlsson KE. A comparison of three injectable corticosteroids for the treatment of patients with seasonal hay fever. *J Int Med Res*. 1980;8(1):63-9. doi:10.1177/030006058000800111

263. Hermance WE, Gerardi A, Popovits CJ, Brown EB. Dexamethasone acetate suspension in the treatment of allergic rhinitis. *Ann Allergy*. Dec 1969;27(12):617-21.

264. Chervinsky P. Treatment of seasonal allergic rhinitis with long-acting steroid injections. A comparison of four preparations. *Ann Allergy*. Apr 1968;26(4):190-3.

265. Laursen LC, Faurschou P, Pals H, Svendsen UG, Weeke B. Intramuscular betamethasone dipropionate vs. oral prednisolone in hay fever patients. *Allergy*. Apr 1987;42(3):168-72. doi:10.1111/j.1398-9995.1987.tb02194.x

266. Pichler WJ, Klint T, Blaser M, et al. Clinical comparison of systemic methylprednisolone acetate versus topical budesonide in patients with seasonal allergic rhinitis. *Allergy*. Feb 1988;43(2):87-92. doi:10.1111/j.1398-9995.1988.tb00399.x

267. Bayoumy AB, van Schie F, Stegeman I, Blijleven EB, van der Veen EL, de Ru JA. Intramuscular corticosteroid injections in seasonal allergic rhinitis: A systematic review. *Laryngoscope Investig Otolaryngol*. Oct 2021;6(5):911-923. doi:10.1002/lio2.645

268. Mygind N, Laursen LC, Dahl M. Systemic corticosteroid treatment for seasonal allergic rhinitis: a common but poorly documented therapy. *Allergy*. Jan 2000;55(1):11-5. doi:10.1034/j.1398-9995.2000.00108.x

269. Aasbjerg K, Torp-Pedersen C, Vaag A, Backer V. Treating allergic rhinitis with depot-steroid injections increase risk of osteoporosis and diabetes. *Respir Med*. Dec 2013;107(12):1852-8. doi:10.1016/j.rmed.2013.09.007

270. Wall JW, Shure N. Intranasal cortisone; preliminary study. *AMA Arch Otolaryngol*. Aug 1952;56(2):172-6.

271. Sidi E, Tardif R. [Treatment of allergic rhinitis accompanied by eczema with hydrocortisone acetate injected into nasal mucous membrane]. *Sem Hop*. May 30 1955;31(33):1922-3. Traitement des rhinites allergiques accompagnees d'eczema par des injections d'acetate d'hydrocortisone au niveau de la muqueuse nasale.

272. Simmons MW. Intranasal injection of corticosteroids. *Calif Med*. Feb 1960;92:155-8.

273. Baker DC, Jr., Strauss RB. Intranasal injections of long acting corticosteroids. *Ann Otol Rhinol Laryngol*. Jun 1962;71:525-31. doi:10.1177/000348946207100224

274. Mabry RL. Intraturbinal steroid injection: indications, results, and complications. *South Med J*. Jul 1978;71(7):789-91, 794. doi:10.1097/00007611-197807000-00015

275. Yang TY, Jung YG, Kim YH, Jang TY. A comparison of the effects of botulinum toxin A and steroid injection on nasal allergy. *Otolaryngol Head Neck Surg*. Sep 2008;139(3):367-71. doi:10.1016/j.otohns.2008.06.031

276. Rowe RJ, Dusler TW, Kinkella AM. Visual changes and triamcinolone. *J Amer Med Assoc*. 1967;201:333.

277. Byers B. Blindness secondary to steroid injections into the nasal turbinates. *Arch Ophthalmol*. Jan 1979;97(1):79-80. doi:10.1001/archopht.1979.01020010019004

278. Martin PA, Church CA, Petti GH, Jr., Hedayi R. Visual loss after intraturbinate steroid injection. *Otolaryngol Head Neck Surg*. Feb 2003;128(2):280-1. doi:10.1067/mhn.2003.81

279. Nagasato D, Ikeda N, Masuda A, Kashimoto R, Ikeda T. Progression of glaucomatous optic neuropathy associated with chorioretinal microvascular embolism after intranasal injection of a corticosteroid suspension. *Indian J Ophthalmol*. Aug 2020;68(8):1686-1687. doi:10.4103/ijo.IJO_2332_19

280. Moss WJ, Kjos KB, Karnezis TT, Lebovits MJ. Intranasal steroid injections and blindness: our personal experience and a review of the past 60 years. *Laryngoscope*. Apr 2015;125(4):796-800. doi:10.1002/lary.25000

281. Eccles R. Substitution of phenylephrine for pseudoephedrine as a nasal decongeststant. An illogical way to control methamphetamine abuse. *Br J Clin Pharmacol*. Jan 2007;63(1):10-4. doi:10.1111/j.1365-2125.2006.02833.x

282. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. *Arch Intern Med*. Aug 8-22 2005;165(15):1686-94. doi:10.1001/archinte.165.15.1686

283. Bronsky E, Boggs P, Findlay S, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Aug 1995;96(2):139-47. doi:10.1016/s0091-6749(95)70001-3

284. Grosclaude M, Mees K, Pinelli ME, Lucas M, Van de Venne H. Cetirizine and pseudoephedrine retard, given alone or in combination, in patients with seasonal allergic rhinitis. *Rhinology*. Jun 1997;35(2):67-73.

285. Dockhorn RJ, Williams BO, Sanders RL. Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed. *Ann Allergy Asthma Immunol*. Feb 1996;76(2):204-8. doi:10.1016/S1081-1206(10)63423-0

286. Grubbe RE, Lumry WR, Anolik R. Efficacy and safety of desloratadine/pseudoephedrine combination vs its components in seasonal allergic rhinitis. *J Investig Allergol Clin Immunol*. 2009;19(2):117-24.

287. Bertrand B, Jamart J, Marchal JL, Arendt C. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: a double-blind multicentre study. *Rhinology*. Jun 1996;34(2):91-6.

288. Sussman GL, Mason J, Compton D, Stewart J, Ricard N. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. *J Allergy Clin Immunol*. Jul 1999;104(1):100-6. doi:10.1016/s0091-6749(99)70120-x

289. Mucha SM, deTineo M, Naclerio RM, Baroody FM. Comparison of montelukast and pseudoephedrine in the treatment of allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. Feb 2006;132(2):164-72. doi:10.1001/archotol.132.2.164

290. Henauer S, Seppey M, Huguenot C, Pecoud A. Effects of terfenadine and pseudoephedrine, alone and in combination in a nasal provocation test and in perennial rhinitis. *Eur J Clin Pharmacol*. 1991;41(4):321-4. doi:10.1007/BF00314960

291. Empey DW, Frosolono MF, Hughes DT, Perkins JG. Comparison of pseudoephedrine and triprolidine, alone and in combination in preventing nasal congestion in subjects with allergic rhinitis using nasal histamine challenge. *Br J Clin Pharmacol*. Jul 1984;18(1):86-9. doi:10.1111/j.1365-2125.1984.tb05026.x

292. Howarth PH, Harrison K, Smith S. The influence of terfenadine and pseudo-ephedrine alone and in combination on allergen-induced rhinitis. *Int Arch Allergy Immunol*. 1993;101(3):318-21. doi:10.1159/000236470

293. Meltzer EO, Ratner PH, McGraw T. Oral Phenylephrine HCl for Nasal Congestion in Seasonal Allergic Rhinitis: A Randomized, Open-label, Placebo-controlled Study. *J Allergy Clin Immunol Pract*. Sep-Oct 2015;3(5):702-8. doi:10.1016/j.jaip.2015.05.007

294. Pleskow W, Grubbe R, Weiss S, Lutsky B. Efficacy and safety of an extended-release formulation of desloratadine and pseudoephedrine vs the individual components in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Mar 2005;94(3):348-54. doi:10.1016/S1081-1206(10)60986-6

295. Svensson C, Pipkorn U, Alkner U, Baumgarten CR, Persson CG. Topical vasoconstrictor (oxymetazoline) does not affect histamine-induced mucosal exudation of plasma in human nasal airways. *Clin Exp Allergy*. Mar 1992;22(3):411-6. doi:10.1111/j.1365-2222.1992.tb03103.x

296. Bickford L, Shakib S, Taverner D. The nasal airways response in normal subjects to oxymetazoline spray: randomized double-blind placebo-controlled trial. *Br J Clin Pharmacol*. Jul 1999;48(1):53-6. doi:10.1046/j.1365-2125.1999.00972.x

297. Gomez-Hervas J, Garcia-Valdecasas Bernal J, Fernandez-Prada M, Palomeque-Vera JM, Garcia-Ramos A, Fernandez-Castanys BF. Effects of oxymetazoline on nasal flow and maximum aerobic exercise performance in patients with inferior turbinate hypertrophy. *Laryngoscope*. Jun 2015;125(6):1301-6. doi:10.1002/lary.25107

298. Taverner D, Bickford L, Shakib S, Tonkin A. Evaluation of the dose-response relationship for intra-nasal oxymetazoline hydrochloride in normal adults. *Eur J Clin Pharmacol*. Sep 1999;55(7):509-13. doi:10.1007/s002280050665

299. Barnes ML, Biallosterski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. *Rhinology*. Dec 2005;43(4):291-5.

300. Pritchard S, Glover M, Guthrie G, et al. Effectiveness of 0.05% oxymetazoline (Vicks Sinex Micromist(R)) nasal spray in the treatment of objective nasal congestion demonstrated to 12 h post-administration by magnetic resonance imaging. *Pulm Pharmacol Ther*. Feb 2014;27(1):121-6. doi:10.1016/j.pupt.2013.08.002

301. Druce HM, Ramsey DL, Karnati S, Carr AN. Topical nasal decongestant oxymetazoline (0.05%) provides relief of nasal symptoms for 12 hours. *Rhinology*. Dec 1 2018;56(4):343-350. doi:10.4193/Rhin17.150

302. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ. An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion. *Am J Rhinol*. Mar-Apr 1997;11(2):109-15. doi:10.2500/105065897782537197

303. Watanabe H, Foo TH, Djazaeri B, Duncombe P, Mackay IS, Durham SR. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. *Rhinology*. Sep 2003;41(3):167-74.

304. Graf P, Hallen H. Effect on the nasal mucosa of long-term treatment with oxymetazoline, benzalkonium chloride, and placebo nasal sprays. *Laryngoscope*. May 1996;106(5 Pt 1):605-9. doi:10.1097/00005537-199605000-00016

305. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. *Laryngoscope*. Jan 1997;107(1):40-3. doi:10.1097/00005537-199701000-00010

306. Petruson B. Treatment with xylometazoline (Otrivin) nosedrops over a six-week period. *Rhinology*. Sep 1981;19(3):167-72.

307. Song XH, Zhang L, Han DM, Wang KJ, Wang H, Zhang W. [Effects of oxymetazoline hydrochloride on ex vivo human nasal cilia movement measured with high-speed digital microscopy]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. Apr 2008;43(4):268-71.

308. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

309. Meltzer EO, Wallace D, Friedman HS, Navaratnam P, Scott EP, Nolte H. Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children. *Rhinology*. Oct 1 2021;59(5):422-432. doi:10.4193/Rhin21.054

310. Krishnamoorthy M, Mohd Noor N, Mat Lazim N, Abdullah B. Efficacy of Montelukast in Allergic Rhinitis Treatment: A Systematic Review and Meta-Analysis. *Drugs*. Nov 2020;80(17):1831-1851. doi:10.1007/s40265-020-01406-9

311. Okubo K, Hashiguchi K, Takeda T, et al. A randomized controlled phase II clinical trial comparing ONO-4053, a novel DP1 antagonist, with a leukotriene receptor antagonist pranlukast in patients with seasonal allergic rhinitis. *Allergy*. Oct 2017;72(10):1565-1575. doi:10.1111/all.13174

312. Wei C. The efficacy and safety of H1-antihistamine versus Montelukast for allergic rhinitis: A systematic review and meta-analysis. *Biomed Pharmacother*. Oct 2016;83:989-997. doi:10.1016/j.biopha.2016.08.003

313. Durham SR, Creticos PS, Nelson HS, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. *J Allergy Clin Immunol*. Oct 2016;138(4):1081-1088 e4. doi:10.1016/j.jaci.2016.04.061

314. Hashiguchi K, Okubo K, Inoue Y, et al. Evaluation of Montelukast for the Treatment of Children With Japanese Cedar Pollinosis Using an Artificial Exposure Chamber (OHIO Chamber). *Allergy Rhinol (Providence)*. Jan-Dec 2018;9:2152656718783599. doi:10.1177/2152656718783599

315. Yoshihara S, Kikuchi Y, Saitou M, et al. Efficacy of a leukotriene receptor antagonist for pediatric cedar pollen allergy complicated by asthma. *Exp Ther Med*. Oct 2017;14(4):3233-3238. doi:10.3892/etm.2017.4893

316. Chen H, Lou H, Wang Y, Cao F, Zhang L, Wang C. Comparison of the efficacy and mechanisms of intranasal budesonide, montelukast, and their combination in treatment of patients with seasonal allergic rhinitis. *Int Forum Allergy Rhinol*. Nov 2018;8(11):1242-1252. doi:10.1002/alr.22197

317. Jindal A, Suriyan S, Sagadevan S, et al. Comparison of Oral Montelukast and Intranasal Fluticasone in Patients with Asthma and Allergic Rhinitis. *J Clin Diagn Res*. Aug 2016;10(8):OC06-10. doi:10.7860/JCDR/2016/20741.8268

318. Dalgic A, Dinc ME, Ulusoy S, Dizdar D, Is A, Topak M. Comparison of the effects of nasal steroids and montelukast on olfactory functions in patients with allergic rhinitis. *Eur Ann Otorhinolaryngol Head Neck Dis*. Sep 2017;134(4):213-216. doi:10.1016/j.anorl.2016.05.012

319. Feng Y, Meng YP, Dong YY, Qiu CY, Cheng L. Management of allergic rhinitis with leukotriene receptor antagonists versus selective H1-antihistamines: a meta-analysis of current evidence. *Allergy Asthma Clin Immunol*. Jun 29 2021;17(1):62. doi:10.1186/s13223-021-00564-z

320. Xiao J, Wu WX, Ye YY, Lin WJ, Wang L. A Network Meta-analysis of Randomized Controlled Trials Focusing on Different Allergic Rhinitis Medications. *Am J Ther*. Nov/Dec 2016;23(6):e1568-e1578. doi:10.1097/MJT.0000000000000242

321. Xu Y, Zhang J, Wang J. The efficacy and safety of selective H1-antihistamine versus leukotriene receptor antagonist for seasonal allergic rhinitis: a meta-analysis. *PLoS One*. 2014;9(11):e112815. doi:10.1371/journal.pone.0112815

322. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med*. May 1 2014;12:71. doi:10.1186/1741-7015-12-71

323. Li YJ, Zong M, Ding LF, Rui XQ, Ma BY, Qin LP. Efficacy of Chinese Medicine Acupoint Application Combined with Montelukast on Children with Perennial Allergic Rhinitis: A Randomized Controlled Trial. *Chin J Integr Med*. Nov 2020;26(11):845-852. doi:10.1007/s11655-020-3099-2

324. U.S. Food and Drug Administration. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. 2020.

325. American Academy of Family Physicians. Clinical practice guidelines: allergic rhinitis. Updated July 6 2020. Accessed Nov 1, 2021, https://www.aafp.org/family-physician/patient-care/clinical-recommendations/all-clinical-recommendations/allergic-rhinitis.html

326. Goodman MJ, Jhaveri M, Saverno K, Meyer K, Nightengale B. Cost-effectiveness of second-generation antihistamines and montelukast in relieving allergic rhinitis nasal symptoms. *Am Health Drug Benefits*. Oct 2008;1(8):26-34.

327. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol*. Oct 2006;31(5):360-7. doi:10.1111/j.1749-4486.2006.01276.x

328. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. *Ann Allergy Asthma Immunol*. Jun 2006;96(6):779-86. doi:10.1016/S1081-1206(10)61339-7

329. Gonyeau MJ, Partisan AM. A clinical review of montelukast in the treatment of seasonal allergic rhinitis. *Formulary*. 2003;38:368-378.

330. Endo S, Gotoh M, Okubo K, Hashiguchi K, Suzuki H, Masuyama K. Trial of pranlukast inhibitory effect for cedar exposure using an OHIO chamber. *J Drug Assess*. 2012;1(1):48-54. doi:10.3109/21556660.2012.703630

331. Wakabayashi K, Hashiguchi K, Kanzaki S, et al. Pranlukast dry syrup inhibits symptoms of Japanese cedar pollinosis in children using OHIO Chamber. *Allergy Asthma Proc*. Jan-Feb 2012;33(1):102-9. doi:10.2500/aap.2012.33.3517

332. Day JH, Briscoe MP, Ratz JD. Efficacy of levocetirizine compared with montelukast in subjects with ragweed-induced seasonal allergic rhinitis in the Environmental Exposure Unit. *Allergy Asthma Proc*. May-Jun 2008;29(3):304-12. doi:10.2500/aap.2008.29.3109

333. Jiang RS. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. *J Otolaryngol*. Apr 2006;35(2):117-21. doi:10.2310/7070.2005.5007

334. Patel P, Philip G, Yang W, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Dec 2005;95(6):551-7. doi:10.1016/S1081-1206(10)61018-6

335. Chervinsky P, Philip G, Malice MP, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol*. Mar 2004;92(3):367-73. doi:10.1016/S1081-1206(10)61576-1

336. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin*. Oct 2004;20(10):1549-58. doi:10.1185/030079904x3348

337. Ratner PH, Howland WC, 3rd, Arastu R, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol*. May 2003;90(5):536-42. doi:10.1016/S1081-1206(10)61847-9

338. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy*. Dec 2003;58(12):1268-76. doi:10.1046/j.1398-9995.2003.00261.x

339. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Feb 2003;90(2):214-22. doi:10.1016/S1081-1206(10)62144-8

340. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy*. Jul 2002;32(7):1020-8. doi:10.1046/j.1365-2222.2002.01422.x

341. Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med*. Jun 1999;159(6):1814-8. doi:10.1164/ajrccm.159.6.9810016

342. Altounyan RE. Review of clinical activity and mode of action of sodium cromoglycate. *Clin Allergy*. Jul 1980;10 Suppl:481-9. doi:10.1111/j.1365-2222.1980.tb02162.x

343. Kay AB, Walsh GM, Moqbel R, et al. Disodium cromoglycate inhibits activation of human inflammatory cells in vitro. *J Allergy Clin Immunol*. Jul 1987;80(1):1-8. doi:10.1016/s0091-6749(87)80183-5

344. Taylor G, Shivalkar PR. Disodium cromoglycate: laboratory studies and clinical trial in allergic rhinitis. *Clin Allergy*. Jun 1971;1(2):189-98. doi:10.1111/j.1365-2222.1971.tb03018.x

345. Pelikan Z. The diagnostic approach to immediate hypersensitivity in patients with allergic rhinitis; a comparison of nasal challenges and serum rast. *Ann Allergy*. Sep 1983;51(3):395-400.

346. Kolly M, Pecoud A. Comparison of levocabastine, a new selective H1-receptor antagonist, and disodium cromoglycate, in a nasal provocation test with allergen. *Br J Clin Pharmacol*. Oct 1986;22(4):389-94. doi:10.1111/j.1365-2125.1986.tb02907.x

347. Davies HJ. Exposure of hay fever subjects to an indoor environmental grass pollen challenge system. *Clin Allergy*. Sep 1985;15(5):419-27. doi:10.1111/j.1365-2222.1985.tb02291.x

348. Ibanez MD, Laso MT, Martinez-San Irineo M, Alonso E. Anaphylaxis to disodium cromoglycate. *Ann Allergy Asthma Immunol*. Sep 1996;77(3):185-6. doi:10.1016/s1081-1206(10)63252-8

349. Wass U, Plaschke P, Bjorkander J, Belin L. Assay of specific IgE antibodies to disodium cromoglycate in serum from a patient with an immediate hypersensitivity reaction. *J Allergy Clin Immunol*. Apr 1988;81(4):750-7. doi:10.1016/0091-6749(88)91049-4

350. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol*. Sep 1997;100(3):301-6. doi:10.1016/s0091-6749(97)70241-0

351. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy. Safety considerations. *Drug Saf*. Apr 1999;20(4):361-75. doi:10.2165/00002018-199920040-00005

352. Meltzer EO, NasalCrom Study G. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther*. Jun 2002;24(6):942-52. doi:10.1016/s0149-2918(02)80009-1

353. Chandra RK, Heresi G, Woodford G. Double-blind controlled crossover trial of 4% intranasal sodium cromoglycate solution in patients with seasonal allergic rhinitis. *Ann Allergy*. Sep 1982;49(3):131-4.

354. Handelman NI, Friday GA, Schwartz HJ, et al. Cromolyn sodium nasal solution in the prophylactic treatment of pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. Mar 1977;59(3):237-42. doi:10.1016/0091-6749(77)90156-7

355. Nizami RM, Baboo MT. Efficacy double-blind, crossover study of sodium cromoglycate in patients with seasonal allergic rhinitis. *Ann Allergy*. Jan 1977;38(1):42-45.

356. Knight A, Underdown BJ, Demanuele F, Hargreave FE. Disodium cromoglycate in ragweed-allergic rhinitis. *J Allergy Clin Immunol*. Aug 1976;58(2):278-83. doi:10.1016/0091-6749(76)90132-9

357. Lejeune M, Lefebvre PP, Delvenne P, El-Shazly AE. Nasal sodium cromoglycate (Lomusol) modulates the early phase reaction of mild to moderate persistent allergic rhinitis in patients mono-sensitized to house dust mite: a preliminary study. *Int Immunopharmacol*. May 2015;26(1):272-6. doi:10.1016/j.intimp.2015.02.004

358. Tandon MK, Strahan EG. Double-blind crossover trial comparing beclomethasone dipropionate and sodium cromoglycate in perennial allergic rhinitis. *Clin Allergy*. Jul 1980;10(4):459-62. doi:10.1111/j.1365-2222.1980.tb02129.x

359. McDowell MK, Spitz E. Treatment of chronic perennial allergic rhinitis: a double-blind trial of cromolyn sodium. *Ann Allergy*. Sep 1977;39(3):169-74.

360. Warland A, Kapstad B. The effect of disodium cromoglycate in perennial allergic rhinitis. A controlled clinical study. *Acta Allergol*. Jun 1977;32(3):195-9. doi:10.1111/j.1398-9995.1977.tb01350.x

361. Cohan RH, Bloom FL, Rhoades RB, Wittig HJ, Haugh LD. Treatment of perennial allergic rhinitis with cromolyn sodium. Double-blind study on 34 adult patients. *J Allergy Clin Immunol*. Jul 1976;58(1 PT. 2):121-8. doi:10.1016/0091-6749(76)90147-0

362. Orgel HA, Meltzer EO, Kemp JP, Ostrom NK, Welch MJ. Comparison of intranasal cromolyn sodium, 4%, and oral terfenadine for allergic rhinitis: symptoms, nasal cytology, nasal ciliary clearance, and rhinomanometry. *Ann Allergy*. Mar 1991;66(3):237-44.

363. Schata M, Jorde W, Richarz-Barthauer U. Levocabastine nasal spray better than sodium cromoglycate and placebo in the topical treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. Apr 1991;87(4):873-8. doi:10.1016/0091-6749(91)90136-c

364. Lange B, Lukat KF, Rettig K, Holtappels G, Bachert C. Efficacy, cost-effectiveness, and tolerability of mometasone furoate, levocabastine, and disodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2005;95(3):272-82. doi:10.1016/S1081-1206(10)61225-2

365. Fisher WG. Comparison of budesonide and disodium cromoglycate for the treatment of seasonal allergic rhinitis in children. *Ann Allergy*. Dec 1994;73(6):515-20.

366. Bousquet J, Chanal I, Alquie MC, et al. Prevention of pollen rhinitis symptoms: comparison of fluticasone propionate aqueous nasal spray and disodium cromoglycate aqueous nasal spray. A multicenter, double-blind, double-dummy, parallel-group study. *Allergy*. Jul 1993;48(5):327-33. doi:10.1111/j.1398-9995.1993.tb02401.x

367. Welsh PW, Stricker WE, Chu CP, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc*. Feb 1987;62(2):125-34. doi:10.1016/s0025-6196(12)61882-5

368. Bjerrum P, Illum P. Treatment of seasonal allergic rhinitis with budesonide and disodium cromoglycate. A double-blind clinical comparison between budesonide and disodium cromoglycate. *Allergy*. Jan 1985;40(1):65-9. doi:10.1111/j.1398-9995.1985.tb04156.x

369. Morrow-Brown H, Jackson FA, Pover GM. A comparison of beclomethasone dipropionate aqueous nasal spray and sodium cromoglycate nasal spray in the management of seasonal allergic rhinitis. *Allergol Immunopathol (Madr)*. Sep-Oct 1984;12(5):355-61.

370. Brown HM, Engler C, English JR. A comparative trial of flunisolide and sodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. *Clin Allergy*. Mar 1981;11(2):169-73. doi:10.1111/j.1365-2222.1981.tb01581.x

371. Wilson JA, Walker SR. A clinical study of the prophylactic use of betamethasone valerate and sodium cromoglycate in the treatment of seasonal allergic rhinitis. *J Laryngol Otol*. Feb 1976;90(2):201-6. doi:10.1017/s0022215100081962

372. Frankland AW, Walker SR. A comparison of intranasal betamethasone valerate and sodium cromoglycate in seasonal allergic rhinitis. *Clin Allergy*. Sep 1975;5(3):295-300. doi:10.1111/j.1365-2222.1975.tb01866.x

373. Pitsios C, Papadopoulos D, Kompoti E, et al. Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. May 2006;96(5):673-8. doi:10.1016/S1081-1206(10)61064-2

374. Schuller DE, Selcow JE, Joos TH, et al. A multicenter trial of nedocromil sodium, 1% nasal solution, compared with cromolyn sodium and placebo in ragweed seasonal allergic rhinitis. *J Allergy Clin Immunol*. Oct 1990;86(4 Pt 1):554-61. doi:10.1016/s0091-6749(05)80212-x

375. Craig S, Rubinstein E, Reisman RE, Arbesman CE. Treatment of ragweed hay fever with intranasally administered disodium cromoglycate. *Clin Allergy*. Nov 1977;7(6):569-76. doi:10.1111/j.1365-2222.1977.tb01487.x

376. Posey WC, Nelson HS. Controlled trials with four per cent cromolyn spray in seasonal allergic rhinitis. *Clin Allergy*. Sep 1977;7(5):485-96. doi:10.1111/j.1365-2222.1977.tb01479.x

377. Becker B, Borum S, Nielsen K, Mygind N, Borum P. A time-dose study of the effect of topical ipratropium bromide on methacholine-induced rhinorrhoea in patients with perennial non-allergic rhinitis. *Clin Otolaryngol Allied Sci*. Apr 1997;22(2):132-4. doi:10.1046/j.1365-2273.1997.00875.x

378. Sanwikarja S, Schmitz PI, Dieges PH. The effect of locally applied ipratropium aerosol on the nasal methacholine challenge in patients with allergic and non-allergic rhinitis. *Ann Allergy*. Feb 1986;56(2):162-6.

379. Ostberg B, Winther B, Mygind N. Cold air-induced rhinorrhea and high-dose ipratropium. *Arch Otolaryngol Head Neck Surg*. Feb 1987;113(2):160-2. doi:10.1001/archotol.1987.01860020052011

380. Kirkegaard J, Mygind N, Molgaard F, et al. Ordinary and high-dose ipratropium in perennial nonallergic rhinitis. *J Allergy Clin Immunol*. Apr 1987;79(4):585-90. doi:10.1016/s0091-6749(87)80153-7

381. Kirkegaard J, Mygind N, Molgaard F, et al. Ipratropium treatment of rhinorrhea in perennial nonallergic rhinitis. A Nordic multicenter study. *Acta Otolaryngol Suppl*. 1988;449:93-5. doi:10.3109/00016488809106386

382. Bonadonna P, Senna G, Zanon P, et al. Cold-induced rhinitis in skiers--clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol*. Sep-Oct 2001;15(5):297-301.

383. Kaiser HB, Findlay SR, Georgitis JW, et al. The anticholinergic agent, ipratropium bromide, is useful in the treatment of rhinorrhea associated with perennial allergic rhinitis. *Allergy Asthma Proc*. Jan-Feb 1998;19(1):23-9. doi:10.2500/108854198778557962

384. Kaiser HB, Findlay SR, Georgitis JW, et al. Long-term treatment of perennial allergic rhinitis with ipratropium bromide nasal spray 0.06%. *J Allergy Clin Immunol*. May 1995;95(5 Pt 2):1128-32. doi:10.1016/s0091-6749(95)70217-2

385. Bronsky EA, Druce H, Findlay SR, et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. *J Allergy Clin Immunol*. May 1995;95(5 Pt 2):1117-22. doi:10.1016/s0091-6749(95)70215-6

386. Kim KT, Kerwin E, Landwehr L, et al. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol*. Jan 2005;94(1):73-9. doi:10.1016/s1081-1206(10)61289-6

387. Ensing K, de Zeeuw RA, Nossent GD, Koeter GH, Cornelissen PJ. Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. *Eur J Clin Pharmacol*. 1989;36(2):189-94. doi:10.1007/BF00609193

388. Meltzer EO, Orgel HA, Biondi R, et al. Ipratropium nasal spray in children with perennial rhinitis. *Ann Allergy Asthma Immunol*. May 1997;78(5):485-91. doi:10.1016/S1081-1206(10)63236-X

389. Milgrom H, Biondi R, Georgitis JW, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children. *Ann Allergy Asthma Immunol*. Aug 1999;83(2):105-11. doi:10.1016/S1081-1206(10)62620-8

390. Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol*. Apr 1999;82(4):349-59. doi:10.1016/S1081-1206(10)63284-X

391. Finn AF, Jr., Aaronson D, Korenblat P, et al. Ipratropium bromide nasal spray 0.03% provides additional relief from rhinorrhea when combined with terfenadine in perennial rhinitis patients; a randomized, double-blind, active-controlled trial. *Am J Rhinol*. Nov-Dec 1998;12(6):441-9. doi:10.2500/105065898780707919

392. Gorski P, Pazdrak K, Ruta U. Effect of ipratropium on nasal reactivity to histamine and eosinophil influx in perennial allergic rhinitis. *Eur J Clin Pharmacol*. 1993;44(6):545-7. doi:10.1007/BF02440856

393. Meltzer EO, Orgel HA, Bronsky EA, et al. Ipratropium bromide aqueous nasal spray for patients with perennial allergic rhinitis: a study of its effect on their symptoms, quality of life, and nasal cytology. *J Allergy Clin Immunol*. Aug 1992;90(2):242-9. doi:10.1016/0091-6749(92)90078-g

394. Schultz Larsen F, Mygind N, Larsen FS. Ipratropium treatment for rhinorrhoea in patients with perennial rhinitis. An open follow-up study of efficacy and safety. *Clin Otolaryngol Allied Sci*. Aug 1983;8(4):267-72. doi:10.1111/j.1365-2273.1983.tb01440.x

395. Borum P, Mygind N, Schultz Larsen F. Intranasal ipratropium: a new treatment for perennial rhinitis. *Clin Otolaryngol Allied Sci*. Dec 1979;4(6):407-11. doi:10.1111/j.1365-2273.1979.tb01773.x

396. Cox L. Biologics and Allergy Immunotherapy in the Treatment of Allergic Diseases. *Immunol Allergy Clin North Am*. Nov 2020;40(4):687-700. doi:10.1016/j.iac.2020.06.008

397. Eschenbacher W, Straesser M, Knoeddler A, Li RC, Borish L. Biologics for the Treatment of Allergic Rhinitis, Chronic Rhinosinusitis, and Nasal Polyposis. *Immunol Allergy Clin North Am*. Nov 2020;40(4):539-547. doi:10.1016/j.iac.2020.06.001

398. Licari A, Marseglia G, Castagnoli R, Marseglia A, Ciprandi G. The discovery and development of omalizumab for the treatment of asthma. *Expert Opin Drug Discov*. 2015;10(9):1033-42. doi:10.1517/17460441.2015.1048220

399. Tsabouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract*. May-Jun 2014;2(3):332-40 e1. doi:10.1016/j.jaip.2014.02.001

400. Yu C, Wang K, Cui X, et al. Clinical Efficacy and Safety of Omalizumab in the Treatment of Allergic Rhinitis: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *Am J Rhinol Allergy*. Mar 2020;34(2):196-208. doi:10.1177/1945892419884774

401. Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol*. Jul 1997;100(1):110-21. doi:10.1016/s0091-6749(97)70202-1

402. Adelroth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. Aug 2000;106(2):253-9. doi:10.1067/mai.2000.108310

403. Casale TB, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. Dec 19 2001;286(23):2956-67. doi:10.1001/jama.286.23.2956

404. Chervinsky P, Casale T, Townley R, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2003;91(2):160-7. doi:10.1016/S1081-1206(10)62171-0

405. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int*. Dec 2006;55(4):379-86. doi:10.2332/allergolint.55.379

406. Corren J, Diaz-Sanchez D, Saxon A, et al. Effects of omalizumab, a humanized monoclonal anti-IgE antibody, on nasal reactivity to allergen and local IgE synthesis. *Ann Allergy Asthma Immunol*. Sep 2004;93(3):243-8. doi:10.1016/S1081-1206(10)61495-0

407. Bez C, Schubert R, Kopp M, et al. Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy*. Jul 2004;34(7):1079-85. doi:10.1111/j.1365-2222.2004.01998.x

408. Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M, Ishikawa T. Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Clin Exp Allergy*. Feb 2008;38(2):329-37. doi:10.1111/j.1365-2222.2007.02894.x

409. Davydov L. Omalizumab (Xolair) for treatment of asthma. *Am Fam Physician*. Jan 15 2005;71(2):341-2.

410. Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy*. Jan 2020;75(1):148-157. doi:10.1111/all.13984

411. Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol*. Jul 2018;142(1):171-177 e1. doi:10.1016/j.jaci.2017.11.051

412. Busse WW, Maspero JF, Lu Y, et al. Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Nov 2020;125(5):565-576 e1. doi:10.1016/j.anai.2020.05.026

413. Corren J, Saini SS, Gagnon R, et al. Short-Term Subcutaneous Allergy Immunotherapy and Dupilumab are Well Tolerated in Allergic Rhinitis: A Randomized Trial. *J Asthma Allergy*. 2021;14:1045-1063. doi:10.2147/JAA.S318892

414. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. Jan 2006;117(1):134-40. doi:10.1016/j.jaci.2005.09.036

415. Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol*. Feb 2002;109(2):274-80. doi:10.1067/mai.2002.121949

416. Cordray S, Harjo JB, Miner L. Comparison of intranasal hypertonic dead sea saline spray and intranasal aqueous triamcinolone spray in seasonal allergic rhinitis. *Ear Nose Throat J*. Jul 2005;84(7):426-30.

417. Rogkakou A, Guerra L, Massacane P, et al. Effects on symptoms and quality of life of hypertonic saline nasal spray added to antihistamine in persistent allergic rhinitis--a randomized controlled study. *Eur Ann Allergy Clin Immunol*. Nov 2005;37(9):353-6.

418. Ural A, Oktemer TK, Kizil Y, Ileri F, Uslu S. Impact of isotonic and hypertonic saline solutions on mucociliary activity in various nasal pathologies: clinical study. *J Laryngol Otol*. May 2009;123(5):517-21. doi:10.1017/S0022215108003964

419. Garavello W, Somigliana E, Acaia B, Gaini L, Pignataro L, Gaini RM. Nasal lavage in pregnant women with seasonal allergic rhinitis: a randomized study. *Int Arch Allergy Immunol*. 2010;151(2):137-41. doi:10.1159/000236003

420. Chusakul S, Warathanasin S, Suksangpanya N, et al. Comparison of buffered and nonbuffered nasal saline irrigations in treating allergic rhinitis. *Laryngoscope*. Jan 2013;123(1):53-6. doi:10.1002/lary.23617

421. Di Berardino F, Zanetti D, D'Amato G. Nasal rinsing with an atomized spray improves mucociliary clearance and clinical symptoms during peak grass pollen season. *Am J Rhinol Allergy*. Jan 26 2017;31(1):40-43. doi:10.2500/ajra.2016.30.4383

422. Sansila K, Eiamprapai P, Sawangjit R. Effects of self-prepared hypertonic nasal saline irrigation in allergic rhinitis: A randomized controlled trial. *Asian Pac J Allergy Immunol*. Sep 2020;38(3):200-207. doi:10.12932/AP-090618-0331

423. Lin L, Chen Z, Cao Y, Sun G. Normal saline solution nasal-pharyngeal irrigation improves chronic cough associated with allergic rhinitis. *Am J Rhinol Allergy*. Mar 1 2017;31(2):96-104. doi:10.2500/ajra.2017.31.4418

424. Yata K, Srivanitchapoom C. The comparison of nasal irrigation outcome between 3% NaCl and 0.9% NaCl in adults majority with intermittent allergic rhinitis: A randomized double-blind study. *Asian Pac J Allergy Immunol*. Mar 2021;39(1):9-14. doi:10.12932/AP-140520-0844

425. Li CL, Lin HC, Lin CY, Hsu TF. Effectiveness of Hypertonic Saline Nasal Irrigation for Alleviating Allergic Rhinitis in Children: A Systematic Review and Meta-Analysis. *J Clin Med*. Jan 9 2019;8(1)doi:10.3390/jcm8010064

426. Li H, Sha Q, Zuo K, et al. Nasal saline irrigation facilitates control of allergic rhinitis by topical steroid in children. *ORL J Otorhinolaryngol Relat Spec*. 2009;71(1):50-5. doi:10.1159/000178165

427. Garavello W, Romagnoli M, Sordo L, Gaini RM, Di Berardino C, Angrisano A. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study. *Pediatr Allergy Immunol*. Apr 2003;14(2):140-3. doi:10.1034/j.1399-3038.2003.00021.x

428. Garavello W, Di Berardino F, Romagnoli M, Sambataro G, Gaini RM. Nasal rinsing with hypertonic solution: an adjunctive treatment for pediatric seasonal allergic rhinoconjunctivitis. *Int Arch Allergy Immunol*. Aug 2005;137(4):310-4. doi:10.1159/000086462

429. Marchisio P, Varricchio A, Baggi E, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. *Int J Immunopathol Pharmacol*. Jul-Sep 2012;25(3):721-30. doi:10.1177/039463201202500318

430. Satdhabudha A, Poachanukoon O. Efficacy of buffered hypertonic saline nasal irrigation in children with symptomatic allergic rhinitis: a randomized double-blind study. *Int J Pediatr Otorhinolaryngol*. Apr 2012;76(4):583-8. doi:10.1016/j.ijporl.2012.01.022

431. Chen JR, Jin L, Li XY. The effectiveness of nasal saline irrigation (seawater) in treatment of allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol*. Jul 2014;78(7):1115-8. doi:10.1016/j.ijporl.2014.04.026

432. Malizia V, Fasola S, Ferrante G, et al. Efficacy of Buffered Hypertonic Saline Nasal Irrigation for Nasal Symptoms in Children with Seasonal Allergic Rhinitis: A Randomized Controlled Trial. *Int Arch Allergy Immunol*. 2017;174(2):97-103. doi:10.1159/000481093

433. Jung M, Lee JY, Ryu G, et al. Beneficial effect of nasal saline irrigation in children with allergic rhinitis and asthma: A randomized clinical trial. *Asian Pac J Allergy Immunol*. Dec 2020;38(4):251-257. doi:10.12932/AP-070918-0403

434. Hermelingmeier KE, Weber RK, Hellmich M, Heubach CP, Mosges R. Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy*. Sep-Oct 2012;26(5):e119-25. doi:10.2500/ajra.2012.26.3787

435. Head K, Snidvongs K, Glew S, et al. Saline irrigation for allergic rhinitis. *Cochrane Database Syst Rev*. Jun 22 2018;6:CD012597. doi:10.1002/14651858.CD012597.pub2

436. Wang Y, Jin L, Liu SX, Fan K, Qin ML, Yu SQ. Role of nasal saline irrigation in the treatment of allergic rhinitis in children and adults: A systematic analysis. *Allergol Immunopathol (Madr)*. Jul - Aug 2020;48(4):360-367. doi:10.1016/j.aller.2020.01.002

437. Ozdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol*. Jun 2010;160(3):295-304. doi:10.1111/j.1365-2249.2010.04109.x

438. Guvenc IA, Muluk NB, Mutlu FS, et al. Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis. *Am J Rhinol Allergy*. Sep 1 2016;30(5):157-175. doi:10.2500/ajra.2016.30.4354

439. Zajac AE, Adams AS, Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis. *Int Forum Allergy Rhinol*. Jun 2015;5(6):524-32. doi:10.1002/alr.21492

440. Du X, Wang L, Wu S, et al. Efficacy of probiotic supplementary therapy for asthma, allergic rhinitis, and wheeze: a meta-analysis of randomized controlled trials. *Allergy Asthma Proc*. Jul 1 2019;40(4):250-260. doi:10.2500/aap.2019.40.4227

441. Zuccotti G, Meneghin F, Aceti A, et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. *Allergy*. Nov 2015;70(11):1356-71. doi:10.1111/all.12700

442. Anania C, Di Marino VP, Olivero F, et al. Treatment with a Probiotic Mixture Containing Bifidobacterium animalis Subsp. Lactis BB12 and Enterococcus faecium L3 for the Prevention of Allergic Rhinitis Symptoms in Children: A Randomized Controlled Trial. *Nutrients*. Apr 16 2021;13(4)doi:10.3390/nu13041315

443. Jalali MM, Soleimani R, Alavi Foumani A, Ganjeh Khosravi H. Add-on probiotics in patients with persistent allergic rhinitis: A randomized crossover clinical trial. *Laryngoscope*. Aug 2019;129(8):1744-1750. doi:10.1002/lary.27858

444. Sumadiono S, Satria CD, Mardhiah N, Susanti GI. Immunotherapy and probiotic treatment for allergic rhinitis in children. *Paediatrica Indonesiana*. 2018;58(6):280-285.

445. Dennis-Wall JC, Culpepper T, Nieves C, Jr., et al. Probiotics (Lactobacillus gasseri KS-13, Bifidobacterium bifidum G9-1, and Bifidobacterium longum MM-2) improve rhinoconjunctivitis-specific quality of life in individuals with seasonal allergies: a double-blind, placebo-controlled, randomized trial. *Am J Clin Nutr*. Mar 2017;105(3):758-767. doi:10.3945/ajcn.116.140012

446. Miraglia Del Giudice M, Indolfi C, Capasso M, Maiello N, Decimo F, Ciprandi G. Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M-16V) treatment in children with seasonal allergic rhinitis and intermittent asthma. *Ital J Pediatr*. Mar 7 2017;43(1):25. doi:10.1186/s13052-017-0340-5

447. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. Jan 29 2015;372(5):456-63. doi:10.1056/NEJMcp1412282

448. Beard S. Rhinitis. *Prim Care*. Mar 2014;41(1):33-46. doi:10.1016/j.pop.2013.10.005

449. North ML, Walker TJ, Steacy LM, et al. Add-on histamine receptor-3 antagonist for allergic rhinitis: a double blind randomized crossover trial using the environmental exposure unit. *Allergy Asthma Clin Immunol*. 2014;10(1):33. doi:10.1186/1710-1492-10-33

450. Nathan RA, Finn AF, Jr., LaForce C, et al. Comparison of cetirizine-pseudoephedrine and placebo in patients with seasonal allergic rhinitis and concomitant mild-to-moderate asthma: randomized, double-blind study. *Ann Allergy Asthma Immunol*. Sep 2006;97(3):389-96. doi:10.1016/S1081-1206(10)60806-X

451. Chervinsky P, Nayak A, Rooklin A, Danzig M. Efficacy and safety of desloratadine/pseudoephedrine tablet, 2.5/120 mg two times a day, versus individual components in the treatment of patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. Sep-Oct 2005;26(5):391-6.

452. Meltzer EO, Casale TB, Gold MS, et al. Efficacy and safety of clemastine-pseudoephedrine-acetaminophen versus pseudoephedrine-acetaminophen in the treatment of seasonal allergic rhinitis in a 1-day, placebo-controlled park study. *Ann Allergy Asthma Immunol*. Jan 2003;90(1):79-86. doi:10.1016/S1081-1206(10)63618-6

453. Berkowitz RB, Woodworth GG, Lutz C, et al. Onset of action, efficacy, and safety of fexofenadine 60 mg/pseudoephedrine 120 mg versus placebo in the Atlanta allergen exposure unit. *Ann Allergy Asthma Immunol*. Jul 2002;89(1):38-45. doi:10.1016/S1081-1206(10)61909-6

454. McFadden EA, Gungor A, Ng B, Mamikoglu B, Moinuddin R, Corey J. Loratadine/pseudoephedrine for nasal symptoms in seasonal allergic rhinitis: a double-blind, placebo-controlled study. *Ear Nose Throat J*. Apr 2000;79(4):254, 257-8, 260 passim.

455. Horak F, Toth J, Marks B, et al. Efficacy and safety relative to placebo of an oral formulation of cetirizine and sustained-release pseudoephedrine in the management of nasal congestion. *Allergy*. Sep 1998;53(9):849-56. doi:10.1111/j.1398-9995.1998.tb03990.x

456. Serra HA, Alves O, Rizzo LF, Devoto FM, Ascierto H. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. *Br J Clin Pharmacol*. Feb 1998;45(2):147-50. doi:10.1046/j.1365-2125.1998.00657.x

457. Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol*. Dec 1997;100(6 Pt 1):781-8. doi:10.1016/s0091-6749(97)70274-4

458. Williams BO, Hull H, McSorley P, Frosolono MF, Sanders RL. Efficacy of acrivastine plus pseudoephedrine for symptomatic relief of seasonal allergic rhinitis due to mountain cedar. *Ann Allergy Asthma Immunol*. May 1996;76(5):432-8. doi:10.1016/S1081-1206(10)63460-6

459. Grossman J, Bronsky EA, Lanier BQ, et al. Loratadine-pseudoephedrine combination versus placebo in patients with seasonal allergic rhinitis. *Ann Allergy*. Oct 1989;63(4):317-21.

460. Storms WW, Bodman SF, Nathan RA, et al. SCH 434: a new antihistamine/decongestant for seasonal allergic rhinitis. *J Allergy Clin Immunol*. Jun 1989;83(6):1083-90. doi:10.1016/0091-6749(89)90450-8

461. Chen YA, Chang KP, Lin YS, Hao SP. A randomized, double-blind, parallel-group study to compare the efficacy and safety of a once-daily loratadine-pseudoephedrine combination with that of a twice-daily loratadine-pseudoephedrine combination in the treatment of allergic rhinitis. *Eur Arch Otorhinolaryngol*. Sep 2007;264(9):1019-25. doi:10.1007/s00405-007-0316-y

462. Chiang YC, Shyur SD, Chen TL, et al. A randomized controlled trial of cetirizine plus pseudoephedrine versus loratadine plus pseudoephedrine for perennial allergic rhinitis. *Asian Pac J Allergy Immunol*. Jun-Sep 2006;24(2-3):97-103.

463. Moinuddin R, deTineo M, Maleckar B, Naclerio RM, Baroody FM. Comparison of the combinations of fexofenadine-pseudoephedrine and loratadine-montelukast in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Jan 2004;92(1):73-9. doi:10.1016/S1081-1206(10)61713-9

464. Simola M, Boss I, Holopainen E, et al. Astemizole in combination with pseudoephedrine in the treatment of seasonal allergic rhinitis. *Rhinology*. Mar 1996;34(1):21-3.

465. Prevost M, Turenne Y, Moote DW, et al. Comparative study of SCH 434 and CTM-D in the treatment of seasonal allergic rhinitis. *Clin Ther*. Jan-Feb 1994;16(1):50-6.

466. Segal AT, Falliers CJ, Grant JA, et al. Safety and efficacy of terfenadine/pseudoephedrine versus clemastine/phenylpropanolamine in the treatment of seasonal allergic rhinitis. *Ann Allergy*. May 1993;70(5):389-94.

467. Zieglmayer UP, Horak F, Toth J, Marks B, Berger UE, Burtin B. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus budesonide nasal spray in the management of nasal congestion in allergic rhinitis. *Treat Respir Med*. 2005;4(4):283-7. doi:10.2165/00151829-200504040-00006

468. Negrini AC, Troise C, Voltolini S, Horak F, Bachert C, Janssens M. Oral antihistamine/decongestant treatment compared with intranasal corticosteroids in seasonal allergic rhinitis. *Clin Exp Allergy*. Jan 1995;25(1):60-5. doi:10.1111/j.1365-2222.1995.tb01003.x

469. Stubner UP, Toth J, Marks B, Berger UE, Burtin B, Horak F. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus xylometazoline nasal spray in nasal congestion. *Arzneimittelforschung*. Nov 2001;51(11):904-10. doi:10.1055/s-0031-1300135

470. Kaiser HB, Banov CH, Berkowitz RR, et al. Comparative efficacy and safety of once-daily versus twice-daily loratadine-pseudoephedrine combinations versus placebo in seasonal allergic rhinitis. *Am J Ther*. Jul 1998;5(4):245-51. doi:10.1097/00045391-199807000-00007

471. Pinar E, Eryigit O, Oncel S, Calli C, Yilmaz O, Yuksel H. Efficacy of nasal corticosteroids alone or combined with antihistamines or montelukast in treatment of allergic rhinitis. *Auris Nasus Larynx*. Mar 2008;35(1):61-6. doi:10.1016/j.anl.2007.06.004

472. Anolik R, Mometasone Furoate Nasal Spray With Loratadine Study G. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Mar 2008;100(3):264-71. doi:10.1016/S1081-1206(10)60452-8

473. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy*. May 2006;36(5):676-84. doi:10.1111/j.1365-2222.2006.02478.x

474. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy*. Feb 2004;34(2):259-67. doi:10.1111/j.1365-2222.2004.01877.x

475. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract*. Aug 1998;47(2):118-25.

476. Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Khattiyawittayakun L, Snidvongs K. Effects of H1 antihistamine addition to intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Oct 2018;8(10):1083-1092. doi:10.1002/alr.22166

477. Wang R, Zhang C. [Clinical evaluation of Montelukast plus Budesonide nasal spray and Desloratadine citrate disodium in treating moderate and severe persistent allergic rhinitis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. Dec 2015;29(23):2041-3.

478. Modgill V, Badyal DK, Verghese A. Efficacy and safety of montelukast add-on therapy in allergic rhinitis. *Methods Find Exp Clin Pharmacol*. Nov 2010;32(9):669-74. doi:10.1358/mf.2010.32.9.1533686

479. Benitez HH, Arvizu VM, Gutierrez DJ, et al. [Nasal budesonide plus zafirlukast vs nasal budesonide plus loratadine-pseudoephedrine for controlling the symptoms of rhinitis and asthma]. *Rev Alerg Mex*. Mar-Apr 2005;52(2):90-5. Budesonida nasal mas zafirlukast vs budesonida nasal mas loratadina- pseudoefedrina en el control de los sintomas de la rinitis y el asma.

480. Lanier BQ, Abelson MB, Berger WE, et al. Comparison of the efficacy of combined fluticasone propionate and olopatadine versus combined fluticasone propionate and fexofenadine for the treatment of allergic rhinoconjunctivitis induced by conjunctival allergen challenge. *Clin Ther*. Jul 2002;24(7):1161-74. doi:10.1016/s0149-2918(02)80027-3

481. Wilson A, Dempsey OJ, Sims EJ, Coutie WJ, Paterson MC, Lipworth BJ. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. *Clin Exp Allergy*. Jun 2000;30(6):833-8. doi:10.1046/j.1365-2222.2000.00749.x

482. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol*. Mar 1989;83(3):627-33. doi:10.1016/0091-6749(89)90075-4

483. Kim MK, Lee SY, Park HS, et al. A Randomized, Multicenter, Double-blind, Phase III Study to Evaluate the Efficacy on Allergic Rhinitis and Safety of a Combination Therapy of Montelukast and

Levocetirizine in Patients With Asthma and Allergic Rhinitis. *Clin Ther*. Jul 2018;40(7):1096-1107 e1. doi:10.1016/j.clinthera.2018.04.021

484. Liu G, Zhou X, Chen J, Liu F. Oral Antihistamines Alone vs in Combination with Leukotriene Receptor Antagonists for Allergic Rhinitis: A Meta-analysis. *Otolaryngol Head Neck Surg*. Mar 2018;158(3):450-458. doi:10.1177/0194599817752624

485. Mahatme MS, Dakhale GN, Tadke K, Hiware SK, Dudhgaonkar SD, Wankhede S. Comparison of efficacy, safety, and cost-effectiveness of montelukast-levocetirizine and montelukast-fexofenadine in patients of allergic rhinitis: A randomized, double-blind clinical trial. *Indian J Pharmacol*. Nov-Dec 2016;48(6):649-653. doi:10.4103/0253-7613.194854

486. Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. *J Asthma*. Nov 2009;46(9):878-83. doi:10.3109/02770900903104540

487. Saengpanich S, deTineo M, Naclerio RM, Baroody FM. Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. May 2003;129(5):557-62. doi:10.1001/archotol.129.5.557

488. Cingi C, Gunhan K, Gage-White L, Unlu H. Efficacy of leukotriene antagonists as concomitant therapy in allergic rhinitis. *Laryngoscope*. Sep 2010;120(9):1718-23. doi:10.1002/lary.20941

489. Li AM, Abdullah VJ, Tsen CS, et al. Leukotriene receptor antagonist in the treatment of childhood allergic rhinitis--a randomized placebo-controlled study. *Pediatr Pulmonol*. Nov 2009;44(11):1085-92. doi:10.1002/ppul.21102

490. Ciebiada M, Barylski M, Gorska Ciebiada M. Nasal eosinophilia and serum soluble intercellular adhesion molecule 1 in patients with allergic rhinitis treated with montelukast alone or in combination with desloratadine or levocetirizine. *Am J Rhinol Allergy*. Mar-Apr 2013;27(2):e58-62. doi:10.2500/ajra.2013.27.3881

491. Yamamoto H, Yamada T, Sakashita M, et al. Efficacy of prophylactic treatment with montelukast and montelukast plus add-on loratadine for seasonal allergic rhinitis. *Allergy Asthma Proc*. Mar-Apr 2012;33(2):e17-22. doi:10.2500/aap.2012.33.3514

492. Watanasomsiri A, Poachanukoon O, Vichyanond P. Efficacy of montelukast and loratadine as treatment for allergic rhinitis in children. *Asian Pac J Allergy Immunol*. Jun-Sep 2008;26(2-3):89-95.

493. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF, Montelukast Fall Rhinitis Investigator G. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol*. Jun 2002;88(6):592-600. doi:10.1016/S1081-1206(10)61891-1

494. Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol*. May 2000;105(5):917-22. doi:10.1067/mai.2000.106040

495. Andrews CP, Mohar D, Salhi Y, Tantry SK. Efficacy and safety of twice-daily and once-daily olopatadine-mometasone combination nasal spray for seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Feb 2020;124(2):171-178 e2. doi:10.1016/j.anai.2019.11.007

496. Segall N, Prenner B, Lumry W, Caracta CF, Tantry SK. Long-term safety and efficacy of olopatadine-mometasone combination nasal spray in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Sep 1 2019;40(5):301-310. doi:10.2500/aap.2019.40.4233

497. Hampel FC, Pedinoff AJ, Jacobs RL, Caracta CF, Tantry SK. Olopatadine-mometasone combination nasal spray: Evaluation of efficacy and safety in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. Jul 3 2019;40(4):261-272. doi:10.2500/aap.2019.40.4223

498. Gross GN, Berman G, Amar NJ, Caracta CF, Tantry SK. Efficacy and safety of olopatadine-mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Jun 2019;122(6):630-638 e3. doi:10.1016/j.anai.2019.03.017

499. Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. *Ann Allergy Asthma Immunol*. Feb 2019;122(2):160-166 e1. doi:10.1016/j.anai.2018.10.011

500. Bousquet J, Meltzer EO, Couroux P, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. *J Allergy Clin Immunol Pract*. Sep - Oct 2018;6(5):1726-1732 e6. doi:10.1016/j.jaip.2018.01.031

501. Kortekaas Krohn I, Callebaut I, Alpizar YA, et al. MP29-02 reduces nasal hyperreactivity and nasal mediators in patients with house dust mite-allergic rhinitis. *Allergy*. May 2018;73(5):1084-1093. doi:10.1111/all.13349

502. Berger W, Meltzer EO, Amar N, et al. Efficacy of MP-AzeFlu in children with seasonal allergic rhinitis: Importance of paediatric symptom assessment. *Pediatr Allergy Immunol*. Mar 2016;27(2):126-33. doi:10.1111/pai.12540

503. Meltzer E, Ratner P, Bachert C, et al. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int Arch Allergy Immunol*. 2013;161(4):369-77. doi:10.1159/000351404

504. Price D, Shah S, Bhatia S, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. *J Investig Allergol Clin Immunol*. 2013;23(7):495-503.

505. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol*. May 2012;129(5):1282-1289 e10. doi:10.1016/j.jaci.2012.01.077

506. Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc*. Jul-Aug 2012;33(4):324-32. doi:10.2500/aap.2012.33.3587

507. Salapatek AM, Lee J, Patel D, et al. Solubilized nasal steroid (CDX-947) when combined in the same solution nasal spray with an antihistamine (CDX-313) provides improved, fast-acting symptom relief in patients with allergic rhinitis. *Allergy Asthma Proc*. May-Jun 2011;32(3):221-9. doi:10.2500/aap.2011.32.3444

508. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol*. Aug 2010;105(2):168-73. doi:10.1016/j.anai.2010.06.008

509. LaForce CF, Carr W, Tilles SA, et al. Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis. *Allergy Asthma Proc*. Mar-Apr 2010;31(2):132-40. doi:10.2500/aap.2010.31.3326

510. Ratner PH, Hampel F, Van Bavel J, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Jan 2008;100(1):74-81. doi:10.1016/S1081-1206(10)60408-5

511. Ilyina NI, Edin AS, Astafieva NG, et al. Efficacy of a Novel Intranasal Formulation of Azelastine Hydrochloride and Fluticasone Propionate, Delivered in a Single Spray, for the Treatment of Seasonal Allergic Rhinitis: Results from Russia. *Int Arch Allergy Immunol*. 2019;178(3):255-263. doi:10.1159/000494507

512. Berger W, Bousquet J, Fox AT, et al. MP-AzeFlu is more effective than fluticasone propionate for the treatment of allergic rhinitis in children. *Allergy*. Aug 2016;71(8):1219-22. doi:10.1111/all.12903

513. Klimek L, Bachert C, Stjarne P, et al. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study. *Allergy Asthma Proc*. Sep 2016;37(5):376-86. doi:10.2500/aap.2016.37.3979

514. Klimek L, Bachert C, Mosges R, et al. Effectiveness of MP29-02 for the treatment of allergic rhinitis in real-life: results from a noninterventional study. *Allergy Asthma Proc*. Jan-Feb 2015;36(1):40-7. doi:10.2500/aap.2015.36.3823

515. Klimek L, Poletti SC, Sperl A, et al. Olfaction in patients with allergic rhinitis: an indicator of successful MP-AzeFlu therapy. *Int Forum Allergy Rhinol*. Mar 2017;7(3):287-292. doi:10.1002/alr.21877

516. Debbaneh PM, Bareiss AK, Wise SK, McCoul ED. Intranasal Azelastine and Fluticasone as Combination Therapy for Allergic Rhinitis: Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Sep 2019;161(3):412-418. doi:10.1177/0194599819841883

517. Du K, Qing H, Zheng M, Wang X, Zhang L. Intranasal antihistamine is superior to oral H1 antihistamine as an add-on therapy to intranasal corticosteroid for treating allergic rhinitis. *Ann Allergy Asthma Immunol*. Nov 2020;125(5):589-596 e3. doi:10.1016/j.anai.2020.06.038

518. Seresirikachorn K, Mullol J, Limitlaohaphan K, Asvapoositkul V, Snidvongs K. Leukotriene receptor antagonist addition to intranasal steroid: systematic review and meta-analysis. *Rhinology*. Feb 1 2021;59(1):2-9. doi:10.4193/Rhin20.126

519. Chen H, Zhang L, Lou H, Wang Y, Cao F, Wang C. A Randomized Trial of Comparing a Combination of Montelukast and Budesonide With Budesonide in Allergic Rhinitis. *Laryngoscope*. Apr 2021;131(4):E1054-E1061. doi:10.1002/lary.28433

520. Goh BS, Ismail MI, Husain S. Quality of life assessment in patients with moderate to severe allergic rhinitis treated with montelukast and/or intranasal steroids: a randomised, double-blind, placebo-controlled study. *J Laryngol Otol*. Mar 2014;128(3):242-8. doi:10.1017/S002221511400036X

521. Esteitie R, deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Aug 2010;105(2):155-61. doi:10.1016/j.anai.2010.05.017

522. Florinescu-Gheorghe N-A, Popescu F, Alexandru DO. Treatment evaluation with mometasone furoate, alone or in combination with desloratadine/montelukast, in moderate severe allergic rhinitis. *Acta Med Marisienis*. 2014;60:106-108.

523. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. *Fundam Clin Pharmacol*. Dec 2010;24(6):729-39. doi:10.1111/j.1472-8206.2009.00805.x

524. Graf P, Hallen H, Juto JE. The pathophysiology and treatment of rhinitis medicamentosa. *Clin Otolaryngol Allied Sci*. Jun 1995;20(3):224-9. doi:10.1111/j.1365-2273.1995.tb01853.x

525. Kirtsreesakul V, Khanuengkitkong T, Ruttanaphol S. Does oxymetazoline increase the efficacy of nasal steroids in treating nasal polyposis? *Am J Rhinol Allergy*. May 2016;30(3):195-200. doi:10.2500/ajra.2016.30.4294

526. Matreja PS, Gupta V, Kaur J, Singh S. Efficacy of fluticasona nd oxymetazoline as the treatment for allergic rhinitis. *J Clin Diagnostic Res*. 2012;6:4.

527. Meltzer EO, Bernstein DI, Prenner BM, Berger WE, Shekar T, Teper AA. Mometasone furoate nasal spray plus oxymetazoline nasal spray: short-term efficacy and safety in seasonal allergic rhinitis. *Am J Rhinol Allergy*. Mar-Apr 2013;27(2):102-8. doi:10.2500/ajra.2013.27.3864

528. Rael EL, Ramey J, Lockey RF. Oxymetazoline hydrochloride combined with mometasone nasal spray for persistent nasal congestion (pilot study). *World Allergy Organ J*. Mar 2011;4(3):65-7. doi:10.1097/WOX.0b013e31820f8fae

529. Thongngarm T, Assanasen P, Pradubpongsa P, Tantilipikorn P. The effectiveness of oxymetazoline plus intranasal steroid in the treatment of chronic rhinitis: A randomised controlled trial. *Asian Pac J Allergy Immunol*. Mar 2016;34(1):30-7. doi:10.12932/AP0649.34.1.2016

530. Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. Apr 2011;127(4):927-34. doi:10.1016/j.jaci.2011.01.037

531. Khattiyawittayakun L, Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Effects of decongestant addition to intranasal corticosteroid for chronic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. Dec 2018;8(12):1445-1453. doi:10.1002/alr.22193

532. Kilic G. Treatment of allergic rhinitis in children. *Anti-inflammatory and anti-allergy agents in medicinal chemistry*. 2008;7:38-44.

533. Scadding GK. Allergic rhinitis in children. *Paediatrics Child Health*. 2008;18:323-328.

534. Yap L, Pothula VB, Warner J, Akhtar S, Yates E. The root and development of otorhinolaryngology in traditional Chinese medicine. *Eur Arch Otorhinolaryngol*. Sep 2009;266(9):1353-9. doi:10.1007/s00405-009-1041-5

535. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med*. Mar 5 2002;136(5):374-83. doi:10.7326/0003-4819-136-5-200203050-00010

536. Yang XY, Shi GX, Li QQ, Zhang ZH, Xu Q, Liu CZ. Characterization of deqi sensation and acupuncture effect. *Evid Based Complement Alternat Med*. 2013;2013:319734. doi:10.1155/2013/319734

537. Petti FB, Liguori A, Ippoliti F. Study on cytokines IL-2, IL-6, IL-10 in patients of chronic allergic rhinitis treated with acupuncture. *J Tradit Chin Med*. Jun 2002;22(2):104-11.

538. Feng S, Han M, Fan Y, et al. Acupuncture for the treatment of allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy*. Jan-Feb 2015;29(1):57-62. doi:10.2500/ajra.2015.29.4116

539. Roberts J, Huissoon A, Dretzke J, Wang D, Hyde C. A systematic review of the clinical effectiveness of acupuncture for allergic rhinitis. *BMC Complement Altern Med*. Apr 22 2008;8:13. doi:10.1186/1472-6882-8-13

540. Lee MS, Pittler MH, Shin BC, Kim JI, Ernst E. Acupuncture for allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol*. Apr 2009;102(4):269-79; quiz 279-81, 307. doi:10.1016/S1081-1206(10)60330-4

541. Brinkhaus B, Ortiz M, Witt CM, et al. Acupuncture in patients with seasonal allergic rhinitis: a randomized trial. *Ann Intern Med*. Feb 19 2013;158(4):225-34. doi:10.7326/0003-4819-158-4-201302190-00002

542. Wu AW, Gettelfinger JD, Ting JY, Mort C, Higgins TS. Alternative therapies for sinusitis and rhinitis: a systematic review utilizing a modified Delphi method. *Int Forum Allergy Rhinol*. Apr 2020;10(4):496-504. doi:10.1002/alr.22488

543. Yin Z, Geng G, Xu G, Zhao L, Liang F. Acupuncture methods for allergic rhinitis: a systematic review and bayesian meta-analysis of randomized controlled trials. *Chin Med*. 2020;15:109. doi:10.1186/s13020-020-00389-9

544. Taw MB, Reddy WD, Omole FS, Seidman MD. Acupuncture and allergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2015;23(3):216-20. doi:10.1097/MOO.0000000000000161

545. Zhang CS, Yang AW, Zhang AL, et al. Ear-acupressure for allergic rhinitis: a systematic review. *Clin Otolaryngol*. Feb 2010;35(1):6-12. doi:10.1111/j.1749-4486.2009.02067.x

546. Li XR, Zhang QX, Liu M, et al. Catgut implantation at acupoints for allergic rhinitis: a systematic review. *Chin J Integr Med*. Mar 2014;20(3):235-40. doi:10.1007/s11655-014-1748-z

547. Zhou F, Yan LJ, Yang GY, Liu JP. Acupoint herbal patching for allergic rhinitis: a systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol*. Dec 2015;40(6):551-68. doi:10.1111/coa.12410

548. Fu Q, Zhang L, Liu Y, et al. Effectiveness of Acupuncturing at the Sphenopalatine Ganglion Acupoint Alone for Treatment of Allergic Rhinitis: A Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med*. 2019;2019:6478102. doi:10.1155/2019/6478102

549. Li X. The mechanism analysis of treating nasal disease by sphenopalatine ganglion (acupoint "ZhiBi 3") stimulation with acupuncture needle and an introduction to the relevant needling method. *J Clin Otorhinolaryngol Head Neck Surg*. 2011;5:193.

550. Li XW, Tian ZP. A preliminary summary of the treatment on rhinitis puncturing sphenopalatine ganglion. *Beijing J Chinese Med*. 1990;9:36-38.

551. Zhang J, Zhang Y, Huang X, et al. Different Acupuncture Therapies for Allergic Rhinitis: Overview of Systematic Reviews and Network Meta-Analysis. *Evid Based Complement Alternat Med*. 2020;2020:8363027. doi:10.1155/2020/8363027

552. Wang LL. [Characteristic of moxibustion and its warming-dredging effect]. *Zhongguo Zhen Jiu*. Oct 2011;31(10):865-8.

553. Yuan T, Xiong J, Yang J, et al. The Effectiveness and Safety of Thunder Fire Moxibustion for Treating Allergic Rhinitis: A PRISMA Compliant Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med*. 2020;2020:6760436. doi:10.1155/2020/6760436

554. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. Mar 2008;100(3 Suppl 3):S1-148. doi:10.1016/s1081-1206(10)60305-5

555. Kacaniova M, Pavlicova S, Hascik P, et al. Microbial communities in bees, pollen and honey from Slovakia. *Acta Microbiol Immunol Hung*. Sep 2009;56(3):285-95. doi:10.1556/AMicr.56.2009.3.7

556. Duddukuri GR, Kumar PS, Kumar VB, Athota RR. Immunosuppressive effect of honey on the induction of allergen-specific humoral antibody response in mice. *Int Arch Allergy Immunol*. Dec 1997;114(4):385-8. doi:10.1159/000237699

557. Ishikawa Y, Tokura T, Nakano N, et al. Inhibitory effect of honeybee-collected pollen on mast cell degranulation in vivo and in vitro. *J Med Food*. Mar 2008;11(1):14-20. doi:10.1089/jmf.2006.163

558. Ishikawa Y, Tokura T, Ushio H, et al. Lipid-soluble components of honeybee-collected pollen exert antiallergic effect by inhibiting IgE-mediated mast cell activation in vivo. *Phytother Res*. Nov 2009;23(11):1581-6. doi:10.1002/ptr.2824

559. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns*. Mar 1998;24(2):157-61. doi:10.1016/s0305-4179(97)00113-7

560. Al-Waili NS, Boni NS. Natural honey lowers plasma prostaglandin concentrations in normal individuals. *J Med Food*. Summer 2003;6(2):129-33. doi:10.1089/109662003322233530

561. Asha'ari ZA, Ahmad MZ, Jihan WS, Che CM, Leman I. Ingestion of honey improves the symptoms of allergic rhinitis: evidence from a randomized placebo-controlled trial in the East coast of Peninsular Malaysia. *Ann Saudi Med*. Sep-Oct 2013;33(5):469-75. doi:10.5144/0256-4947.2013.469

562. Saarinen K, Jantunen J, Haahtela T. Birch pollen honey for birch pollen allergy--a randomized controlled pilot study. *Int Arch Allergy Immunol*. 2011;155(2):160-6. doi:10.1159/000319821

563. Rajan TV, Tennen H, Lindquist RL, Cohen L, Clive J. Effect of ingestion of honey on symptoms of rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. Feb 2002;88(2):198-203. doi:10.1016/S1081-1206(10)61996-5

564. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: a review. *J Am Coll Nutr*. Dec 2008;27(6):677-89. doi:10.1080/07315724.2008.10719745

565. Passalacqua G, Bousquet PJ, Carlsen KH, et al. ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma. *J Allergy Clin Immunol*. May 2006;117(5):1054-62. doi:10.1016/j.jaci.2005.12.1308

566. Enomoto T, Nagasako-Akazome Y, Kanda T, Ikeda M, Dake Y. Clinical effects of apple polyphenols on persistent allergic rhinitis: A randomized double-blind placebo-controlled parallel arm study. *J Investig Allergol Clin Immunol*. 2006;16(5):283-9.

567. Matkovic Z, Zivkovic V, Korica M, Plavec D, Pecanic S, Tudoric N. Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. *Phytother Res*. Feb 2010;24(2):175-81. doi:10.1002/ptr.2877

568. D'Souza P, Amit A, Saxena VS, Bagchi D, Bagchi M, Stohs SJ. Antioxidant properties of Aller-7, a novel polyherbal formulation for allergic rhinitis. *Drugs Exp Clin Res*. 2004;30(3):99-109.

569. Pratibha N, Saxena VS, Amit A, D'Souza P, Bagchi M, Bagchi D. Anti-inflammatory activities of Aller-7, a novel polyherbal formulation for allergic rhinitis. *Int J Tissue React*. 2004;26(1-2):43-51.

570. Amit A, Saxena VS, Pratibha N, et al. Mast cell stabilization, lipoxygenase inhibition, hyaluronidase inhibition, antihistaminic and antispasmodic activities of Aller-7, a novel botanical formulation for allergic rhinitis. *Drugs Exp Clin Res*. 2003;29(3):107-15.

571. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol*. Dec 2007;99(6):483-95. doi:10.1016/S1081-1206(10)60375-4

572. Suzuki M, Yoshino K, Maeda-Yamamoto M, Miyase T, Sano M. Inhibitory effects of tea catechins and O-methylated derivatives of (-)-epigallocatechin-3-O-gallate on mouse type IV allergy. *J Agric Food Chem*. Nov 2000;48(11):5649-53. doi:10.1021/jf000313d

573. Maeda-Yamamoto M, Inagaki N, Kitaura J, et al. O-methylated catechins from tea leaves inhibit multiple protein kinases in mast cells. *J Immunol*. Apr 1 2004;172(7):4486-92. doi:10.4049/jimmunol.172.7.4486

574. Masuda S, Maeda-Yamamoto M, Usui S, Fujisawa T. 'Benifuuki' green tea containing o-methylated catechin reduces symptoms of Japanese cedar pollinosis: a randomized, double-blind, placebo-controlled trial. *Allergol Int*. Jun 2014;63(2):211-7. doi:10.2332/allergolint.13-OA-0620

575. Hu G, Walls RS, Bass D, et al. The Chinese herbal formulation biminne in management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-week clinical trial. *Ann Allergy Asthma Immunol*. May 2002;88(5):478-87. doi:10.1016/s1081-1206(10)62386-1

576. Shimoda H, Tanaka J, Yamada E, Morikawa T, Kasajima N, Yoshikawa M. Anti type I allergic property of Japanese butterbur extract and its mast cell degranulation inhibitory ingredients. *J Agric Food Chem*. Apr 19 2006;54(8):2915-20. doi:10.1021/jf052994o

577. Russell LC, Burchiel KJ. Neurophysiological effects of capsaicin. *Brain Res*. Dec 1984;320(2-3):165-76. doi:10.1016/0165-0173(84)90005-5

578. Philip G, Baroody FM, Proud D, Naclerio RM, Togias AG. The human nasal response to capsaicin. *J Allergy Clin Immunol*. Dec 1994;94(6 Pt 1):1035-45. doi:10.1016/0091-6749(94)90122-8

579. Cheng J, Yang XN, Liu X, Zhang SP. Capsaicin for allergic rhinitis in adults. *Cochrane Database Syst Rev*. Apr 19 2006;(2):CD004460. doi:10.1002/14651858.CD004460.pub2

580. Gerth Van Wijk R, Terreehorst IT, Mulder PG, Garrelds IM, Blom HM, Popering S. Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study. *Clin Exp Allergy*. Dec 2000;30(12):1792-8. doi:10.1046/j.1365-2222.2000.00920.x

581. Fujiwara T, Nishida N, Nota J, et al. Efficacy of chlorophyll c2 for seasonal allergic rhinitis: single-center double-blind randomized control trial. *Eur Arch Otorhinolaryngol*. Dec 2016;273(12):4289-4294. doi:10.1007/s00405-016-4133-z

582. Corren J, Lemay M, Lin Y, Rozga L, Randolph RK. Clinical and biochemical effects of a combination botanical product (ClearGuard) for allergy: a pilot randomized double-blind placebo-controlled trial. *Nutr J*. Jul 14 2008;7:20. doi:10.1186/1475-2891-7-20

583. Turpeinen AM, Ylonen N, von Willebrand E, Basu S, Aro A. Immunological and metabolic effects of cis-9, trans-11-conjugated linoleic acid in subjects with birch pollen allergy. *Br J Nutr*. Jul 2008;100(1):112-9. doi:10.1017/S0007114507886326

584. Bernstein DI, Bernstein CK, Deng C, et al. Evaluation of the clinical efficacy and safety of grapeseed extract in the treatment of fall seasonal allergic rhinitis: a pilot study. *Ann Allergy Asthma Immunol*. Mar 2002;88(3):272-8. doi:10.1016/S1081-1206(10)62008-X

585. Hirano T, Kawai M, Arimitsu J, et al. Preventative effect of a flavonoid, enzymatically modified isoquercitrin on ocular symptoms of Japanese cedar pollinosis. *Allergol Int*. Sep 2009;58(3):373-82. doi:10.2332/allergolint.08-OA-0070

586. Kawai M, Hirano T, Arimitsu J, et al. Effect of enzymatically modified isoquercitrin, a flavonoid, on symptoms of Japanese cedar pollinosis: a randomized double-blind placebo-controlled trial. *Int Arch Allergy Immunol*. 2009;149(4):359-68. doi:10.1159/000205582

587. Yamprasert R, Chanvimalueng W, Mukkasombut N, Itharat A. Ginger extract versus Loratadine in the treatment of allergic rhinitis: a randomized controlled trial. *BMC Complement Med Ther*. Apr 20 2020;20(1):119. doi:10.1186/s12906-020-2875-z

588. Hewlings S, Kalman DS. Evaluating the Impacts of Methylsulfonylmethane on Allergic Rhinitis After a Standard Allergen Challenge: Randomized Double-Blind Exploratory Study. *JMIR Res Protoc*. Nov 29 2018;7(11):e11139. doi:10.2196/11139

589. Chakravarty N. Inhibition of histamine release from mast cells by nigellone. *Ann Allergy*. Mar 1993;70(3):237-42.

590. El Gazzar M, El Mezayen R, Marecki JC, Nicolls MR, Canastar A, Dreskin SC. Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation. *Int Immunopharmacol*. Jul 2006;6(7):1135-42. doi:10.1016/j.intimp.2006.02.004

591. Kalus U, Pruss A, Bystron J, et al. Effect of Nigella sativa (black seed) on subjective feeling in patients with allergic diseases. *Phytother Res*. Dec 2003;17(10):1209-14. doi:10.1002/ptr.1356

592. Nikakhlagh S, Rahim F, Aryani FH, Syahpoush A, Brougerdnya MG, Saki N. Herbal treatment of allergic rhinitis: the use of Nigella sativa. *Am J Otolaryngol*. Sep-Oct 2011;32(5):402-7. doi:10.1016/j.amjoto.2010.07.019

593. Alsamarai AM, Abdulsatar M, Ahmed Alobaidi AH. Evaluation of topical black seed oil in the treatment of allergic rhinitis. *Antiinflamm Antiallergy Agents Med Chem*. Mar 2014;13(1):75-82. doi:10.2174/18715230113129990014

594. Rotondo S, Rajtar G, Manarini S, et al. Effect of trans-resveratrol, a natural polyphenolic compound, on human polymorphonuclear leukocyte function. *Br J Pharmacol*. Apr 1998;123(8):1691-9. doi:10.1038/sj.bjp.0701784

595. Varilek GW, Yang F, Lee EY, et al. Green tea polyphenol extract attenuates inflammation in interleukin-2-deficient mice, a model of autoimmunity. *J Nutr*. Jul 2001;131(7):2034-9. doi:10.1093/jn/131.7.2034

596. Yang F, de Villiers WJ, McClain CJ, Varilek GW. Green tea polyphenols block endotoxin-induced tumor necrosis factor-production and lethality in a murine model. *J Nutr*. Dec 1998;128(12):2334-40. doi:10.1093/jn/128.12.2334

597. Makino T, Furuta Y, Wakushima H, Fujii H, Saito K, Kano Y. Anti-allergic effect of Perilla frutescens and its active constituents. *Phytother Res*. Mar 2003;17(3):240-3. doi:10.1002/ptr.1115

598. Takano H, Osakabe N, Sanbongi C, et al. Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic rhinoconjunctivitis in humans. *Exp Biol Med (Maywood)*. Mar 2004;229(3):247-54. doi:10.1177/153537020422900305

599. Wassenberg J, Nutten S, Audran R, et al. Effect of Lactobacillus paracasei ST11 on a nasal provocation test with grass pollen in allergic rhinitis. *Clin Exp Allergy*. Apr 2011;41(4):565-73. doi:10.1111/j.1365-2222.2011.03695.x

600. Perrin Y, Nutten S, Audran R, et al. Comparison of two oral probiotic preparations in a randomized crossover trial highlights a potentially beneficial effect of Lactobacillus paracasei NCC2461 in patients with allergic rhinitis. *Clin Transl Allergy*. Jan 6 2014;4(1):1. doi:10.1186/2045-7022-4-1

601. Lenon GB, Xue CC, Story DF, Thien FC, McPhee S, Li CG. Inhibition of release of inflammatory mediators in primary and cultured cells by a Chinese herbal medicine formula for allergic rhinitis. *Chin Med*. Feb 15 2007;2:2. doi:10.1186/1749-8546-2-2

602. Lenon GB, Li CG, Xue CC, Thien FC, Story DF. Inhibition of release of vasoactive and inflammatory mediators in airway and vascular tissues and macrophages by a chinese herbal medicine formula for allergic rhinitis. *Evid Based Complement Alternat Med*. Jun 2007;4(2):209-17. doi:10.1093/ecam/nel083

603. Xue CC, Thien FC, Zhang JJ, Da Costa C, Li CG. Treatment for seasonal allergic rhinitis by Chinese herbal medicine: a randomized placebo controlled trial. *Altern Ther Health Med*. Sep-Oct 2003;9(5):80-7.

604. Mao TK, Van de Water J, Gershwin ME. Effects of a Spirulina-based dietary supplement on cytokine production from allergic rhinitis patients. *J Med Food*. Spring 2005;8(1):27-30. doi:10.1089/jmf.2005.8.27

605. Karkos PD, Leong SC, Karkos CD, Sivaji N, Assimakopoulos DA. Spirulina in clinical practice: evidence-based human applications. *Evid Based Complement Alternat Med*. 2011;2011:531053. doi:10.1093/ecam/nen058

606. Cingi C, Conk-Dalay M, Cakli H, Bal C. The effects of spirulina on allergic rhinitis. *Eur Arch Otorhinolaryngol*. Oct 2008;265(10):1219-23. doi:10.1007/s00405-008-0642-8

607. Ishikura Y, Suwa Y, Okada T. Anti-allergic effects of Rubus suavissimus extract. *Japanese J Inflamm*. 1995;15:167-173.

608. Yonekura S, Okamoto Y, Yamasaki K, et al. A randomized, double-blind, placebo-controlled study of ten-cha (Rubus suavissimus) on house dust mite allergic rhinitis. *Auris Nasus Larynx*. Oct 2011;38(5):600-7. doi:10.1016/j.anl.2010.11.017

609. Das AK, Mizuguchi H, Kodama M, et al. Sho-seiryu-to suppresses histamine signaling at the transcriptional level in TDI-sensitized nasal allergy model rats. *Allergol Int*. Mar 2009;58(1):81-8. doi:10.2332/allergolint.O-07-526

610. Baba S. Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial allergic rhinitis. *Pract Otol*. 1995;88:389-405.

611. Badar VA, Thawani VR, Wakode PT, et al. Efficacy of Tinospora cordifolia in allergic rhinitis. *J Ethnopharmacol*. Jan 15 2005;96(3):445-9. doi:10.1016/j.jep.2004.09.034

612. Yoshimura M, Enomoto T, Dake Y, et al. An evaluation of the clinical efficacy of tomato extract for perennial allergic rhinitis. *Allergol Int*. Sep 2007;56(3):225-30. doi:10.2332/allergolint.O-06-443

613. Roschek B, Jr., Fink RC, McMichael M, Alberte RS. Nettle extract (Urtica dioica) affects key receptors and enzymes associated with allergic rhinitis. *Phytother Res*. Jul 2009;23(7):920-6. doi:10.1002/ptr.2763

614. Mittman P. Randomized, double-blind study of freeze-dried Urtica dioica in the treatment of allergic rhinitis. *Planta Med*. Feb 1990;56(1):44-7. doi:10.1055/s-2006-960881

615. Podoshin L, Gertner R, Fradis M. Treatment of perennial allergic rhinitis with ascorbic acid solution. *Ear Nose Throat J*. Jan 1991;70(1):54-5.

616. Jerzynska J, Stelmach W, Rychlik B, et al. Clinical and immunological effects of vitamin D supplementation during the pollen season in children with allergic rhinitis. *Arch Med Sci*. Jan 2018;14(1):122-131. doi:10.5114/aoms.2016.61978

617. Shahar E, Hassoun G, Pollack S. Effect of vitamin E supplementation on the regular treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Jun 2004;92(6):654-8. doi:10.1016/S1081-1206(10)61432-9

618. Montano Velazquez BB, Jauregui-Renaud K, Banuelos Arias Adel C, et al. Vitamin E effects on nasal symptoms and serum specific IgE levels in patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. Jan 2006;96(1):45-50. doi:10.1016/s1081-1206(10)61039-3

619. Cheng L, Chen J, Fu Q, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. *Allergy Asthma Immunol Res*. Jul 2018;10(4):300-353. doi:10.4168/aair.2018.10.4.300

620. Chen S, Guo SN, Marmori F, et al. Clinical Practice Guideline for Allergic Rhinitis Treatment with Acupuncture. *Chin J Integr Med*. Feb 2021;27(2):83-90. doi:10.1007/s11655-020-3161-0

621. Fjermedal O, Saunte C, Pedersen S. Septoplasty and/or submucous resection? 5 years nasal septum operations. *J Laryngol Otol*. Sep 1988;102(9):796-8. doi:10.1017/s0022215100106486

622. Karatzanis AD, Fragiadakis G, Moshandrea J, Zenk J, Iro H, Velegrakis GA. Septoplasty outcome in patients with and without allergic rhinitis. *Rhinology*. Dec 2009;47(4):444-9. doi:10.4193/Rhin08.126

623. Mondina M, Marro M, Maurice S, Stoll D, de Gabory L. Assessment of nasal septoplasty using NOSE and RhinoQoL questionnaires. *Eur Arch Otorhinolaryngol*. Oct 2012;269(10):2189-95. doi:10.1007/s00405-011-1916-0

624. Stoksted P, Gutierrez C. The nasal passage following rhinoplastic surgery. *J Laryngol Otol*. Jan 1983;97(1):49-54. doi:10.1017/s0022215100093798

625. Stewart MG, Smith TL, Weaver EM, et al. Outcomes after nasal septoplasty: results from the Nasal Obstruction Septoplasty Effectiveness (NOSE) study. *Otolaryngol Head Neck Surg*. Mar 2004;130(3):283-90. doi:10.1016/j.otohns.2003.12.004

626. Bugten V, Nilsen AH, Thorstensen WM, Moxness MH, Amundsen MF, Nordgard S. Quality of life and symptoms before and after nasal septoplasty compared with healthy individuals. *BMC Ear Nose Throat Disord*. 2016;16:13. doi:10.1186/s12901-016-0031-7

627. Manteghi A, Din H, Bundogji N, Leuin SC. Pediatric septoplasty and functional septorhinoplasty: A quality of life outcome study. *Int J Pediatr Otorhinolaryngol*. Aug 2018;111:16-20. doi:10.1016/j.ijporl.2018.05.016

628. Sokoya M, Gonzalez JR, Winkler AA. Effect of allergic rhinitis on nasal obstruction outcomes after functional open septorhinoplasty. *Am J Otolaryngol*. May - Jun 2018;39(3):303-306. doi:10.1016/j.amjoto.2018.03.014

629. Gillman GS, Staltari GV, Chang YF, Mattos JL. A Prospective Study of Outcomes of Septoplasty with Turbinate Reductions in Patients with Allergic Rhinitis. *Otolaryngol Head Neck Surg*. Jun 2019;160(6):1118-1123. doi:10.1177/0194599819838761

630. Kokubo LCP, Carvalho TBO, Fornazieri MA, Gomes EMC, Alves CMF, Sampaio ALL. Effects of septorhinoplasty on smell perception. *Eur Arch Otorhinolaryngol*. Apr 2019;276(4):1247-1250. doi:10.1007/s00405-019-05356-1

631. Gerecci D, Casanueva FJ, Mace JC, et al. Nasal obstruction symptom evaluation (NOSE) score outcomes after septorhinoplasty. *Laryngoscope*. Apr 2019;129(4):841-846. doi:10.1002/lary.27578

632. Kim SD, Jung DW, Lee JW, Park JH, Mun SJ, Cho KS. Relationship between allergic rhinitis and nasal surgery success in patients with obstructive sleep apnea. *Am J Otolaryngol*. Nov-Dec 2021;42(6):103079. doi:10.1016/j.amjoto.2021.103079

633. Ghosh SK, Dutta M, Haldar D. Role of Bilateral Inferior Turbinoplasty as an Adjunct to Septoplasty in Improving Nasal Obstruction and Subjective Performance in Patients With Deviated Nasal Septum Associated With Allergic Rhinitis: An Interventional, Prospective Study. *Ear Nose Throat J*. May 10 2021:1455613211015440. doi:10.1177/01455613211015440

634. Topal O, Celik SB, Erbek S, Erbek SS. Risk of nasal septal perforation following septoplasty in patients with allergic rhinitis. *Eur Arch Otorhinolaryngol*. Feb 2011;268(2):231-3. doi:10.1007/s00405-010-1323-y

635. Eren E, Balci MK, Islek A. Analysis of patient- and procedure-related risk factors for nasal septal perforations following septoplasty. *Eur Arch Otorhinolaryngol*. Mar 2022;279(3):1357-1361. doi:10.1007/s00405-021-06887-2

636. Kim YH, Kim BJ, Bang KH, Hwang Y, Jang TY. Septoplasty improves life quality related to allergy in patients with septal deviation and allergic rhinitis. *Otolaryngol Head Neck Surg*. Dec 2011;145(6):910-4. doi:10.1177/0194599811424119

637. Chhabra N, Houser SM. The surgical management of allergic rhinitis. *Otolaryngol Clin North Am*. Jun 2011;44(3):779-95, xi. doi:10.1016/j.otc.2011.03.007

638. Chhabra N, Houser SM. Surgery for allergic rhinitis. *Int Forum Allergy Rhinol*. Sep 2014;4 Suppl 2:S79-83. doi:10.1002/alr.21387

639. Aksoy F, Yildirim YS, Veyseller B, Ozturan O, Demirhan H. Midterm outcomes of outfracture of the inferior turbinate. *Otolaryngol Head Neck Surg*. Oct 2010;143(4):579-84. doi:10.1016/j.otohns.2010.06.915

640. Mori S, Fujieda S, Igarashi M, Fan GK, Saito H. Submucous turbinectomy decreases not only nasal stiffness but also sneezing and rhinorrhea in patients with perennial allergic rhinitis. *Clin Exp Allergy*. Nov 1999;29(11):1542-8. doi:10.1046/j.1365-2222.1999.00645.x

641. Kaymakci M, Gur OE, Ozdem C. Nasal obstruction: comparison of radiofrequency with lateral displacement of the inferior turbinate and radiofrequency alone. *J Pak Med Assoc*. Jan 2014;64(1):33-7.

642. Assanasen P, Banhiran W, Tantilipikorn P, Pinkaew B. Combined radiofrequency volumetric tissue reduction and lateral outfracture of hypertrophic inferior turbinate in the treatment of chronic rhinitis: short-term and long-term outcome. *Int Forum Allergy Rhinol*. Apr 2014;4(4):339-44. doi:10.1002/alr.21278

643. Li KK, Powell NB, Riley RW, Troell RJ, Guilleminault C. Radiofrequency volumetric tissue reduction for treatment of turbinate hypertrophy: a pilot study. *Otolaryngol Head Neck Surg*. Dec 1998;119(6):569-73. doi:10.1016/S0194-5998(98)70013-0

644. Passali D, Lauriello M, Anselmi M, Bellussi L. Treatment of hypertrophy of the inferior turbinate: long-term results in 382 patients randomly assigned to therapy. *Ann Otol Rhinol Laryngol*. Jun 1999;108(6):569-75. doi:10.1177/000348949910800608

645. Zagolski O. [Effectiveness of bipolar coagulation in treatment of post-nasal drip in patients with chronic rhinitis--preliminary report]. *Przegl Lek*. 2007;64(1):9-11. Skutecznosc mukotomii przy uzyciu pesety bipolarnej w leczeniu splywania do gardla u chorych z przewleklym niezytem nosa--doniesienie wstepne.

646. Tani T, Seno S, Hanamitsu M, Shimizu T. [Clinical effectiveness of coblation-assisted inferior turbinoplasty]. *Arerugi*. Aug 2008;57(8):1053-60.

647. Liu CM, Tan CD, Lee FP, Lin KN, Huang HM. Microdebrider-assisted versus radiofrequency-assisted inferior turbinoplasty. *Laryngoscope*. Feb 2009;119(2):414-8. doi:10.1002/lary.20088

648. Hytonen ML, Back LJ, Malmivaara AV, Roine RP. Radiofrequency thermal ablation for patients with nasal symptoms: a systematic review of effectiveness and complications. *Eur Arch Otorhinolaryngol*. Aug 2009;266(8):1257-66. doi:10.1007/s00405-009-0914-y

649. Iwasaki A, Tokano H, Kamiyama R, Suzuki Y, Kitamura K. A 24-month-follow-up study of argon plasma coagulation of the inferior turbinate in patients with perennial nasal allergy. *J Med Dent Sci*. Mar 2010;57(1):11-5.

650. Zagolski O. Factors affecting outcome of inferior turbinate mucotomy in treatment of postnasal drip syndrome. *Am J Rhinol Allergy*. Nov-Dec 2010;24(6):459-63. doi:10.2500/ajra.2010.24.3524

651. Lin HC, Lin PW, Friedman M, et al. Long-term results of radiofrequency turbinoplasty for allergic rhinitis refractory to medical therapy. *Arch Otolaryngol Head Neck Surg*. Sep 2010;136(9):892-5. doi:10.1001/archoto.2010.135

652. Simeon R, Soufflet B, Souchal Delacour I. Coblation turbinate reduction in childhood allergic rhinitis. *Eur Ann Otorhinolaryngol Head Neck Dis*. May 2010;127(2):77-82. doi:10.1016/j.anorl.2010.04.004

653. Gunhan K, Unlu H, Yuceturk AV, Songu M. Intranasal steroids or radiofrequency turbinoplasty in persistent allergic rhinitis: effects on quality of life and objective parameters. *Eur Arch Otorhinolaryngol*. Jun 2011;268(6):845-50. doi:10.1007/s00405-010-1462-1

654. Di Rienzo Businco L, Di Rienzo Businco A, Ventura L, Laurino S, Lauriello M. Turbinoplasty with quantic molecular resonance in the treatment of persistent moderate-severe allergic rhinitis: Comparative analysis of efficacy. *Am J Rhinol Allergy*. Mar-Apr 2014;28(2):164-8. doi:10.2500/ajra.2014.28.3990

655. Garzaro M, Pezzoli M, Pecorari G, Landolfo V, Defilippi S, Giordano C. Radiofrequency inferior turbinate reduction: an evaluation of olfactory and respiratory function. *Otolaryngol Head Neck Surg*. Sep 2010;143(3):348-52. doi:10.1016/j.otohns.2010.06.908

656. Banhiran W, Tantilipikorn P, Metheetrairut C, Assanasen P, Bunnag C. Quality of life in patients with chronic rhinitis after radiofrequency inferior turbinate reduction. *J Med Assoc Thai*. Aug 2010;93(8):950-60.

657. Deenadayal DS, Kumar MN, Sudhakshin P, Hameed S. Radiofrequency reduction of inferior turbinates in allergic and non allergic rhinitis. *Indian J Otolaryngol Head Neck Surg*. Jan 2014;66(Suppl 1):231-6. doi:10.1007/s12070-011-0445-x

658. Ungkhara G, Purpermpulsiri P. Acoustic rhinometry evaluation in allergic rhinitis patients before and after turbinate radiofrequency ablation. *J Med Assoc Thai*. Feb 2011;94(2):200-4.

659. Parida PK, Santhosh K, Ganesan S, Surianarayanan G, Saxena SK. The efficacy of radiofrequency volumetric tissue reduction of hypertrophied inferior turbinate in allergic rhinitis. *Indian J Med Sci*. Jul 2011;65(7):269-77.

660. Lavinsky-Wolff M, Camargo HL, Jr., Barone CR, et al. Effect of turbinate surgery in rhinoseptoplasty on quality-of-life and acoustic rhinometry outcomes: a randomized clinical trial. *Laryngoscope*. Jan 2013;123(1):82-9. doi:10.1002/lary.23628

661. Garzaro M, Pezzoli M, Landolfo V, Defilippi S, Giordano C, Pecorari G. Radiofrequency inferior turbinate reduction: long-term olfactory and functional outcomes. *Otolaryngol Head Neck Surg*. Jan 2012;146(1):146-50. doi:10.1177/0194599811423008

662. Incandela C, Calamusa G, Massenti MF, Incandela S, Speciale R, Amodio E. Long-term efficacy of radiofrequency treatment of turbinate hypertrophy: a patient based point of view. *Indian J Otolaryngol Head Neck Surg*. Aug 2013;65(Suppl 2):226-30. doi:10.1007/s12070-011-0337-0

663. Fradis M, Malatskey S, Magamsa I, Golz A. Effect of submucosal diathermy in chronic nasal obstruction due to turbinate enlargement. *Am J Otolaryngol*. Nov-Dec 2002;23(6):332-6. doi:10.1053/ajot.2002.126857

664. Kojima Y, Tsuzuki K, Takebayashi H, Oka H, Sakagami M. Therapeutic evaluation of outpatient submucosal inferior turbinate surgery for patients with severe allergic rhinitis. *Allergol Int*. Dec 2013;62(4):479-85. doi:10.2332/allergolint.12-OA-0533

665. Bitar MA, Kanaan AA, Sinno S. Efficacy and safety of inferior turbinates coblation in children. *J Laryngol Otol*. Jul 2014;128 Suppl 2:S48-54. doi:10.1017/S0022215114000206

666. Akdag M, Dasdag S, Ozkurt FE, et al. Long-term effect of radiofrequency turbinoplasty in nasal obstruction. *Biotechnol Biotechnol Equip*. Mar 4 2014;28(2):285-294. doi:10.1080/13102818.2014.909083

667. Assanasen P, Choochurn P, Banhiran W, Bunnag C. Radiofrequency inferior turbinate reduction improves smell ability of patients with chronic rhinitis and inferior turbinate hypertrophy. *Allergy Rhinol (Providence)*. Mar 2014;5(1):12-6. doi:10.2500/ar.2014.5.0077

668. Acevedo JL, Camacho M, Brietzke SE. Radiofrequency Ablation Turbinoplasty versus Microdebrider-Assisted Turbinoplasty: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. Dec 2015;153(6):951-6. doi:10.1177/0194599815607211

669. Arganbright JM, Jensen EL, Mattingly J, Gao D, Chan KH. Utility of Inferior Turbinoplasty for the Treatment of Nasal Obstruction in Children: A 10-Year Review. *JAMA Otolaryngol Head Neck Surg*. Oct 2015;141(10):901-4. doi:10.1001/jamaoto.2015.1560

670. Shah AN, Brewster D, Mitzen K, Mullin D. Radiofrequency Coblation Versus Intramural Bipolar Cautery for the Treatment of Inferior Turbinate Hypertrophy. *Ann Otol Rhinol Laryngol*. Sep 2015;124(9):691-7. doi:10.1177/0003489415578709

671. Banhiran W, Assanasen P, Tantilipikorn P, Nujchanart N, Voraprayoon S, Bunnag C. A randomized study of temperature-controlled versus bipolar radiofrequency for inferior turbinate reduction. *Eur Arch Otorhinolaryngol*. Oct 2015;272(10):2877-84. doi:10.1007/s00405-014-3410-y

672. Sinno S, Mehta K, Lee ZH, Kidwai S, Saadeh PB, Lee MR. Inferior Turbinate Hypertrophy in Rhinoplasty: Systematic Review of Surgical Techniques. *Plast Reconstr Surg*. Sep 2016;138(3):419e-429e. doi:10.1097/PRS.0000000000002433

673. Ishida H, Yoshida T, Hasegawa T, Mohri M, Amatsu M. Submucous electrocautery following submucous resection of turbinate bone--a rationale of surgical treatment for allergic rhinitis. *Auris Nasus Larynx*. May 2003;30(2):147-52. doi:10.1016/s0385-8146(03)00010-5

674. De Corso E, Bastanza G, Di Donfrancesco V, et al. Radiofrequency volumetric inferior turbinate reduction: long-term clinical results. *Acta Otorhinolaryngol Ital*. Jun 2016;36(3):199-205. Riduzione volumetrica dei turbinati inferiori con radiofrequenze: risultati clinici a lungo termine. doi:10.14639/0392-100X-964

675. Lukka VK, Jacob TM, Jeyaseelan V, Rupa V. Do turbinate reduction procedures restore epithelial integrity in patients with turbinate hypertrophy secondary to allergic rhinitis? A histopathological study. *Eur Arch Otorhinolaryngol*. Jun 2018;275(6):1457-1467. doi:10.1007/s00405-018-4955-y

676. Turk B, Korkut AY, Kaya KS, et al. Results of Radiofrequency Ablation of Inferior Turbinate Hypertrophy in Patients with Allergic and Non-Allergic Rhinitis. *Sisli Etfal Hastan Tip Bul*. 2018;52(4):296-301. doi:10.14744/SEMB.2018.77992

677. Zhong B, Li LK, Deng D, et al. Effect of High-Intensity Focused Ultrasound Versus Plasma Radiofrequency Ablation on Recurrent Allergic Rhinitis. *Med Sci Monit*. Sep 9 2019;25:6775-6781. doi:10.12659/MSM.916228

678. Kang T, Sung CM, Yang HC. Radiofrequency ablation of turbinates after septoplasty has no effect on allergic rhinitis symptoms other than nasal obstruction. *Int Forum Allergy Rhinol*. Nov 2019;9(11):1257-1262. doi:10.1002/alr.22420

679. Mun IK, Yoo SH, Mo JH. Long-term outcome of concurrent coblator turbinoplasty with adenotonsillectomy in children with allergic rhinitis. *Acta Otolaryngol*. Mar 2021;141(3):286-292. doi:10.1080/00016489.2020.1846782

680. Pecorari G, Riva G, Bartoli C, et al. Nasal Cytology in Radiofrequency Turbinate Volume Reduction. *ORL J Otorhinolaryngol Relat Spec*. 2021;83(4):252-257. doi:10.1159/000513629

681. Whelan RL, Shaffer AD, Stapleton AL. Efficacy of inferior turbinate reduction in pediatric patients: a prospective analysis. *Int Forum Allergy Rhinol*. Dec 2021;11(12):1654-1662. doi:10.1002/alr.22849

682. Ogino-Nishimura E, Okamura HO, Takiguchi Y. Argon plasma coagulation for intractable nasal obstruction occurring in patients with allergic rhinitis. *Fukushima J Med Sci*. Jun 2003;49(1):15-22. doi:10.5387/fms.49.15

683. Lin HC, Lin PW, Su CY, Chang HW. Radiofrequency for the treatment of allergic rhinitis refractory to medical therapy. *Laryngoscope*. Apr 2003;113(4):673-8. doi:10.1097/00005537-200304000-00017

684. Tokano H, Maehara H, Nakamura H, Makino N, Iwasaki A, Kitamura K. Short-term effect of argon plasma coagulation of the inferior turbinate in patients with perennial nasal allergy. *Auris Nasus Larynx*. Jun 2005;32(2):145-50. doi:10.1016/j.anl.2005.01.002

685. Fang CX, Zhen SS. [Nasal endoscopy combined with multiple radiofrequency for perennial allergic rhinitis]. *Di Yi Jun Yi Da Xue Xue Bao*. Jul 2005;25(7):876-7.

686. Ding H, Liu J, Wang T, Xia G, Liu W. [Combination application of radiofrequency ablation in nasal operation]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi*. Oct 2005;19(20):918-9, 922.

687. Quine SM, Aitken PM, Eccles R. Effect of submucosal diathermy to the inferior turbinates on unilateral and total nasal airflow in patients with rhinitis. *Acta Otolaryngol*. 1999;119(8):911-5. doi:10.1080/00016489950180270

688. Sroka R, Janda P, Killian T, Vaz F, Betz CS, Leunig A. Comparison of long term results after Ho:YAG and diode laser treatment of hyperplastic inferior nasal turbinates. *Lasers Surg Med*. Apr 2007;39(4):324-31. doi:10.1002/lsm.20479

689. Chusakul S, Choktaweekarn T, Snidvongs K, Phannaso C, Aeumjaturapat S. Effect of the KTP laser in inferior turbinate surgery on eosinophil influx in allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2011;144(2):237-40. doi:10.1177/0194599810390448

690. Caffier PP, Scherer H, Neumann K, Luck S, Enzmann H, Haisch A. Diode laser treatment in therapy-resistant allergic rhinitis: impact on nasal obstruction and associated symptoms. *Lasers Med Sci*. Jan 2011;26(1):57-67. doi:10.1007/s10103-010-0813-x

691. Gupta P, Kc T, Regmi D. Diode Laser Turbinate Reduction in Allergic Rhinitis: A Cross-sectional Study. *JNMA J Nepal Med Assoc*. Nov-Dec 2018;56(214):949-952.

692. Sasaki K, Ohshiro T, Sakio R, et al. Efficacy of seasonal allergic rhinitis using an 810 nm diode laser system. *Laser Ther*. Mar 31 2019;28(1):11-18. doi:10.5978/islsm.28_19-OR-01

693. Tanigawa T, Yashiki T, Hayashi K, Sato T. Carbon dioxide laser vaporization for turbinate: optimal conditions and indications. *Auris Nasus Larynx*. Apr 2000;27(2):137-40. doi:10.1016/s0385-8146(99)00061-9

694. Kunachak S, Kulapaditharom B, Prakunhungsit S. Minimally invasive KTP laser treatment of perennial allergic rhinitis: a preliminary report. *J Otolaryngol*. Jun 2000;29(3):139-43.

695. Janda P, Sroka R, Betz CS, Grevers G, Leunig A. [Ho:YAG and diode laser treatment of hyperplastic inferior nasal turbinates]. *Laryngorhinootologie*. Jul 2002;81(7):484-90. Die Laserkonchotomie mit Ho:YAG- und Dioden-Laser zur Behandlung von hyperplastischen Nasenmuscheln. doi:10.1055/s-2002-33288

696. Janda P, Sroka R, Tauber S, Baumgartner R, Grevers G, Leunig A. Diode laser treatment of hyperplastic inferior nasal turbinates. *Lasers Surg Med*. 2000;27(2):129-39. doi:10.1002/1096-9101(2000)27:2<129::aid-lsm4>3.0.co;2-r

697. Takeno S, Osada R, Ishino T, Yajin K. Laser surgery of the inferior turbinate for allergic rhinitis with seasonal exacerbation: an acoustic rhinometry study. *Ann Otol Rhinol Laryngol*. May 2003;112(5):455-60. doi:10.1177/000348940311200513

698. Imamura S, Honda H. Carbon dioxide laser vaporization of the inferior turbinate for allergic rhinitis: short-term results. *Ann Otol Rhinol Laryngol*. Dec 2003;112(12):1043-9. doi:10.1177/000348940311201209

699. Sandhu AS, Temple RH, Timms MS. Partial laser turbinectomy: two year outcomes in patients with allergic and non-allergic rhinitis. *Rhinology*. Jun 2004;42(2):81-4.

700. Takeno S, Osada R, Furukido K, Yajin K. Analysis of local cytokine gene expression in patients with allergic rhinitis treated with CO2 laser surgery. *Laryngoscope*. Nov 2000;110(11):1968-74. doi:10.1097/00005537-200011000-00038

701. Lee JY. Efficacy of intra- and extraturbinal microdebrider turbinoplasty in perennial allergic rhinitis. *Laryngoscope*. Dec 2013;123(12):2945-9. doi:10.1002/lary.24215

702. Parthasarathi K, Christensen JM, Alvarado R, Barham HP, Sacks R, Harvey RJ. Airflow and symptom outcomes between allergic and non-allergic rhinitis patients from turbinoplasty. *Rhinology*. Dec 1 2017;55(4):332-338. doi:10.4193/Rhin16.210

703. Ikeda K, Oshima T, Suzuki M, Suzuki H, Shimomura A. Functional inferior turbinosurgery (FITS) for the treatment of resistant chronic rhinitis. *Acta Otolaryngol*. Jul 2006;126(7):739-45. doi:10.1080/00016480500472853

704. Huang TW, Cheng PW. Changes in nasal resistance and quality of life after endoscopic microdebrider-assisted inferior turbinoplasty in patients with perennial allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. Sep 2006;132(9):990-3. doi:10.1001/archotol.132.9.990

705. Wu CC, Lee SY, Hsu CJ, Yeh TH. Patients with positive allergen test have less favorable outcome after endoscopic microdebrider-assisted inferior turbinoplasty. *Am J Rhinol*. Jan-Feb 2008;22(1):20-3. doi:10.2500/ajr.2008.22.3116

706. Chen YL, Tan CT, Huang HM. Long-term efficacy of microdebrider-assisted inferior turbinoplasty with lateralization for hypertrophic inferior turbinates in patients with perennial allergic rhinitis. *Laryngoscope*. Jul 2008;118(7):1270-4. doi:10.1097/MLG.0b013e31816d728e

707. Neri G, Mastronardi V, Traini T, D'Orazio F, Pugliese M, Cazzato F. Respecting nasal mucosa during turbinate surgery: end of the dogma? *Rhinology*. Dec 2013;51(4):368-75. doi:10.4193/Rhino12.124

708. de Moura BH, Migliavacca RO, Lima RK, et al. Partial inferior turbinectomy in rhinoseptoplasty has no effect in quality-of-life outcomes: A randomized clinical trial. *Laryngoscope*. Jan 2018;128(1):57-63. doi:10.1002/lary.26831

709. Suzuki M, Yokota M, Ozaki S, Murakami S. The effects of resection of the peripheral branches of the posterior nasal nerves in the inferior turbinate, with special focus on olfactory dysfunction. *J Laryngol Otol*. Dec 2019;133(12):1046-1049. doi:10.1017/S0022215119002238

710. Mori S, Fujieda S, Yamada T, Kimura Y, Takahashi N, Saito H. Long-term effect of submucous turbinectomy in patients with perennial allergic rhinitis. *Laryngoscope*. May 2002;112(5):865-9. doi:10.1097/00005537-200205000-00016

711. Ogawa T, Takeno S, Ishino T, Hirakawa K. Submucous turbinectomy combined with posterior nasal neurectomy in the management of severe allergic rhinitis: clinical outcomes and local cytokine changes. *Auris Nasus Larynx*. Sep 2007;34(3):319-26. doi:10.1016/j.anl.2007.01.008

712. Tan G, Ma Y, Li H, Li W, Wang J. Long-term results of bilateral endoscopic vidian neurectomy in the management of moderate to severe persistent allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. May 2012;138(5):492-7. doi:10.1001/archoto.2012.284

713. Hamerschmidt R, Hamerschmidt R, Moreira AT, Tenorio SB, Timi JR. Comparison of turbinoplasty surgery efficacy in patients with and without allergic rhinitis. *Braz J Otorhinolaryngol*. Mar-Apr 2016;82(2):131-9. doi:10.1016/j.bjorl.2015.10.010

714. Piromchai P, Pornumnouy W, Saeseow P, Chainansamit S. The minimum effective dose of abobotulinum toxin A injection for allergic rhinitis: A dose-escalation randomized controlled trial. *Laryngoscope Investig Otolaryngol*. Feb 2021;6(1):6-12. doi:10.1002/lio2.499

715. Abtahi SM, Hashemi SM, Abtahi SH, Bastani B. Septal injection in comparison with inferior turbinates injection of botulinum toxin A in patients with allergic rhinitis. *J Res Med Sci*. May 2013;18(5):400-4.

716. Unal M, Sevim S, Dogu O, Vayisoglu Y, Kanik A. Effect of botulinum toxin type A on nasal symptoms in patients with allergic rhinitis: a double-blind, placebo-controlled clinical trial. *Acta Otolaryngol*. Dec 2003;123(9):1060-3. doi:10.1080/00016480310000755

717. Wei H, Zhang Y, Shi L, et al. Higher dosage of HIFU treatment may lead to higher and longer efficacy for moderate to severe perennial allergic rhinitis. *Int J Med Sci*. 2013;10(13):1914-20. doi:10.7150/ijms.7117

718. Wei H, Shi L, Zhang J, et al. High-intensity focused ultrasound leads to histopathologic changes of the inferior turbinate mucosa with allergic inflammation. *Ultrasound Med Biol*. Oct 2014;40(10):2425-30. doi:10.1016/j.ultrasmedbio.2014.05.016

719. Ibrahim N, Tyler MA, Borchard NA, Rathor A, Nayak JV. Nasal vestibular body treatment for recalcitrant nasal obstruction. *Int Forum Allergy Rhinol*. Mar 2020;10(3):388-394. doi:10.1002/alr.22463

720. Kim SJ, Kim HT, Park YH, Kim JY, Bae JH. Coblation nasal septal swell body reduction for treatment of nasal obstruction: a preliminary report. *Eur Arch Otorhinolaryngol*. Sep 2016;273(9):2575-8. doi:10.1007/s00405-016-3946-0

721. Karpishchenko S, Ulupov M, Gindryuk capital A C, Kaplun D. Using thermal effect of 970 nm diode laser to reduce nasal swell body. *Am J Otolaryngol*. Nov-Dec 2021;42(6):103165. doi:10.1016/j.amjoto.2021.103165

722. Catalano P, Ashmead MG, Carlson D. Radiofrequency ablation of septal swell body. *Ann Otolaryngol Rhinol*. 2015;2(11):1069.

723. Yu MS, Kim JY, Kim BH, Kang SH, Lim DJ. Feasibility of septal body volume reduction for patients with nasal obstruction. *Laryngoscope*. Jul 2015;125(7):1523-8. doi:10.1002/lary.25154

724. Lai WS, Cheng SY, Lin YY, et al. Clinical assessment of diode laser-assisted endoscopic intrasphenoidal vidian neurectomy in the treatment of refractory rhinitis. *Lasers Med Sci*. Dec 2017;32(9):2097-2104. doi:10.1007/s10103-017-2330-7

725. Su WF, Liu SC, Chiu FS, Lee CH. Antegrade transsphenoidal vidian neurectomy: short-term surgical outcome analysis. *Am J Rhinol Allergy*. Nov-Dec 2011;25(6):e217-20. doi:10.2500/ajra.2011.25.3704

726. Ai J, Xie Z, Qing X, et al. Clinical Effect of Endoscopic Vidian Neurectomy on Bronchial Asthma Outcomes in Patients with Coexisting Refractory Allergic Rhinitis and Asthma. *Am J Rhinol Allergy*. May 2018;32(3):139-146. doi:10.1177/1945892418764964

727. Shen L, Wang J, Kang X, et al. Clinical Efficacy and Possible Mechanism of Endoscopic Vidian Neurectomy for House Dust Mite-Sensitive Allergic Rhinitis. *ORL J Otorhinolaryngol Relat Spec*. 2021;83(2):75-84. doi:10.1159/000511711

728. Maimaitiaili G, Kahaer K, Tang L, Zhang J. The Effect of Vidian Neurectomy on Pulmonary Function in Patients with Allergic Rhinitis and Chronic Rhinosinusitis with Nasal Polyps. *Am J Med Sci*. Aug 2020;360(2):137-145. doi:10.1016/j.amjms.2020.04.024

729. Qi Y, Liu J, Peng S, Hou S, Zhang M, Wang Z. Efficacy of Selective Vidian Neurectomy for Allergic Rhinitis Combined with Chronic Rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec*. 2021;83(5):327-334. doi:10.1159/000512083

730. Konno A. Historical, pathophysiological, and therapeutic aspects of vidian neurectomy. *Curr Allergy Asthma Rep*. Mar 2010;10(2):105-12. doi:10.1007/s11882-010-0093-3

731. Bleier BS, Schlosser RJ. Endoscopic anatomy of the postganglionic pterygopalatine innervation of the posterolateral nasal mucosa. *Int Forum Allergy Rhinol*. Mar-Apr 2011;1(2):113-7. doi:10.1002/alr.20011

732. Wang EW, Gardner PA, Fraser S, Stefko ST, Fernandez-Miranda JC, Snyderman CH. Reduced Tearing With Stable Quality of Life After Vidian Neurectomy: A Prospective Controlled Trial. *Laryngoscope*. Jul 2021;131(7):1487-1491. doi:10.1002/lary.29287

733. Makihara S, Okano M, Miyamoto S, et al. Underwater posterior nasal neurectomy compared to resection of peripheral branches of posterior nerve in severe allergic rhinitis. *Acta Otolaryngol*. Aug 2021;141(8):780-785. doi:10.1080/00016489.2021.1925151

734. Hua H, Wang G, Zhao Y, Wang D, Qiu Z, Fang P. The long-term outcomes of posterior nasal neurectomy with or without pharyngeal neurectomy in patients with allergic rhinitis: a randomized controlled trial. *Braz J Otorhinolaryngol*. May 29 2021;doi:10.1016/j.bjorl.2021.05.006

735. Wang L, Chen M, Xu M. Effect of posterior nasal neurectomy on the suppression of allergic rhinitis. *Am J Otolaryngol*. May - Jun 2020;41(3):102410. doi:10.1016/j.amjoto.2020.102410

736. Li S, Cheng J, Yang J, et al. Efficacy of posterior nasal neurectomy for allergic rhinitis combined with chronic rhinosinusitis with nasal polyps. *Acta Otolaryngol*. Oct 2019;139(10):890-894. doi:10.1080/00016489.2019.1654132

737. Takahara D, Takeno S, Hamamoto T, Ishino T, Hirakawa K. Management of Intractable Nasal Hyperreactivity by Selective Resection of Posterior Nasal Nerve Branches. *Int J Otolaryngol*. 2017;2017:1907862. doi:10.1155/2017/1907862

738. Ogi K, Manabe Y, Mori S, et al. Long-term effect of combined submucous turbinectomy and posterior nasal neurectomy in patients with allergic rhinitis. *SN Comp Clin Med*. 2019;1:540-546.

739. Marshak T, Yun WK, Hazout C, Sacks R, Harvey RJ. A systematic review of the evidence base for vidian neurectomy in managing rhinitis. *J Laryngol Otol*. Jul 2016;130 Suppl 4:S7-S28. doi:10.1017/S0022215116008008

740. Albu S, Trombitas V, Nagy A. Endoscopic microdebrider-assisted inferior turbinoplasty with and without posterior nasal neurectomy. *Auris Nasus Larynx*. Jun 2014;41(3):273-7. doi:10.1016/j.anl.2013.10.018

741. Terao A, Meshitsuka K, Suzaki H, Fukuda S. Cryosurgery on postganglionic fibers (posterior nasal branches) of the pterygopalatine ganglion for vasomotor rhinitis. *Acta Otolaryngol*. Jul-Aug 1983;96(1-2):139-48. doi:10.3109/00016488309132884

742. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol*. Oct 2017;7(10):952-956. doi:10.1002/alr.21991

743. D MY, D BC, O'Malley EM, Byerly TA, Johnson J. Multiple Site Cryoablation Treatment of the Posterior Nasal Nerve for Treatment of Chronic Rhinitis: An Observational Feasibility Study. *Allergy Rhinol (Providence)*. Jan-Dec 2020;11:2152656720946996. doi:10.1177/2152656720946996

744. Del Signore AG, Greene JB, Russell JL, Yen DM, O'Malley EM, Schlosser RJ. Cryotherapy for treatment of chronic rhinitis: 3-month outcomes of a randomized, sham-controlled trial. *Int Forum Allergy Rhinol*. Jan 2022;12(1):51-61. doi:10.1002/alr.22868

745. Ow RA, O'Malley EM, Han JK, Lam KK, Yen DM. Cryosurgical Ablation for Treatment of Rhinitis: Two-Year Results of a Prospective Multicenter Study. *Laryngoscope*. Sep 2021;131(9):1952-1957. doi:10.1002/lary.29453

746. Gerka Stuyt JA, Luk L, Keschner D, Garg R. Evaluation of In-Office Cryoablation of Posterior Nasal Nerves for the Treatment of Rhinitis. *Allergy Rhinol (Providence)*. Jan-Dec 2021;12:2152656720988565. doi:10.1177/2152656720988565

747. Chang MT, Song S, Hwang PH. Cryosurgical ablation for treatment of rhinitis: A prospective multicenter study. *Laryngoscope*. Aug 2020;130(8):1877-1884. doi:10.1002/lary.28301

748. Yoo F, Kuan EC, Batra PS, Chan CK, Tajudeen BA, Craig JR. Predictors of rhinorrhea response after posterior nasal nerve cryoablation for chronic rhinitis. *Int Forum Allergy Rhinol*. Jul 2020;10(7):913-919. doi:10.1002/alr.22574

749. Ehmer D, McDuffie CM, Scurry WC, Jr., et al. Temperature-Controlled Radiofrequency Neurolysis for the Treatment of Rhinitis. *Am J Rhinol Allergy*. Jan 2022;36(1):149-156. doi:10.1177/19458924211033400

750. Stolovitzky JP, Ow RA, Silvers SL, Bikhazi NB, Johnson CD, Takashima M. Effect of Radiofrequency Neurolysis on the Symptoms of Chronic Rhinitis: A Randomized Controlled Trial. *OTO Open*. Jul-Sep 2021;5(3):2473974X211041124. doi:10.1177/2473974X211041124

751. Krespi YP, Wilson KA, Kizhner V. Laser ablation of posterior nasal nerves for rhinitis. *Am J Otolaryngol*. May - Jun 2020;41(3):102396. doi:10.1016/j.amjoto.2020.102396

752. Singh AK, Kasle DA, Torabi SJ, Manes RP. Adverse Events Associated With ClariFix Posterior Nasal Nerve Cryoablation: A MAUDE Database Analysis. *Otolaryngol Head Neck Surg*. Oct 2021;165(4):597-601. doi:10.1177/0194599820986581

753. Jose J, Coatesworth AP. Inferior turbinate surgery for nasal obstruction in allergic rhinitis after failed medical treatment. *Cochrane Database Syst Rev*. Dec 8 2010;(12):CD005235. doi:10.1002/14651858.CD005235.pub2

754. Langille M, El-Hakim H. Pediatric inferior turbinoplasty with or without adenoidectomy: preliminary report on improvement of quality of life, symptom control, and safety. *J Otolaryngol Head Neck Surg*. Oct 2011;40(5):420-6.

755. Di Rienzo Businco L, Di Rienzo Businco A, Lauriello M. Comparative study on the effectiveness of Coblation-assisted turbinoplasty in allergic rhinitis. *Rhinology*. Jun 2010;48(2):174-8. doi:10.4193/Rhin09.149

756. Kobayashi T, Hyodo M, Nakamura K, Komobuchi H, Honda N. Resection of peripheral branches of the posterior nasal nerve compared to conventional posterior neurectomy in severe allergic rhinitis. *Auris Nasus Larynx*. Dec 2012;39(6):593-6. doi:10.1016/j.anl.2011.11.006

757. Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. Apr 2018;73(4):765-798. doi:10.1111/all.13317

758. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. Jan 2011;127(1 Suppl):S1-55. doi:10.1016/j.jaci.2010.09.034

759. Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol*. Oct 2011;128(4):791-799 e6. doi:10.1016/j.jaci.2011.03.049

760. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. Dec 8 2010;(12):CD002893. doi:10.1002/14651858.CD002893.pub2

761. Tie K, Miller C, Zanation AM, Ebert CS, Jr. Subcutaneous Versus Sublingual Immunotherapy for Adults with Allergic Rhinitis: A Systematic Review with Meta-Analyses. *Laryngoscope*. Mar 2022;132(3):499-508. doi:10.1002/lary.29586

762. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. Aug 12 1999;341(7):468-75. doi:10.1056/NEJM199908123410702

763. Ebner C, Kraft D, Ebner H. Booster immunotherapy (BIT). *Allergy*. Jan 1994;49(1):38-42. doi:10.1111/j.1398-9995.1994.tb00771.x

764. Arroabarren E, Tabar AI, Echechipia S, Cambra K, Garcia BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. *Pediatr Allergy Immunol*. Feb 2015;26(1):34-41. doi:10.1111/pai.12296

765. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. Feb 2017;28(1):18-29. doi:10.1111/pai.12661

766. Schmitt J, Schwarz K, Stadler E, Wustenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: Results from a large retrospective cohort study. *J Allergy Clin Immunol*. Dec 2015;136(6):1511-1516. doi:10.1016/j.jaci.2015.07.038

767. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. Aug 2007;62(8):943-8. doi:10.1111/j.1398-9995.2007.01451.x

768. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*. Feb 2018;141(2):529-538 e13. doi:10.1016/j.jaci.2017.06.014

769. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol*. Sep 2005;95(3):254-8. doi:10.1016/S1081-1206(10)61222-7

770. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy*. Jan 2005;60(1):133. doi:10.1111/j.1398-9995.2004.00616.x

771. Darsow U. Allergen-specific immunotherapy for atopic eczema: updated. *Curr Opin Allergy Clin Immunol*. Dec 2012;12(6):665-9. doi:10.1097/ACI.0b013e3283588cf4

772. Passalacqua G, Canonica GW. Allergen Immunotherapy: History and Future Developments. *Immunol Allergy Clin North Am*. Feb 2016;36(1):1-12. doi:10.1016/j.iac.2015.08.001

773. Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol*. Mar 2017;118(3):276-282 e2. doi:10.1016/j.anai.2016.12.009

774. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol*. Mar 2014;133(3):621-31. doi:10.1016/j.jaci.2013.12.1088

775. Nelson HS, Makatsori M, Calderon MA. Subcutaneous Immunotherapy and Sublingual Immunotherapy: Comparative Efficacy, Current and Potential Indications, and Warnings--United States Versus Europe. *Immunol Allergy Clin North Am*. Feb 2016;36(1):13-24. doi:10.1016/j.iac.2015.08.005

776. Lawrence MG, Steinke JW, Borish L. Basic science for the clinician: Mechanisms of sublingual and subcutaneous immunotherapy. *Ann Allergy Asthma Immunol*. Aug 2016;117(2):138-42. doi:10.1016/j.anai.2016.06.027

777. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. *Allergy*. Nov 2017;72(11):1597-1631. doi:10.1111/all.13201

778. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic overview of systematic reviews. *Clin Transl Allergy*. 2017;7:24. doi:10.1186/s13601-017-0159-6

779. Lin SY, Erekosima N, Suarez-Cuervo C, et al. *Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review*. 2013. *AHRQ Comparative Effectiveness Reviews*.

780. Epstein TG, Murphy-Berendts K, Liss GM, Bernstein DI. Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): postinjection monitoring and severe asthma. *Ann Allergy Asthma Immunol*. Jul 2021;127(1):64-69 e1. doi:10.1016/j.anai.2021.03.011

781. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee AAoAA, Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol*. Jun 2004;113(6):1129-36. doi:10.1016/j.jaci.2004.02.006

782. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol*. Apr 2013;110(4):274-8, 278 e1. doi:10.1016/j.anai.2013.01.015

783. Lee S, Hess EP, Nestler DM, et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. *J Allergy Clin Immunol*. Apr 2013;131(4):1103-8. doi:10.1016/j.jaci.2013.01.011

784. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol*. Mar 2005;115(3):606-10. doi:10.1016/j.jaci.2004.11.012

785. Pitsios C, Tsoumani M, Bilo MB, et al. Contraindications to immunotherapy: a global approach. *Clin Transl Allergy*. 2019;9:45. doi:10.1186/s13601-019-0285-4

786. Wohrl S, Kinaciyan T, Jalili A, Stingl G, Moritz KB. Malignancy and specific allergen immunotherapy: the results of a case series. *Int Arch Allergy Immunol*. 2011;156(3):313-9. doi:10.1159/000323519

787. Linneberg A, Jacobsen RK, Jespersen L, Abildstrom SZ. Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischemic heart disease, and mortality. *J Allergy Clin Immunol*. Feb 2012;129(2):413-9. doi:10.1016/j.jaci.2011.09.007

788. Bozek A, Kolodziejczyk K, Bednarski P. The relationship between autoimmunity and specific immunotherapy for allergic diseases. *Hum Vaccin Immunother*. 2015;11(12):2764-8. doi:10.1080/21645515.2015.1087627

789. Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. *Clin Exp Allergy*. Oct 1993;23(10):857-60. doi:10.1111/j.1365-2222.1993.tb00264.x

790. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. *Allergy*. Jun 2012;67(6):741-3. doi:10.1111/j.1398-9995.2012.02815.x

791. Odactra House Dust Mite (Dermatophagoides farinae and Dermatophagoides pteronyssinus) allergen extract tablet for sublingual use. Accessed October 8, 2021, fda.gov/media/103380/download

792. ORALAIR (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/87935/download

793. Grastek Timothy grass pollen extract tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/88510/download

794. Ragwitek short ragweed pollen extract tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/88712/download

795. Osguthorpe JD. The evolution of understanding inhalant allergy. *Otolaryngol Clin North Am*. Jun 2011;44(3):519-35, vii. doi:10.1016/j.otc.2011.03.008

796. Noon L. Prophylactic inoculation against hayfever. *Lancet*. 1911;1:1572-1573.

797. Mason WW, Ward WA. Standardized extracts. *Otolaryngol Clin North Am*. Feb 1992;25(1):101-17.

798. Zimmer J, Vieths S, Kaul S. Standardization and Regulation of Allergen Products in the European Union. *Curr Allergy Asthma Rep*. Mar 2016;16(3):21. doi:10.1007/s11882-016-0599-4

799. Carnes J, Iraola V, Gallego M, Leonor JR. Control Process for Manufacturing and Standardization of Allergenic Molecules. *Curr Allergy Asthma Rep*. Jul 2015;15(7):37. doi:10.1007/s11882-015-0541-1

800. Zimmer J, Bridgewater J, Ferreira F, van Ree R, Rabin RL, Vieths S. The History, Present and Future of Allergen Standardization in the United States and Europe. *Front Immunol*. 2021;12:725831. doi:10.3389/fimmu.2021.725831

801. Park KH, Son M, Choi SY, et al. In vitro evaluation of allergen potencies of commercial house dust mite sublingual immunotherapy reagents. *Allergy Asthma Immunol Res*. Mar 2015;7(2):124-9. doi:10.4168/aair.2015.7.2.124

802. Thomsen GF, Schlunssen V, Skadhauge LR, et al. Are allergen batch differences and the use of double skin prick test important? *BMC Pulm Med*. Apr 9 2015;15:33. doi:10.1186/s12890-015-0021-3

803. Slater JE. Standardized allergen extracts in the United States. *Clin Allergy Immunol*. 2004;18:421-32.

804. Jutel M, Agache I, Bonini S, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol*. Feb 2016;137(2):358-68. doi:10.1016/j.jaci.2015.12.1300

805. Zakzuk J, Kilimajer J, Lockey R. World Allergy Organization Allergen Standardization and Characterization. Updated January 2019. Accessed June 3, 2022, https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/allergen-standardization-and-characterization

806. van Ree R, Chapman MD, Ferreira F, et al. The CREATE project: development of certified reference materials for allergenic products and validation of methods for their quantification. *Allergy*. Mar 2008;63(3):310-26. doi:10.1111/j.1398-9995.2007.01612.x

807. Mucci T, Govindaraj S, Tversky J. Allergic rhinitis. *Mt Sinai J Med*. Sep-Oct 2011;78(5):634-44. doi:10.1002/msj.20287

808. Petrovsky N. Comparative Safety of Vaccine Adjuvants: A Summary of Current Evidence and Future Needs. *Drug Saf*. Nov 2015;38(11):1059-74. doi:10.1007/s40264-015-0350-4

809. Gunawardana NC, Durham SR. New approaches to allergen immunotherapy. *Ann Allergy Asthma Immunol*. Sep 2018;121(3):293-305. doi:10.1016/j.anai.2018.07.014

810. Leuthard DS, Duda A, Freiberger SN, et al. Microcrystalline Tyrosine and Aluminum as Adjuvants in Allergen-Specific Immunotherapy Protect from IgE-Mediated Reactivity in Mouse Models and Act Independently of Inflammasome and TLR Signaling. *J Immunol*. May 1 2018;200(9):3151-3159. doi:10.4049/jimmunol.1800035

811. Zubeldia JM, Ferrer M, Davila I, Justicia JL. Adjuvants in Allergen-Specific Immunotherapy: Modulating and Enhancing the Immune Response. *J Investig Allergol Clin Immunol*. 2019;29(2):103-111. doi:10.18176/jiaci.0349

812. Johnson L, Duschl A, Himly M. Nanotechnology-Based Vaccines for Allergen-Specific Immunotherapy: Potentials and Challenges of Conventional and Novel Adjuvants under Research. *Vaccines (Basel)*. May 20 2020;8(2)doi:10.3390/vaccines8020237

813. Kirtland ME, Tsitoura DC, Durham SR, Shamji MH. Toll-Like Receptor Agonists as Adjuvants for Allergen Immunotherapy. *Front Immunol*. 2020;11:599083. doi:10.3389/fimmu.2020.599083

814. Feng Z, Yi X, Hajavi J. New and old adjuvants in allergen-specific immunotherapy: With a focus on nanoparticles. *J Cell Physiol*. Feb 2021;236(2):863-876. doi:10.1002/jcp.29941

815. Norman PS, Lichtenstein LM. Comparisons of alum-precipitated and unprecipitated aqueous ragweed pollen extracts in the treatment of hay fever. *J Allergy Clin Immunol*. Jun 1978;61(6):384-9. doi:10.1016/0091-6749(78)90118-5

816. Jensen-Jarolim E, Bachmann MF, Bonini S, et al. State-of-the-art in marketed adjuvants and formulations in Allergen Immunotherapy: A position paper of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy*. Apr 2020;75(4):746-760. doi:10.1111/all.14134

817. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A, Study G. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy*. Jun 2005;60(6):801-7. doi:10.1111/j.1398-9995.2005.00790.x

818. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy*. Jun 2001;56(6):498-505. doi:10.1034/j.1398-9995.2001.056006498.x

819. Tulic MK, Fiset PO, Christodoulopoulos P, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol*. Feb 2004;113(2):235-41. doi:10.1016/j.jaci.2003.11.001

820. Torii Y, Ito T, Amakawa R, et al. Imidazoquinoline acts as immune adjuvant for functional alteration of thymic stromal lymphopoietin-mediated allergic T cell response. *J Immunol*. Oct 15 2008;181(8):5340-9. doi:10.4049/jimmunol.181.8.5340

821. Tversky JR, Bieneman AP, Chichester KL, Hamilton RG, Schroeder JT. Subcutaneous allergen immunotherapy restores human dendritic cell innate immune function. *Clin Exp Allergy*. Jan 2010;40(1):94-102. doi:10.1111/j.1365-2222.2009.03388.x

822. Tversky JR, Le TV, Bieneman AP, Chichester KL, Hamilton RG, Schroeder JT. Human blood dendritic cells from allergic subjects have impaired capacity to produce interferon-alpha via Toll-like receptor 9. *Clin Exp Allergy*. May 2008;38(5):781-8. doi:10.1111/j.1365-2222.2008.02954.x

823. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. Oct 5 2006;355(14):1445-55. doi:10.1056/NEJMoa052916

824. Busse W, Korenblat P, Nayak A, et al. Phase 2/3 study of the novel vaccine Amb a 1 immunostimulatory oligodeoxyriboneucleotide conjugate AIC in ragweed allergic adults. *J Allergy Clin Immunol*. 2006;117:S88-89.

825. Leonard C, Montamat G, Davril C, et al. Comprehensive mapping of immune tolerance yields a regulatory TNF receptor 2 signature in a murine model of successful Fel d 1-specific immunotherapy using high-dose CpG adjuvant. *Allergy*. Jul 2021;76(7):2153-2165. doi:10.1111/all.14716

826. Senti G, Johansen P, Haug S, et al. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/IIa clinical trial. *Clin Exp Allergy*. Apr 2009;39(4):562-70. doi:10.1111/j.1365-2222.2008.03191.x

827. Rosewich M, Lee D, Zielen S. Pollinex Quattro: an innovative four injections immunotherapy in allergic rhinitis. *Hum Vaccin Immunother*. Jul 2013;9(7):1523-31. doi:10.4161/hv.24631

828. DuBuske LM, Frew AJ, Horak F, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc*. Nov 1 2011;32(6):466. doi:10.2500/108854111798840203

829. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. Jan 2014;133(1):121-9 e1-2. doi:10.1016/j.jaci.2013.05.032

830. Feynman R. *Plenty of room at the bottom*. 1959. *Lecture to the American Physical Society*.

831. Marty JJ, Oppenheim RC, Speiser P. Nanoparticles--a new colloidal drug delivery system. *Pharm Acta Helv*. 1978;53(1):17-23.

832. Toh ZQ, Anzela A, Tang ML, Licciardi PV. Probiotic therapy as a novel approach for allergic disease. *Front Pharmacol*. 2012;3:171. doi:10.3389/fphar.2012.00171

833. Ho HE, Bunyavanich S. Microbial Adjuncts for Food Allergen Immunotherapy. *Curr Allergy Asthma Rep*. Mar 22 2019;19(5):25. doi:10.1007/s11882-019-0859-1

834. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*. Mar 24 2006;311(5768):1770-3. doi:10.1126/science.1123933

835. Hesse L, van Ieperen N, Petersen AH, Elberink J, van Oosterhout AJM, Nawijn MC. High dose vitamin D3 empowers effects of subcutaneous immunotherapy in a grass pollen-driven mouse model of asthma. *Sci Rep*. Nov 30 2020;10(1):20876. doi:10.1038/s41598-020-77947-6

836. Heine G, Francuzik W, Doelle-Bierke S, et al. Immunomodulation of high-dose vitamin D supplementation during allergen-specific immunotherapy. *Allergy*. Mar 2021;76(3):930-933. doi:10.1111/all.14541

837. Grundstrom J, Neimert-Andersson T, Kemi C, et al. Covalent coupling of vitamin D3 to the major cat allergen Fel d 1 improves the effects of allergen-specific immunotherapy in a mouse model for cat allergy. *Int Arch Allergy Immunol*. 2012;157(2):136-46. doi:10.1159/000327546

838. Liu C, Yang N, Song Y, et al. Ganoderic acid C1 isolated from the anti-asthma formula, ASHMI suppresses TNF-alpha production by mouse macrophages and peripheral blood mononuclear cells from asthma patients. *Int Immunopharmacol*. Aug 2015;27(2):224-31. doi:10.1016/j.intimp.2015.05.018

839. Wen MC, Wei CH, Hu ZQ, et al. Efficacy and tolerability of anti-asthma herbal medicine intervention in adult patients with moderate-severe allergic asthma. *J Allergy Clin Immunol*. Sep 2005;116(3):517-24. doi:10.1016/j.jaci.2005.05.029

840. Mahler V, Esch RE, Kleine-Tebbe J, et al. Understanding differences in allergen immunotherapy products and practices in North America and Europe. *J Allergy Clin Immunol*. Mar 2019;143(3):813-828. doi:10.1016/j.jaci.2019.01.024

841. Valenta R, Niespodziana K, Focke-Tejkl M, et al. Recombinant allergens: what does the future hold? *J Allergy Clin Immunol*. Apr 2011;127(4):860-4. doi:10.1016/j.jaci.2011.02.016

842. Zhernov Y, Curin M, Khaitov M, Karaulov A, Valenta R. Recombinant allergens for immunotherapy: state of the art. *Curr Opin Allergy Clin Immunol*. Aug 2019;19(4):402-414. doi:10.1097/ACI.0000000000000536

843. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol*. Sep 2005;116(3):608-13. doi:10.1016/j.jaci.2005.06.004

844. Klimek L, Schendzielorz P, Pinol R, Pfaar O. Specific subcutaneous immunotherapy with recombinant grass pollen allergens: first randomized dose-ranging safety study. *Clin Exp Allergy*. Jun 2012;42(6):936-45. doi:10.1111/j.1365-2222.2012.03971.x

845. Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Nov 2008;122(5):951-60. doi:10.1016/j.jaci.2008.09.017

846. Nony E, Bouley J, Le Mignon M, et al. Development and evaluation of a sublingual tablet based on recombinant Bet v 1 in birch pollen-allergic patients. *Allergy*. Jul 2015;70(7):795-804. doi:10.1111/all.12622

847. Ellis AK, Frankish CW, O'Hehir RE, et al. Treatment with grass allergen peptides improves symptoms of grass pollen-induced allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Aug 2017;140(2):486-496. doi:10.1016/j.jaci.2016.11.043

848. Litwin A, Pesce AJ, Fischer T, Michael M, Michael JG. Regulation of the human immune response to ragweed pollen by immunotherapy. A controlled trial comparing the effect of immunosuppressive peptic fragments of short ragweed with standard treatment. *Clin Exp Allergy*. Jul 1991;21(4):457-65. doi:10.1111/j.1365-2222.1991.tb01686.x

849. Purohit A, Niederberger V, Kronqvist M, et al. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy*. Sep 2008;38(9):1514-25. doi:10.1111/j.1365-2222.2008.03042.x

850. Patel D, Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. Jan 2013;131(1):103-9 e1-7. doi:10.1016/j.jaci.2012.07.028

851. Couroux P, Patel D, Armstrong K, Larche M, Hafner RP. Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects. *Clin Exp Allergy*. May 2015;45(5):974-981. doi:10.1111/cea.12488

852. Maguire P, Nicodemus C, Robinson D, Aaronson D, Umetsu DT. The safety and efficacy of ALLERVAX CAT in cat allergic patients. *Clin Immunol*. Dec 1999;93(3):222-31. doi:10.1006/clim.1999.4795

853. Norman PS, Ohman JL, Jr., Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med*. Dec 1996;154(6 Pt 1):1623-8. doi:10.1164/ajrccm.154.6.8970345

854. Spertini F, Perrin Y, Audran R, et al. Safety and immunogenicity of immunotherapy with Bet v 1-derived contiguous overlapping peptides. *J Allergy Clin Immunol*. Jul 2014;134(1):239-240 e13. doi:10.1016/j.jaci.2014.04.001

855. Spertini F, DellaCorte G, Kettner A, et al. Efficacy of 2 months of allergen-specific immunotherapy with Bet v 1-derived contiguous overlapping peptides in patients with allergic rhinoconjunctivitis: Results of a phase IIb study. *J Allergy Clin Immunol*. Jul 2016;138(1):162-8. doi:10.1016/j.jaci.2016.02.044

856. Kettner A, DellaCorte G, de Blay F, et al. Benefit of Bet v 1 contiguous overlapping peptide immunotherapy persists during first follow-up season. *J Allergy Clin Immunol*. Aug 2018;142(2):678-680 e7. doi:10.1016/j.jaci.2018.01.052

857. Jutel M, Kosowska A, Smolinska S. Allergen Immunotherapy: Past, Present, and Future. *Allergy Asthma Immunol Res*. May 2016;8(3):191-7. doi:10.4168/aair.2016.8.3.191

858. Valenta R, Campana R, Focke-Tejkl M, Niederberger V. Vaccine development for allergen-specific immunotherapy based on recombinant allergens and synthetic allergen peptides: Lessons from the past and novel mechanisms of action for the future. *J Allergy Clin Immunol*. Feb 2016;137(2):351-7. doi:10.1016/j.jaci.2015.12.1299

859. Norman PS, Lichtenstein LM, Marsh DG. Studies on allergoids from naturally occurring allergens. IV. Efficacy and safety of long-term allergoid treatment of ragweed hay fever. *J Allergy Clin Immunol*. Dec 1981;68(6):460-70. doi:10.1016/0091-6749(81)90200-1

860. Grammer LC, Zeiss CR, Suszko IM, Shaughnessy MA, Patterson R. A double-blind, placebo-controlled trial of polymerized whole ragweed for immunotherapy of ragweed allergy. *J Allergy Clin Immunol*. Jun 1982;69(6):494-9. doi:10.1016/0091-6749(82)90173-7

861. Bousquet J, Hejjaoui A, Soussana M, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol*. Feb 1990;85(2):490-7. doi:10.1016/0091-6749(90)90160-6

862. Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol*. Oct 1989;84(4 Pt 1):546-56. doi:10.1016/0091-6749(89)90369-2

863. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy*. Sep-Oct 2010;24(5):e104-9. doi:10.2500/ajra.2010.24.3508

864. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet*. Feb 28 1998;351(9103):629-32. doi:10.1016/S0140-6736(97)07055-4

865. Rauber MM, Wu HK, Adams B, et al. Birch pollen allergen-specific immunotherapy with glutaraldehyde-modified allergoid induces IL-10 secretion and protective antibody responses. *Allergy*. Aug 2019;74(8):1575-1579. doi:10.1111/all.13774

866. Ramesh M, Karagic M. New modalities of allergen immunotherapy. *Hum Vaccin Immunother*. 2018;14(12):2848-2863. doi:10.1080/21645515.2018.1502126

867. Pohlit H, Bellinghausen I, Frey H, Saloga J. Recent advances in the use of nanoparticles for allergen-specific immunotherapy. *Allergy*. Oct 2017;72(10):1461-1474. doi:10.1111/all.13199

868. Basomba A, Tabar AI, de Rojas DH, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol*. Jun 2002;109(6):943-8. doi:10.1067/mai.2002.124465

869. TePas EC, Hoyte EG, McIntire JJ, Umetsu DT. Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals. *Ann Allergy Asthma Immunol*. Jan 2004;92(1):25-31. doi:10.1016/S1081-1206(10)61706-1

870. Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. *Lancet*. May 22 1954;266(6821):1055-7. doi:10.1016/s0140-6736(54)91620-7

871. Penagos M, Eifan AO, Durham SR, Scadding GW. Duration of Allergen Immunotherapy for Long-Term Efficacy in Allergic Rhinoconjunctivitis. *Curr Treat Options Allergy*. 2018;5(3):275-290. doi:10.1007/s40521-018-0176-2

872. Bachert C, Larche M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. *World Allergy Organ J*. 2015;8(1):29. doi:10.1186/s40413-015-0078-8

873. McEldowney SJ, Bush RK. Pollen immunotherapy: selection,prevention, and future directions. *Curr Allergy Asthma Rep*. Sep 2006;6(5):420-6. doi:10.1007/s11882-996-0016-5

874. Coop CA. Immunotherapy for mold allergy. *Clin Rev Allergy Immunol*. Dec 2014;47(3):289-98. doi:10.1007/s12016-013-8389-4

875. Nelson HS. Immunotherapy for house-dust mite allergy. *Allergy Asthma Proc*. Jul 1 2018;39(4):264-272. doi:10.2500/aap.2018.39.4145

876. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy*. Jul 2017;47(7):856-889. doi:10.1111/cea.12953

877. Dhami S, Agarwal A. Does evidence support the use of cat allergen immunotherapy? *Curr Opin Allergy Clin Immunol*. Aug 2018;18(4):350-355. doi:10.1097/ACI.0000000000000457

878. Larenas-Linnemann D. Allergen immunotherapy: an update on protocols of administration. *Curr Opin Allergy Clin Immunol*. Dec 2015;15(6):556-67. doi:10.1097/ACI.0000000000000220

879. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract*. Mar-Apr 2014;2(2):161-7. doi:10.1016/j.jaip.2014.01.004

880. Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013-2017): Fatalities, Infections, Delayed Reactions, and Use of Epinephrine Autoinjectors. *J Allergy Clin Immunol Pract*. Jul - Aug 2019;7(6):1996-2003 e1. doi:10.1016/j.jaip.2019.01.058

881. DaVeiga SP, Liu X, Caruso K, Golubski S, Xu M, Lang DM. Systemic reactions associated with subcutaneous allergen immunotherapy: timing and risk assessment. *Ann Allergy Asthma Immunol*. Jun 2011;106(6):533-537 e2. doi:10.1016/j.anai.2011.02.007

882. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol*. Jan 2008;121(1):227-32. doi:10.1016/j.jaci.2007.10.026

883. Hankin CS, Cox L, Lang D, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol*. Jan 2010;104(1):79-85. doi:10.1016/j.anai.2009.11.010

884. Sun D, Cafone J, Shaker M, Greenhawt M. The cost-effectiveness of requiring universal vs contextual self-injectable epinephrine autoinjector for allergen immunotherapy. *Ann Allergy Asthma Immunol*. Dec 2019;123(6):582-589. doi:10.1016/j.anai.2019.09.009

885. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. Feb 2006;61(2):198-201. doi:10.1111/j.1398-9995.2006.01011.x

886. Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol*. Dec 2017;28(8):728-745. doi:10.1111/pai.12807

887. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. Apr 1997;99(4):450-3. doi:10.1016/s0091-6749(97)70069-1

888. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy*. Sep 2001;31(9):1392-7. doi:10.1046/j.1365-2222.2001.01161.x

889. Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. *JAMA*. Feb 14 2017;317(6):615-625. doi:10.1001/jama.2016.21040

890. Worm M, Rak S, Samolinski B, et al. Efficacy and safety of birch pollen allergoid subcutaneous immunotherapy: A 2-year double-blind, placebo-controlled, randomized trial plus 1-year open-label extension. *Clin Exp Allergy*. Apr 2019;49(4):516-525. doi:10.1111/cea.13331

891. Xian M, Feng M, Dong Y, Wei N, Su Q, Li J. Changes in CD4+CD25+FoxP3+ Regulatory T Cells and Serum Cytokines in Sublingual and Subcutaneous Immunotherapy in Allergic Rhinitis with or without Asthma. *Int Arch Allergy Immunol*. 2020;181(1):71-80. doi:10.1159/000503143

892. Wang ZX, Shi H. Single-allergen sublingual immunotherapy versus multi-allergen subcutaneous immunotherapy for children with allergic rhinitis. *J Huazhong Univ Sci Technolog Med Sci*. Jun 2017;37(3):407-411. doi:10.1007/s11596-017-1748-2

893. Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, Jarzab J. Pre-seasonal, subcutaneous immunotherapy: a double-blinded, placebo-controlled study in elderly patients with an allergy to grass. *Ann Allergy Asthma Immunol*. Feb 2016;116(2):156-61. doi:10.1016/j.anai.2015.12.013

894. Bozek A, Kolodziejczyk K, Kozlowska R, Canonica GW. Evidence of the efficacy and safety of house dust mite subcutaneous immunotherapy in elderly allergic rhinitis patients: a randomized, double-blind placebo-controlled trial. *Clin Transl Allergy*. 2017;7:43. doi:10.1186/s13601-017-0180-9

895. Pfaar O, Hohlfeld JM, Al-Kadah B, et al. Dose-response relationship of a new Timothy grass pollen allergoid in comparison with a 6-grass pollen allergoid. *Clin Exp Allergy*. Nov 2017;47(11):1445-1455. doi:10.1111/cea.12977

896. Kim JY, Jang MJ, Kim DY, Park SW, Han DH. Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis-Based Comparison. *J Allergy Clin Immunol Pract*. Dec 2021;9(12):4450-4458 e6. doi:10.1016/j.jaip.2021.08.018

897. Schmid JM, Wurtzen PA, Siddhuraj P, et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. *Allergy*. May 2021;76(5):1528-1538. doi:10.1111/all.14264

898. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. Sep 2015;136(3):556-68. doi:10.1016/j.jaci.2015.04.047

899. Shamji MH, Larson D, Eifan A, et al. Differential induction of allergen-specific IgA responses following timothy grass subcutaneous and sublingual immunotherapy. *J Allergy Clin Immunol*. Oct 2021;148(4):1061-1071 e11. doi:10.1016/j.jaci.2021.03.030

900. Rondon C, Campo P, Salas M, et al. Efficacy and safety of D. pteronyssinus immunotherapy in local allergic rhinitis: a double-blind placebo-controlled clinical trial. *Allergy*. Jul 2016;71(7):1057-61. doi:10.1111/all.12889

901. Kleine-Tebbe J, Walmar M, Bitsch-Jensen K, et al. Negative clinical results from a randomised, double-blind, placebo-controlled trial evaluating the efficacy of two doses of immunologically enhanced, grass subcutaneous immunotherapy despite dose-dependent immunological response. *Clin Drug Investig*. Aug 2014;34(8):577-86. doi:10.1007/s40261-014-0216-z

902. Klimek L, Uhlig J, Mosges R, Rettig K, Pfaar O. A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. *Allergy*. Dec 2014;69(12):1629-38. doi:10.1111/all.12513

903. Tworek D, Bochenska-Marciniak M, Kuprys-Lipinska I, Kupczyk M, Kuna P. Perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. *Am J Rhinol Allergy*. Jul-Aug 2013;27(4):304-8. doi:10.2500/ajra.2013.27.3935

904. James LK, Shamji MH, Walker SM, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol*. Feb 2011;127(2):509-516 e1-5. doi:10.1016/j.jaci.2010.12.1080

905. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. *J Allergy Clin Immunol*. Feb 2011;127(2):502-508 e1-6. doi:10.1016/j.jaci.2010.11.036

906. Hoiby AS, Strand V, Robinson DS, Sager A, Rak S. Efficacy, safety, and immunological effects of a 2-year immunotherapy with Depigoid birch pollen extract: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. Jul 2010;40(7):1062-70. doi:10.1111/j.1365-2222.2010.03521.x

907. Pfaar O, Robinson DS, Sager A, Emuzyte R. Immunotherapy with depigmented-polymerized mixed tree pollen extract: a clinical trial and responder analysis. *Allergy*. Dec 2010;65(12):1614-21. doi:10.1111/j.1398-9995.2010.02413.x

908. Tabar AI, Lizaso MT, Garcia BE, et al. Double-blind, placebo-controlled study of Alternaria alternata immunotherapy: clinical efficacy and safety. *Pediatr Allergy Immunol*. Feb 2008;19(1):67-75. doi:10.1111/j.1399-3038.2007.00589.x

909. Charpin D, Gouitaa M, Dron-Gonzalvez M, et al. Immunotherapy with an aluminum hydroxide-adsorbed Juniperus ashei foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol*. 2007;143(2):83-91. doi:10.1159/000098656

910. Powell RJ, Frew AJ, Corrigan CJ, Durham SR. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy*. Nov 2007;62(11):1335-8. doi:10.1111/j.1398-9995.2007.01455.x

911. Colas C, Monzon S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of Salsola kali (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol*. Apr 2006;117(4):810-6. doi:10.1016/j.jaci.2005.11.039

912. Alvarez-Cuesta E, Aragoneses-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy*. May 2005;35(5):572-8. doi:10.1111/j.1365-2222.2005.02245.x

913. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Prilozi*. Dec 2005;26(2):113-29.

914. Ferrer M, Burches E, Pelaez A, et al. Double-blind, placebo-controlled study of immunotherapy with Parietaria judaica: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol*. 2005;15(4):283-92.

915. Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. *J Allergy Clin Immunol*. Jul 2005;116(1):109-18. doi:10.1016/j.jaci.2005.05.005

916. Crimi N, Li Gotti F, Mangano G, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect on bronchial

hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int*. Apr-Jun 2004;19(2):98-108.

917. Mirone C, Albert F, Tosi A, et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of Ambrosia artemisiifolia pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy*. Sep 2004;34(9):1408-14. doi:10.1111/j.1365-2222.2004.02056.x

918. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ*. Aug 2 2003;327(7409):251-4. doi:10.1136/bmj.327.7409.251

919. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy*. Aug 2003;33(8):1076-82. doi:10.1046/j.1365-2222.2003.01735.x

920. Arvidsson MB, Lowhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol*. May 2002;109(5):777-83. doi:10.1067/mai.2002.123868

921. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. *Allergy*. Apr 2002;57(4):297-305. doi:10.1034/j.1398-9995.2002.1o3532.x

922. Drachenberg K, Heinzkill M, Urban E. Short-term immunotherapy with tree pollen allergoids and the adjuvant monophosphoryl lipid-A - Results from a multicentre, placebo-controlled, randomised, double-blind study..[Kurzzeit-Immuntherapie mit Baumpollen- Allergoiden und dem Adjuvans Monophosphoryl Lipid-A]. *Allergologie*. 2002;9:466-474.

923. Leynadier F, Banoun L, Dollois B, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy*. Jul 2001;31(7):988-96. doi:10.1046/j.1365-2222.2001.01145.x

924. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol*. Jan 2001;107(1):87-93. doi:10.1067/mai.2001.112027

925. Balda BR, Wolf H, Baumgarten C, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. *Allergy*. Aug 1998;53(8):740-8. doi:10.1111/j.1398-9995.1998.tb03969.x

926. Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. Jul 1997;100(1):23-9. doi:10.1016/s0091-6749(97)70190-8

927. Olsen OT, Frolund L, Heinig J, Jacobsen L, Svendsen UG. A double-blind, randomized study investigating the efficacy and specificity of immunotherapy with Artemisia vulgaris or Phleum pratense/betula verrucosa. *Allergol Immunopathol (Madr)*. Mar-Apr 1995;23(2):73-8.

928. Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. *Allergy*. Jan 1994;49(1):13-21. doi:10.1111/j.1398-9995.1994.tb00767.x

929. Pastorello EA, Pravettoni V, Incorvaia C, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. *Allergy*. Aug 1992;47(4 Pt 1):281-90. doi:10.1111/j.1398-9995.1992.tb02054.x

930. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ*. Feb 2 1991;302(6771):265-9. doi:10.1136/bmj.302.6771.265

931. Grammer LC, Shaughnessy MA, Suszko IM, Shaughnessy JJ, Patterson R. A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. *J Allergy Clin Immunol*. Nov 1983;72(5 Pt 1):448-53. doi:10.1016/0091-6749(83)90580-8

932. Weyer A, Donat N, L'Heritier C, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. *Allergy*. Jul 1981;36(5):309-17. doi:10.1111/j.1398-9995.1981.tb01582.x

933. Moreno V, Alvarino M, Rodriguez F, et al. Randomized dose-response study of subcutaneous immunotherapy with a Dermatophagoides pteronyssinus extract in patients with respiratory allergy. *Immunotherapy*. 2016;8(3):265-77. doi:10.2217/imt.15.124

934. Pfaar O, Urry Z, Robinson DS, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. *Allergy*. Feb 2012;67(2):272-9. doi:10.1111/j.1398-9995.2011.02736.x

935. DuBuske LM, Frew AJ, Horak F, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc*. May-Jun 2011;32(3):239-47. doi:10.2500/aap.2011.32.3453

936. Ceuppens JL, Bullens D, Kleinjans H, van der Werf J, Group PBES. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects. *Clin Exp Allergy*. Dec 2009;39(12):1903-9. doi:10.1111/j.1365-2222.2009.03379.x

937. Chakraborty P, Roy I, Chatterjee S, Chanda S, Gupta-Bharracharya S. Phoenix sylvestris Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. *J Investig Allergol Clin Immunol*. 2006;16(6):377-84.

938. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, Group UKIS. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Feb 2006;117(2):319-25. doi:10.1016/j.jaci.2005.11.014

939. Rak S, Heinrich C, Jacobsen L, Scheynius A, Venge P. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. *J Allergy Clin Immunol*. Dec 2001;108(6):921-8. doi:10.1067/mai.2001.119743

940. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with Parietaria. Clinical and immunologic effects in a randomized, controlled trial. *Allergy*. Apr 1999;54(4):313-9. doi:10.1034/j.1398-9995.1999.00900.x

941. Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed Parietaria-pollen allergoid: a 2-year, double-blind, placebo-controlled study. *Allergy*. Jan 1997;52(1):65-74. doi:10.1111/j.1398-9995.1997.tb02547.x

942. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy*. Jul 1996;51(7):489-500. doi:10.1111/j.1398-9995.1996.tb04655.x

943. Brunet C, Bedard PM, Lavoie A, Jobin M, Hebert J. Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses. *J Allergy Clin Immunol*. Jan 1992;89(1 Pt 1):76-86. doi:10.1016/s0091-6749(05)80043-0

944. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol*. Jul 1991;88(1):43-53. doi:10.1016/0091-6749(91)90299-4

945. Iliopoulos O, Proud D, Adkinson NF, Jr., et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. *J Allergy Clin Immunol*. Apr 1991;87(4):855-66. doi:10.1016/0091-6749(91)90134-a

946. Fell P, Brostoff J. A single dose desensitization for summer hay fever. Results of a double blind study-1988. *Eur J Clin Pharmacol*. 1990;38(1):77-9. doi:10.1007/BF00314808

947. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. *J Allergy Clin Immunol*. Feb 1990;85(2):460-72. doi:10.1016/0091-6749(90)90156-x

948. Juniper EF, Kline PA, Ramsdale EH, Hargreave FE. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Mar 1990;85(3):606-11. doi:10.1016/0091-6749(90)90100-i

949. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Allergy*. Sep 1988;18(5):501-8. doi:10.1111/j.1365-2222.1988.tb02900.x

950. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. *J Allergy Clin Immunol*. Oct 1987;80(4):591-8. doi:10.1016/0091-6749(87)90013-3

951. Grammer LC, Shaughnessy MA, Bernhard MI, et al. The safety and activity of polymerized ragweed: a double-blind, placebo-controlled trial in 81 patients with ragweed rhinitis. *J Allergy Clin Immunol*. Aug 1987;80(2):177-83. doi:10.1016/0091-6749(87)90127-8

952. Grammer LC, Shaughnessy MA, Suszko IM, Shaughnessy JJ, Patterson R. Persistence of efficacy after a brief course of polymerized ragweed allergen: a controlled study. *J Allergy Clin Immunol*. Apr 1984;73(4):484-9. doi:10.1016/0091-6749(84)90359-2

953. Metzger WJ, Dorminey HC, Richerson HB, Weiler JM, Donnelly A, Moran D. Clinical and immunologic evaluation of glutaraldehyde-modified tyrosine-adsorbed short ragweed extract: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. Dec 1981;68(6):442-8. doi:10.1016/0091-6749(81)90198-6

954. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. *Ann Allergy Asthma Immunol*. Aug 2006;97(2):126-37; quiz 137-40, 202. doi:10.1016/S1081-1206(10)60003-8

955. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol*. Apr 2002;88(4):391-4. doi:10.1016/S1081-1206(10)62370-8

956. Pfaar O, Biedermann T, Klimek L, Sager A, Robinson DS. Depigmented-polymerized mixed grass/birch pollen extract immunotherapy is effective in polysensitized patients. *Allergy*. Oct 2013;68(10):1306-13. doi:10.1111/all.12219

957. Klunker S, Saggar LR, Seyfert-Margolis V, et al. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: Inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol*. Sep 2007;120(3):688-95. doi:10.1016/j.jaci.2007.05.034

958. Morais-Almeida M, Arede C, Sampaio G, Borrego LM. Ultrarush schedule of subcutaneous immunotherapy with modified allergen extracts is safe in paediatric age. *Asia Pac Allergy*. Jan 2016;6(1):35-42. doi:10.5415/apallergy.2016.6.1.35

959. Akmanlar N, Altintas DU, Guneser KS, Yilmaz M, Bingol G. Comparison of conventional and rush immunotherapy with der PI in childhood respiratory allergy. *Allergol Immunopathol (Madr)*. Jul-Aug 2000;28(4):213-8.

960. Lilja G, Sundin B, Graff-Lonnevig V, et al. Immunotherapy with cat- and dog-dander extracts. IV. Effects of 2 years of treatment. *J Allergy Clin Immunol*. Jan 1989;83(1):37-44. doi:10.1016/0091-6749(89)90475-2

961. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol*. Apr 1989;83(4):797-802. doi:10.1016/0091-6749(89)90017-1

962. Winslow AW, Turbyville JC, Sublett JW, Sublett JL, Pollard SJ. Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy. *Ann Allergy Asthma Immunol*. Nov 2016;117(5):542-545. doi:10.1016/j.anai.2016.09.005

963. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Int Arch Allergy Immunol*. 2006;139(2):153-8. doi:10.1159/000090392

964. Cook KA, Kelso JM, White AA. Increased risk of systemic reactions extends beyond completion of rush immunotherapy. *J Allergy Clin Immunol Pract*. Nov - Dec 2017;5(6):1773-1775. doi:10.1016/j.jaip.2017.04.015

965. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy*. Nov 1994;73(5):409-18.

966. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. IV. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol*. Feb 1990;85(2):473-9. doi:10.1016/0091-6749(90)90157-y

967. Feng S, Xu Y, Ma R, Sun Y, Luo X, Li H. Cluster subcutaneous allergen specific immunotherapy for the treatment of allergic rhinitis: a systematic review and meta-analysis. *PLoS One*. 2014;9(1):e86529. doi:10.1371/journal.pone.0086529

968. Jiang Z, Xiao H, Zhang H, Liu S, Meng J. Comparison of adverse events between cluster and conventional immunotherapy for allergic rhinitis patients with or without asthma: A systematic review and meta-analysis. *Am J Otolaryngol*. Nov - Dec 2019;40(6):102269. doi:10.1016/j.amjoto.2019.07.013

969. Fan Q, Liu X, Gao J, Huang S, Ni L. Comparative analysis of cluster versus conventional immunotherapy in patients with allergic rhinitis. *Exp Ther Med*. Feb 2017;13(2):717-722. doi:10.3892/etm.2017.4032

970. Nanda A, O'Connor M, Anand M, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. *J Allergy Clin Immunol*. Dec 2004;114(6):1339-44. doi:10.1016/j.jaci.2004.08.049

971. Subiza J, Feliu A, Subiza JL, Uhlig J, Fernandez-Caldas E. Cluster immunotherapy with a glutaraldehyde-modified mixture of grasses results in an improvement in specific nasal provocation tests in less than 2.5 months of treatment. *Clin Exp Allergy*. Jun 2008;38(6):987-94. doi:10.1111/j.1365-2222.2008.02995.x

972. Yu J, Zhong N, Luo Q, et al. Early Efficacy Analysis of Cluster and Conventional Immunotherapy in Patients With Allergic Rhinitis. *Ear Nose Throat J*. Jun 2021;100(5):378-385. doi:10.1177/0145561319863370

973. Zhang L, Wang C, Han D, Wang X, Zhao Y, Liu J. Comparative study of cluster and conventional immunotherapy schedules with dermatophagoides pteronyssinus in the treatment of persistent allergic rhinitis. *Int Arch Allergy Immunol*. 2009;148(2):161-9. doi:10.1159/000155747

974. Wang CS, Zhang W, Wang XD, et al. [Comparative study on cluster and conventional immunotherapy with Dermatophagoides pteronyssinus in patients with allergic rhinitis]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. Dec 2011;46(12):981-5.

975. Cook KA, Ford CM, Leyvas EA, Waalen J, White AA. Half of systemic reactions to allergen immunotherapy are delayed, majority require treatment with epinephrine. *J Allergy Clin Immunol Pract*. Sep - Oct 2017;5(5):1415-1417. doi:10.1016/j.jaip.2017.03.025

976. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol*. Jun 1996;97(6):1207-13. doi:10.1016/s0091-6749(96)70186-0

977. Larenas Linnemann DE. One hundred years of immunotherapy: review of the first landmark studies. *Allergy Asthma Proc*. Mar-Apr 2012;33(2):122-8. doi:10.2500/aap.2012.33.3515

978. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy*. Sep 1986;16(5):483-91. doi:10.1111/j.1365-2222.1986.tb01983.x

979. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Apr 2006;117(4):802-9. doi:10.1016/j.jaci.2005.12.1358

980. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol*. Dec 2007;120(6):1338-45. doi:10.1016/j.jaci.2007.07.046

981. Calderon MA. Meta-analyses of specific immunotherapy trials. *Drugs Today (Barc)*. Dec 2008;44 Suppl B:31-4.

982. Cohen J. *Statistical power analysis for the behavioral scienes*. 2nd ed ed. Lawrence Erlbaum Associates; 1988.

983. de Bot CM, Moed H, Berger MY, Roder E, van Wijk RG, van der Wouden JC. Sublingual immunotherapy in children with allergic rhinitis: quality of systematic reviews. *Pediatr Allergy Immunol*. Sep 2011;22(6):548-58. doi:10.1111/j.1399-3038.2011.01165.x

984. Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics*. Jun 2013;131(6):1155-67. doi:10.1542/peds.2013-0343

985. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012. *Ann Allergy Asthma Immunol*. Jun 2013;110(6):402-415 e9. doi:10.1016/j.anai.2013.02.017

986. Chen L, Lei L, Cai Y, Li T. Specific sublingual immunotherapy in children with perennial rhinitis: a systemic review and meta-analysis. *Int Forum Allergy Rhinol*. Nov 2020;10(11):1226-1235. doi:10.1002/alr.22589

987. Feng B, Wu J, Chen B, et al. Efficacy and safety of sublingual immunotherapy for allergic rhinitis in pediatric patients: A meta-analysis of randomized controlled trials. *Am J Rhinol Allergy*. Jan 1 2017;31(1):27-35. doi:10.2500/ajra.2017.31.4382

988. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol*. Nov 2012;130(5):1097-1107 e2. doi:10.1016/j.jaci.2012.08.012

989. Nelson H, Cartier S, Allen-Ramey F, Lawton S, Calderon MA. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol Pract*. Mar-Apr 2015;3(2):256-266 e3. doi:10.1016/j.jaip.2014.09.018

990. Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. *J Eval Clin Pract*. Jun 2014;20(3):225-38. doi:10.1111/jep.12112

991. Chelladurai Y, Suarez-Cuervo C, Erekosima N, et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Allergy Clin Immunol Pract*. Jul-Aug 2013;1(4):361-9. doi:10.1016/j.jaip.2013.04.005

992. Aasbjerg K, Dalhoff KP, Backer V. Adverse Events During Immunotherapy Against Grass Pollen-Induced Allergic Rhinitis - Differences Between Subcutaneous and Sublingual Treatment. *Basic Clin Pharmacol Toxicol*. Aug 2015;117(2):73-84. doi:10.1111/bcpt.12416

993. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol*. Dec 2013;132(6):1322-36. doi:10.1016/j.jaci.2013.09.004

994. Ji DX, Tan JR, Yu HW. [Efficacy, safety and compliance of immunotherapy in the treatment of allergic rhinitis: a Meta-analysis]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. Dec 7 2019;54(12):894-901. doi:10.3760/cma.j.issn.1673-0860.2019.12.003

995. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Macchia L, Di Lorenzo G. Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy*. May 2017;72(5):691-704. doi:10.1111/all.13104

996. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis. *JAMA Intern Med*. Aug 2015;175(8):1301-9. doi:10.1001/jamainternmed.2015.2840

997. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy*. Jun 2009;64(6):963-4. doi:10.1111/j.1398-9995.2009.01998.x

998. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. *J Allergy Clin Immunol*. Aug 2009;124(2):378-9. doi:10.1016/j.jaci.2009.04.040

999. Janssens NS, van Ouwerkerk L, Gerth van Wijk R, Karim F. Acute systemic reactions to sublingual immunotherapy for house dust mite. *Allergy*. Nov 2020;75(11):2962-2963. doi:10.1111/all.14417

1000. Creticos PS, Bernstein DI, Casale TB, Lockey RF, Maloney J, Nolte H. Coseasonal Initiation of Allergen Immunotherapy: A Systematic Review. *J Allergy Clin Immunol Pract*. Nov - Dec 2016;4(6):1194-1204 e4. doi:10.1016/j.jaip.2016.05.014

1001. Maloney J, Durham S, Skoner D, et al. Safety of sublingual immunotherapy Timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. *Allergy*. Mar 2015;70(3):302-9. doi:10.1111/all.12560

1002. Makatsori M, Scadding GW, Lombardo C, et al. Dropouts in sublingual allergen immunotherapy trials - a systematic review. *Allergy*. May 2014;69(5):571-80. doi:10.1111/all.12385

1003. Cafone J, Capucilli P, Hill DA, Spergel JM. Eosinophilic esophagitis during sublingual and oral allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. Aug 2019;19(4):350-357. doi:10.1097/ACI.0000000000000537

1004. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol*. 2015;11:31. doi:10.1186/s13223-015-0096-7

1005. Larenas-Linnemann D. How does the efficacy and safety of Oralair((R)) compare to other products on the market? *Ther Clin Risk Manag*. 2016;12:831-50. doi:10.2147/TCRM.S70363

1006. Larenas-Linnemann D. Direct comparison of efficacy of sublingual immunotherapy tablets for rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. Apr 2016;116(4):274-86. doi:10.1016/j.anai.2016.02.008

1007. Meadows A, Kaambwa B, Novielli N, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess*. Jul 2013;17(27):vi, xi-xiv, 1-322. doi:10.3310/hta17270

1008. Asaria M, Dhami S, van Ree R, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: A systematic overview. *Allergy*. Feb 2018;73(2):269-283. doi:10.1111/all.13254

1009. Yonekura S, Gotoh M, Kaneko S, Maekawa Y, Okubo K, Okamoto Y. Disease-Modifying Effect of Japanese Cedar Pollen Sublingual Immunotherapy Tablets. *J Allergy Clin Immunol Pract*. Nov 2021;9(11):4103-4116 e14. doi:10.1016/j.jaip.2021.06.060

1010. Nolte H, Waserman S, Ellis AK, Biedermann T, Wurtzen PA. Treatment Effect of the Tree Pollen SLIT-Tablet on Allergic Rhinoconjunctivitis During Oak Pollen Season. *J Allergy Clin Immunol Pract*. May 2021;9(5):1871-1878. doi:10.1016/j.jaip.2021.01.035

1011. Kim JY, Hwang D, Jang M, Rhee CS, Han DH. Clinical effectiveness of house dust mite immunotherapy in mono- versus poly-sensitised patients with allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. Aug 1 2021;59(4):352-359. doi:10.4193/Rhin20.588

1012. Boldovjakova D, Cordoni S, Fraser CJ, et al. Sublingual immunotherapy vs placebo in the management of grass pollen-induced allergic rhinitis in adults: A systematic review and meta-analysis. *Clin Otolaryngol*. Jan 2021;46(1):52-59. doi:10.1111/coa.13651

1013. Blanco C, Bazire R, Argiz L, Hernandez-Pena J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. *Drugs Context*. 2018;7:212552. doi:10.7573/dic.212552

1014. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. Jun 2011;66(6):740-52. doi:10.1111/j.1398-9995.2011.02583.x

1015. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol*. Sep 2010;126(3):558-66. doi:10.1016/j.jaci.2010.06.013

1016. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. Mar 27 2013;309(12):1278-88. doi:10.1001/jama.2013.2049

1017. Ortiz AS, McMains KC, Laury AM. Single vs multiallergen sublingual immunotherapy in the polysensitized patient: a pilot study. *Int Forum Allergy Rhinol*. Apr 2018;8(4):490-494. doi:10.1002/alr.22071

1018. Li P, Li Q, Huang Z, Chen W, Lu Y, Tian M. Efficacy and safety of house dust mite sublingual immunotherapy in monosensitized and polysensitized children with respiratory allergic diseases. *Int Forum Allergy Rhinol*. Oct 2014;4(10):796-801. doi:10.1002/alr.21397

1019. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. Jul 2009;124(1):150-156 e1-5. doi:10.1016/j.jaci.2009.04.037

1020. Moreno-Ancillo A, Moreno C, Ojeda P, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without updosing. *J Investig Allergol Clin Immunol*. 2007;17(6):399-405.

1021. Lee JE, Choi YS, Kim MS, et al. Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis. *Ann Allergy Asthma Immunol*. Jul 2011;107(1):79-84. doi:10.1016/j.anai.2011.03.012

1022. Li Y, Yu SY, Tang R, Zhao ZT, Sun JL. Sublingual Immunotherapy Tablets Relieve Symptoms in Adults with Allergic Rhinitis: A Meta-analysis of Randomized Clinical Trials. *Chin Med J (Engl)*. Nov 5 2018;131(21):2583-2588. doi:10.4103/0366-6999.244108

1023. Roder E, Berger MY, de Groot H, van Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol*. May 2008;19(3):197-207. doi:10.1111/j.1399-3038.2007.00648.x

1024. Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol*. May 2013;131(5):1361-6. doi:10.1016/j.jaci.2013.02.013

1025. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. Mar 2012;129(3):717-725 e5. doi:10.1016/j.jaci.2011.12.973

1026. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy*. 2015;5:12. doi:10.1186/s13601-015-0057-8

1027. Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy*. Oct 2006;61(10):1177-83. doi:10.1111/j.1398-9995.2006.01190.x

1028. Nolte H, Hebert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol*. Jun 2013;110(6):450-456 e4. doi:10.1016/j.anai.2013.03.013

1029. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol*. May 2013;131(5):1342-9 e6. doi:10.1016/j.jaci.2013.03.019

1030. Skoner D, Gentile D, Bush R, Fasano MB, McLaughlin A, Esch RE. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol*. Mar 2010;125(3):660-6, 666 e1-666 e4. doi:10.1016/j.jaci.2009.12.931

1031. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. Jun 2015;135(6):1494-501 e6. doi:10.1016/j.jaci.2014.12.1911

1032. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol*. Jun 2014;133(6):1608-14 e6. doi:10.1016/j.jaci.2013.11.012

1033. Mosbech H, Canonica GW, Backer V, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol*. Feb 2015;114(2):134-40. doi:10.1016/j.anai.2014.11.015

1034. Cortellini G, Spadolini I, Patella V, et al. Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol*. Nov 2010;105(5):382-6. doi:10.1016/j.anai.2010.08.007

1035. Horak F, Jaeger S, Worm M, Melac M, Didier A. Implementation of pre-seasonal sublingual immunotherapy with a five-grass pollen tablet during optimal dosage assessment. *Clin Exp Allergy*. Mar 2009;39(3):394-400. doi:10.1111/j.1365-2222.2008.03153.x

1036. Malling HJ, Montagut A, Melac M, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy*. Mar 2009;39(3):387-93. doi:10.1111/j.1365-2222.2008.03152.x

1037. Gotoh M, Okubo K, Yuta A, et al. Safety profile and immunological response of dual sublingual immunotherapy with house dust mite tablet and Japanese cedar pollen tablet. *Allergol Int*. Jan 2020;69(1):104-110. doi:10.1016/j.alit.2019.07.007

1038. Leatherman BD, Khalid A, Lee S, et al. Dosing of sublingual immunotherapy for allergic rhinitis: evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Sep 2015;5(9):773-83. doi:10.1002/alr.21561

1039. Jin JJ, Li JT, Klimek L, Pfaar O. Sublingual Immunotherapy Dosing Regimens: What Is Ideal? *J Allergy Clin Immunol Pract*. Jan - Feb 2017;5(1):1-10. doi:10.1016/j.jaip.2016.09.027

1040. Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol*. Mar 2007;98(3):274-80. doi:10.1016/S1081-1206(10)60718-1

1041. Pfaar O, Nell MJ, Boot JD, et al. A randomized, 5-arm dose finding study with a mite allergoid SCIT in allergic rhinoconjunctivitis patients. *Allergy*. Jul 2016;71(7):967-76. doi:10.1111/all.12860

1042. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy*. Feb 2013;43(2):242-8. doi:10.1111/cea.12039

1043. Didier A, Melac M, Montagut A, Lheritier-Barrand M, Tabar A, Worm M. Agreement of efficacy assessments for five-grass pollen sublingual tablet immunotherapy. *Allergy*. Jan 2009;64(1):166-71. doi:10.1111/j.1398-9995.2008.01767.x

1044. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. Feb 2016;137(2):444-451 e8. doi:10.1016/j.jaci.2015.06.036

1045. Saporta D. Efficacy of sublingual immunotherapy versus subcutaneous injection immunotherapy in allergic patients. *J Environ Public Health*. 2012;2012:492405. doi:10.1155/2012/492405

1046. Tsabouri S, Mavroudi A, Feketea G, Guibas GV. Subcutaneous and Sublingual Immunotherapy in Allergic Asthma in Children. *Front Pediatr*. 2017;5:82. doi:10.3389/fped.2017.00082

1047. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. *Allergy*. Dec 2017;72(12):1825-1848. doi:10.1111/all.13208

1048. Rice JL, Diette GB, Suarez-Cuervo C, et al. Allergen-Specific Immunotherapy in the Treatment of Pediatric Asthma: A Systematic Review. *Pediatrics*. May 2018;141(5)doi:10.1542/peds.2017-3833

1049. Epstein TG, Calabria C, Cox LS, Dreborg S. Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States. *J Allergy Clin Immunol Pract*. Jan - Feb 2017;5(1):34-40 e2. doi:10.1016/j.jaip.2016.09.017

1050. Seiberling K, Hiebert J, Nyirady J, Lin S, Chang D. Cost of allergy immunotherapy: sublingual vs subcutaneous administration. *Int Forum Allergy Rhinol*. Nov 2012;2(6):460-4. doi:10.1002/alr.21061

1051. Reinhold T, Bruggenjurgen B. Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment. *Allergo J Int*. 2017;26(1):7-15. doi:10.1007/s40629-016-0002-y

1052. Drazdauskaite G, Layhadi JA, Shamji MH. Mechanisms of Allergen Immunotherapy in Allergic Rhinitis. *Curr Allergy Asthma Rep*. Dec 12 2020;21(1):2. doi:10.1007/s11882-020-00977-7

1053. Pfaar O, Bachert C, Bufe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23(8):282-319. doi:10.1007/s40629-014-0032-2

1054. Ott H, Sieber J, Brehler R, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy*. Sep 2009;64(9):1394-401. doi:10.1111/j.1398-9995.2009.02194.x

1055. Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol*. Sep 1997;100(3):293-300. doi:10.1016/s0091-6749(97)70240-9

1056. Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract*. Mar-Apr 2014;2(2):156-60. doi:10.1016/j.jaip.2014.01.010

1057. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy*. May 2010;65(5):668-9. doi:10.1111/j.1398-9995.2009.02223.x

1058. Hura N, Song S, Kamil RJ, Pierre G, Lin SY. Predictors of Completion of Sublingual Immunotherapy. *Laryngoscope*. Jul 2021;131(7):E2111-E2115. doi:10.1002/lary.29272

1059. Chaaban MR, Mansi A, Tripple JW, Wise SK. SCIT Versus SLIT: Which One Do You Recommend, Doc? *Am J Med Sci*. May 2019;357(5):442-447. doi:10.1016/j.amjms.2019.02.004

1060. Lin CH, Alandijani S, Lockey RF. Subcutaneous versus sublingual immunotherapy. *Expert Rev Clin Immunol*. Aug 2016;12(8):801-3. doi:10.1080/1744666X.2016.1196137

1061. Borg M, Lokke A, Hilberg O. Compliance in subcutaneous and sublingual allergen immunotherapy: A nationwide study. *Respir Med*. Aug - Sep 2020;170:106039. doi:10.1016/j.rmed.2020.106039

1062. Gotoh M, Kaminuma O. Sublingual Immunotherapy: How Sublingual Allergen Administration Heals Allergic Diseases; Current Perspective about the Mode of Action. *Pathogens*. Feb 2 2021;10(2)doi:10.3390/pathogens10020147

1063. Allergenics. FDA. Accessed October 29, 2021, https://www.fda.gov/vaccines-blood-biologics/allergenics

1064. Creticos PS. Sublingual immunotherapy for allergic rhinoconjunctivitis and asthma. Accessed October 26, 2021, https://www.uptodate.com/contents/sublingual-immunotherapy-for-allergic-rhinoconjunctivitis-and-asthma

1065. Nolte H, Casale TB, Lockey RF, et al. Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets. *J Allergy Clin Immunol Pract*. Jan - Feb 2017;5(1):84-89 e3. doi:10.1016/j.jaip.2016.08.017

1066. Clark S, Wei W, Rudders SA, Camargo CA, Jr. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. *J Allergy Clin Immunol*. Nov 2014;134(5):1125-30. doi:10.1016/j.jaci.2014.05.018

1067. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy*. Jun 1996;51(6):430-3. doi:10.1111/j.1398-9995.1996.tb04643.x

1068. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol*. Sep 1988;82(3 Pt 1):439-46. doi:10.1016/0091-6749(88)90017-6

1069. Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol*. Dec 2005;116(6):1380-1. doi:10.1016/j.jaci.2005.07.034

1070. Kiel MA, Roder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Molken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol*. Aug 2013;132(2):353-60 e2. doi:10.1016/j.jaci.2013.03.013

1071. Sieber J, De Geest S, Shah-Hosseini K, Mosges R. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. *Curr Med Res Opin*. Apr 2011;27(4):855-61. doi:10.1185/03007995.2011.559538

1072. Senna G, Ridolo E, Calderon M, Lombardi C, Canonica GW, Passalacqua G. Evidence of adherence to allergen-specific immunotherapy. *Curr Opin Allergy Clin Immunol*. Dec 2009;9(6):544-8. doi:10.1097/ACI.0b013e328332b8df

1073. Leader BA, Rotella M, Stillman L, DelGaudio JM, Patel ZM, Wise SK. Immunotherapy compliance: comparison of subcutaneous versus sublingual immunotherapy. *Int Forum Allergy Rhinol*. May 2016;6(5):460-4. doi:10.1002/alr.21699

1074. Creticos PS. Subcutaneous immunotherapy (SCIT) for allergic disease: Indications and efficacy. Accessed October 26, 2021, https://www.uptodate.com/contents/subcutaneous-immunotherapy-scit-for-allergic-disease-indications-and-efficacy

1075. Nelson H. Preparation of allergen extracts fro therapeutic use. Accessed October 26, 2021, https://www.uptodate.com/contents/scit-preparation-of-allergen-extracts-for-therapeutic-use

1076. Egan M, Atkins D. What Is the Relationship Between Eosinophilic Esophagitis (EoE) and Aeroallergens? Implications for Allergen Immunotherapy. *Curr Allergy Asthma Rep*. Jun 16 2018;18(8):43. doi:10.1007/s11882-018-0798-2

1077. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol*. Jun 2000;9(3):165-9. doi:10.1034/j.1600-0625.2000.009003165.x

1078. Senti G, Kundig TM. Novel Delivery Routes for Allergy Immunotherapy: Intralymphatic, Epicutaneous, and Intradermal. *Immunol Allergy Clin North Am*. Feb 2016;36(1):25-37. doi:10.1016/j.iac.2015.08.006

1079. Wang Y, Kong Y, Wu MX. Innovative Systems to Deliver Allergen Powder for Epicutaneous Immunotherapy. *Front Immunol*. 2021;12:647954. doi:10.3389/fimmu.2021.647954

1080. Esposito S, Isidori C, Pacitto A, et al. Epicutaneous immunotherapy in rhino-conjunctivitis and food allergies: a review of the literature. *J Transl Med*. Nov 27 2018;16(1):329. doi:10.1186/s12967-018-1701-6

1081. Senti G, Graf N, Haug S, et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J Allergy Clin Immunol*. Nov 2009;124(5):997-1002. doi:10.1016/j.jaci.2009.07.019

1082. Agostinis F, Forti S, Di Berardino F. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. *Allergy*. Mar 2010;65(3):410-1. doi:10.1111/j.1398-9995.2009.02189.x

1083. Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol*. Jan 2012;129(1):128-35. doi:10.1016/j.jaci.2011.08.036

1084. Senti G, von Moos S, Tay F, Graf N, Johansen P, Kundig TM. Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. *Allergy*. Jun 2015;70(6):707-10. doi:10.1111/all.12600

1085. Xiong L, Lin J, Luo Y, Chen W, Dai J. The Efficacy and Safety of Epicutaneous Immunotherapy for Allergic Diseases: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol*. 2020;181(3):170-182. doi:10.1159/000504366

1086. Senti G, Freiburghaus AU, Larenas-Linnemann D, et al. Intralymphatic Immunotherapy: Update and Unmet Needs. *Int Arch Allergy Immunol*. 2019;178(2):141-149. doi:10.1159/000493647

1087. Hoang MP, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Rhinology*. Jun 1 2021;59(3):236-244. doi:10.4193/Rhin20.572

1088. Aini NR, Mohd Noor N, Md Daud MK, Wise SK, Abdullah B. Efficacy and safety of intralymphatic immunotherapy in allergic rhinitis: A systematic review and meta-analysis. *Clin Transl Allergy*. Aug 2021;11(6):e12055. doi:10.1002/clt2.12055

1089. Hylander T, Latif L, Petersson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. Feb 2013;131(2):412-20. doi:10.1016/j.jaci.2012.10.056

1090. Senti G, Prinz Vavricka BM, Erdmann I, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc Natl Acad Sci U S A*. Nov 18 2008;105(46):17908-12. doi:10.1073/pnas.0803725105

1091. Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol*. May 2012;129(5):1290-6. doi:10.1016/j.jaci.2012.02.026

1092. Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK. Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy? *J Allergy Clin Immunol*. Nov 2013;132(5):1248-1252 e5. doi:10.1016/j.jaci.2013.07.033

1093. Patterson AM, Bonny AE, Shiels WE, 2nd, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. Feb 2016;116(2):168-70. doi:10.1016/j.anai.2015.11.010

1094. Hylander T, Larsson O, Petersson-Westin U, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. *Respir Res*. Jan 27 2016;17:10. doi:10.1186/s12931-016-0324-9

1095. Hellkvist L, Hjalmarsson E, Kumlien Georen S, et al. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: A randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. Oct 2018;142(4):1338-1341 e9. doi:10.1016/j.jaci.2018.05.030

1096. Konradsen JR, Grundstrom J, Hellkvist L, et al. Intralymphatic immunotherapy in pollen-allergic young adults with rhinoconjunctivitis and mild asthma: A randomized trial. *J Allergy Clin Immunol*. Mar 2020;145(3):1005-1007 e7. doi:10.1016/j.jaci.2019.11.017

1097. Skaarup SH, Schmid JM, Skjold T, Graumann O, Hoffmann HJ. Intralymphatic immunotherapy improves grass pollen allergic rhinoconjunctivitis: A 3-year randomized placebo-controlled trial. *J Allergy Clin Immunol*. Mar 2021;147(3):1011-1019. doi:10.1016/j.jaci.2020.07.002

1098. Thompson CP, Silvers S, Shapiro MA. Intralymphatic immunotherapy for mountain cedar pollinosis: A randomized, double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol*. Sep 2020;125(3):311-318 e2. doi:10.1016/j.anai.2020.04.030

1099. Terada T, Omura S, Kikuoka Y, et al. Sustained effects of intralymphatic pollen-specific immunotherapy on Japanese cedar pollinosis. *Rhinology*. Jun 1 2020;58(3):241-247. doi:10.4193/Rhin19.301

1100. Wang K, Zheng R, Chen Y, et al. Clinical efficacy and safety of cervical intralymphatic immunotherapy for house dust mite allergic rhinitis: A pilot study. *Am J Otolaryngol*. Nov - Dec 2019;40(6):102280. doi:10.1016/j.amjoto.2019.102280

1101. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. Aug 2017;72(8):1156-1173. doi:10.1111/all.13138

1102. Lee SP, Choi SJ, Joe E, et al. A Pilot Study of Intralymphatic Immunotherapy for House Dust Mite, Cat, and Dog Allergies. *Allergy Asthma Immunol Res*. May 2017;9(3):272-277. doi:10.4168/aair.2017.9.3.272

1103. Schmid JM, Nezam H, Madsen HH, Schmitz A, Hoffmann HJ. Intralymphatic immunotherapy induces allergen specific plasmablasts and increases tolerance to skin prick testing in a pilot study. *Clin Transl Allergy*. 2016;6:19. doi:10.1186/s13601-016-0107-x

1104. Taudorf E, Laursen LC, Lanner A, et al. Oral immunotherapy in birch pollen hay fever. *J Allergy Clin Immunol*. Aug 1987;80(2):153-61. doi:10.1016/0091-6749(87)90124-2

1105. Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat extract. *J Allergy Clin Immunol*. Jan 1994;93(1 Pt 1):61-7. doi:10.1016/0091-6749(94)90233-x

1106. Van Deusen MA, Angelini BL, Cordoro KM, Seiler BA, Wood L, Skoner DP. Efficacy and safety of oral immunotherapy with short ragweed extract. *Ann Allergy Asthma Immunol*. Jun 1997;78(6):573-80. doi:10.1016/S1081-1206(10)63218-8

1107. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med*. Nov 22 2018;379(21):1991-2001. doi:10.1056/NEJMoa1812856

1108. Allam JP, Stojanovski G, Friedrichs N, et al. Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy? *Allergy*. Jun 2008;63(6):720-7. doi:10.1111/j.1398-9995.2007.01611.x

1109. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. Mar 28 2014;7(1):6. doi:10.1186/1939-4551-7-6

1110. Reisacher WR, Suurna MV, Rochlin K, Bremberg MG, Tropper G. Oral mucosal immunotherapy for allergic rhinitis: A pilot study. *Allergy Rhinol (Providence)*. Jan 2016;7(1):21-8. doi:10.2500/ar.2016.7.0150

1111. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to Parietaria: evidence of reduction of local allergic inflammation. *Am J Respir Crit Care Med*. Aug 1995;152(2):461-6. doi:10.1164/ajrccm.152.2.7633693

1112. Andri L, Senna G, Betteli C, Givanni S, Andri G, Falagiani P. Local nasal immunotherapy for Dermatophagoides-induced rhinitis: efficacy of a powder extract. *J Allergy Clin Immunol*. May 1993;91(5):987-96. doi:10.1016/0091-6749(93)90211-w

1113. Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma--a double-blind study. *J Investig Allergol Clin Immunol*. Mar-Apr 1992;2(2):59-67.

1114. Saco T, Ugalde IC, Cardet JC, Casale TB. Strategies for choosing a biologic for your patient with allergy or asthma. *Ann Allergy Asthma Immunol*. Dec 2021;127(6):627-637. doi:10.1016/j.anai.2021.09.009

1115. Kamin W, Kopp MV, Erdnuess F, Schauer U, Zielen S, Wahn U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol*. Feb 2010;21(1 Pt 2):e160-5. doi:10.1111/j.1399-3038.2009.00900.x

1116. Rolinck-Werninghaus C, Hamelmann E, Keil T, et al. The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. *Allergy*. Sep 2004;59(9):973-9. doi:10.1111/j.1398-9995.2004.00552.x

1117. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. *J Allergy Clin Immunol*. Feb 2004;113(2):297-302. doi:10.1016/j.jaci.2003.11.044

1118. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. *J Allergy Clin Immunol*. Dec 2003;112(6):1147-54. doi:10.1016/j.jaci.2003.10.003

1119. Kopp MV, Hamelmann E, Zielen S, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy*. Feb 2009;39(2):271-9. doi:10.1111/j.1365-2222.2008.03121.x

1120. Kopp MV, Hamelmann E, Bendiks M, et al. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. *Pediatr Allergy Immunol*. Aug 2013;24(5):427-33. doi:10.1111/pai.12098

1121. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol*. Feb 2010;125(2):383-9. doi:10.1016/j.jaci.2009.11.022

1122. Slater JE. Preparation and standardization of allergen extracts. In: Adkinson NF, Burks AW, Busse WW, Holgate ST, Lemanske RFJ, eds. *Allergy Principlses and Practice*. 8 ed. Mosbe; 2014:470-81.

1123. Calderon MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol*. Apr 2012;129(4):929-34. doi:10.1016/j.jaci.2011.11.019

1124. Zuberbier T, Bachert C, Bousquet PJ, et al. GA(2) LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy*. Dec 2010;65(12):1525-30. doi:10.1111/j.1398-9995.2010.02474.x

1125. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. *Allergy Asthma Clin Immunol*. 2016;12:2. doi:10.1186/s13223-015-0109-6

1126. Wahn U, Calderon MA, Demoly P. Real-life clinical practice and management of polysensitized patients with respiratory allergies: a large, global survey of clinicians prescribing allergen immunotherapy. *Expert Rev Clin Immunol*. Mar 2017;13(3):283-289. doi:10.1080/1744666X.2017.1277142

1127. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol*. May 2016;27 Suppl 23:1-250. doi:10.1111/pai.12563

1128. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. *JAMA*. Sep 18 1967;201(12):915-7.

1129. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injecton therapy in ragweed hay fever. *N Engl J Med*. Sep 23 1965;273(13):675-9. doi:10.1056/NEJM196509232731302

1130. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children--a 14-year study. *Pediatrics*. Nov 1968;42(5):793-802.

1131. Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol*. Oct 1986;78(4 Pt 1):590-600. doi:10.1016/0091-6749(86)90076-x

1132. El-Qutob D, Raducan I, Mencia G. A preliminary study to investigate effectiveness of a mixed extract of Dermatophagoides sp. house dust mites and Alternaria sp. mold. *Eur Ann Allergy Clin Immunol*. Sep 2021;53(5):234-239. doi:10.23822/EurAnnACI.1764-1489.185

1133. Nevot-Falco S, Mancebo EG, Martorell A, et al. Safety and Effectiveness of a Single Multiallergen Subcutaneous Immunotherapy in Polyallergic Patients. *Int Arch Allergy Immunol*. 2021;182(12):1226-1230. doi:10.1159/000517473

1134. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol*. Apr 2009;123(4):763-9. doi:10.1016/j.jaci.2008.12.013

1135. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy*. Jun 2006;61(6):693-8. doi:10.1111/j.1398-9995.2006.01054.x

1136. Blume SW, Yeomans K, Allen-Ramey F, et al. Administration and Burden of Subcutaneous Immunotherapy for Allergic Rhinitis in U.S. and Canadian Clinical Practice. *J Manag Care Spec Pharm*. Nov 2015;21(11):982-90. doi:10.18553/jmcp.2015.21.11.982

1137. Kim JY, Han DH, Won TB, et al. Immunologic modification in mono- and poly-sensitized patients after sublingual immunotherapy. *Laryngoscope*. May 2019;129(5):E170-E177. doi:10.1002/lary.27721

1138. Soyyigit S, Guloglu D, Ikinciogullari A, et al. Immunologic alterations and efficacy of subcutaneous immunotherapy with Dermatophagoides pteronyssinus in monosensitized and polysensitized patients. *Ann Allergy Asthma Immunol*. Mar 2016;116(3):244-251 e2. doi:10.1016/j.anai.2016.01.002

1139. Song Y, Long J, Wang T, Xie J, Wang M, Tan G. Long-term efficacy of standardised specific subcutaneous immunotherapy in children with persistent allergic rhinitis due to multiple allergens including house dust mites. *J Laryngol Otol*. Mar 2018;132(3):230-235. doi:10.1017/S0022215117002547

1140. Search of: allergy immunotherapy | Recruiting, Not yet recruiting, Active, not recruiting Studies | Allergic Rhinitis - List Results Accessed November 8, 2021, https://clinicaltrials.gov/ct2/results?term=allergy+immunotherapy&cond=Allergic+Rhinitis&Search=Apply&recrs=b&recrs=a&recrs=d&age_v=&gndr=&type=&rslt=

1141. Nelson HS. Subcutaneous injection immunotherapy for optimal effectiveness. *Immunol Allergy Clin North Am*. May 2011;31(2):211-26, viii. doi:10.1016/j.iac.2011.02.010

1142. Esch RE. Allergen immunotherapy: what can and cannot be mixed? *J Allergy Clin Immunol*. Sep 2008;122(3):659-60. doi:10.1016/j.jaci.2008.07.018

1143. Grier TJ, LeFevre DM, Duncan EA, Esch RE, Coyne TC. Allergen stabilities and compatibilities in mixtures of high-protease fungal and insect extracts. *Ann Allergy Asthma Immunol*. Jun 2012;108(6):439-47. doi:10.1016/j.anai.2012.04.012

1144. Bozek A, Kolodziejczyk K, Warkocka-Szoltysek B, Jarzab J. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*. Sep-Oct 2014;28(5):423-7. doi:10.2500/ajra.2014.28.4091

1145. Bozek A, Cudak A, Walter Canonica G. Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis. *Allergy Asthma Proc*. Jul 1 2020;41(4):271-277. doi:10.2500/aap.2020.41.200035

1146. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol*. Feb 2006;117(2):263-8. doi:10.1016/j.jaci.2005.09.054

1147. Cools M, Van Bever HP, Weyler JJ, Stevens WJ. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. *Allergy*. Jan 2000;55(1):69-73. doi:10.1034/j.1398-9995.2000.00191.x

1148. Stelmach I, Sobocinska A, Majak P, Smejda K, Jerzynska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann Allergy Asthma Immunol*. Oct 2012;109(4):274-8. doi:10.1016/j.anai.2012.07.015

1149. Pfaar O, Sager A, Robinson DS. Safety and effect on reported symptoms of depigmented polymerized allergen immunotherapy: a retrospective study of 2927 paediatric patients. *Pediatr Allergy Immunol*. May 2015;26(3):280-286. doi:10.1111/pai.12347

1150. Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy*. Mar 2019;74(3):594-604. doi:10.1111/all.13598

1151. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol*. Nov 2010;126(5):942-9. doi:10.1016/j.jaci.2010.06.002

1152. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. Feb 2002;109(2):251-6. doi:10.1067/mai.2002.121317

1153. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*. Jul 2006;61(7):855-9. doi:10.1111/j.1398-9995.2006.01068.x

1154. Devillier P, Molimard M, Ansolabehere X, et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: A retrospective database study in France. *Allergy*. Jul 2019;74(7):1317-1326. doi:10.1111/all.13705

1155. Lim CE, Sison CP, Ponda P. Comparison of Pediatric and Adult Systemic Reactions to Subcutaneous Immunotherapy. *J Allergy Clin Immunol Pract*. Sep - Oct 2017;5(5):1241-1247 e2. doi:10.1016/j.jaip.2017.01.014

1156. Liu JL, Ning WX, Li SX, et al. The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China. *Allergol Immunopathol (Madr)*. Nov - Dec 2017;45(6):541-548. doi:10.1016/j.aller.2017.04.002

1157. Bousquet PJ, Castelli C, Daures JP, et al. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). *Ann Epidemiol*. Nov 2010;20(11):797-803. doi:10.1016/j.annepidem.2010.05.012

1158. Arbes SJ, Jr., Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. Aug 2005;116(2):377-83. doi:10.1016/j.jaci.2005.05.017

1159. Anto JM, Bousquet J, Akdis M, et al. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol*. Feb 2017;139(2):388-399. doi:10.1016/j.jaci.2016.12.940

1160. Ballardini N, Bergstrom A, Wahlgren CF, et al. IgE antibodies in relation to prevalence and multimorbidity of eczema, asthma, and rhinitis from birth to adolescence. *Allergy*. Mar 2016;71(3):342-9. doi:10.1111/all.12798

1161. Hauser M, Roulias A, Ferreira F, Egger M. Panallergens and their impact on the allergic patient. *Allergy Asthma Clin Immunol*. Jan 18 2010;6(1):1. doi:10.1186/1710-1492-6-1

1162. Aalberse RC, Aalberse JA. Molecular Allergen-Specific IgE Assays as a Complement to Allergen Extract-Based Sensitization Assessment. *J Allergy Clin Immunol Pract*. Nov-Dec 2015;3(6):863-9; quiz 870. doi:10.1016/j.jaip.2015.09.013

1163. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint. *J Allergy Clin Immunol*. Sep 2010;126(3):668-9. doi:10.1016/j.jaci.2010.06.045

1164. Kiotseridis H, Arvidsson P, Backer V, Braendholt V, Tunsater A. Adherence and quality of life in adults and children during 3-years of SLIT treatment with Grazax-a real life study. *NPJ Prim Care Respir Med*. Feb 12 2018;28(1):4. doi:10.1038/s41533-018-0072-z

1165. Chen H, Chen Y, Lin B, et al. Efficacy and adherence of sublingual immunotherapy in patients aged 60 to 75 years old with house dust mite-induced allergic rhinitis. *Am J Otolaryngol*. Jul - Aug 2020;41(4):102538. doi:10.1016/j.amjoto.2020.102538

1166. Vogelberg C, Bruggenjurgen B, Richter H, Jutel M. Real-World Adherence and Evidence of Subcutaneous and Sublingual Immunotherapy in Grass and Tree Pollen-Induced Allergic Rhinitis and Asthma. *Patient Prefer Adherence*. 2020;14:817-827. doi:10.2147/PPA.S242957

1167. Lemberg ML, Berk T, Shah-Hosseini K, Kasche EM, Mosges R. Sublingual versus subcutaneous immunotherapy: patient adherence at a large German allergy center. *Patient Prefer Adherence*. 2017;11:63-70. doi:10.2147/PPA.S122948

1168. Stone B, Rance K, Waddell D, Aagren M, Hammerby E, Tkacz JP. Real-world mapping of allergy immunotherapy in the United States: The argument for improving adherence. *Allergy Asthma Proc*. Jan 1 2021;42(1):55-64. doi:10.2500/aap.2021.42.200114

1169. Liu W, Zeng Q, He C, et al. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. *Pediatr Allergy Immunol*. Jan 2021;32(1):86-91. doi:10.1111/pai.13332

1170. Hsu NM, Reisacher WR. A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. *Int Forum Allergy Rhinol*. Jul-Aug 2012;2(4):280-4. doi:10.1002/alr.21037

1171. Allam JP, Andreasen JN, Mette J, Serup-Hansen N, Wustenberg EG. Comparison of allergy immunotherapy medication persistence with a sublingual immunotherapy tablet versus subcutaneous immunotherapy in Germany. *J Allergy Clin Immunol*. May 2018;141(5):1898-1901 e5. doi:10.1016/j.jaci.2017.12.999

1172. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. *Rhinology*. Jun 1980;18(2):83-6.

1173. Incuado GA. Diagnosis and treatment of allergic rhinitis and sinusitis during pregnancy and lactation. *Clin Rev Allergy Immunol*. 2004;27(2):159-77.

1174. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. Feb 2006;61(2):169-76. doi:10.1136/thx.2005.049718

1175. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol*. Apr 1978;61(4):268-72. doi:10.1016/0091-6749(78)90202-6

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]

REFERENCES

1. Dowdee A, Ossege J. Assessment of childhood allergy for the primary care practitioner. *J Am Acad Nurse Pract*. Feb 2007;19(2):53-62. doi:10.1111/j.1745-7599.2006.00195.x

2. Berger WE. Allergic rhinitis in children : diagnosis and management strategies. *Paediatr Drugs*. 2004;6(4):233-50. doi:10.2165/00148581-200406040-00003

3. Doulaptsi M, Aoi N, Kawauchi H, Milioni A, Karatzanis A, Prokopakis E. Differentiating Rhinitis in the Paediatric Population by Giving Focus on Medical History and Clinical Examination. *Med Sci (Basel)*. Feb 26 2019;7(3)doi:10.3390/medsci7030038

4. Tharpe CA, Kemp SF. Pediatric allergic rhinitis. *Immunol Allergy Clin North Am*. Feb 2015;35(1):185-98. doi:10.1016/j.iac.2014.09.003

5. Sanford T. Allergic rhinitis in children. *Mo Med*. May-Jun 2008;105(3):230-4.

6. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. Sep 2013;68(9):1102-16. doi:10.1111/all.12235

7. Izquierdo-Dominguez A, Valero AL, Mullol J. Comparative analysis of allergic rhinitis in children and adults. *Curr Allergy Asthma Rep*. Apr 2013;13(2):142-51. doi:10.1007/s11882-012-0331-y

8. Reshma A, Baranwal AK. Child with Allergies or Allergic Reactions. *Indian J Pediatr*. Jan 2018;85(1):60-65. doi:10.1007/s12098-017-2436-8

9. Lee VS, Lin SY. Allergy and the Pediatric Otolaryngologist. *Otolaryngol Clin North Am*. Oct 2019;52(5):863-873. doi:10.1016/j.otc.2019.05.005

10. Mims JW, Veling MC. Inhalant allergies in children. *Otolaryngol Clin North Am*. Jun 2011;44(3):797-814, xi. doi:10.1016/j.otc.2011.03.013

11. Lin SY, Melvin TA, Boss EF, Ishman SL. The association between allergic rhinitis and sleep-disordered breathing in children: a systematic review. *Int Forum Allergy Rhinol*. Jun 2013;3(6):504-9. doi:10.1002/alr.21123

12. Kwon C, Lee HY, Kim MG, Boo SH, Yeo SG. Allergic diseases in children with otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. Feb 2013;77(2):158-61. doi:10.1016/j.ijporl.2012.09.039

13. Roditi RE, Veling M, Shin JJ. Age: An effect modifier of the association between allergic rhinitis and Otitis media with effusion. *Laryngoscope*. Jul 2016;126(7):1687-92. doi:10.1002/lary.25682

14. Olusesi AD, Undie NB, Amodu JE. Allergy history as a predictor of early onset adenoids/adenotonsillar hypertrophy among Nigerian children. *Int J Pediatr Otorhinolaryngol*. Jun 2013;77(6):1032-5. doi:10.1016/j.ijporl.2013.04.004

15. Evcimik MF, Dogru M, Cirik AA, Nepesov MI. Adenoid hypertrophy in children with allergic disease and influential factors. *Int J Pediatr Otorhinolaryngol*. May 2015;79(5):694-7. doi:10.1016/j.ijporl.2015.02.017

16. Huang SW, Giannoni C. The risk of adenoid hypertrophy in children with allergic rhinitis. *Ann Allergy Asthma Immunol*. Oct 2001;87(4):350-5. doi:10.1016/S1081-1206(10)62251-X

17. La Mantia I, Andaloro C. Demographics and clinical features predictive of allergic versus non-allergic rhinitis in children aged 6-18 years: A single-center experience of 1535 patients. *Int J Pediatr Otorhinolaryngol*. Jul 2017;98:103-109. doi:10.1016/j.ijporl.2017.04.044

18. Brown T. Diagnosis and Management of Allergic Rhinitis in Children. *Pediatr Ann*. Dec 1 2019;48(12):e485-e488. doi:10.3928/19382359-20191111-01

19. Ameli F, Brocchetti F, Tosca MA, Signori A, Ciprandi G. Nasal endoscopy in children with suspected allergic rhinitis. *Laryngoscope*. Oct 2011;121(10):2055-9. doi:10.1002/lary.22156

20. Eigenmann PA, Atanaskovic-Markovic M, J OBH, et al. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatr Allergy Immunol*. Mar 2013;24(2):195-209. doi:10.1111/pai.12066

21. Host A, Andrae S, Charkin S, et al. Allergy testing in children: why, who, when and how? *Allergy*. Jul 2003;58(7):559-69. doi:10.1034/j.1398-9995.2003.00238.x

22. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. Feb 2015;152(1 Suppl):S1-43. doi:10.1177/0194599814561600

23. Chawes BLK, Kreiner-Moller E, Bisgaard H. Objective assessments of allergic and nonallergic rhinitis in young children. *Allergy*. Oct 2009;64(10):1547-1553. doi:10.1111/j.1398-9995.2009.02085.x

24. Miller RE, Paradise JL, Friday GA, Fireman P, Voith D. The nasal smear for eosinophils. Its value in children with seasonal allergic rhinitis. *Am J Dis Child*. Nov 1982;136(11):1009-11. doi:10.1001/archpedi.1982.03970470053015

25. Mierzejewska A, Jung A, Kalicki B. Nasal Cytology as a Marker of Atopy in Children. *Dis Markers*. 2017;2017:4159251. doi:10.1155/2017/4159251

26. Lee KS, Yu J, Shim D, et al. Local Immune Responses in Children and Adults with Allergic and Nonallergic Rhinitis. *PLoS One*. 2016;11(6):e0156979. doi:10.1371/journal.pone.0156979

27. Jirapongsananuruk O, Vichyanond P. Nasal cytology in the diagnosis of allergic rhinitis in children. *Ann Allergy Asthma Immunol*. Feb 1998;80(2):165-70. doi:10.1016/S1081-1206(10)62950-X

28. Ogulur I, Kiykim A, Baris S, Ozen A, Yuce EG, Karakoc-Aydiner E. Basophil activation test for inhalant allergens in pediatric patients with allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Jun 2017;97:197-201. doi:10.1016/j.ijporl.2017.04.006

29. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. Jan 2020;145(1):70-80 e3. doi:10.1016/j.jaci.2019.06.049

30. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. Oct 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

31. Horak F, Zieglmayer UP, Zieglmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin*. Jan 2006;22(1):151-7. doi:10.1185/030079906X80305

32. Kaliner MA, Berger WE, Ratner PH, Siegel CJ. The efficacy of intranasal antihistamines in the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol*. Feb 2011;106(2 Suppl):S6-S11. doi:10.1016/j.anai.2010.08.010

33. Herman H. Once-daily administration of intranasal corticosteroids for allergic rhinitis: a comparative review of efficacy, safety, patient preference, and cost. *Am J Rhinol*. Jan-Feb 2007;21(1):70-9. doi:10.2500/ajr.2007.21.2896

34. Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy*. Feb 2011;41(2):160-70. doi:10.1111/j.1365-2222.2010.03654.x

35. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy*. Oct 2008;63(10):1280-91. doi:10.1111/j.1398-9995.2008.01808.x

36. Dibildox J. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. *J Allergy Clin Immunol*. Jul 2001;108(1 Suppl):S54-8. doi:10.1067/mai.2001.115567

37. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol*. Oct 2006;31(5):360-7. doi:10.1111/j.1749-4486.2006.01276.x

38. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. *Ann Allergy Asthma Immunol*. Jun 2006;96(6):779-86. doi:10.1016/S1081-1206(10)61339-7

39. Ratner PH, Howland WC, 3rd, Arastu R, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol*. May 2003;90(5):536-42. doi:10.1016/S1081-1206(10)61847-9

40. Pitsios C, Papadopoulos D, Kompoti E, et al. Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. May 2006;96(5):673-8. doi:10.1016/S1081-1206(10)61064-2

41. Lange B, Lukat KF, Rettig K, Holtappels G, Bachert C. Efficacy, cost-effectiveness, and tolerability of mometasone furoate, levocabastine, and disodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2005;95(3):272-82. doi:10.1016/S1081-1206(10)61225-2

42. Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol*. Apr 1999;82(4):349-59. doi:10.1016/S1081-1206(10)63284-X

43. Roberge RJ, Hirani KH, Rowland PL, 3rd, Berkeley R, Krenzelok EP. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med*. Mar-Apr 1999;17(2):285-8. doi:10.1016/s0736-4679(98)00193-0

44. Sauder KL, Brady WJ, Jr., Hennes H. Visual hallucinations in a toddler: accidental ingestion of a sympathomimetic over-the-counter nasal decongestant. *Am J Emerg Med*. Sep 1997;15(5):521-6. doi:10.1016/s0735-6757(97)90200-x

45. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. Jan 2011;127(1 Suppl):S1-55. doi:10.1016/j.jaci.2010.09.034

46. Creticos PS, Bernstein DI, Casale TB, Lockey RF, Maloney J, Nolte H. Coseasonal Initiation of Allergen Immunotherapy: A Systematic Review. *J Allergy Clin Immunol Pract*. Nov - Dec 2016;4(6):1194-1204 e4. doi:10.1016/j.jaip.2016.05.014

47. Halken S, Lau S, Valovirta E. New visions in specific immunotherapy in children: an iPAC summary and future trends. *Pediatr Allergy Immunol*. Aug 2008;19 Suppl 19:60-70. doi:10.1111/j.1399-3038.2008.00768.x

48. Roder E, Berger MY, de Groot H, van Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol*. May 2008;19(3):197-207. doi:10.1111/j.1399-3038.2007.00648.x

49. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. Mar 27 2013;309(12):1278-88. doi:10.1001/jama.2013.2049

50. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. Feb 2017;28(1):18-29. doi:10.1111/pai.12661

51. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol*. Aug 2008;101(2):206-11. doi:10.1016/s1081-1206(10)60211-6

52. Bousquet J, Pfaar O, Agache I, et al. ARIA-EAACI care pathways for allergen immunotherapy in respiratory allergy. *Clin Transl Allergy*. Jun 2021;11(4):e12014. doi:10.1002/clt2.12014

53. Pitsios C, Demoly P, Bilo MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. Aug 2015;70(8):897-909. doi:10.1111/all.12638

54. Odactra House Dust Mite (Dermatophagoides farinae and Dermatophagoides pteronyssinus) allergen extract tablet for sublingual use. Accessed October 8, 2021, fda.gov/media/103380/download

55. ORALAIR (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/87935/download

56. Grastek Timothy grass pollen extract tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/88510/download

57. Ragwitek short ragweed pollen extract tablet for sublingual use. Accessed July 3, 2022, https://www.fda.gov/media/88712/download

58. Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. Apr 2018;73(4):765-798. doi:10.1111/all.13317

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-sectional studies	General public, asthma patients, n=3182	Asthma+AR prevalence	-Asthma and AR are often comorbid diseases -Asthma+AR prevalence 39%
Tohinidik et al[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	General public	Prevalence of AR in pediatric asthma patients	-54.9% prevalence of AR in pediatric asthma -Prevalence of AR higher

			studies			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	2000	3	Cohort	University	Asthma	Allergic asthma depends on elevated IgE,

et al[41]				students	development	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	2003	2	RCT	Seasonal AR and asthma, n=924:	-TASS -FEV_1	-Desloratadine versus placebo: reduction in mean TASS,

al[92]				-Desloratadine 5mg -Montelukast 10mg -Placebo	-β-agonist use	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	2005	2	RCT	Seasonal AR and persistent asthma,	-Daily PEF	-INFP added to FSC improved nasal

al[109]				n=863; all received FSC: -INFP 200µg and FSC daily -MON 10mg + FSC -Placebo + FSC	-Daily asthma and AR symptoms -Rescue albuterol use	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 -Placebo nasal spray + Bdp MDI 1000µg -Bdp nasal spray 400µg + Bdp MDI 1000µg daily	-Asthma and AR symptom scores -PEF -FEV_1 and BHR (PC_{20}) -Proxy indicators of asthma-related morbidity (work absence, emergency visits, etc)	-Reductions of AR and asthma symptoms in all groups -No change PEF or BHR -Increased FEV_1 with nasal Bdp alone and for Bdp MDI alone -Asthma morbidity reduced for all
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	1993	3*	RCT	AR and controlled	-Asthma and rhinitis	-No difference in asthma

al[116]				asthma, n=21: -Intranasal Bdp 100µg twice daily, then placebo -Placebo nasal spray, then intranasal Bdp 100µg twice daily	symptoms -PC_{20} -Bdp deposition**	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	MON-levocetirizine safe and more effective than MON alone across all observed endpoints

					-FEV_1, FVC, FEV_1/FVC -Asthma Control Test -Rescue medication usage	
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	2003	2	RCT	Seasonal AR and asthma,	-TASS	Desloratadine vs

et al[92]				n=924: -Desloratadine 5mg -MON 10mg -placebo	-FEV_1 -β-agonist use	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	Omalizumab: -Reduced asthma exacerbations -Increased AQLQ and RQLQ -Reduced asthma symptoms -Increased FEV_1, FVC,

					-FEV_1, FVC, AM PEF	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,	New allergic sensitization	Low evidence that AIT prevents further allergic sensitization among mono- and polysensitized patients with AR

				treated with AIT vs not treated with AIT		
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	-Development of persistent asthma (not at baseline) -Symptom and medication scores of allergic symptoms	-Persistent asthma incidence lower with SLIT vs control -Methacholine-positive patients after 3 years reduced with SLIT

				-Standard drug therapy plus SLIT*	-Daily medication use -New sensitization	-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	-BHR increased with SCIT -No HDM IgE difference -Increased med use and visits with placebo

					symptoms -Development of asthma	-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	2008	2	RCT	CRSsNP with or without	Reactivity in ragweed season	Allergic patients have increased reactivity

al[156]				ragweed allergy, n=18	determined by symptoms and sinus inflammation	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,	-Postoperative course	No difference between allergic and

				n=63	-Recurrence	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,	-Skin test against aspergillin antigen, n=47 -Histopathologic monitoring for the	Type 1 hypersensitivity was significantly associated with the AFRS group ($p<0.05$)

				n=36) -M+F- (likely EMCRS, n=12) -M-F+ (likely sinus mycetoma, n=4) -M-F- (CRS from other causes, n=18)	presence of mucin -Mycologic monitoring for the presence of fungus	
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	-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

				AIT		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 -AFRS-like mucin, n=18	Culture results of 31 of the 44 AFRS patients	19 of the 31 had negative culture results

Manning et al[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	-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

					pattern of disease	(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:	Allergy and asthma prevalence by	-Allergen sensitivity increased in CCAD, AERD and AFRS compared with

				-AFRS -AERD -CCAD -CRSwNP NOS	subtype	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	-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

					-Eos, tIgE	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	2021	3	Retrospective	380 CRS patients, including 28 patients	-Prevalence of atopy in	-75.3% of CRS patients were

al[226]			cohort	with comorbid AERD	CRS subtypes -Clinical characteristics, histopathology, serum IgE, symptom and radiographic scores -Atopy defined by clinical symptoms + SPT	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 -SPT, spirometry, nasal lavage, bronchoscopy -Cytokine and eicosanoid levels in bronchoalveolar lavage	-36% of AERD patients with positive SPT -SPT positivity did not differ between eosinophilic and non-eosinophilic AERD endotypes 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	-80.6% of AERD subjects had CC disease -100% of CC-AERD patients had atopic history, 93.8% had

					and positive SPT	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	2021	3	Retrospective	Patients referred for allergy	-History	-33% diagnosed with AC -AC associated with AR in

et al[245]			cohort analysis	evaluation, n=2914	-Skin test -sIgE -Provocation tests	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	-Physical examination -Skin prick test	-73.8% of patients with perennial AC had associated AR -Most common sensitization was house

				eyes		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	Children with AD/eczema in	-SPT -Symptoms upon	AD associated with AR (-asthma) in White (3x

			cohort	Cincinnati enrolled ≤2 years old, n=601	allergen exposure	risk) and Black (6x risk) children
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 of US children, n=38,408	Prevalence of shellfish food allergy, associated factors	History of AR independently associated with shellfish allergy (OR 2.0; 95% CI 1.4-2.9)
Alm et al[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	Children referred	-Endoscopic	AH negatively

			cohort	from pediatric allergy to otolaryngology	adenoid size -SPT	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	-Passive opening and closing pressures of the ET -Active clearance of	Sensitized rats had significant increases in passive and active opening pressures, decreased

				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	positive and negative pressure -MCTT	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	1987	3**	Double-blind	-Adults with AR, n=5	-Nine-step tympanometric ET	-All AR subjects had ET obstruction after histamine

al[382]			crossover	-Adults without AR, n=5	function test	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	1997	4	Retrospective	Patients with ETD and positive allergy	Ratings of fullness, allergy symptoms,	Majority improved on all three symptoms - fullness

et al[394]			case series	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)	and well-being as "improved", "no change", or "worse"	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	-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

				-Controls, n=4504		
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 persistent OME after 3 months	Prevalence of AR in OME children was 52.3% and 80.3% for those with persistent OME
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	2010	2	RCT	Children with OME,	Clearance of effusion at 1 month	Montelukast is no more effective than placebo in

al[435]				n=38	after montelukast or placebo	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	-Atopic patients had higher levels of ECP, MPO and tryptase in effusions vs non-

					-Serum tIgE	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	Higher levels of IgE in MEE of allergic children than non-allergic children

					-MEE IgE	
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	-Serum tIgE -Serum sIgE -ECoG SP/AP ratio	-Patients with acute low frequency SNHL have higher serum tIgE and sIgE

				patients, n=115		-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 -Provocative food	-82% had normal serum IgE -AIT improved vertigo in 62%

					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	-Questionnaire	-*D. pteronyssinus* most common allergen

				symptoms from 2011-2014, n=2713	-Allergen profile -Clinical features of AR	-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	Assess safety of nasal allergen challenge, and the use of certain parameters	Extra-nasal symptoms observed early in reaction, namely cough and breathlessness, and more common in those

				-Controls, n=30	applied in assessing the condition of the respiratory system.	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 confirmed via skin test) -OVA group -Control group	-Symptoms of AR induced by intranasal application of 15µl 0.5 % HDM -Cough challenge with citric acid performed -Airway resistance measured in vivo by Pennock's method.	-HDM and OVA-sensitized groups showed a significantly enhanced nasal reactivity and cough response vs controls -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	-4-question allergy questionnaire	-AR patients had more voice symptoms during allergy and

				-Controls without AR, matched for gender and age, n=30	-Swedish questionnaire about voice symptoms -Acoustic analysis of voice recordings	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	Prevalence of AR and LPR	3 times as many patients had allergies vs LPR, not

				sensation		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	Demographic and clinical characteristics	50-80% had AR and sensitization to

				patients		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 allergies treated with AIT	Clinicohistologic remission	EoE remission observed after treatment with multiallergen SCIT as monotherapy
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	Rate of EoE diagnosis in patients with AR	AR diagnosis associated with an increased rate of

				-Controls, n=22,272		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, aged 3-14 years, n=660	-PSG -Sleep questionnaire	-Prevalence of AR in SDB (25.8%), OSA (19.4%) -Regardless of OSA status, AR children had more daytime hypersomnolence, behavioral symptoms,

						and shorter sleep time -Children with AR without OSA spent shorter time in REM -Children with AR had shorter sleep time
Na et al[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	-HDM AR patients more likely to have REM-RDI and REM-AHI in

					-PSG	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

REFERENCES

1. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. May 4 2012;18(5):716-25. doi:10.1038/nm.2678

2. von Mutius E, Drazen JM. A patient with asthma seeks medical advice in 1828, 1928, and 2012. *N Engl J Med*. Mar 1 2012;366(9):827-34. doi:10.1056/NEJMra1102783

3. Global strategy for asthma management and prevention, 2021. Accessed November 6, 2021, www.ginasthma.org

4. Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe (Sheff)*. Mar 2019;15(1):e20-e27. doi:10.1183/20734735.0362-2018

5. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. Jan 27 2018;391(10118):350-400. doi:10.1016/S0140-6736(17)30879-6

6. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. Feb 2014;43(2):343-73. doi:10.1183/09031936.00202013

7. Pedersen CJ, Uddin MJ, Saha SK, Darmstadt GL. Prevalence of atopic dermatitis, asthma and rhinitis from infancy through adulthood in rural Bangladesh: a population-based, cross-sectional survey. *BMJ Open*. Nov 4 2020;10(11):e042380. doi:10.1136/bmjopen-2020-042380

8. Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. *World Allergy Organ J*. Oct 2019;12(10):100069. doi:10.1016/j.waojou.2019.100069

9. Machluf Y, Farkash R, Rotkopf R, Fink D, Chaiter Y. Asthma phenotypes and associated comorbidities in a large cohort of adolescents in Israel. *J Asthma*. Jul 2020;57(7):722-735. doi:10.1080/02770903.2019.1604743

10. Heck S, Al-Shobash S, Rapp D, et al. High probability of comorbidities in bronchial asthma in Germany. *NPJ Prim Care Respir Med*. Apr 21 2017;27(1):28. doi:10.1038/s41533-017-0026-x

11. Pols DHJ, Bohnen AM, Nielen MMJ, Korevaar JC, Bindels PJE. Risks for comorbidity in children with atopic disorders: an observational study in Dutch general practices. *BMJ Open*. Nov 12 2017;7(11):e018091. doi:10.1136/bmjopen-2017-018091

12. Ozoh OB, Aderibigbe SA, Ayuk AC, et al. The prevalence of asthma and allergic rhinitis in Nigeria: A nationwide survey among children, adolescents and adults. *PLoS One*. 2019;14(9):e0222281. doi:10.1371/journal.pone.0222281

13. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy*. Mar 2008;63(3):292-8. doi:10.1111/j.1398-9995.2007.01584.x

14. de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax*. Jul 2012;67(7):582-7. doi:10.1136/thoraxjnl-2011-201168

15. Tay TR, Radhakrishna N, Hore-Lacy F, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology*. Nov 2016;21(8):1384-1390. doi:10.1111/resp.12838

16. Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. *Allergy*. Nov 2014;69(11):1515-21. doi:10.1111/all.12467

17. Holgate ST, Wenzel S, Postma DS, Weiss ST, Renz H, Sly PD. Asthma. *Nat Rev Dis Primers*. Sep 10 2015;1:15025. doi:10.1038/nrdp.2015.25

18. Togias A, Gergen PJ, Hu JW, et al. Rhinitis in children and adolescents with asthma: Ubiquitous, difficult to control, and associated with asthma outcomes. *J Allergy Clin Immunol*. Mar 2019;143(3):1003-1011 e10. doi:10.1016/j.jaci.2018.07.041

19. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. Sep 20 2008;372(9643):1049-57. doi:10.1016/S0140-6736(08)61446-4

20. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol*. Jan 2015;15(1):57-65. doi:10.1038/nri3786

21. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. *Clin Rev Allergy Immunol*. Apr 2019;56(2):219-233. doi:10.1007/s12016-018-8712-1

22. Todd S, Walsted ES, Grillo L, Livingston R, Menzies-Gow A, Hull JH. Novel assessment tool to detect breathing pattern disorder in patients with refractory asthma. *Respirology*. Mar 2018;23(3):284-290. doi:10.1111/resp.13173

23. Barker N, Thevasagayam R, Ugonna K, Kirkby J. Pediatric Dysfunctional Breathing: Proposed Components, Mechanisms, Diagnosis, and Management. *Front Pediatr*. 2020;8:379. doi:10.3389/fped.2020.00379

24. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. Dec 2017;49(12):1752-1757. doi:10.1038/ng.3985

25. Seumois G, Zapardiel-Gonzalo J, White B, et al. Transcriptional Profiling of Th2 Cells Identifies Pathogenic Features Associated with Asthma. *J Immunol*. Jul 15 2016;197(2):655-64. doi:10.4049/jimmunol.1600397

26. Samitas K, Carter A, Kariyawasam HH, Xanthou G. Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: The one airway concept revisited. *Allergy*. May 2018;73(5):993-1002. doi:10.1111/all.13373

27. Ullmann N, Mirra V, Di Marco A, et al. Asthma: Differential Diagnosis and Comorbidities. *Front Pediatr*. 2018;6:276. doi:10.3389/fped.2018.00276

28. Shen Y, Zeng JH, Hong SL, Kang HY. Prevalence of allergic rhinitis comorbidity with asthma and asthma with allergic rhinitis in China: A meta-analysis. *Asian Pac J Allergy Immunol*. Dec 2019;37(4):220-225. doi:10.12932/AP-120417-0072

29. Kou W, Li X, Yao H, Wei P. Meta-analysis of the comorbidity rate of allergic rhinitis and asthma in Chinese children. *Int J Pediatr Otorhinolaryngol*. Apr 2018;107:131-134. doi:10.1016/j.ijporl.2018.02.001

30. Carr TF, Stern DA, Halonen M, Wright AL, Martinez FD. Non-atopic rhinitis at age 6 is associated with subsequent development of asthma. *Clin Exp Allergy*. Jan 2019;49(1):35-43. doi:10.1111/cea.13276

31. Tosca MA, Duse M, Marseglia G, Ciprandi G, ControL'Asma" Study G. The practical clinical relevance of rhinitis classification in children with asthma: outcomes of the "ControL'Asma" study. *Ann Allergy Asthma Immunol*. Nov 2019;123(5):516-519. doi:10.1016/j.anai.2019.08.003

32. Kisiel MA, Zhou X, Sundh J, et al. Data-driven questionnaire-based cluster analysis of asthma in Swedish adults. *NPJ Prim Care Respir Med*. Apr 6 2020;30(1):14. doi:10.1038/s41533-020-0168-0

33. Heffler E, Blasi F, Latorre M, et al. The Severe Asthma Network in Italy: Findings and Perspectives. *J Allergy Clin Immunol Pract*. May - Jun 2019;7(5):1462-1468. doi:10.1016/j.jaip.2018.10.016

34. Huang K, Yang T, Xu J, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet*. Aug 3 2019;394(10196):407-418. doi:10.1016/S0140-6736(19)31147-X

35. Ji H, Hu Y, Zhang T, et al. Allergic Comorbidity of Asthma or Wheezing, Allergic Rhinitis, and Eczema: Result From 333 029 Allergic Children in Shanghai, China. *Am J Rhinol Allergy*. Mar 2020;34(2):189-195. doi:10.1177/1945892419883238

36. Sonia T, Meriem M, Yacine O, et al. Prevalence of asthma and rhinitis in a Tunisian population. *Clin Respir J*. Feb 2018;12(2):608-615. doi:10.1111/crj.12570

37. Ziyab AH. Prevalence and Risk Factors of Asthma, Rhinitis, and Eczema and Their Multimorbidity among Young Adults in Kuwait: A Cross-Sectional Study. *Biomed Res Int*. 2017;2017:2184193. doi:10.1155/2017/2184193

38. Testa D, M DIB, Nunziata M, et al. Allergic rhinitis and asthma assessment of risk factors in pediatric patients: A systematic review. *Int J Pediatr Otorhinolaryngol*. Feb 2020;129:109759. doi:10.1016/j.ijporl.2019.109759

39. Lipiec A, Sybilski A, Komorowski J, et al. Sensitisation to airborne allergens as a risk factor for allergic rhinitis and asthma in the Polish population. *Postepy Dermatol Alergol*. Oct 2020;37(5):751-759. doi:10.5114/ada.2019.84231

40. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics*. Dec 1994;94(6 Pt 1):895-901.

41. Settipane RJ, Settipane GA. IgE and the allergy-asthma connection in the 23-year follow-up of Brown University students. *Allergy Asthma Proc*. Jul-Aug 2000;21(4):221-5. doi:10.2500/108854100778248890

42. Guerra S, Sherrill DL, Baldacci S, et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy*. Mar 2005;60(3):343-9. doi:10.1111/j.1398-9995.2005.00717.x

43. Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma--a Swedish population-based case-control study (MAP-study). *Respir Med*. Aug 2002;96(8):635-41. doi:10.1053/rmed.2002.1319

44. Shaaban R, Zureik M, Soussan D, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. *Am J Respir Crit Care Med*. Oct 1 2007;176(7):659-66. doi:10.1164/rccm.200703-427OC

45. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. Dec 2010;126(6):1170-5 e2. doi:10.1016/j.jaci.2010.09.008

46. Hamouda S, Karila C, Connault T, Scheinmann P, de Blic J. Allergic rhinitis in children with asthma: a questionnaire-based study. *Clin Exp Allergy*. May 2008;38(5):761-6. doi:10.1111/j.1365-2222.2008.02953.x

47. Antonicelli L, Micucci C, Voltolini S, et al. Allergic rhinitis and asthma comorbidity: ARIA classification of rhinitis does not correlate with the prevalence of asthma. *Clin Exp Allergy*. Jun 2007;37(6):954-60. doi:10.1111/j.1365-2222.2007.02729.x

48. Jung S, Lee SY, Yoon J, et al. Risk Factors and Comorbidities Associated With the Allergic Rhinitis Phenotype in Children According to the ARIA Classification. *Allergy Asthma Immunol Res*. Jan 2020;12(1):72-85. doi:10.4168/aair.2020.12.1.72

49. Sio YY, Pang SL, Say YH, et al. Sensitization to Airborne Fungal Allergens Associates with Asthma and Allergic Rhinitis Presentation and Severity in the Singaporean/Malaysian Population. *Mycopathologia*. Oct 2021;186(5):583-588. doi:10.1007/s11046-021-00532-6

50. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics*. Aug 2001;108(2):E33. doi:10.1542/peds.108.2.e33

51. Bonay M, Neukirch C, Grandsaigne M, et al. Changes in airway inflammation following nasal allergic challenge in patients with seasonal rhinitis. *Allergy*. Jan 2006;61(1):111-8. doi:10.1111/j.1398-9995.2006.00967.x

52. Moscato G, Vandenplas O, Van Wijk RG, et al. EAACI position paper on occupational rhinitis. *Respir Res*. Mar 3 2009;10:16. doi:10.1186/1465-9921-10-16

53. Panganiban RP, Wang Y, Howrylak J, et al. Circulating microRNAs as biomarkers in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol*. May 2016;137(5):1423-32. doi:10.1016/j.jaci.2016.01.029

54. Deng Q, Lu C, Yu Y, Li Y, Sundell J, Norback D. Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children. *Respir Med*. Dec 2016;121:67-73. doi:10.1016/j.rmed.2016.10.016

55. Wang J, Zhang Y, Li B, et al. Asthma and allergic rhinitis among young parents in China in relation to outdoor air pollution, climate and home environment. *Sci Total Environ*. Jan 10 2021;751:141734. doi:10.1016/j.scitotenv.2020.141734

56. Nordeide Kuiper I, Svanes C, Markevych I, et al. Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. *Environ Int*. Jan 2021;146:106219. doi:10.1016/j.envint.2020.106219

57. Polosa R, Knoke JD, Russo C, et al. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol*. Jun 2008;121(6):1428-34. doi:10.1016/j.jaci.2008.02.041

58. Ma T, Chen Y, Pang Y, et al. Prevalence and risk factors of allergic rhinitis and asthma in the southern edge of the plateau grassland region of northern China: A cross-sectional study. *World Allergy Organ J*. Jul 2021;14(7):100537. doi:10.1016/j.waojou.2021.100537

59. Ibanez MD, Valero AL, Montoro J, et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. *Pediatr Allergy Immunol*. Nov 2013;24(7):678-84. doi:10.1111/pai.12126

60. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. Jan 2012;67(1):91-8. doi:10.1111/j.1398-9995.2011.02709.x

61. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol*. Oct 2007;120(4):863-9. doi:10.1016/j.jaci.2007.07.020

62. Bodtger U, Poulsen LK, Linneberg A. Rhinitis symptoms and IgE sensitization as risk factors for development of later allergic rhinitis in adults. *Allergy*. Jun 2006;61(6):712-6. doi:10.1111/j.1398-9995.2006.01140.x

63. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest*. Feb 2006;129(2):309-316. doi:10.1378/chest.129.2.309

64. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med*. Sep 2000;162(3 Pt 1):920-4. doi:10.1164/ajrccm.162.3.9912030

65. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol*. Feb 1997;99(2):S781-6. doi:10.1016/s0091-6749(97)70127-1

66. Corren J. The impact of allergic rhinitis on bronchial asthma. *J Allergy Clin Immunol*. Feb 1998;101(2 Pt 2):S352-6. doi:10.1016/s0091-6749(98)70218-0

67. Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in a one-airway condition. *BMC Pulm Med*. Nov 30 2006;6 Suppl 1:S5. doi:10.1186/1471-2466-6-S1-S5

68. Bhimrao SK, Wilson SJ, Howarth PH. Airway inflammation in atopic patients: a comparison of the upper and lower airways. *Otolaryngol Head Neck Surg*. Sep 2011;145(3):396-400. doi:10.1177/0194599811410531

69. Eriksson J, Bjerg A, Lotvall J, et al. Rhinitis phenotypes correlate with different symptom presentation and risk factor patterns of asthma. *Respir Med*. Nov 2011;105(11):1611-21. doi:10.1016/j.rmed.2011.06.004

70. Kersten ET, van Leeuwen JC, Brand PL, et al. Effect of an intranasal corticosteroid on exercise induced bronchoconstriction in asthmatic children. *Pediatr Pulmonol*. Jan 2012;47(1):27-35. doi:10.1002/ppul.21511

71. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy*. 2013;68(5):569-79. doi:10.1111/all.12124

72. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. *J Allergy Clin Immunol*. May 1988;81(5 Pt 2):1042-7. doi:10.1016/0091-6749(88)90177-7

73. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol*. Aug 1992;90(2):250-6. doi:10.1016/0091-6749(92)90079-h

74. De Jong HJI, Voorham J, Scadding GK, et al. Evaluating the real-life effect of MP-AzeFlu on asthma outcomes in patients with allergic rhinitis and asthma in UK primary care. *World Allergy Organ J*. Dec 2020;13(12):100490. doi:10.1016/j.waojou.2020.100490

75. Chyrek-Borowska S, Siergiejko Z, Michalska I. The effects of a new generation of H1 antihistamines (cetirizine and loratadine) on histamine release and the bronchial response to histamine in atopic patients. *J Investig Allergol Clin Immunol*. Mar-Apr 1995;5(2):103-7.

76. Wasserfallen JB, Leuenberger P, Pecoud A. Effect of cetirizine, a new H1 antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. *J Allergy Clin Immunol*. Jun 1993;91(6):1189-97. doi:10.1016/0091-6749(93)90322-7

77. Nishimura M, Koga T, Kamimura T, et al. Comparison of leukotriene receptor antagonists and anti-histamines as an add-on therapy in patients with asthma complicated by allergic rhinitis. *Kurume Med J*. 2011;58(1):9-14. doi:10.2739/kurumemedj.58.9

78. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. Dec 2000;162(6):2048-52. doi:10.1164/ajrccm.162.6.9909087

79. Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics*. Jun 2013;131(6):1155-67. doi:10.1542/peds.2013-0343

80. Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. *J Allergy Clin Immunol*. Sep 1988;82(3 Pt 1):470-80. doi:10.1016/0091-6749(88)90021-8

81. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol*. Aug 2008;101(2):206-11. doi:10.1016/s1081-1206(10)60211-6

82. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. Feb 2002;109(2):251-6. doi:10.1067/mai.2002.121317

83. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Oct 2004;114(4):851-7. doi:10.1016/j.jaci.2004.07.012

84. Suissa S, Ernst P. Bias in observational study of the effectiveness of nasal corticosteroids in asthma. *J Allergy Clin Immunol*. Apr 2005;115(4):714-9. doi:10.1016/j.jaci.2004.12.1118

85. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis executive summary. *Otolaryngol Head Neck Surg*. Feb 2015;152(2):197-206. doi:10.1177/0194599814562166

86. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. Oct 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

87. D'Amato G, Ortega OPM, Annesi-Maesano I, D'Amato M. Prevention of Allergic Asthma with Allergen Avoidance Measures and the Role of Exposome. *Curr Allergy Asthma Rep*. Feb 26 2020;20(3):8. doi:10.1007/s11882-020-0901-3

88. Gotzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database Syst Rev*. Apr 16 2008;(2):CD001187. doi:10.1002/14651858.CD001187.pub3

89. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. Apr 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

90. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, et al. The effect of encasings on quality of life in adult house dust mite allergic patients with rhinitis, asthma and/or atopic dermatitis. *Allergy*. Jul 2005;60(7):888-93. doi:10.1111/j.1398-9995.2004.00677.x

91. Pasquali M, Baiardini I, Rogkakou A, et al. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. *Clin Exp Allergy*. Sep 2006;36(9):1161-7. doi:10.1111/j.1365-2222.2006.02548.x

92. Baena-Cagnani CE, Berger WE, DuBuske LM, et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol*. Apr 2003;130(4):307-13. doi:10.1159/000070218

93. Berger WE, Schenkel EJ, Mansfield LE, Desloratadine Study G. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. *Ann Allergy Asthma Immunol*. Nov 2002;89(5):485-91. doi:10.1016/S1081-1206(10)62086-8

94. Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. May 1995;95(5 Pt 1):923-32. doi:10.1016/s0091-6749(95)70090-0

95. Aubier M, Neukirch C, Peiffer C, Melac M. Effect of cetirizine on bronchial hyperresponsiveness in patients with seasonal allergic rhinitis and asthma. *Allergy*. Jan 2001;56(1):35-42. doi:10.1034/j.1398-9995.2001.00629.x

96. Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol*. May 1996;76(5):440-6. doi:10.1016/S1081-1206(10)63461-8

97. Simons FE. Is antihistamine (H1-receptor antagonist) therapy useful in clinical asthma? *Clin Exp Allergy*. Jul 1999;29 Suppl 3:98-104. doi:10.1046/j.1365-2222.1999.0290s3098.x

98. Bousquet J, Emonot A, Germouty J, et al. Double-blind multicenter study of cetirizine in grass-pollen-induced asthma. *Ann Allergy*. Dec 1990;65(6):504-8.

99. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J*. Oct 1997;10(10):2216-24. doi:10.1183/09031936.97.10102216

100. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. *Pediatr Allergy Immunol*. Aug 1998;9(3):116-24.

101. Bhargava S, Prakash A, Rehan HS, Gupta LK. Effect of systemic corticosteroids on serum apoptotic markers and quality of life in patients with asthma. *Allergy Asthma Proc*. Jul-Aug 2015;36(4):275-82. doi:10.2500/aap.2015.36.3834

102. Brooks CD, Karl KJ, Francom SF. Oral methylprednisolone acetate (Medrol Tablets) for seasonal rhinitis: examination of dose and symptom response. *J Clin Pharmacol*. Sep 1993;33(9):816-22. doi:10.1002/j.1552-4604.1993.tb01957.x

103. Sood V, Rogers L, Khurana S. Managing Corticosteroid-Related Comorbidities in Severe Asthma. *Chest*. Nov 2021;160(5):1614-1623. doi:10.1016/j.chest.2021.05.021

104. Welsh PW, Stricker WE, Chu CP, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc*. Feb 1987;62(2):125-34. doi:10.1016/s0025-6196(12)61882-5

105. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis*. Dec 1984;130(6):1014-8. doi:10.1164/arrd.1984.130.6.1014

106. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev*. 2003;(4):CD003570. doi:10.1002/14651858.CD003570

107. Jindal A, Suriyan S, Sagadevan S, et al. Comparison of Oral Montelukast and Intranasal Fluticasone in Patients with Asthma and Allergic Rhinitis. *J Clin Diagn Res*. Aug 2016;10(8):OC06-10. doi:10.7860/JCDR/2016/20741.8268

108. Dahl R, Nielsen LP, Kips J, et al. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy*. Jul 2005;60(7):875-81. doi:10.1111/j.1398-9995.2005.00819.x

109. Nathan RA, Yancey SW, Waitkus-Edwards K, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. Oct 2005;128(4):1910-20. doi:10.1378/chest.128.4.1910

110. Stelmach R, do Patrocinio TNM, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest*. Nov 2005;128(5):3140-7. doi:10.1378/chest.128.5.3140

111. Thio BJ, Slingerland GL, Fredriks AM, et al. Influence of intranasal steroids during the grass pollen season on bronchial responsiveness in children and young adults with asthma and hay fever. *Thorax*. Oct 2000;55(10):826-32. doi:10.1136/thorax.55.10.826

112. Baiardini I, Villa E, Rogkakou A, et al. Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire. *Clin Exp Allergy*. Mar 2011;41(3):417-23. doi:10.1111/j.1365-2222.2010.03660.x

113. Nair A, Vaidyanathan S, Clearie K, Williamson P, Meldrum K, Lipworth BJ. Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis. *Allergy*. Mar 2010;65(3):359-67. doi:10.1111/j.1398-9995.2009.02187.x

114. Agondi RC, Machado ML, Kalil J, Giavina-Bianchi P. Intranasal corticosteroid administration reduces nonspecific bronchial hyperresponsiveness and improves asthma symptoms. *J Asthma*. Nov 2008;45(9):754-7. doi:10.1080/02770900802249149

115. Pedroletti C, Lundahl J, Alving K, Hedlin G. Effect of nasal steroid treatment on airway inflammation determined by exhaled nitric oxide in allergic schoolchildren with perennial rhinitis and asthma. *Pediatr Allergy Immunol*. May 2008;19(3):219-26. doi:10.1111/j.1399-3038.2007.00613.x

116. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol*. Jan 1993;91(1 Pt 1):97-101. doi:10.1016/0091-6749(93)90301-u

117. Gani F, Pozzi E, Crivellaro MA, et al. The role of patient training in the management of seasonal rhinitis and asthma: clinical implications. *Allergy*. Jan 2001;56(1):65-8. doi:10.1034/j.1398-9995.2001.00794.x

118. Meltzer EO. Role for cysteinyl leukotriene receptor antagonist therapy in asthma and their potential role in allergic rhinitis based on the concept of "one linked airway disease". *Ann Allergy Asthma Immunol*. Feb 2000;84(2):176-85; quiz 185-7. doi:10.1016/S1081-1206(10)62750-0

119. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. Sep 2010;126(3):466-76. doi:10.1016/j.jaci.2010.06.047

120. Egan M, Bunyavanich S. Allergic rhinitis: the "Ghost Diagnosis" in patients with asthma. *Asthma Res Pract*. 2015;1:8. doi:10.1186/s40733-015-0008-0

121. Nowak D. Management of asthma with anti-immunoglobulin E: a review of clinical trials of omalizumab. *Respir Med*. Nov 2006;100(11):1907-17. doi:10.1016/j.rmed.2005.10.004

122. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy*. Mar 2005;60(3):302-8. doi:10.1111/j.1398-9995.2004.00770.x

123. Casale TB, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. Dec 19 2001;286(23):2956-67. doi:10.1001/jama.286.23.2956

124. D'Amato G, Salzillo A, Piccolo A, D'Amato M, Liccardi G. A review of anti-IgE monoclonal antibody (omalizumab) as add on therapy for severe allergic (IgE-mediated) asthma. *Ther Clin Risk Manag*. Aug 2007;3(4):613-9.

125. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. Jan 13 2014;(1):CD003559. doi:10.1002/14651858.CD003559.pub4

126. Humbert M, Boulet LP, Niven RM, Panahloo Z, Blogg M, Ayre G. Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. *Allergy*. Jan 2009;64(1):81-4. doi:10.1111/j.1398-9995.2008.01846.x

127. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy*. Jul 2004;59(7):709-17. doi:10.1111/j.1398-9995.2004.00550.x

128. Kopp MV, Hamelmann E, Zielen S, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy*. Feb 2009;39(2):271-9. doi:10.1111/j.1365-2222.2008.03121.x

129. Erekosima N, Suarez-Cuervo C, Ramanathan M, et al. Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: a systematic review. *Laryngoscope*. Mar 2014;124(3):616-27. doi:10.1002/lary.24295

130. Lin SY, Erekosima N, Suarez-Cuervo C, et al. *Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review*. 2013. *AHRQ Comparative Effectiveness Reviews*.

131. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. *Allergy*. Nov 2017;72(11):1597-1631. doi:10.1111/all.13201

132. Blanco C, Bazire R, Argiz L, Hernandez-Pena J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. *Drugs Context*. 2018;7:212552. doi:10.7573/dic.212552

133. Sidenius K, Arvidsson P, Indbryn R, Emanuelsson CA. A Real-Life One-Year Non-Interventional Study Assessing Safety, Tolerability, and Treatment Outcome of the SQ HDM SLIT-Tablet (Acarizax((R))) in House Dust Mite Allergic Rhinitis With or Without Asthma. *Pulm Ther*. Jun 2021;7(1):221-236. doi:10.1007/s41030-021-00150-z

134. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. Feb 2006;61(2):198-201. doi:10.1111/j.1398-9995.2006.01011.x

135. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol*. 2007;17(2):85-91.

136. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. Aug 2007;62(8):943-8. doi:10.1111/j.1398-9995.2007.01451.x

137. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*. Jul 2006;61(7):855-9. doi:10.1111/j.1398-9995.2006.01068.x

138. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy*. Aug 2001;31(8):1295-302. doi:10.1046/j.1365-2222.2001.01027.x

139. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. Feb 2017;28(1):18-29. doi:10.1111/pai.12661

140. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Macchia L, Di Lorenzo G. Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy*. May 2017;72(5):691-704. doi:10.1111/all.13104

141. Di Lorenzo G, Leto-Barone MS, La Piana S, Plaia A, Di Bona D. The effect of allergen immunotherapy in the onset of new sensitizations: a meta-analysis. *Int Forum Allergy Rhinol*. Jul 2017;7(7):660-669. doi:10.1002/alr.21946

142. Fortescue R, Kew KM, Leung MST. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. Sep 14 2020;9:CD011293. doi:10.1002/14651858.CD011293.pub3

143. Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, 2019. Accessed July 4, 2022, www.ginasthma.org

144. 2020 Focused Update to the Asthma Management Guidelines: Clinician's Guide. Accessed July 4, 2022, https://www.nhlbi.nih.gov/sites/default/files/publications/AsthmaCliniciansGuideDesign-508.pdf

145. Kim MK, Lee SY, Park HS, et al. A Randomized, Multicenter, Double-blind, Phase III Study to Evaluate the Efficacy on Allergic Rhinitis and Safety of a Combination Therapy of Montelukast and

Levocetirizine in Patients With Asthma and Allergic Rhinitis. *Clin Ther*. Jul 2018;40(7):1096-1107 e1. doi:10.1016/j.clinthera.2018.04.021

146. Katial RK, Oppenheimer JJ, Ostrom NK, et al. Adding montelukast to fluticasone propionate/salmeterol for control of asthma and seasonal allergic rhinitis. *Allergy Asthma Proc*. Jan-Feb 2010;31(1):68-75. doi:10.2500/aap.2010.31.3306

147. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. Jun 2006;61(6):737-42. doi:10.1111/j.1398-9995.2006.01007.x

148. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin*. Oct 2004;20(10):1549-58. doi:10.1185/030079904x3348

149. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. Mar 27 2013;309(12):1278-88. doi:10.1001/jama.2013.2049

150. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. Mar 2021;11(3):213-739. doi:10.1002/alr.22741

151. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. Feb 20 2020;58(Suppl S29):1-464. doi:10.4193/Rhin20.600

152. Helman SN, Barrow E, Edwards T, DelGaudio JM, Levy JM, Wise SK. The Role of Allergic Rhinitis in Chronic Rhinosinusitis. *Immunol Allergy Clin North Am*. May 2020;40(2):201-214. doi:10.1016/j.iac.2019.12.010

153. Marcus S, Roland LT, DelGaudio JM, Wise SK. The relationship between allergy and chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol*. Feb 2019;4(1):13-17. doi:10.1002/lio2.236

154. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. Feb 2018;8(2):108-352. doi:10.1002/alr.22073

155. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. Feb 2014;4(2):93-103. doi:10.1002/alr.21258

156. Baroody FM, Mucha SM, Detineo M, Naclerio RM. Nasal challenge with allergen leads to maxillary sinus inflammation. *J Allergy Clin Immunol*. May 2008;121(5):1126-1132 e7. doi:10.1016/j.jaci.2008.02.010

157. Tan BK, Zirkle W, Chandra RK, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Mar-Apr 2011;1(2):88-94. doi:10.1002/alr.20025

158. Pearlman AN, Chandra RK, Chang D, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. *Am J Rhinol Allergy*. Mar-Apr 2009;23(2):145-8. doi:10.2500/ajra.2009.23.3284

159. Gelincik A, Buyukozturk S, Aslan I, et al. Allergic vs nonallergic rhinitis: which is more predisposing to chronic rhinosinusitis? *Ann Allergy Asthma Immunol*. Jul 2008;101(1):18-22. doi:10.1016/S1081-1206(10)60829-0

160. Kirtsreesakul V, Ruttanaphol S. The relationship between allergy and rhinosinusitis. *Rhinology*. Sep 2008;46(3):204-8.

161. Robinson S, Douglas R, Wormald PJ. The relationship between atopy and chronic rhinosinusitis. *Am J Rhinol*. Nov-Dec 2006;20(6):625-8. doi:10.2500/ajr.2006.20.2907

162. Alho OP, Karttunen R, Karttunen TJ. Nasal mucosa in natural colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. *Clin Exp Immunol*. Aug 2004;137(2):366-72. doi:10.1111/j.1365-2249.2004.02530.x

163. Van Zele T, Gevaert P, Watelet JB, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. *J Allergy Clin Immunol*. Oct 2004;114(4):981-3. doi:10.1016/j.jaci.2004.07.013

164. Berrettini S, Carabelli A, Sellari-Franceschini S, et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. *Allergy*. Mar 1999;54(3):242-8. doi:10.1034/j.1398-9995.1999.00813.x

165. Al-Qudah M. Food Sensitization in Medically Resistant Chronic Rhinosinusitis with or without Nasal Polyposis. *Int Arch Allergy Immunol*. 2016;169(1):40-4. doi:10.1159/000443737

166. Li QC, Cheng KJ, Wang F, Zhou SH. Role of atopy in chronic rhinosinusitis with nasal polyps: does an atopic condition affect the severity and recurrence of disease? *J Laryngol Otol*. Jul 2016;130(7):640-4. doi:10.1017/S0022215116008112

167. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. *Laryngoscope*. Sep 2008;118(9):1521-7. doi:10.1097/MLG.0b013e31817d01b8

168. Kirtsreesakul V. Role of allergy in the therapeutic response of nasal polyps. *Asian Pac J Allergy Immunol*. Sep 2002;20(3):141-6.

169. Gorgulu O, Ozdemir S, Canbolat EP, Sayar C, Olgun MK, Akbas Y. Analysis of the roles of smoking and allergy in nasal polyposis. *Ann Otol Rhinol Laryngol*. Sep 2012;121(9):615-9. doi:10.1177/000348941212100909

170. Lill C, Loader B, Seemann R, et al. Milk allergy is frequent in patients with chronic sinusitis and nasal polyposis. *Am J Rhinol Allergy*. Nov-Dec 2011;25(6):e221-4. doi:10.2500/ajra.2011.25.3686

171. Munoz del Castillo F, Jurado-Ramos A, Fernandez-Conde BL, et al. Allergenic profile of nasal polyposis. *J Investig Allergol Clin Immunol*. 2009;19(2):110-6.

172. Bonfils P, Malinvaud D. Influence of allergy in patients with nasal polyposis after endoscopic sinus surgery. *Acta Otolaryngol*. Feb 2008;128(2):186-92. doi:10.1080/00016480701387165

173. Erbek SS, Erbek S, Topal O, Cakmak O. The role of allergy in the severity of nasal polyposis. *Am J Rhinol*. Nov-Dec 2007;21(6):686-90. doi:10.2500/ajr.2007.21.3062

174. Bonfils P, Avan P, Malinvaud D. Influence of allergy on the symptoms and treatment of nasal polyposis. *Acta Otolaryngol*. Aug 2006;126(8):839-44. doi:10.1080/00016480500504226

175. Collins MM, Loughran S, Davidson P, Wilson JA. Nasal polyposis: prevalence of positive food and inhalant skin tests. *Otolaryngol Head Neck Surg*. Nov 2006;135(5):680-3. doi:10.1016/j.otohns.2006.07.005

176. Asero R, Bottazzi G. Nasal polyposis: a study of its association with airborne allergen hypersensitivity. *Ann Allergy Asthma Immunol*. Mar 2001;86(3):283-5. doi:10.1016/S1081-1206(10)63299-1

177. Voegels RL, Santoro P, Butugan O, Formigoni LG. Nasal polyposis and allergy: is there a correlation? *Am J Rhinol*. Jan-Feb 2001;15(1):9-14. doi:10.2500/105065801781329365

178. Asero R, Bottazzi G. Hypersensitivity to molds in patients with nasal polyposis: A clinical study. *J Allergy Clin Immunol*. Jan 2000;105(1 Pt 1):186-8. doi:10.1016/s0091-6749(00)90198-2

179. Pang YT, Eskici O, Wilson JA. Nasal polyposis: role of subclinical delayed food hypersensitivity. *Otolaryngol Head Neck Surg*. Feb 2000;122(2):298-301. doi:10.1016/S0194-5998(00)70259-2

180. Pumhirun P, Limitlaohapanth C, Wasuwat P. Role of allergy in nasal polyps of Thai patients. *Asian Pac J Allergy Immunol*. Mar 1999;17(1):13-5.

181. Keith PK, Conway M, Evans S, et al. Nasal polyps: effects of seasonal allergen exposure. *J Allergy Clin Immunol*. Mar 1994;93(3):567-74. doi:10.1016/s0091-6749(94)70068-0

182. Ence BK, Gourley DS, Jorgensen NL, al e. Allergic fungal sinusitis. *Amer J Rhinol*. 1990;4:169-78.

183. Schubert MS. Allergic fungal sinusitis. *Otolaryngol Clin North Am*. Apr 2004;37(2):301-26. doi:10.1016/S0030-6665(03)00152-X

184. Bent JP, 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg*. Nov 1994;111(5):580-8. doi:10.1177/019459989411100508

185. Saravanan K, Panda NK, Chakrabarti A, Das A, Bapuraj RJ. Allergic fungal rhinosinusitis: an attempt to resolve the diagnostic dilemma. *Arch Otolaryngol Head Neck Surg*. Feb 2006;132(2):173-8. doi:10.1001/archotol.132.2.173

186. Hutcheson PS, Schubert MS, Slavin RG. Distinctions between allergic fungal rhinosinusitis and chronic rhinosinusitis. *Am J Rhinol Allergy*. Nov-Dec 2010;24(6):405-8. doi:10.2500/ajra.2010.24.3533

187. Manning SC, Mabry RL, Schaefer SD, Close LG. Evidence of IgE-mediated hypersensitivity in allergic fungal sinusitis. *Laryngoscope*. Jul 1993;103(7):717-21. doi:10.1288/00005537-199307000-00002

188. Stewart AE, Hunsaker DH. Fungus-specific IgG and IgE in allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. Oct 2002;127(4):324-32. doi:10.1067/mhn.2002.126801

189. Ryan MW, Marple BF. Allergic fungal rhinosinusitis: diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg*. Feb 2007;15(1):18-22. doi:10.1097/MOO.0b013e328013dbd9

190. Collins M, Nair S, Smith W, Kette F, Gillis D, Wormald PJ. Role of local immunoglobulin E production in the pathophysiology of noninvasive fungal sinusitis. *Laryngoscope*. Jul 2004;114(7):1242-6. doi:10.1097/00005537-200407000-00019

191. Wise SK, Ahn CN, Lathers DM, Mulligan RM, Schlosser RJ. Antigen-specific IgE in sinus mucosa of allergic fungal rhinosinusitis patients. *Am J Rhinol*. Sep-Oct 2008;22(5):451-6. doi:10.2500/ajr.2008.22.3227

192. Chang YT, Fang SY. Tissue-specific immunoglobulin E in maxillary sinus mucosa of allergic fungal sinusitis. *Rhinology*. Sep 2008;46(3):226-30.

193. Kuhn FA, Swain R, Jr. Allergic fungal sinusitis: diagnosis and treatment. *Curr Opin Otolaryngol Head Neck Surg*. Feb 2003;11(1):1-5. doi:10.1097/00020840-200302000-00001

194. Marcus S, Schertzer J, Roland LT, Wise SK, Levy JM, DelGaudio JM. Central compartment atopic disease: prevalence of allergy and asthma compared with other subtypes of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. Feb 2020;10(2):183-189. doi:10.1002/alr.22454

195. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. Feb 2016;6 Suppl 1:S22-209. doi:10.1002/alr.21695

196. Mabry RL, Marple BF, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: three years' experience. *Otolaryngol Head Neck Surg*. Dec 1998;119(6):648-51. doi:10.1016/S0194-5998(98)70027-0

197. Folker RJ, Marple BF, Mabry RL, Mabry CS. Treatment of allergic fungal sinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. *Laryngoscope*. Nov 1998;108(11 Pt 1):1623-7. doi:10.1097/00005537-199811000-00007

198. Gan EC, Thamboo A, Rudmik L, Hwang PH, Ferguson BJ, Javer AR. Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: an evidence-based review and recommendations. *Int Forum Allergy Rhinol*. Sep 2014;4(9):702-15. doi:10.1002/alr.21352

199. Doellman MS, Dion GR, Weitzel EK, Reyes EG. Immunotherapy in allergic fungal sinusitis: The controversy continues. A recent review of literature. *Allergy Rhinol (Providence)*. Spring 2013;4(1):e32-5. doi:10.2500/ar.2013.4.0045

200. Pant H, Kette FE, Smith WB, Wormald PJ, Macardle PJ. Fungal-specific humoral response in eosinophilic mucus chronic rhinosinusitis. *Laryngoscope*. Apr 2005;115(4):601-6. doi:10.1097/01.mlg.0000161341.00258.54

201. Clark DW, Wenaas A, Luong A, Citardi MJ, Fakhri S. Staphylococcus aureus prevalence in allergic fungal rhinosinusitis vs other subsets of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. Feb 2013;3(2):89-93. doi:10.1002/alr.21090

202. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc*. Sep 1999;74(9):877-84. doi:10.4065/74.9.877

203. Cody DT, 2nd, Neel HB, 3rd, Ferreiro JA, Roberts GD. Allergic fungal sinusitis: the Mayo Clinic experience. *Laryngoscope*. Sep 1994;104(9):1074-9. doi:10.1288/00005537-199409000-00005

204. Dykewicz MS, Rodrigues JM, Slavin RG. Allergic fungal rhinosinusitis. *J Allergy Clin Immunol*. Aug 2018;142(2):341-351. doi:10.1016/j.jaci.2018.06.023

205. Tyler MA, Luong AU. Current understanding of allergic fungal rhinosinusitis. *World J Otorhinolaryngol Head Neck Surg*. Sep 2018;4(3):179-185. doi:10.1016/j.wjorl.2018.08.003

206. DelGaudio JM, Loftus PA, Hamizan AW, Harvey RJ, Wise SK. Central compartment atopic disease. *Am J Rhinol Allergy*. Jul 1 2017;31(4):228-234. doi:10.2500/ajra.2017.31.4443

207. White LJ, Rotella MR, DelGaudio JM. Polypoid changes of the middle turbinate as an indicator of atopic disease. *Int Forum Allergy Rhinol*. May 2014;4(5):376-80. doi:10.1002/alr.21290

208. Hamizan AW, Christensen JM, Ebenzer J, et al. Middle turbinate edema as a diagnostic marker of inhalant allergy. *Int Forum Allergy Rhinol*. Jan 2017;7(1):37-42. doi:10.1002/alr.21835

209. Brunner JP, Jawad BA, McCoul ED. Polypoid Change of the Middle Turbinate and Paranasal Sinus Polyposis Are Distinct Entities. *Otolaryngol Head Neck Surg*. Sep 2017;157(3):519-523. doi:10.1177/0194599817711887

210. Roland LT, Marcus S, Schertzer JS, Wise SK, Levy JM, DelGaudio JM. Computed Tomography Findings Can Help Identify Different Chronic Rhinosinusitis With Nasal Polyp Phenotypes. *Am J Rhinol Allergy*. Sep 2020;34(5):679-685. doi:10.1177/1945892420923926

211. Hamizan AW, Loftus PA, Alvarado R, et al. Allergic phenotype of chronic rhinosinusitis based on radiologic pattern of disease. *Laryngoscope*. Sep 2018;128(9):2015-2021. doi:10.1002/lary.27180

212. Abdullah B, Vengathajalam S, Md Daud MK, Wan Mohammad Z, Hamizan A, Husain S. The Clinical and Radiological Characterizations of the Allergic Phenotype of Chronic Rhinosinusitis with Nasal Polyps. *J Asthma Allergy*. 2020;13:523-531. doi:10.2147/JAA.S275536

213. Lee K, Kim TH, Lee SH, Kang CH, Je BK, Oh S. Predictive Value of Radiologic Central Compartment Atopic Disease for Identifying Allergy and Asthma in Pediatric Patients. *Ear Nose Throat J*. Mar 9 2021:145561321997546. doi:10.1177/0145561321997546

214. Lin YT, Lin CF, Liao CK, Chiang BL, Yeh TH. Clinical characteristics and cytokine profiles of central-compartment-type chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Jul 2021;11(7):1064-1073. doi:10.1002/alr.22759

215. DelGaudio JM, Levy JM, Wise SK. Central compartment involvement in aspirin-exacerbated respiratory disease: the role of allergy and previous sinus surgery. *Int Forum Allergy Rhinol*. Sep 2019;9(9):1017-1022. doi:10.1002/alr.22367

216. Makary CA, Falco J, Sussman S, et al. Disease involvement in the central compartment in eosinophilic chronic rhinosinusitis. *Int Forum Allergy Rhinol*. Oct 2021;11(10):1417-1423. doi:10.1002/alr.22803

217. Schertzer JS, Levy JM, Wise SK, Magliocca KR, DelGaudio JM. Is Respiratory Epithelial Adenomatoid Hamartoma Related to Central Compartment Atopic Disease? *Am J Rhinol Allergy*. Sep 2020;34(5):610-617. doi:10.1177/1945892420914212

218. Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. *Immunol Allergy Clin North Am*. May 2013;33(2):195-210. doi:10.1016/j.iac.2012.11.006

219. Samter M, Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med*. May 1968;68(5):975-83. doi:10.7326/0003-4819-68-5-975

220. Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol*. Jan 2014;133(1):98-103 e1-6. doi:10.1016/j.jaci.2013.07.004

221. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. Nov 2002;89(5):474-8. doi:10.1016/S1081-1206(10)62084-4

222. Jakiela B, Soja J, Sladek K, et al. Heterogeneity of lower airway inflammation in patients with NSAID-exacerbated respiratory disease. *J Allergy Clin Immunol*. Apr 2021;147(4):1269-1280. doi:10.1016/j.jaci.2020.08.007

223. Dona I, Barrionuevo E, Salas M, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Sci Rep*. Nov 12 2018;8(1):16710. doi:10.1038/s41598-018-34668-1

224. Bochenek G, Nizankowska E, Szczeklik A. The atopy trait in hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. Jan 1996;51(1):16-23. doi:10.1111/j.1398-9995.1996.tb04544.x

225. Stevens WW, Peters AT, Hirsch AG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract*. Jul - Aug 2017;5(4):1061-1070 e3. doi:10.1016/j.jaip.2016.12.027

226. Brown HJ, Tajudeen BA, Kuhar HN, Gattuso P, Batra PS, Mahdavinia M. Defining the Allergic Endotype of Chronic Rhinosinusitis by Structured Histopathology and Clinical Variables. *J Allergy Clin Immunol Pract*. Oct 2021;9(10):3797-3804. doi:10.1016/j.jaip.2021.06.013

227. Buchheit KM, Dwyer DF, Ordovas-Montanes J, et al. IL-5Ralpha marks nasal polyp IgG4- and IgE-expressing cells in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Jun 2020;145(6):1574-1584. doi:10.1016/j.jaci.2020.02.035

228. Ta V, White AA. Survey-Defined Patient Experiences With Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract*. Sep-Oct 2015;3(5):711-8. doi:10.1016/j.jaip.2015.03.001

229. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. Jan 2011;127(1 Suppl):S1-55. doi:10.1016/j.jaci.2010.09.034

230. Haque R, White AA, Jackson DJ, Hopkins C. Clinical evaluation and diagnosis of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. Aug 2021;148(2):283-291. doi:10.1016/j.jaci.2021.06.018

231. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol*. Oct 2015;15(5):482-8. doi:10.1097/ACI.0000000000000204

232. Miyazaki D, Fukagawa K, Okamoto S, et al. Epidemiological aspects of allergic conjunctivitis. *Allergol Int*. Oct 2020;69(4):487-495. doi:10.1016/j.alit.2020.06.004

233. Ait-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. Jan 2009;64(1):123-48. doi:10.1111/j.1398-9995.2008.01884.x

234. Strachan DP, Rutter CE, Asher MI, et al. Worldwide time trends in prevalence of symptoms of rhinoconjunctivitis in children: Global Asthma Network Phase I. *Pediatr Allergy Immunol*. Jan 2022;33(1):e13656. doi:10.1111/pai.13656

235. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. Oct 2010;126(4):778-783 e6. doi:10.1016/j.jaci.2010.06.050

236. Navarro A, Colas C, Anton E, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergologica-2005. *J Investig Allergol Clin Immunol*. 2009;19 Suppl 2:7-13.

237. Kosrirukvongs P, Visitsunthorn N, Vichyanond P, Bunnag C. Allergic conjunctivitis. *Asian Pac J Allergy Immunol*. Dec 2001;19(4):237-44.

238. Kim DH, Park YS, Jang HJ, Kim JH, Lim DH. Prevalence and allergen of allergic rhinitis in Korean children. *Am J Rhinol Allergy*. May 2016;30(3):72-8. doi:10.2500/ajra.2013.27.4317

239. Han DH, Ahn JC, Mun SJ, Park SK, Oh SY, Rhee CS. Novel Risk Factors for Allergic Rhinitis in Korean Elementary School Children: ARCO-kids Phase II in a Community. *Allergy Asthma Immunol Res*. May 2015;7(3):234-40. doi:10.4168/aair.2015.7.3.234

240. Cibella F, Ferrante G, Cuttitta G, et al. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res*. Jan 2015;7(1):44-50. doi:10.4168/aair.2015.7.1.44

241. Gradman J, Wolthers OD. Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic. *Pediatr Allergy Immunol*. Nov 2006;17(7):524-6. doi:10.1111/j.1399-3038.2006.00429.x

242. Williams DC, Edney G, Maiden B, Smith PK. Recognition of allergic conjunctivitis in patients with allergic rhinitis. *World Allergy Organ J*. Feb 12 2013;6(1):4. doi:10.1186/1939-4551-6-4

243. Wuthrich B, Brignoli R, Canevascini M, Gerber M. Epidemiological survey in hay fever patients: symptom prevalence and severity and influence on patient management. *Schweiz Med Wochenschr*. Jan 31 1998;128(5):139-43.

244. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol*. Nov 1997;8(4):161-76. doi:10.1111/j.1399-3038.1997.tb00156.x

245. Sanchez-Hernandez MC, Dordal MT, Navarro AM, et al. Severity and duration of allergic conjunctivitis: are they associated with severity and duration of allergic rhinitis and asthma? *Eur Ann Allergy Clin Immunol*. Jul 27 2021;doi:10.23822/EurAnnACI.1764-1489.231

246. Zhang SY, Li J, Liu R, et al. Association of Allergic Conjunctivitis With Health-Related Quality of Life in Children and Their Parents. *JAMA Ophthalmol*. Aug 1 2021;139(8):830-837. doi:10.1001/jamaophthalmol.2021.1708

247. Bielory L, Katelaris CH, Lightman S, Naclerio RM. Treating the ocular component of allergic rhinoconjunctivitis and related eye disorders. *MedGenMed*. Aug 15 2007;9(3):35.

248. Bielory L, Skoner DP, Blaiss MS, et al. Ocular and nasal allergy symptom burden in America: the Allergies, Immunotherapy, and RhinoconjunctivitiS (AIRS) surveys. *Allergy Asthma Proc*. May-Jun 2014;35(3):211-8. doi:10.2500/aap.2014.35.3750

249. Frolund L, Durham SR, Calderon M, et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy*. Jun 1 2010;65(6):753-7. doi:10.1111/j.1398-9995.2009.02238.x

250. Sayed KM, Kamel AG, Ali AH. One-year evaluation of clinical and immunological efficacy and safety of sublingual versus subcutaneous allergen immunotherapy in allergic conjunctivitis. *Graefes Arch Clin Exp Ophthalmol*. Sep 2019;257(9):1989-1996. doi:10.1007/s00417-019-04389-w

251. Alexandropoulos T, Haidich AB, Pilalas D, Dardavessis T, Daniilidis M, Arvanitidou M. Characteristics of patients with allergic rhinitis in an outpatient clinic: a retrospective study. *Allergol Immunopathol (Madr)*. May-Jun 2013;41(3):194-200. doi:10.1016/j.aller.2011.12.008

252. Almaliotis D, Michailopoulos P, Gioulekas D, et al. Allergic conjunctivitis and the most common allergens in Northern Greece. *World Allergy Organ J*. Jul 16 2013;6(1):12. doi:10.1186/1939-4551-6-12

253. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. Aug 1 2020;396(10247):345-360. doi:10.1016/S0140-6736(20)31286-1

254. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. *Br J Dermatol*. Feb 2021;184(2):304-309. doi:10.1111/bjd.19580

255. Dierick BJH, van der Molen T, Flokstra-de Blok BMJ, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. *Expert Rev Pharmacoecon Outcomes Res*. Oct 2020;20(5):437-453. doi:10.1080/14737167.2020.1819793

256. Gabryszewski SJ, Chang X, Dudley JW, et al. Unsupervised modeling and genome-wide association identify novel features of allergic march trajectories. *J Allergy Clin Immunol*. Feb 2021;147(2):677-685 e10. doi:10.1016/j.jaci.2020.06.026

257. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. *J Allergy Clin Immunol Pract*. Sep - Oct 2018;6(5):1528-1533. doi:10.1016/j.jaip.2018.05.010

258. Tan R, Cvetkovski B, Kritikos V, et al. Identifying the hidden burden of allergic rhinitis (AR) in community pharmacy: a global phenomenon. *Asthma Res Pract*. 2017;3:8. doi:10.1186/s40733-017-0036-z

259. Gonzalez-Mendoza T, Bedolla-Barajas M, Bedolla-Pulido TR, et al. [The prevalence of allergic rhinitis and atopic dermatitis in late adolescents differs according to their gender]. *Rev Alerg Mex*. Apr-Jun 2019;66(2):147-153. La prevalencia de rinitis alergica y dermatitis atopica en adolescentes tardios difiere de acuerdo con el sexo. doi:10.29262/ram.v66i2.521

260. Bekic S, Martinek V, Talapko J, Majnaric L, Vasilj Mihaljevic M, Skrlec I. Atopic Dermatitis and Comorbidity. *Healthcare (Basel)*. Mar 25 2020;8(2)doi:10.3390/healthcare8020070

261. Huang YH, Huang LH, Kuo CF, Yu KH. Familial aggregation of atopic dermatitis and co-aggregation of allergic diseases in affected families in Taiwan. *J Dermatol Sci*. Oct 2020;100(1):15-22. doi:10.1016/j.jdermsci.2020.07.007

262. Schoos AM, Chawes BL, Bonnelykke K, Stokholm J, Rasmussen MA, Bisgaard H. Increasing severity of early-onset atopic dermatitis, but not late-onset, associates with development of aeroallergen sensitization and allergic rhinitis in childhood. *Allergy*. Sep 24 2021;doi:10.1111/all.15108

263. Mortz CG, Andersen KE, Poulsen LK, Kjaer HF, Broesby-Olsen S, Bindslev-Jensen C. Atopic diseases and type I sensitization from adolescence to adulthood in an unselected population (TOACS) with focus on predictors for allergic rhinitis. *Allergy*. Feb 2019;74(2):308-317. doi:10.1111/all.13630

264. Wang LC, Chiang BL. Early-onset-early-resolving atopic dermatitis does not increase the risk of development of allergic diseases at 3 Years old. *J Formos Med Assoc*. Dec 2020;119(12):1854-1861. doi:10.1016/j.jfma.2020.02.014

265. Dharma C, Lefebvre DL, Tran MM, et al. Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: Effects on allergic diseases. *Clin Exp Allergy*. Jan 2018;48(1):48-59. doi:10.1111/cea.13063

266. Huang Y, Zhang Y, Zhang L. Prevalence of allergic and nonallergic rhinitis in a rural area of northern China based on sensitization to specific aeroallergens. *Allergy Asthma Clin Immunol*. 2018;14:77. doi:10.1186/s13223-018-0299-9

267. Biagini JM, Kroner JW, Baatyrbek Kyzy A, et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. *J Allergy Clin Immunol*. Oct 18 2021;doi:10.1016/j.jaci.2021.09.036

268. Jeong JW, Lim KH, Lee WH, Won JY, Kwon JW. Heterogeneity of Adult Rhinitis for Multimorbidity and Age at Onset among Non-Sensitized Rhinitis and Mono-/Poly-Sensitized Rhinitis: A Retrospective Cross-Sectional Study. *Int Arch Allergy Immunol*. 2020;181(7):512-521. doi:10.1159/000507444

269. Raciborski F, Bousquet J, Bousqet J, et al. Dissociating polysensitization and multimorbidity in children and adults from a Polish general population cohort. *Clin Transl Allergy*. 2019;9:4. doi:10.1186/s13601-019-0246-y

270. Moreno-Lopez S, Perez-Herrera LC, Penaranda D, Hernandez DC, Garcia E, Penaranda A. Prevalence and associated factors of allergic diseases in school children and adolescents aged 6-7 and 13-14 years from two rural areas in Colombia. *Allergol Immunopathol (Madr)*. 2021;49(3):153-161. doi:10.15586/aei.v49i3.183

271. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol*. Jan 1999;103(1 Pt 1):125-38. doi:10.1016/s0091-6749(99)70536-1

272. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. *J Am Acad Dermatol*. Oct 2016;75(4):681-687 e11. doi:10.1016/j.jaad.2016.05.028

273. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med*. Jan 15 2002;165(2):176-80. doi:10.1164/ajrccm.165.2.2104032

274. Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis--a prospective follow-up to 7 years of age. *Allergy*. Mar 2000;55(3):240-5. doi:10.1034/j.1398-9995.2000.00391.x

275. Schneider L, Hanifin J, Boguniewicz M, et al. Study of the Atopic March: Development of Atopic Comorbidities. *Pediatr Dermatol*. Jul 2016;33(4):388-98. doi:10.1111/pde.12867

276. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy*. Jul 2015;70(7):836-45. doi:10.1111/all.12619

277. Sybilski AJ, Raciborski F, Lipiec A, et al. Atopic dermatitis is a serious health problem in Poland. Epidemiology studies based on the ECAP study. *Postepy Dermatol Alergol*. Feb 2015;32(1):1-10. doi:10.5114/pdia.2014.40935

278. Bozek A, Jarzab J. Epidemiology of IgE-dependent allergic diseases in elderly patients in Poland. *Am J Rhinol Allergy*. Sep-Oct 2013;27(5):e140-5. doi:10.2500/ajra.2013.27.3920

279. Lowe AJ, Hosking CS, Bennett CM, et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. *Clin Exp Allergy*. Nov 2007;37(11):1624-31. doi:10.1111/j.1365-2222.2007.02822.x

280. Karaman O, Turgut CS, Uzuner N, et al. The determination of asthma, rhinitis, eczema, and atopy prevalence in 9- to 11-year-old children in the city of Izmir. *Allergy Asthma Proc*. Jul-Aug 2006;27(4):319-24. doi:10.2500/aap.2006.27.2877

281. Kuyucu S, Saraclar Y, Tuncer A, et al. Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr Allergy Immunol*. Jun 2006;17(4):269-77. doi:10.1111/j.1399-3038.2006.00407.x

282. Yemaneberhan H, Flohr C, Lewis SA, et al. Prevalence and associated factors of atopic dermatitis symptoms in rural and urban Ethiopia. *Clin Exp Allergy*. May 2004;34(5):779-85. doi:10.1111/j.1365-2222.2004.1946.x

283. Min YG, Choi BY, Kwon SK, et al. Multicenter study on the prevalence of perennial allergic rhinitis and allergy-associated disorders. *J Korean Med Sci*. Dec 2001;16(6):697-701. doi:10.3346/jkms.2001.16.6.697

284. Leung R, Ho P. Asthma, allergy, and atopy in three south-east Asian populations. *Thorax*. Dec 1994;49(12):1205-10. doi:10.1136/thx.49.12.1205

285. Batlles Garrido J, Torres-Borrego J, Bonillo Perales A, et al. Prevalence and factors linked to atopic eczema in 10- and 11-year-old schoolchildren. Isaac 2 in Almeria, Spain. *Allergol Immunopathol (Madr)*. Jul-Aug 2010;38(4):174-80. doi:10.1016/j.aller.2009.10.008

286. Peroni DG, Piacentini GL, Bodini A, Rigotti E, Pigozzi R, Boner AL. Prevalence and risk factors for atopic dermatitis in preschool children. *Br J Dermatol*. Mar 2008;158(3):539-43. doi:10.1111/j.1365-2133.2007.08344.x

287. Kidon MI, Chiang WC, Liew WK, et al. Sensitization to dust mites in children with allergic rhinitis in Singapore: does it matter if you scratch while you sneeze? *Clin Exp Allergy*. Apr 2005;35(4):434-40. doi:10.1111/j.1365-2222.2005.02208.x

288. Kusel MM, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol*. Nov 2005;116(5):1067-72. doi:10.1016/j.jaci.2005.06.038

289. Peroni DG, Piacentini GL, Alfonsi L, et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy*. Oct 2003;33(10):1349-54. doi:10.1046/j.1365-2222.2003.01766.x

290. Ozdemir N, Ucgun I, Metintas S, Kolsuz M, Metintas M. The prevalence of asthma and allergy among university freshmen in Eskisehir, Turkey. *Respir Med*. Jun 2000;94(6):536-41. doi:10.1053/rmed.1999.0728

291. Garcia-Gonzalez JJ, Vega-Chicote JM, Rico P, et al. Prevalence of atopy in students from Malaga, Spain. *Ann Allergy Asthma Immunol*. Mar 1998;80(3):237-44. doi:10.1016/s1081-1206(10)62964-x

292. Cosme-Blanco W, Arroyo-Flores E, Ale H. Food Allergies. *Pediatr Rev*. Aug 2020;41(8):403-415. doi:10.1542/pir.2019-0037

293. Katelaris CH. Food allergy and oral allergy or pollen-food syndrome. *Curr Opin Allergy Clin Immunol*. Jun 2010;10(3):246-51. doi:10.1097/ACI.0b013e32833973fb

294. Ebner C, Birkner T, Valenta R, et al. Common epitopes of birch pollen and apples--studies by western and northern blot. *J Allergy Clin Immunol*. Oct 1991;88(4):588-94. doi:10.1016/0091-6749(91)90152-e

295. American Academy of Asthma Allergy & Immunology: Oral allergy syndrome – pollens and cross-reacting foods. Accessed March 19, 2022, https://www.aaaai.org/Aaaai/media/Media-Library-PDFs/Tools%20for%20the%20Public/Conditions%20Library/Library%20-%20Allergies/OAS-table_revised.pdf

296. Carlson G, Coop C. Pollen food allergy syndrome (PFAS): A review of current available literature. *Ann Allergy Asthma Immunol*. Oct 2019;123(4):359-365. doi:10.1016/j.anai.2019.07.022

297. Dondi A, Tripodi S, Panetta V, et al. Pollen-induced allergic rhinitis in 1360 Italian children: comorbidities and determinants of severity. *Pediatr Allergy Immunol*. Dec 2013;24(8):742-51. doi:10.1111/pai.12136

298. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. *J Allergy Clin Immunol Pract*. Jun 2020;8(6):1854-1864. doi:10.1016/j.jaip.2020.02.010

299. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. Nov 2014;134(5):1016-25 e43. doi:10.1016/j.jaci.2014.05.013

300. Ortolani C, Pastorello EA, Farioli L, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy*. Nov 1993;71(5):470-6.

301. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. *Ann Allergy Asthma Immunol*. Nov 2015;115(5):341-84. doi:10.1016/j.anai.2015.07.019

302. Skamstrup Hansen K, Vestergaard H, Stahl Skov P, et al. Double-blind, placebo-controlled food challenge with apple. *Allergy*. Feb 2001;56(2):109-17. doi:10.1034/j.1398-9995.2001.056002109.x

303. Rosen JP, Selcow JE, Mendelson LM, Grodofsky MP, Factor JM, Sampson HA. Skin testing with natural foods in patients suspected of having food allergies: is it a necessity? *J Allergy Clin Immunol*. Jun 1994;93(6):1068-70. doi:10.1016/s0091-6749(94)70056-7

304. de Jong NW, Terlouw S, van Boven FE, et al. Birch Pollen Related Pear Allergy: A Single-Blind Oral Challenge TRIAL with 2 Pear Cultivars. *Nutrients*. Apr 18 2021;13(4)doi:10.3390/nu13041355

305. Lee SC, Kim SR, Park KH, Lee JH, Park JW. Clinical Features and Culprit Food Allergens of Korean Adult Food Allergy Patients: A Cross-Sectional Single-Institute Study. *Allergy Asthma Immunol Res*. Sep 2019;11(5):723-735. doi:10.4168/aair.2019.11.5.723

306. Fuhrmann V, Huang HJ, Akarsu A, et al. From Allergen Molecules to Molecular Immunotherapy of Nut Allergy: A Hard Nut to Crack. *Front Immunol*. 2021;12:742732. doi:10.3389/fimmu.2021.742732

307. Thompson JC, Kroker GF. The role of component-resolved testing in food allergy and oral allergy syndrome. *Ann Allergy Asthma Immunol*. Jun 2010;104(6):543; author reply 543-4. doi:10.1016/j.anai.2010.03.011

308. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol*. Jan 2010;125(1):191-7 e1-13. doi:10.1016/j.jaci.2009.10.008

309. Bolhaar ST, Tiemessen MM, Zuidmeer L, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy*. May 2004;34(5):761-9. doi:10.1111/j.1365-2222.2004.1939.x

310. Inuo C, Kondo Y, Tanaka K, et al. Japanese cedar pollen-based subcutaneous immunotherapy decreases tomato fruit-specific basophil activation. *Int Arch Allergy Immunol*. 2015;167(2):137-45. doi:10.1159/000437325

311. Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy*. Nov 1998;28(11):1368-73. doi:10.1046/j.1365-2222.1998.00399.x

312. Mauro M, Russello M, Incorvaia C, et al. Birch-apple syndrome treated with birch pollen immunotherapy. *Int Arch Allergy Immunol*. 2011;156(4):416-22. doi:10.1159/000323909

313. Krouse JH, Chadwick SJ, Gordon BR, Derebery J. *Allergy and immunology: an otolaryngic approach*. Lippincott Williams & Wilkins; 2002.

314. Cudowska B, Pawlowicz M, Lebensztejn DM. Pollen-related food allergy in children with seasonal allergic rhinitis. *Postepy Dermatol Alergol*. Feb 2021;38(2):96-101. doi:10.5114/ada.2021.104284

315. Thong BY, Arulanandam S, Tan SC, et al. Shellfish/crustacean oral allergy syndrome among national service pre-enlistees in Singapore. *Asia Pac Allergy*. Apr 2018;8(2):e18. doi:10.5415/apallergy.2018.8.e18

316. Diaz-Cabrera NM, Sanchez-Borges MA, Ledford DK. Atopy: A Collection of Comorbid Conditions. *J Allergy Clin Immunol Pract*. Nov 2021;9(11):3862-3866. doi:10.1016/j.jaip.2021.09.002

317. Matsumoto M, Takenaka M, Aoyagi K, et al. Factors associated with the development of oral allergy syndrome: A retrospective questionnaire survey of Japanese university students. *Allergol Int*. Oct 2021;70(4):458-462. doi:10.1016/j.alit.2021.02.003

318. Ota M, Nishida Y, Yagi H, et al. Regional differences in the prevalence of oral allergy syndrome among Japanese children: A questionnaire-based survey. *Asian Pac J Allergy Immunol*. Jun 21 2020;doi:10.12932/AP-130120-0739

319. Anvari S, Miller J, Yeh CY, Davis CM. IgE-Mediated Food Allergy. *Clin Rev Allergy Immunol*. Oct 2019;57(2):244-260. doi:10.1007/s12016-018-8710-3

320. Tong X, Tong H, Gao L, et al. A Multicenter Study of Prevalence and Risk Factors for Allergic Rhinitis in Primary School Children in 5 Cities of Hubei Province, China. *Int Arch Allergy Immunol*. 2022;183(1):34-44. doi:10.1159/000517948

321. Celakovska J, Bukac J. Analysis of food allergy in atopic dermatitis patients - association with concomitant allergic diseases. *Indian J Dermatol*. Sep 2014;59(5):445-50. doi:10.4103/0019-5154.139867

322. Bilaver LA, Kanaley MK, Fierstein JL, Gupta RS. Prevalence and Correlates of Food Allergy Among Medicaid-Enrolled United States Children. *Acad Pediatr*. Jan-Feb 2021;21(1):84-92. doi:10.1016/j.acap.2020.03.005

323. Wang HT, Warren CM, Gupta RS, Davis CM. Prevalence and Characteristics of Shellfish Allergy in the Pediatric Population of the United States. *J Allergy Clin Immunol Pract*. Apr 2020;8(4):1359-1370 e2. doi:10.1016/j.jaip.2019.12.027

324. Ruffner MA, Wang KY, Dudley JW, et al. Elevated Atopic Comorbidity in Patients with Food Protein-Induced Enterocolitis. *J Allergy Clin Immunol Pract*. Mar 2020;8(3):1039-1046. doi:10.1016/j.jaip.2019.10.047

325. Bedolla-Pulido TR, Bedolla-Barajas M, Morales-Romero J, et al. Self-reported hypersensitivity and allergy to foods amongst Mexican adolescents: Prevalence and associated factors. *Allergol Immunopathol (Madr)*. May - Jun 2019;47(3):246-253. doi:10.1016/j.aller.2018.09.004

326. Hill DA, Grundmeier RW, Ram G, Spergel JM. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. *BMC Pediatr*. Aug 20 2016;16:133. doi:10.1186/s12887-016-0673-z

327. Alm B, Goksor E, Thengilsdottir H, et al. Early protective and risk factors for allergic rhinitis at age 4(1/2) yr. *Pediatr Allergy Immunol*. Jun 2011;22(4):398-404. doi:10.1111/j.1399-3038.2011.01153.x

328. Huang Y, Wang C, Zhang Y, Zhang L. Developing nomograms for identifying allergic rhinitis among chronic rhinitis: A real-world study. *World Allergy Organ J*. Apr 2021;14(4):100534. doi:10.1016/j.waojou.2021.100534

329. Sultesz M, Horvath A, Molnar D, et al. Prevalence of allergic rhinitis, related comorbidities and risk factors in schoolchildren. *Allergy Asthma Clin Immunol*. Nov 11 2020;16(1):98. doi:10.1186/s13223-020-00495-1

330. Walter G, Kalicinsky C. Adult-onset IgE-mediated food allergy at a Winnipeg allergy clinic: a case series. *Allergy Asthma Clin Immunol*. 2020;16:85. doi:10.1186/s13223-020-00483-5

331. Lyons SA, Knulst AC, Burney PGJ, et al. Predicting food allergy: The value of patient history reinforced. *Allergy*. May 2021;76(5):1454-1462. doi:10.1111/all.14583

332. Tong H, Gao L, Deng Y, et al. Prevalence of Allergic Rhinitis and Associated Risk Factors in 6 to 12 Years Schoolchildren From Wuhan in Central China: A Cross-sectional Study. *Am J Rhinol Allergy*. Sep 2020;34(5):632-641. doi:10.1177/1945892420920499

333. Blaiss MS, Meadows JA, Yu S, et al. Economic burden of peanut allergy in pediatric patients with evidence of reactions to peanuts in the United States. *J Manag Care Spec Pharm*. Apr 2021;27(4):516-527. doi:10.18553/jmcp.2021.20389

334. Blumchen K, DunnGalvin A, Timmermans F, et al. APPEAL-1: A pan-European survey of patient/caregiver perceptions of peanut allergy management. *Allergy*. Nov 2020;75(11):2920-2935. doi:10.1111/all.14414

335. Scott LA, Jones BI, Berni TR, Berni ER, De Vries J, Currie CJ. Evaluation of the epidemiology of peanut allergy in the United Kingdom. *Expert Rev Clin Immunol*. Dec 2019;15(12):1333-1339. doi:10.1080/1744666X.2020.1693264

336. Bedolla-Barajas M, Bedolla-Pulido TR, Macriz-Romero N, Morales-Romero J, Robles-Figueroa M. Prevalence of Peanut, Tree Nut, Sesame, and Seafood Allergy in Mexican Adults. *Rev Invest Clin*. Nov-Dec 2015;67(6):379-86.

337. Taylor-Black S, Wang J. The prevalence and characteristics of food allergy in urban minority children. *Ann Allergy Asthma Immunol*. Dec 2012;109(6):431-7. doi:10.1016/j.anai.2012.09.012

338. Diez S, Puerta L, Martinez D, Munoz M, Hernandez K, Sanchez J. Clinical Relevance of Shrimp Sensitization in Patients with Allergic Rhinitis: Anti-Der p 10 IgE as Predictor. *Int Arch Allergy Immunol*. 2021;182(10):971-979. doi:10.1159/000516005

339. Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol*. Jan 2013;131(1):135-43 e1-12. doi:10.1016/j.jaci.2012.09.015

340. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-risk Infants. *Pediatrics*. Sep 2015;136(3):600-604. doi:10.1542/peds.2015-2394

341. Logan K, Du Toit G, Giovannini M, Turcanu V, Lack G. Pediatric Allergic Diseases, Food Allergy, and Oral Tolerance. *Annu Rev Cell Dev Biol*. Oct 6 2020;36:511-528. doi:10.1146/annurev-cellbio-100818-125346

342. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. *JAMA*. Sep 20 2016;316(11):1181-1192. doi:10.1001/jama.2016.12623

343. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. *Ann Allergy Asthma Immunol*. Feb 2010;104(2):101-8; quiz 109-10, 117. doi:10.1016/j.anai.2009.11.007

344. American College of Allergy Asthma Immunology — Food allergy: a practice parameter. *Ann Allergy Asthma Immunol*. Mar 2006;96(3 Suppl 2):S1-68.

345. Lam HY, Tergaonkar V, Ahn KS. Mechanisms of allergen-specific immunotherapy for allergic rhinitis and food allergies. *Biosci Rep*. Apr 30 2020;40(4)doi:10.1042/BSR20200256

346. Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. *JAMA*. Feb 14 2017;317(6):615-625. doi:10.1001/jama.2016.21040

347. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy*. 2015;5:12. doi:10.1186/s13601-015-0057-8

348. Schoos AM, Bullens D, Chawes BL, et al. Immunological Outcomes of Allergen-Specific Immunotherapy in Food Allergy. *Front Immunol*. 2020;11:568598. doi:10.3389/fimmu.2020.568598

349. Tordesillas L, Berin MC, Sampson HA. Immunology of Food Allergy. *Immunity*. Jul 18 2017;47(1):32-50. doi:10.1016/j.immuni.2017.07.004

350. Marseglia GL, Poddighe D, Caimmi D, et al. Role of adenoids and adenoiditis in children with allergy and otitis media. *Curr Allergy Asthma Rep*. Nov 2009;9(6):460-4. doi:10.1007/s11882-009-0068-4

351. Cassano P, Gelardi M, Cassano M, Fiorella ML, Fiorella R. Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management. *Int J Pediatr Otorhinolaryngol*. Dec 2003;67(12):1303-9. doi:10.1016/j.ijporl.2003.07.018

352. Evcimik MF, Dogru M, Cirik AA, Nepesov MI. Adenoid hypertrophy in children with allergic disease and influential factors. *Int J Pediatr Otorhinolaryngol*. May 2015;79(5):694-7. doi:10.1016/j.ijporl.2015.02.017

353. Dogru M, Evcimik MF, Calim OF. Does adenoid hypertrophy affect disease severity in children with allergic rhinitis? *Eur Arch Otorhinolaryngol*. Jan 2017;274(1):209-213. doi:10.1007/s00405-016-4196-x

354. Modrzynski M, Zawisza E. The influence of birch pollination on the adenoid size in children with intermittent allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Jul 2007;71(7):1017-23. doi:10.1016/j.ijporl.2007.02.018

355. Atan Sahin O, Kececioglu N, Serdar M, Ozpinar A. The association of residential mold exposure and adenotonsillar hypertrophy in children living in damp environments. *Int J Pediatr Otorhinolaryngol*. Sep 2016;88:233-8. doi:10.1016/j.ijporl.2016.07.018

356. Huang SW, Giannoni C. The risk of adenoid hypertrophy in children with allergic rhinitis. *Ann Allergy Asthma Immunol*. Oct 2001;87(4):350-5. doi:10.1016/S1081-1206(10)62251-X

357. Karaca CT, Toros SZ, Noseri H, et al. Role of allergy in children with adenotonsillar hypertrophy. *J Craniofac Surg*. Nov 2012;23(6):e611-3. doi:10.1097/SCS.0b013e31826cf562

358. Ameli F, Brocchetti F, Tosca MA, Signori A, Ciprandi G. Adenoidal hypertrophy and allergic rhinitis: is there an inverse relationship? *Am J Rhinol Allergy*. Jan 2013;27(1):e5-10. doi:10.2500/ajra.2013.27.3854

359. Sadeghi-Shabestari M, Jabbari Moghaddam Y, Ghaharri H. Is there any correlation between allergy and adenotonsillar tissue hypertrophy? *Int J Pediatr Otorhinolaryngol*. Apr 2011;75(4):589-91. doi:10.1016/j.ijporl.2011.01.026

360. Eren E, Arslanoglu S, Erdem SB, et al. Chicken or the egg: the dilemma of allergic rhinitis versus adenoid hypertrophy. *Rhinology*. Jun 2015;53(2):154-9. doi:10.4193/Rhino14.013

361. Karabulut B, Sahin-Onder S, Erkmen B, Cetemen A, Gergin O. Predictive fiberoptic endoscopic findings of upper airway in children with allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Sep 2019;124:143-146. doi:10.1016/j.ijporl.2019.06.004

362. Ni K, Zhao L, Wu J, Chen W, HongyaYang, Li X. Th17/Treg balance in children with obstructive sleep apnea syndrome and the relationship with allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. Sep 2015;79(9):1448-54. doi:10.1016/j.ijporl.2015.06.026

363. Masieri S, Trabattoni D, Incorvaia C, et al. A role for Waldeyer's ring in immunological response to allergens. *Curr Med Res Opin*. Feb 2014;30(2):203-5. doi:10.1185/03007995.2013.855185

364. Zhu F, Sun K, Yu L, Sun S, Wan Y, Shi L. Tissue Cytokine Adenoid Experssion in Hypertrophic Adenoid Gland in Children with Allergic Rhinitis. *J Coll Physicians Surg Pak*. Aug 2021;31(8):903-909. doi:10.29271/jcpsp.2021.08.903

365. Cho KS, Kim SH, Hong SL, et al. Local Atopy in Childhood Adenotonsillar Hypertrophy. *Am J Rhinol Allergy*. May 2018;32(3):160-166. doi:10.1177/1945892418765003

366. Shin SY, Choi SJ, Hur GY, et al. Local production of total IgE and specific antibodies to the house dust mite in adenoid tissue. *Pediatr Allergy Immunol*. Mar 2009;20(2):134-41. doi:10.1111/j.1399-3038.2008.00756.x

367. Shin SY, Ye YM, Eun YG, Kim SW, Cho JS, Park HS. Local IgE-mediated hypersensitivity to Alternaria in pediatric adenoid tissue. *Int J Pediatr Otorhinolaryngol*. Oct 2012;76(10):1423-8. doi:10.1016/j.ijporl.2012.06.015

368. Scadding G. Non-surgical treatment of adenoidal hypertrophy: the role of treating IgE-mediated inflammation. *Pediatr Allergy Immunol*. Dec 2010;21(8):1095-106. doi:10.1111/j.1399-3038.2010.01012.x

369. Zhang L, Mendoza-Sassi RA, Cesar JA, Chadha NK. Intranasal corticosteroids for nasal airway obstruction in children with moderate to severe adenoidal hypertrophy. *Cochrane Database Syst Rev*. Jul 16 2008;(3):CD006286. doi:10.1002/14651858.CD006286.pub2

370. Chohan A, Lal A, Chohan K, Chakravarti A, Gomber S. Systematic review and meta-analysis of randomized controlled trials on the role of mometasone in adenoid hypertrophy in children. *Int J Pediatr Otorhinolaryngol*. Oct 2015;79(10):1599-608. doi:10.1016/j.ijporl.2015.07.009

371. Warman M, Granot E, Halperin D. Improvement in allergic and nonallergic rhinitis: A secondary benefit of adenoidectomy in children. *Ear Nose Throat J*. Jun 2015;94(6):220;222;224-7. doi:10.1177/014556131509400607

372. Patel A, Brook CD, Levi JR. Factors Associated with Refractory Nasal Congestion Following Adenoidectomy. *Ann Otol Rhinol Laryngol*. Feb 2021;130(2):148-152. doi:10.1177/0003489420940349

373. De Corso E, Galli J, Di Cesare T, et al. A systematic review of the clinical evidence and biomarkers linking allergy to adeno-tonsillar disease. *Int J Pediatr Otorhinolaryngol*. Aug 2021;147:110799. doi:10.1016/j.ijporl.2021.110799

374. Pagella F, De Amici M, Pusateri A, et al. Adenoids and clinical symptoms: Epidemiology of a cohort of 795 pediatric patients. *Int J Pediatr Otorhinolaryngol*. Dec 2015;79(12):2137-41. doi:10.1016/j.ijporl.2015.09.035

375. Schilder AG, Bhutta MF, Butler CC, et al. Eustachian tube dysfunction: consensus statement on definition, types, clinical presentation and diagnosis. *Clin Otolaryngol*. Oct 2015;40(5):407-11. doi:10.1111/coa.12475

376. Yang B, Brook CD. The Role of Allergy in Otologic Disease. *Otolaryngol Clin North Am*. Dec 2017;50(6):1091-1101. doi:10.1016/j.otc.2017.08.005

377. Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. *J Allergy Clin Immunol*. Feb 1997;99(2):S787-97. doi:10.1016/s0091-6749(97)70130-1

378. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. *J Allergy Clin Immunol*. Dec 1990;86(6 Pt 1):924-35. doi:10.1016/s0091-6749(05)80156-3

379. Skoner DP, Doyle WJ, Boehm S, Fireman P. Priming of the nose and eustachian tube during nasal pollen exposure. *Amer J Rhinol*. 1989;3(2):53-57.

380. Friedman RA, Doyle WJ, Casselbrant ML, Bluestone C, Fireman P. Immunologic-mediated eustachian tube obstruction: a double-blind crossover study. *J Allergy Clin Immunol*. May 1983;71(5):442-7. doi:10.1016/0091-6749(83)90459-1

381. Skoner DP, Doyle WJ, Chamovitz AH, Fireman P. Eustachian tube obstruction after intranasal challenge with house dust mite. *Arch Otolaryngol Head Neck Surg*. Aug 1986;112(8):840-2. doi:10.1001/archotol.1986.03780080040008

382. Skoner DP, Doyle WJ, Fireman P. Eustachian tube obstruction (ETO) after histamine nasal provocation--a double-blind dose-response study. *J Allergy Clin Immunol*. Jan 1987;79(1):27-31. doi:10.1016/s0091-6749(87)80012-x

383. O'Connor RD, Ort H, Leong AB, Cook DA, Street D, Hamburger RN. Tympanometric changes following nasal antigen challenge in children with allergic rhinitis. *Ann Allergy*. Dec 1984;53(6):468-71.

384. Downs BW, Butehorn HF, 3rd, Prazma J, Rose AS, Stamat JC, Pillsbury HC, 3rd. Action of histamine on eustachian tube function. *Otolaryngol Head Neck Surg*. Apr 2001;124(4):414-20. doi:10.1067/mhn.2001.113943

385. Ebert CS, Jr., Pollock HW, Dubin MG, et al. Effect of intranasal histamine challenge on Eustachian tube function. *Int J Pediatr Otorhinolaryngol*. May 15 2002;63(3):189-98. doi:10.1016/s0165-5876(02)00007-1

386. Hardy SM, Heavner SB, White DR, McQueen CT, Prazma J, Pillsbury HC. Late-phase allergy and eustachian tube dysfunction. *Otolaryngol Head Neck Surg*. Oct 2001;125(4):339-45. doi:10.1067/mhn.2001.119140

387. Osur SL, Volovitz B, Dickson S, Enck DC, Bernstein JM. Eustachian tube dysfunction in children with ragweed hayfever during natural pollen exposure. *Allergy Proc*. Mar-Apr 1989;10(2):133-9. doi:10.2500/108854189778961071

388. Knight LC, Eccles R, Morris S. Seasonal allergic rhinitis and its effects on eustachian tube function and middle ear pressure. *Clin Otolaryngol Allied Sci*. Aug 1992;17(4):308-12. doi:10.1111/j.1365-2273.1992.tb01002.x

389. Juszczak H, Aubin-Pouliot A, Sharon JD, Loftus PA. Sinonasal risk factors for eustachian tube dysfunction: Cross-sectional findings from NHANES 2011-2012. *Int Forum Allergy Rhinol*. May 2019;9(5):466-472. doi:10.1002/alr.22275

390. Lazo-Saenz JG, Galvan-Aguilera AA, Martinez-Ordaz VA, Velasco-Rodriguez VM, Nieves-Renteria A, Rincon-Castaneda C. Eustachian tube dysfunction in allergic rhinitis. *Otolaryngol Head Neck Surg*. Apr 2005;132(4):626-9. doi:10.1016/j.otohns.2005.01.029

391. Gluth MB, McDonald DR, Weaver AL, Bauch CD, Beatty CW, Orvidas LJ. Management of eustachian tube dysfunction with nasal steroid spray: a prospective, randomized, placebo-controlled trial. *Arch Otolaryngol Head Neck Surg*. May 2011;137(5):449-55. doi:10.1001/archoto.2011.56

392. Tucci DL, McCoul ED, Rosenfeld RM, et al. Clinical Consensus Statement: Balloon Dilation of the Eustachian Tube. *Otolaryngol Head Neck Surg*. Jul 2019;161(1):6-17. doi:10.1177/0194599819848423

393. Pollock HW, Ebert CS, Dubin MG, White DR, Prazma J, Pillsbury HC, 3rd. The role of soluble interleukin-4 receptor and interleukin-5 antibody in preventing late-phase allergy-induced eustachian tube dysfunction. *Otolaryngol Head Neck Surg*. Sep 2002;127(3):169-76. doi:10.1067/mhn.2002.126901

394. Derebery MJ, Berliner KI. Allergic eustachian tube dysfunction: diagnosis and treatment. *Am J Otol*. Mar 1997;18(2):160-5.

395. Palmu A, Puhakka H, Rahko T, Takala AK. Diagnostic value of tympanometry in infants in clinical practice. *Int J Pediatr Otorhinolaryngol*. Aug 20 1999;49(3):207-13. doi:10.1016/s0165-5876(99)00207-4

396. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical Practice Guideline: Otitis Media with Effusion (Update). *Otolaryngol Head Neck Surg*. Feb 2016;154(1 Suppl):S1-S41. doi:10.1177/0194599815623467

397. Caffarelli C, Savini E, Giordano S, Gianlupi G, Cavagni G. Atopy in children with otitis media with effusion. *Clin Exp Allergy*. May 1998;28(5):591-6. doi:10.1046/j.1365-2222.1998.00284.x

398. Yeo SG, Park DC, Eun YG, Cha CI. The role of allergic rhinitis in the development of otitis media with effusion: effect on eustachian tube function. *Am J Otolaryngol*. May-Jun 2007;28(3):148-52. doi:10.1016/j.amjoto.2006.07.011

399. Borge P. Atopy and secretory otitis media. Immunological studies and responses to topical corticosteroid therapy. *J Laryngol Otol*. Feb 1983;97(2):117-29. doi:10.1017/s0022215100093890

400. Tomonaga K, Kurono Y, Mogi G. The role of nasal allergy in otitis media with effusion. A clinical study. *Acta Otolaryngol Suppl*. 1988;458:41-7. doi:10.3109/00016488809125100

401. Corey JP, Adham RE, Abbass AH, Seligman I. The role of IgE-mediated hypersensitivity in otitis media with effusion. *Am J Otolaryngol*. Mar-Apr 1994;15(2):138-44. doi:10.1016/0196-0709(94)90063-9

402. Chantzi FM, Kafetzis DA, Bairamis T, et al. IgE sensitization, respiratory allergy symptoms, and heritability independently increase the risk of otitis media with effusion. *Allergy*. Mar 2006;61(3):332-6. doi:10.1111/j.1398-9995.2006.00971.x

403. Gultekin E, Develioglu ON, Yener M, Ozdemir I, Kulekci M. Prevalence and risk factors for persistent otitis media with effusion in primary school children in Istanbul, Turkey. *Auris Nasus Larynx*. Apr 2010;37(2):145-9. doi:10.1016/j.anl.2009.05.002

404. Kwon C, Lee HY, Kim MG, Boo SH, Yeo SG. Allergic diseases in children with otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. Feb 2013;77(2):158-61. doi:10.1016/j.ijporl.2012.09.039

405. Sharifian MR, Mahmoudi M, Pourmomenarabi B, Keramati MR. Correlation between Allergic Rhinitis and Otitis Media with Effusion. *Iran J Otorhinolaryngol*. Jul 2019;31(105):209-215.

406. Songu M, Islek A, Imre A, et al. Risk factors for otitis media with effusion in children with adenoid hypertrophy. *Acta Otorhinolaryngol Ital*. Apr 2020;40(2):133-137. doi:10.14639/0392-100X-2456

407. McMahan JT, Calenoff E, Croft DJ, Barenholtz L, Weber LD. Chronic otitis media with effusion and allergy: modified RAST analysis of 119 cases. *Otolaryngol Head Neck Surg*. May-Jun 1981;89(3 Pt 1):427-31. doi:10.1177/019459988108900315

408. Hurst DS. Allergy management of refractory serous otitis media. *Otolaryngol Head Neck Surg*. Jun 1990;102(6):664-9. doi:10.1177/019459989010200607

409. Hurst DS. Association of otitis media with effusion and allergy as demonstrated by intradermal skin testing and eosinophil cationic protein levels in both middle ear effusions and mucosal biopsies. *Laryngoscope*. Sep 1996;106(9 Pt 1):1128-37. doi:10.1097/00005537-199609000-00017

410. Alles R, Parikh A, Hawk L, Darby Y, Romero JN, Scadding G. The prevalence of atopic disorders in children with chronic otitis media with effusion. *Pediatr Allergy Immunol*. Apr 2001;12(2):102-6. doi:10.1046/j.0905-6157.2000.00008.x

411. Hurst DS. Efficacy of allergy immunotherapy as a treatment for patients with chronic otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. Aug 2008;72(8):1215-23. doi:10.1016/j.ijporl.2008.04.013

412. Norhafizah S, Salina H, Goh BS. Prevalence of allergic rhinitis in children with otitis media with effusion. *Eur Ann Allergy Clin Immunol*. May 2020;52(3):121-130. doi:10.23822/EurAnnACI.1764-1489.119

413. Kreiner-Moller E, Chawes BL, Caye-Thomasen P, Bonnelykke K, Bisgaard H. Allergic rhinitis is associated with otitis media with effusion: a birth cohort study. *Clin Exp Allergy*. Nov 2012;42(11):1615-20. doi:10.1111/j.1365-2222.2012.04038.x

414. Cheng X, Sheng H, Ma R, et al. Allergic rhinitis and allergy are risk factors for otitis media with effusion: A meta-analysis. *Allergol Immunopathol (Madr)*. Jan - Feb 2017;45(1):25-32. doi:10.1016/j.aller.2016.03.004

415. Byeon H. The association between allergic rhinitis and otitis media: A national representative sample of in South Korean children. *Sci Rep*. Feb 7 2019;9(1):1610. doi:10.1038/s41598-018-38369-7

416. Roditi RE, Veling M, Shin JJ. Age: An effect modifier of the association between allergic rhinitis and Otitis media with effusion. *Laryngoscope*. Jul 2016;126(7):1687-92. doi:10.1002/lary.25682

417. Torretta S, Pignataro L, Carioli D, et al. Phenotype Profiling and Allergy in Otitis-Prone Children. *Front Pediatr*. 2018;6:383. doi:10.3389/fped.2018.00383

418. Bluestone CD. Current concepts in eustachian tube function as related to otitis media. *Auris Nasus Larynx*. 1985;12 Suppl 1:S1-4. doi:10.1016/s0385-8146(85)80083-3

419. Bluestone CD. Eustachian tube function: physiology, pathophysiology, and role of allergy in pathogenesis of otitis media. *J Allergy Clin Immunol*. Sep 1983;72(3):242-51. doi:10.1016/0091-6749(83)90027-1

420. Bernstein JM, Ellis E, Li P. The role of IgE-mediated hypersensitivity in otitis media with effusion. *Otolaryngol Head Neck Surg*. Sep-Oct 1981;89(5):874-8. doi:10.1177/019459988108900534

421. Bernstein JM, Lee J, Conboy K, Ellis E, Li P. The role of IgE mediated hypersensitivity in recurrent otitis media with effusion. *Am J Otol*. Jul 1983;5(1):66-9.

422. Bernstein JM, Lee J, Conboy K, Ellis E, Li P. Further observations on the role of IgE-mediated hypersensitivity in recurrent otitis media with effusion. *Otolaryngol Head Neck Surg*. Oct 1985;93(5):611-5. doi:10.1177/019459988509300508

423. Hurst DS, Weekley M, Ramanarayanan MP. Evidence of possible localized specific immunoglobulin E production in middle ear fluid as demonstrated by ELISA testing. *Otolaryngol Head Neck Surg*. Sep 1999;121(3):224-30. doi:10.1016/S0194-5998(99)70176-2

424. Hurst DS, Venge P. Evidence of eosinophil, neutrophil, and mast-cell mediators in the effusion of OME patients with and without atopy. *Allergy*. May 2000;55(5):435-41. doi:10.1034/j.1398-9995.2000.00289.x

425. Sobol SE, Taha R, Schloss MD, et al. T(H)2 cytokine expression in atopic children with otitis media with effusion. *J Allergy Clin Immunol*. Jul 2002;110(1):125-30. doi:10.1067/mai.2002.125697

426. Tewfik TL, Mazer B. The links between allergy and otitis media with effusion. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2006;14(3):187-90. doi:10.1097/01.moo.0000193190.24849.f0

427. Wright ED, Hurst D, Miotto D, Giguere C, Hamid Q. Increased expression of major basic protein (MBP) and interleukin-5(IL-5) in middle ear biopsy specimens from atopic patients with persistent otitis media with effusion. *Otolaryngol Head Neck Surg*. Nov 2000;123(5):533-8. doi:10.1067/mhn.2000.109472

428. Jang CH, Kim YH. Characterization of cytokines present in pediatric otitis media with effusion: comparison of allergy positive and negative. *Int J Pediatr Otorhinolaryngol*. Oct 21 2002;66(1):37-40. doi:10.1016/s0165-5876(02)00185-4

429. Jang CH, Kim YH. Demonstration of RANTES and eosinophilic cataionic protein in otitis media with effusion with allergy. *Int J Pediatr Otorhinolaryngol*. May 2003;67(5):531-3. doi:10.1016/s0165-5876(03)00015-6

430. Nguyen LH, Manoukian JJ, Tewfik TL, et al. Evidence of allergic inflammation in the middle ear and nasopharynx in atopic children with otitis media with effusion. *J Otolaryngol*. Dec 2004;33(6):345-51. doi:10.2310/7070.2004.03073

431. Lildholdt T, Kortholm B. Beclomethasone nasal spray in the treatment of middle-ear effusion - a double-blind study. *Int J Pediatr Otorhinolaryngol*. Jun 1982;4(2):133-7. doi:10.1016/0165-5876(82)90088-x

432. Williamson I, Benge S, Barton S, et al. Topical intranasal corticosteroids in 4-11 year old children with persistent bilateral otitis media with effusion in primary care: double blind randomised placebo controlled trial. *BMJ*. Dec 16 2009;339:b4984. doi:10.1136/bmj.b4984

433. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database Syst Rev*. Sep 7 2011;(9):CD003423. doi:10.1002/14651858.CD003423.pub3

434. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. *Cochrane Database Syst Rev*. May 11 2011;(5):CD001935. doi:10.1002/14651858.CD001935.pub3

435. Schoem SR, Willard A, Combs JT. A prospective, randomized, placebo-controlled, double-blind study of montelukast's effect on persistent middle ear effusion. *Ear Nose Throat J*. Sep 2010;89(9):434-7.

436. Ertugay CK, Cingi C, Yaz A, et al. Effect of combination of montelukast and levocetirizine on otitis media with effusion: a prospective, placebo-controlled trial. *Acta Otolaryngol*. Dec 2013;133(12):1266-72. doi:10.3109/00016489.2013.824113

437. Sajjadi H, Paparella MM. Meniere's disease. *Lancet*. Aug 2 2008;372(9636):406-14. doi:10.1016/S0140-6736(08)61161-7

438. Derebery MJ. Allergic and immunologic aspects of Meniere's disease. *Otolaryngol Head Neck Surg*. Mar 1996;114(3):360-5. doi:10.1016/s0194-5998(96)70204-8

439. Derebery MJ, Berliner KI. Prevalence of allergy in Meniere's disease. *Otolaryngol Head Neck Surg*. Jul 2000;123(1 Pt 1):69-75. doi:10.1067/mhn.2000.105715

440. Tyrrell JS, Whinney DJ, Ukoumunne OC, Fleming LE, Osborne NJ. Prevalence, associated factors, and comorbid conditions for Meniere's disease. *Ear Hear*. Jul-Aug 2014;35(4):e162-9. doi:10.1097/AUD.0000000000000041

441. Sen P, Georgalas C, Papesch M. Co-morbidity of migraine and Meniere's disease -- is allergy the link? *J Laryngol Otol*. Jun 2005;119(6):455-60. doi:10.1258/0022215054273133

442. Keles E, Godekmerdan A, Kalidag T, et al. Meniere's disease and allergy: allergens and cytokines. *J Laryngol Otol*. Sep 2004;118(9):688-93. doi:10.1258/0022215042244822

443. Roomiani M, Dehghani Firouzabadi F, Delbandi AA, et al. Evaluation of Serum Immunoreactivity to Common Indigenous Iranian Inhalation and Food Allergens in Patients with Meniere's Disease. *Immunol Invest*. Jan 8 2021:1-10. doi:10.1080/08820139.2020.1869252

444. Ma Y, Sun Q, Zhang K, Bai L, Du L. High level of IgE in acute low-tone sensorineural hearing loss: A predictor for recurrence and Meniere Disease transformation. *Am J Otolaryngol*. Mar-Apr 2021;42(2):102856. doi:10.1016/j.amjoto.2020.102856

445. Hsu L, Zhu XN, Zhao YS. Immunoglobulin E and circulating immune complexes in endolymphatic hydrops. *Ann Otol Rhinol Laryngol*. Jul 1990;99(7 Pt 1):535-8. doi:10.1177/000348949009900707

446. Viscomi GJ, Bojrab DI. Use of electrocochleography to monitor antigenic challenge in Meniere's disease. *Otolaryngol Head Neck Surg*. Dec 1992;107(6 Pt 1):733-7. doi:10.1177/019459988910700604.1

447. Gibbs SR, Mabry RL, Roland PS, Shoup AG, Mabry CS. Electrocochleographic changes after intranasal allergen challenge: A possible diagnostic tool in patients with Meniere's disease. *Otolaryngol Head Neck Surg*. Sep 1999;121(3):283-4. doi:10.1016/S0194-5998(99)70186-5

448. Derebery MJ, Valenzuela S. Meniere's syndrome and allergy. *Otolaryngol Clin North Am*. Feb 1992;25(1):213-24.

449. Derebery MJ. Allergic management of Meniere's disease: an outcome study. *Otolaryngol Head Neck Surg*. Feb 2000;122(2):174-82. doi:10.1016/S0194-5998(00)70235-X

450. NCT04815187 - Repurposed use of allergic rhinitis and allergic asthma drug to reduce vertigo and hearing loss in Meniere's disease. Accessed March 6, 2021, https://clinicaltrials.gov/show/NCT04815187

451. Singh S, Nagarkar AN, Bansal S, Vir D, Gupta AK. Audiological manifestations of allergic rhinitis. *J Laryngol Otol*. Sep 2011;125(9):906-10. doi:10.1017/S0022215111001137

452. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. Jan 2006;129(1 Suppl):1S-23S. doi:10.1378/chest.129.1_suppl.1S

453. Passali D, Benedetto de F, Benedetto de M, et al. Rhino-Bronchial Syndrome. The SIO-AIMAR (Italian Society of Otorhinolaryngology, Head Neck Surgery-Interdisciplinary Scientific Association for the Study of the Respiratory Diseases) survey. *Acta Otorhinolaryngol Ital*. Feb 2011;31(1):27-34.

454. Krzych-Falta E, Piekarska B, Sybilski A, Wojas O, Samolinski B. The Safety of Nasal Allergen Challenge Test Assessed in Lower Airways. *Iran J Allergy Asthma Immunol*. Dec 2015;14(6):581-8.

455. Chakir J, Laviolette M, Turcotte H, Boutet M, Boulet LP. Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis: influence of natural allergen exposure. *J Allergy Clin Immunol*. Nov 2000;106(5):904-10. doi:10.1067/mai.2000.110100

456. Chakir J, Laviolette M, Boutet M, Laliberte R, Dube J, Boulet LP. Lower airways remodeling in nonasthmatic subjects with allergic rhinitis. *Lab Invest*. Nov 1996;75(5):735-44.

457. Buday T, Gavliakova S, Mokry J, Medvedova I, Kavalcikova-Bogdanova N, Plevkova J. The Guinea Pig Sensitized by House Dust Mite: A Model of Experimental Cough Studies. *Adv Exp Med Biol*. 2016;905:87-95. doi:10.1007/5584_2016_217

458. Lin HC, Cho SH, Ghoshal AG, et al. Respiratory diseases and the impact of cough in Taiwan: Results from the APBORD observational study. *Medicine (Baltimore)*. Jul 2016;95(27):e3854. doi:10.1097/MD.0000000000003854

459. Ghoshal AG, Ravindran GD, Gangwal P, et al. The burden of segregated respiratory diseases in India and the quality of care in these patients: Results from the Asia-Pacific Burden of Respiratory Diseases study. *Lung India*. Nov-Dec 2016;33(6):611-619. doi:10.4103/0970-2113.192878

460. Cho SH, Lin HC, Ghoshal AG, et al. Respiratory disease in the Asia-Pacific region: Cough as a key symptom. *Allergy Asthma Proc*. Mar-Apr 2016;37(2):131-40. doi:10.2500/aap.2016.37.3925

461. He S, Li YJ, Chen J. Clinical features of allergic rhinitis in children of Shanghai, China. *Genet Mol Res*. May 9 2016;15(2)doi:10.4238/gmr.15028118

462. Dicpinigiatis P, Birring S, McGarvey L, Schelfhout J, Tzontcheva A, Muccino D. Comorbid conditions and medical history among patients with refractory or unexplained chronic cough in two phase 3 clinical trials (COUGH-1 and COUGH-2). *J Allergy Clin Immunol*. 2021;147(2):AB61.

463. Kim JH, Kim SA, Ku JY, Cho WK, Shin CH. Comparison of allergens and symptoms in patients with allergic rhinitis between 1990s and 2010s. *Allergy Asthma Clin Immunol*. 2020;16:58. doi:10.1186/s13223-020-00455-9

464. Tang W, Zhou J, Miao L, Shi G. Clinical features in patients of cough variant asthma with normal and high level of exhaled fractional nitric oxide. *Clin Respir J*. Feb 2018;12(2):595-600. doi:10.1111/crj.12568

465. Nakajima T, Nagano T, Nishimura Y. Retrospective Study of the Effects of Post-nasal Drip Symptoms on Cough Duration. *In Vivo*. May-Jun 2021;35(3):1799-1803. doi:10.21873/invivo.12440

466. Chen LC, Zeng GS, Wu LL, et al. Diagnostic value of FeNO and MMEF for predicting cough variant asthma in chronic cough patients with or without allergic rhinitis. *J Asthma*. Mar 2021;58(3):326-333. doi:10.1080/02770903.2019.1694035

467. Liu X, Wang X, Yao X, Wang Y, Sun Y, Zhang L. Value of Exhaled Nitric Oxide and FEF25-75 in Identifying Factors Associated With Chronic Cough in Allergic Rhinitis. *Allergy Asthma Immunol Res*. Nov 2019;11(6):830-845. doi:10.4168/aair.2019.11.6.830

468. Deot N, Barr J, Mankowski N, Brunner J, McCoul ED. Effect of Intranasal Corticosteroids on Secondary Sinonasal Symptoms: A Systematic Review of Randomized Trials. *Am J Rhinol Allergy*. Sep 2019;33(5):601-607. doi:10.1177/1945892419844397

469. Hua H, Wang G, Zhao Y, Wang D, Qiu Z, Fang P. The long-term outcomes of posterior nasal neurectomy with or without pharyngeal neurectomy in patients with allergic rhinitis: a randomized controlled trial. *Braz J Otorhinolaryngol*. May 29 2021;doi:10.1016/j.bjorl.2021.05.006

470. Lin L, Chen Z, Cao Y, Sun G. Normal saline solution nasal-pharyngeal irrigation improves chronic cough associated with allergic rhinitis. *Am J Rhinol Allergy*. Mar 1 2017;31(2):96-104. doi:10.2500/ajra.2017.31.4418

471. Reidy PM, Dworkin JP, Krouse JH. Laryngeal effects of antigen stimulation challenge with perennial allergen Dermatophagoides pteronyssinus. *Otolaryngol Head Neck Surg*. Apr 2003;128(4):455-62. doi:10.1016/s0194-5998(03)00003-2

472. Lee K, Young Kang C, Lee H, Choi IH, Lee SH, Kim TH. Association of Sinonasal Factors With Chronic Laryngitis in Korean Adults. *JAMA Otolaryngol Head Neck Surg*. Oct 1 2019;145(10):919-925. doi:10.1001/jamaoto.2019.2134

473. Wang YT, Chang GH, Yang YH, et al. Allergic Rhinitis and Laryngeal Pathology: Real-World Evidence. *Healthcare (Basel)*. Jan 3 2021;9(1)doi:10.3390/healthcare9010036

474. Millqvist E, Bende M, Brynnel M, Johansson I, Kappel S, Ohlsson AC. Voice change in seasonal allergic rhinitis. *J Voice*. Jul 2008;22(4):512-5. doi:10.1016/j.jvoice.2006.12.003

475. Koc EA, Koc B, Erbek S. Comparison of Acoustic and Stroboscopic Findings and Voice Handicap Index between Allergic Rhinitis Patients and Controls. *Balkan Med J*. Dec 2014;31(4):340-4. doi:10.5152/balkanmedj.2014.14511

476. Krouse JH, Dworkin JP, Carron MA, Stachler RJ. Baseline laryngeal effects among individuals with dust mite allergy. *Otolaryngol Head Neck Surg*. Jul 2008;139(1):149-51. doi:10.1016/j.otohns.2008.04.001

477. Randhawa PS, Nouraei S, Mansuri S, Rubin JS. Allergic laryngitis as a cause of dysphonia: a preliminary report. *Logoped Phoniatr Vocol*. Dec 2010;35(4):169-74. doi:10.3109/14015431003599012

478. Ohlsson AC, Drevsater A, Brynnel M, Johansson I. Allergic rhinitis and voice change. *Logoped Phoniatr Vocol*. Dec 2016;41(4):143-8. doi:10.3109/14015439.2015.1049288

479. Velickovic V, Simovic S, Zovanovic S, Stojanovic J, Koravovic M, Mihailovic N. The factors asociated with allergic rhinitis in dysphonic professional voice users. *Mediconski Casopis*. 2017;51(3):73-78.

480. Hamdan AL, Sibai A, Youssef M, Deeb R, Zaitoun F. The use of a screening questionnaire to determine the incidence of allergic rhinitis in singers with dysphonia. *Arch Otolaryngol Head Neck Surg*. May 2006;132(5):547-9. doi:10.1001/archotol.132.5.547

481. Turley R, Cohen SM, Becker A, Ebert CS, Jr. Role of rhinitis in laryngitis: another dimension of the unified airway. *Ann Otol Rhinol Laryngol*. Aug 2011;120(8):505-10. doi:10.1177/000348941112000803

482. Simberg S, Sala E, Tuomainen J, Ronnemaa AM. Vocal symptoms and allergy--a pilot study. *J Voice*. Jan 2009;23(1):136-9. doi:10.1016/j.jvoice.2007.03.010

483. Randhawa PS, Mansuri S, Rubin JS. Is dysphonia due to allergic laryngitis being misdiagnosed as laryngopharyngeal reflux? *Logoped Phoniatr Vocol*. Apr 2010;35(1):1-5. doi:10.1080/14015430903002262

484. Alharethy S, Baqays A, Mesallam TA, et al. Correlation between Allergic Rhinitis and Laryngopharyngeal Reflux. *Biomed Res Int*. 2018;2018:2951928. doi:10.1155/2018/2951928

485. Roth DF, Ferguson BJ. Vocal allergy: recent advances in understanding the role of allergy in dysphonia. *Curr Opin Otolaryngol Head Neck Surg*. Jun 2010;18(3):176-81. doi:10.1097/MOO.0b013e32833952af

486. Eren E, Arslanoglu S, Aktas A, et al. Factors confusing the diagnosis of laryngopharyngeal reflux: the role of allergic rhinitis and inter-rater variability of laryngeal findings. *Eur Arch Otorhinolaryngol*. Apr 2014;271(4):743-7. doi:10.1007/s00405-013-2682-y

487. Jackson-Menaldi CA, Dzul AI, Holland RW. Allergies and vocal fold edema: a preliminary report. *J Voice*. Mar 1999;13(1):113-22. doi:10.1016/s0892-1997(99)80065-4

488. Belafsky PC, Peake J, Smiley-Jewell SM, Verma SP, Dworkin-Valenti J, Pinkerton KE. Soot and house dust mite allergen cause eosinophilic laryngitis in an animal model. *Laryngoscope*. Jan 2016;126(1):108-12. doi:10.1002/lary.25467

489. Mouadeb DA, Belafsky PC, Birchall M, Hood C, Konia T, Pinkerton KE. The effects of allergens and tobacco smoke on the laryngeal mucosa of guinea pigs. *Otolaryngol Head Neck Surg*. Apr 2009;140(4):493-7. doi:10.1016/j.otohns.2008.12.034

490. Dworkin JP, Reidy PM, Stachler RJ, Krouse JH. Effects of sequential Dermatophagoides pteronyssinus antigen stimulation on anatomy and physiology of the larynx. *Ear Nose Throat J*. Feb 2009;88(2):793-9.

491. Roth DF, Abbott KV, Carroll TL, Ferguson BJ. Evidence for primary laryngeal inhalant allergy: a randomized, double-blinded crossover study. *Int Forum Allergy Rhinol*. Jan 2013;3(1):10-8. doi:10.1002/alr.21051

492. Suzuki T, Okamoto Y, Yonekura S, Okuma Y, Sakurai T, Sakurai D. Characteristics of laryngeal symptoms induced in patients with allergic rhinitis in an environmental challenge chamber. *Ann Allergy Asthma Immunol*. Jun 2016;116(6):491-6. doi:10.1016/j.anai.2016.03.011

493. Brook CD, Platt MP, Reese S, Noordzij JP. Utility of Allergy Testing in Patients with Chronic Laryngopharyngeal Symptoms: Is It Allergic Laryngitis? *Otolaryngol Head Neck Surg*. Jan 2016;154(1):41-5. doi:10.1177/0194599815607850

494. Brook C, Noordzij JP, Russell K, Aliphas A, Platt M. Predictive findings of allergic disease in fiberoptic nasolaryngoscopy. *Laryngoscope*. Feb 2015;125(2):286-90. doi:10.1002/lary.24880

495. Leigh LY, Spergel JM. An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. Jan 2019;122(1):65-72 e1. doi:10.1016/j.anai.2018.09.452

496. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. Oct 2007;133(4):1342-63. doi:10.1053/j.gastro.2007.08.017

497. Benninger MS, Strohl M, Holy CE, Hanick AL, Bryson PC. Prevalence of atopic disease in patients with eosinophilic esophagitis. *Int Forum Allergy Rhinol*. Aug 2017;7(8):757-762. doi:10.1002/alr.21968

498. Azzano P, Villard Truc F, Collardeau-Frachon S, Lachaux A. Children with eosinophilic esophagitis in real life: 10 years' experience with a focus on allergic management. *Allergol Immunopathol (Madr)*. May - Jun 2020;48(3):244-250. doi:10.1016/j.aller.2019.07.013

499. Ancellin M, Ricolfi-Waligova L, Clerc-Urmes I, et al. Management of eosinophilic esophagitis in children according to atopic status: A retrospective cohort in northeast of France. *Arch Pediatr*. Apr 2020;27(3):122-127. doi:10.1016/j.arcped.2020.02.001

500. Mohammad AA, Wu SZ, Ibrahim O, et al. Prevalence of atopic comorbidities in eosinophilic esophagitis: A case-control study of 449 patients. *J Am Acad Dermatol*. Mar 2017;76(3):559-560. doi:10.1016/j.jaad.2016.08.068

501. Alves Marcelino JL, Cardoso de Aguiar R, Cabral Duarte F, Celia Costa A, Pereira-Barbosa MA. Pediatric eosinophilic esophagitis in Portugal. *Eur Ann Allergy Clin Immunol*. Mar 2017;49(2):66-74.

502. Olson AA, Evans MD, Johansson MW, et al. Role of food and aeroallergen sensitization in eosinophilic esophagitis in adults. *Ann Allergy Asthma Immunol*. Oct 2016;117(4):387-393 e2. doi:10.1016/j.anai.2016.08.008

503. Vernon N, Shah S, Lehman E, Ghaffari G. Comparison of atopic features between children and adults with eosinophilic esophagitis. *Allergy Asthma Proc*. Sep-Oct 2014;35(5):409-14. doi:10.2500/aap.2014.35.3768

504. Chadha SN, Wang L, Correa H, Moulton D, Hummell DS. Pediatric eosinophilic esophagitis: the Vanderbilt experience. *Ann Allergy Asthma Immunol*. Oct 2014;113(4):445-51. doi:10.1016/j.anai.2014.07.020

505. Castro Jimenez A, Gomez Torrijos E, Garcia Rodriguez R, et al. Demographic, clinical and allergological characteristics of Eosinophilic Esophagitis in a Spanish central region. *Allergol Immunopathol (Madr)*. Sep-Oct 2014;42(5):407-14. doi:10.1016/j.aller.2013.04.004

506. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr*. Jan 2009;48(1):30-6. doi:10.1097/MPG.0b013e3181788282

507. Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. May 2008;6(5):531-5. doi:10.1016/j.cgh.2007.12.045

508. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol*. Mar 2007;119(3):731-8. doi:10.1016/j.jaci.2006.10.044

509. Plaza-Martin AM, Jimenez-Feijoo R, Andaluz C, et al. Polysensitization to aeroallergens and food in eosinophilic esophagitis in a pediatric population. *Allergol Immunopathol (Madr)*. Jan-Feb 2007;35(1):35-7. doi:10.1016/s0301-0546(07)70227-6

510. Sugnanam KK, Collins JT, Smith PK, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy*. Nov 2007;62(11):1257-60. doi:10.1111/j.1398-9995.2007.01454.x

511. Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc*. Jan 2006;63(1):3-12. doi:10.1016/j.gie.2005.07.049

512. Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr*. Oct 2002;141(4):576-81. doi:10.1067/mpd.2002.127663

513. Gonzalez-Cervera J, Arias A, Redondo-Gonzalez O, Cano-Mollinedo MM, Terreehorst I, Lucendo AJ. Association between atopic manifestations and eosinophilic esophagitis: A systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. May 2017;118(5):582-590 e2. doi:10.1016/j.anai.2017.02.006

514. Imamura K, Haruma K, Matsumoto H, et al. Clinical and endoscopic characteristics of eosinophilic esophagitis in Japan: a case-control study. *Asia Pac Allergy*. Apr 2020;10(2):e16. doi:10.5415/apallergy.2020.10.e16

515. Armentia A, Martin-Armentia S, Alvarez-Nogal R, Armentia BM, Gayoso MJ, Fernandez-Gonzalez D. Germination of pollen grains in the oesophagus of individuals with eosinophilic oesophagitis. *Clin Exp Allergy*. Apr 2019;49(4):471-473. doi:10.1111/cea.13312

516. Reed CC, Iglesia EGA, Commins SP, Dellon ES. Seasonal exacerbation of eosinophilic esophagitis histologic activity in adults and children implicates role of aeroallergens. *Ann Allergy Asthma Immunol*. Mar 2019;122(3):296-301. doi:10.1016/j.anai.2018.12.013

517. Fahey L, Robinson G, Weinberger K, Giambrone AE, Solomon AB. Correlation Between Aeroallergen Levels and New Diagnosis of Eosinophilic Esophagitis in New York City. *J Pediatr Gastroenterol Nutr*. Jan 2017;64(1):22-25. doi:10.1097/MPG.0000000000001245

518. Ram G, Lee J, Ott M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. *Ann Allergy Asthma Immunol*. Sep 2015;115(3):224-228 e1. doi:10.1016/j.anai.2015.07.004

519. Moawad FJ, Veerappan GR, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergens. *Aliment Pharmacol Ther*. Feb 15 2010;31(4):509-15. doi:10.1111/j.1365-2036.2009.04199.x

520. Almansa C, Krishna M, Buchner AM, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol*. Apr 2009;104(4):828-33. doi:10.1038/ajg.2008.169

521. Wang FY, Gupta SK, Fitzgerald JF. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? *J Clin Gastroenterol*. May-Jun 2007;41(5):451-3. doi:10.1097/01.mcg.0000248019.16139.67

522. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol*. Oct 2003;112(4):796-7. doi:10.1016/s0091-6749(03)01715-9

523. Armentia A, Martin-Armentia S, Martin-Armentia B, et al. Is eosinophilic esophagitis an equivalent of pollen allergic asthma? Analysis of biopsies and therapy guided by component resolved diagnosis. *Allergol Immunopathol (Madr)*. Mar - Apr 2018;46(2):181-189. doi:10.1016/j.aller.2017.11.001

524. Iglesia EGA, Commins SP, Dellon ES. Complete remission of eosinophilic esophagitis with multi-aeroallergen subcutaneous immunotherapy: A case report. *J Allergy Clin Immunol Pract*. Jun 2021;9(6):2517-2519 e2. doi:10.1016/j.jaip.2021.01.045

525. Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol*. Aug 2013;132(2):503-4. doi:10.1016/j.jaci.2013.04.053

526. Cafone J, Capucilli P, Hill DA, Spergel JM. Eosinophilic esophagitis during sublingual and oral allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. Aug 2019;19(4):350-357. doi:10.1097/ACI.0000000000000537

527. Lucendo AJ, Arias A, Redondo-Gonzalez O, Gonzalez-Cervera J. Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis. *Allergy*. Dec 2015;70(12):1640-50. doi:10.1111/all.12767

528. Elias MK, Kopacova J, Arora AS, et al. The diagnosis of esophageal eosinophilia is not increased in the summer months. *Dysphagia*. Feb 2015;30(1):67-73. doi:10.1007/s00455-014-9574-1

529. Frederickson NW, Bayman L, Valestin J, et al. Lack of seasonal variation in the incidence of eosinophilic oesophagitis in adolescent and adult non-PPI-responsive oesophageal eosinophilia midwestern US populations. *United European Gastroenterol J*. Apr 2014;2(2):69-76. doi:10.1177/2050640614525152

530. Pace A, Iannella G, Rossetti V, et al. Diagnosis of Obstructive Sleep Apnea in Patients with Allergic and Non-Allergic Rhinitis. *Medicina (Kaunas)*. Sep 8 2020;56(9)doi:10.3390/medicina56090454

531. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol*. Sep 2009;124(3 Suppl):S43-70. doi:10.1016/j.jaci.2009.05.013

532. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc*. May-Jun 2009;30(3):244-54. doi:10.2500/aap.2009.30.3230

533. Eifan AO, Durham SR. Pathogenesis of rhinitis. *Clin Exp Allergy*. Sep 2016;46(9):1139-51. doi:10.1111/cea.12780

534. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol*. May 1998;101(5):633-7. doi:10.1016/s0091-6749(98)70171-x

535. Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. *Arch Intern Med*. Jun 25 2001;161(12):1514-9. doi:10.1001/archinte.161.12.1514

536. Staevska MT, Mandajieva MA, Dimitrov VD. Rhinitis and sleep apnea. *Curr Allergy Asthma Rep*. May 2004;4(3):193-9. doi:10.1007/s11882-004-0026-0

537. Morris LG, Burschtin O, Lebowitz RA, Jacobs JB, Lee KC. Nasal obstruction and sleep-disordered breathing: a study using acoustic rhinometry. *Am J Rhinol*. Jan-Feb 2005;19(1):33-9.

538. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. *J Allergy Clin Immunol*. Feb 1997;99(2):S757-62. doi:10.1016/s0091-6749(97)70124-6

539. Storms WW. Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis. *J Allergy Clin Immunol*. Nov 2004;114(5 Suppl):S146-53. doi:10.1016/j.jaci.2004.08.045

540. Roxbury CR, Qiu M, Shargorodsky J, Lin SY. Association between allergic rhinitis and poor sleep parameters in U.S. adults. *Int Forum Allergy Rhinol*. Oct 2018;8(10):1098-1106. doi:10.1002/alr.22174

541. Camhi SL, Morgan WJ, Pernisco N, Quan SF. Factors affecting sleep disturbances in children and adolescents. *Sleep Med*. Apr 1 2000;1(2):117-123. doi:10.1016/s1389-9457(99)00005-2

542. Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis: findings from a large online survey. *Treat Respir Med*. 2005;4(6):439-46. doi:10.2165/00151829-200504060-00007

543. Reinberg A, Gervais P, Levi F, Smolensky M, Del Cerro L, Ugolini C. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol*. Jan 1988;81(1):51-62. doi:10.1016/0091-6749(88)90220-5

544. Liu J, Wu Y, Wu P, Xu Z, Ni X. Analysis of the impact of allergic rhinitis on the children with sleep disordered breathing. *Int J Pediatr Otorhinolaryngol*. Nov 2020;138:110380. doi:10.1016/j.ijporl.2020.110380

545. Tobaldini E, Costantino G, Solbiati M, et al. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. *Neurosci Biobehav Rev*. Mar 2017;74(Pt B):321-329. doi:10.1016/j.neubiorev.2016.07.004

546. Ferguson BJ. Influences of allergic rhinitis on sleep. *Otolaryngol Head Neck Surg*. May 2004;130(5):617-29. doi:10.1016/j.otohns.2004.02.001

547. Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci*. Dec 20 2002;72(4-5):409-14. doi:10.1016/s0024-3205(02)02276-2

548. Sri Kantha S, Matsumura H, Kubo E, et al. Effects of prostaglandin D2, lipoxins and leukotrienes on sleep and brain temperature of rats. *Prostaglandins Leukot Essent Fatty Acids*. Aug 1994;51(2):87-93. doi:10.1016/0952-3278(94)90083-3

549. Pasha S, Kumar S, Chatterjee AB, Krishnaswamy G. An obstructive sleep apnea primer: What the practicing allergist needs to know. *Ann Allergy Asthma Immunol*. Mar 2017;118(3):259-268. doi:10.1016/j.anai.2016.07.033

550. Chirakalwasan N, Ruxrungtham K. The linkage of allergic rhinitis and obstructive sleep apnea. *Asian Pac J Allergy Immunol*. Dec 2014;32(4):276-86.

551. Krouse HJ, Davis JE, Krouse JH. Immune mediators in allergic rhinitis and sleep. *Otolaryngol Head Neck Surg*. Jun 2002;126(6):607-13. doi:10.1067/mhn.2002.125300

552. Mullington JM, Hinze-Selch D, Pollmacher T. Mediators of inflammation and their interaction with sleep: relevance for chronic fatigue syndrome and related conditions. *Ann N Y Acad Sci*. Mar 2001;933:201-10. doi:10.1111/j.1749-6632.2001.tb05825.x

553. Tan SN, Abdullah B. The association between obstructive aleep apnea and allergic rhinitis: current literature review. *Current Respiratory Medicine Reviews*. 2021;17(1):13-19.

554. Tankere F, Maisonobe T, Naccache L, et al. Further evidence for a central reorganisation of synaptic connectivity in patients with hypoglossal-facial anastomosis in man. *Brain Res*. May 2 2000;864(1):87-94. doi:10.1016/s0006-8993(00)02177-6

555. Horner RL, Innes JA, Murphy K, Guz A. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol*. May 1991;436:15-29. doi:10.1113/jphysiol.1991.sp018536

556. White DP, Edwards JK, Shea SA. Local reflex mechanisms: influence on basal genioglossal muscle activation in normal subjects. *Sleep*. Nov 1 1998;21(7):719-28. doi:10.1093/sleep/21.7.719

557. Lo YL, Jordan AS, Malhotra A, et al. Influence of wakefulness on pharyngeal airway muscle activity. *Thorax*. Sep 2007;62(9):799-805. doi:10.1136/thx.2006.072488

558. Baraniuk JN, Merck SJ. Nasal reflexes: implications for exercise, breathing, and sex. *Curr Allergy Asthma Rep*. Apr 2008;8(2):147-53. doi:10.1007/s11882-008-0025-7

559. Basner RC, Simon PM, Schwartzstein RM, Weinberger SE, Weiss JW. Breathing route influences upper airway muscle activity in awake normal adults. *J Appl Physiol (1985)*. Apr 1989;66(4):1766-71. doi:10.1152/jappl.1989.66.4.1766

560. Shintaro C, Park CS. Establishing a Patent Nasal Passage in Obstructive Sleep Apnea. *Sleep Med Clin*. Mar 2019;14(1):41-50. doi:10.1016/j.jsmc.2018.10.005

561. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. May 11 2000;342(19):1378-84. doi:10.1056/NEJM200005113421901

562. Kuniyoshi FH, Garcia-Touchard A, Gami AS, et al. Day-night variation of acute myocardial infarction in obstructive sleep apnea. *J Am Coll Cardiol*. Jul 29 2008;52(5):343-6. doi:10.1016/j.jacc.2008.04.027

563. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med*. Dec 1 2005;172(11):1447-51. doi:10.1164/rccm.200505-702OC

564. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. May 27 2003;107(20):2589-94. doi:10.1161/01.CIR.0000068337.25994.21

565. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol*. Apr 17 2007;49(15):1625-1631. doi:10.1016/j.jacc.2006.12.046

566. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. Sep 2012;130(3):576-84. doi:10.1542/peds.2012-1671

567. Ali NJ, Pitson D, Stradling JR. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. *Arch Dis Child*. Jul 1994;71(1):74-6. doi:10.1136/adc.71.1.74

568. Isaiah A, Ernst T, Cloak CC, Clark DB, Chang L. Association Between Habitual Snoring and Cognitive Performance Among a Large Sample of Preadolescent Children. *JAMA Otolaryngol Head Neck Surg*. May 1 2021;147(5):426-433. doi:10.1001/jamaoto.2020.5712

569. Jan JE, Reiter RJ, Bax MC, Ribary U, Freeman RD, Wasdell MB. Long-term sleep disturbances in children: a cause of neuronal loss. *Eur J Paediatr Neurol*. Sep 2010;14(5):380-90. doi:10.1016/j.ejpn.2010.05.001

570. Di Francesco RC, Alvarez J. Allergic rhinitis affects the duration of rapid eye movement sleep in children with sleep-disordered breathing without sleep apnea. *Int Forum Allergy Rhinol*. May 2016;6(5):465-71. doi:10.1002/alr.21689

571. Berson SR, Klimczak J, Prezio EA, Hu S, Abraham M. Clinical associations between allergies and rapid eye movement sleep disturbances. *Int Forum Allergy Rhinol*. Jul 2018;8(7):817-824. doi:10.1002/alr.22099

572. Morris LG, Burschtin O, Setlur J, et al. REM-associated nasal obstruction: a study with acoustic rhinometry during sleep. *Otolaryngol Head Neck Surg*. Nov 2008;139(5):619-23. doi:10.1016/j.otohns.2008.08.017

573. Huseni S, Gutierrez MJ, Rodriguez-Martinez CE, et al. The link between rhinitis and rapid-eye-movement sleep breathing disturbances in children with obstructive sleep apnea. *Am J Rhinol Allergy*. Jan 1 2014;28(1):56-61. doi:10.2500/ajra.2014.28.3994

574. Kimura A, Chiba S, Capasso R, et al. Phase of nasal cycle during sleep tends to be associated with sleep stage. *Laryngoscope*. Aug 2013;123(8):2050-5. doi:10.1002/lary.23986

575. Berson SR, Klimczak JA, Prezio EA, Abraham MT. House Dust Mite Related Allergic Rhinitis and REM Sleep Disturbances. *Am J Otolaryngol*. Nov - Dec 2020;41(6):102709. doi:10.1016/j.amjoto.2020.102709

576. Skirko JR, James KT, Shusterman DJ, Weaver EM. Association of Allergic Rhinitis With Change in Nasal Congestion in New Continuous Positive Airway Pressure Users. *JAMA Otolaryngol Head Neck Surg*. Jun 1 2020;146(6):523-529. doi:10.1001/jamaoto.2020.0261

577. Inoue A, Chiba S, Matsuura K, Osafune H, Capasso R, Wada K. Nasal function and CPAP compliance. *Auris Nasus Larynx*. Aug 2019;46(4):548-558. doi:10.1016/j.anl.2018.11.006

578. Iwata N, Nakata S, Inada H, Kimura A, Hirata M, Yasuma F. Clinical indication of nasal surgery for the CPAP intolerance in obstructive sleep apnea with nasal obstruction. *Auris Nasus Larynx*. Dec 2020;47(6):1018-1022. doi:10.1016/j.anl.2020.06.005

579. Camacho M, Riaz M, Capasso R, et al. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. *Sleep*. Feb 1 2015;38(2):279-86. doi:10.5665/sleep.4414

580. Nakata S, Noda A, Yagi H, et al. Nasal resistance for determinant factor of nasal surgery in CPAP failure patients with obstructive sleep apnea syndrome. *Rhinology*. Dec 2005;43(4):296-9.

581. Poirier J, George C, Rotenberg B. The effect of nasal surgery on nasal continuous positive airway pressure compliance. *Laryngoscope*. Jan 2014;124(1):317-9. doi:10.1002/lary.24131

582. Awad MI, Kacker A. Nasal Obstruction Considerations in Sleep Apnea. *Otolaryngol Clin North Am*. Oct 2018;51(5):1003-1009. doi:10.1016/j.otc.2018.05.012

583. Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep*. Mar 2010;10(2):113-21. doi:10.1007/s11882-010-0091-5

584. Kim SD, Jung DW, Lee JW, Park JH, Mun SJ, Cho KS. Relationship between allergic rhinitis and nasal surgery success in patients with obstructive sleep apnea. *Am J Otolaryngol*. Nov-Dec 2021;42(6):103079. doi:10.1016/j.amjoto.2021.103079

585. Jalalia MM, Soleimanib R, Jalali SM, Mohisafata B. Evaluation of the effects of allergic rhinitis treatment on sexual functioning, sleep, and fatigue. *Revue Francaise d-Allergologie*. 2020;60(2):55-60.

586. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. *Thorax*. Jan 2004;59(1):50-5.

587. Hughes K, Glass C, Ripchinski M, et al. Efficacy of the topical nasal steroid budesonide on improving sleep and daytime somnolence in patients with perennial allergic rhinitis. *Allergy*. May 2003;58(5):380-5. doi:10.1034/j.1398-9995.2003.00093.x

588. Gurevich F, Glass C, Davies M, et al. The effect of intranasal steroid budesonide on the congestion-related sleep disturbance and daytime somnolence in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. Jul-Aug 2005;26(4):268-74.

589. Jacobi H, Rehm D, Nolte H, Andersen KF, Demoly P. Effect of house dust mite SLIT-tablet treatment on quality of sleep in allergic rhinitis patients. *J Allergy Clin Immunol*. 2019;143:AB286.

590. Novakova SM, Staevska MT, Novakova PI, et al. Quality of life improvement after a three-year course of sublingual immunotherapy in patients with house dust mite and grass pollen induced allergic rhinitis: results from real-life. *Health Qual Life Outcomes*. Sep 29 2017;15(1):189. doi:10.1186/s12955-017-0764-z

591. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice. *BMJ*. Apr 29 2000;320(7243):1184-6. doi:10.1136/bmj.320.7243.1184

592. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy*. Jul 1999;29 Suppl 3:133-42. doi:10.1046/j.1365-2222.1999.0290s3133.x

593. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs*. 2005;65(3):341-84. doi:10.2165/00003495-200565030-00004

594. Chen ST, Lu KH, Sun HL, Chang WT, Lue KH, Chou MC. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr. *Pediatr Allergy Immunol*. Feb 2006;17(1):49-54. doi:10.1111/j.1399-3038.2005.00351.x

595. Seresirikachorn K, Mullol J, Limitlaohaphan K, Asvapoositkul V, Snidvongs K. Leukotriene receptor antagonist addition to intranasal steroid: systematic review and meta-analysis. *Rhinology*. Feb 1 2021;59(1):2-9. doi:10.4193/Rhin20.126

596. Clarenbach CF, Kohler M, Senn O, Thurnheer R, Bloch KE. Does nasal decongestion improve obstructive sleep apnea? *J Sleep Res*. Dec 2008;17(4):444-9. doi:10.1111/j.1365-2869.2008.00667.x

597. Liu J, Zhang X, Zhao Y, Wang Y. The association between allergic rhinitis and sleep: A systematic review and meta-analysis of observational studies. *PLoS One*. 2020;15(2):e0228533. doi:10.1371/journal.pone.0228533

598. Na HG, Sung CM, Yang HC. Effect of continuous positive airway pressure on symptoms of allergic rhinitis in patients with obstructive sleep apnea. *World Allergy Organization J*. 2020;13(8):100271.

599. Chuang C, Tsai M, Tsai Y, Kuo C, Hsu C, Hung J. Increased risk of sleep apnea in patients of allergic rhinitis: a nationwide population-based study. presented at: American Thoracic Society; 2019; Dallas, TX.

600. Lee K, Choi IH, Hong Y, Lee H, Lee SH, Kim TH. Association between allergic rhinitis-related factors and sleep duration in adolescents: Korea National Health and Nutrition Examination Survey V (2010-2012). *Int J Pediatr Otorhinolaryngol*. Mar 2021;142:110613. doi:10.1016/j.ijporl.2021.110613

601. Bosnic-Anticevich S, Smith P, Abramson M, et al. Impact of allergic rhinitis on the day-to-day lives of children: insights from an Australian cross-sectional study. *BMJ Open*. Nov 24 2020;10(11):e038870. doi:10.1136/bmjopen-2020-038870

602. Giraldo-Cadavid LF, Perdomo-Sanchez K, Cordoba-Gravini JL, et al. Allergic Rhinitis and OSA in Children Residing at a High Altitude. *Chest*. Feb 2020;157(2):384-393. doi:10.1016/j.chest.2019.09.018

603. Wongvilairat S, Assanasen P, Banhiran W, Tantilipikorn P, Bunnag C. The prevalence of high risk of obstructive sleep apnea in patients with allergic rhinitis. *Asian Pac J Allergy Immunol*. Nov 3 2019;doi:10.12932/AP-141218-0458

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.

REFERENCES

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Accessed November 13, 2021, https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

2. Mustafa SS, Shaker MS, Munblit D, Greenhawt M. Paediatric allergy practice in the era of coronavirus disease 2019. *Curr Opin Allergy Clin Immunol*. Apr 1 2021;21(2):159-165. doi:10.1097/ACI.0000000000000727

3. Shaker MS, Oppenheimer J, Grayson M, et al. COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic. *J Allergy Clin Immunol Pract*. May 2020;8(5):1477-1488 e5. doi:10.1016/j.jaip.2020.03.012

4. Izquierdo-Dominguez A, Rojas-Lechuga MJ, Alobid I. Management of Allergic Diseases During COVID-19 Outbreak. *Curr Allergy Asthma Rep*. Feb 9 2021;21(2):8. doi:10.1007/s11882-021-00989-x

5. Searing DA, Dutmer CM, Fleischer DM, et al. A Phased Approach to Resuming Suspended Allergy/Immunology Clinical Services. *J Allergy Clin Immunol Pract*. Jul - Aug 2020;8(7):2125-2134. doi:10.1016/j.jaip.2020.05.012

6. Pfaar O, Klimek L, Jutel M, et al. COVID-19 pandemic: Practical considerations on the organization of an allergy clinic-An EAACI/ARIA Position Paper. *Allergy*. Mar 2021;76(3):648-676. doi:10.1111/all.14453

7. Ozturk AB, Baccioglu A, Soyer O, Civelek E, Sekerel BE, Bavbek S. Change in Allergy Practice during the COVID-19 Pandemic. *Int Arch Allergy Immunol*. 2021;182(1):49-52. doi:10.1159/000512079

8. Winders T, DuBuske L, Bukstein DA, Meltzer EO, Wallace D, Rance K. Shifts in allergy practice in a COVID-19 world: Implications of pre-COVID-19 national health care provider and patient surveys of treatments for nasal allergies. *Allergy Asthma Proc*. Jul 24 2021;42(4):301-309. doi:10.2500/aap.2021.42.210035

9. Tsao LR, Villanueva SA, Pines DA, et al. Impact of Rapid Transition to Telemedicine-Based Delivery on Allergy/Immunology Care During COVID-19. *J Allergy Clin Immunol Pract*. Jul 2021;9(7):2672-2679 e2. doi:10.1016/j.jaip.2021.04.018

10. Ren J, Pang W, Luo Y, et al. Impact of Allergic Rhinitis and Asthma on COVID-19 Infection, Hospitalization, and Mortality. *J Allergy Clin Immunol Pract*. Jan 2022;10(1):124-133. doi:10.1016/j.jaip.2021.10.049

11. Beken B, Ozturk GK, Aygun FD, Aydogmus C, Akar HH. Asthma and allergic diseases are not risk factors for hospitalization in children with coronavirus disease 2019. *Ann Allergy Asthma Immunol*. May 2021;126(5):569-575. doi:10.1016/j.anai.2021.01.018

12. Yao Y, Wang H, Liu Z. Expression of ACE2 in airways: Implication for COVID-19 risk and disease management in patients with chronic inflammatory respiratory diseases. *Clin Exp Allergy*. Dec 2020;50(12):1313-1324. doi:10.1111/cea.13746

13. Keswani A, Dhana K, Rosenthal JA, Moore D, Mahdavinia M. Atopy is predictive of a decreased need for hospitalization for coronavirus disease 2019. *Ann Allergy Asthma Immunol*. Oct 2020;125(4):479-481. doi:10.1016/j.anai.2020.07.012

14. Du H, Dong X, Zhang JJ, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. *Allergy*. Feb 2021;76(2):510-532. doi:10.1111/all.14452

15. Darabi A, Dehghanfard M, Jozan S, et al. Investigating the association between allergic diseases and COVID-19 in 400 Iranian patients. *Allergol Immunopathol (Madr)*. 2021;49(5):9-15. doi:10.15586/aei.v49i5.105

16. Ming W, Zuo J, Han J, Chen J. The impact of comorbid allergic airway disease on the severity and mortality of COVID-19: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. Sep 14 2021;doi:10.1007/s00405-021-07072-1

17. Guvey A. How does allergic rhinitis impact the severity of COVID-19?: a case-control study. *Eur Arch Otorhinolaryngol*. Nov 2021;278(11):4367-4371. doi:10.1007/s00405-021-06836-z

18. Hagemann J, Onorato GL, Jutel M, et al. Differentiation of COVID-19 signs and symptoms from allergic rhinitis and common cold: An ARIA-EAACI-GA(2) LEN consensus. *Allergy*. Aug 2021;76(8):2354-2366. doi:10.1111/all.14815

19. Bruno C, Locatello LG, Cilona M, et al. Seasonal Allergic Rhinitis Symptoms in Relation to COVID-19. *Allergy Rhinol (Providence)*. Jan-Dec 2020;11:2152656720968804. doi:10.1177/2152656720968804

20. Ferreli F, Gaino F, Russo E, et al. Clinical presentation at the onset of COVID-19 and allergic rhinoconjunctivitis. *J Allergy Clin Immunol Pract*. Nov - Dec 2020;8(10):3587-3589. doi:10.1016/j.jaip.2020.08.009

21. Jin L, Fan K, Tan S, Liu S, Wang Y, Yu S. Analysis of the characteristics of outpatient and emergency diseases in the department of otolaryngology during the "COVID-19" pandemic. *Sci Prog*. Jul-Sep 2021;104(3):368504211036319. doi:10.1177/00368504211036319

22. Yoon D, Kim KE, Lee JE, Kim M, Kim JH. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Medical Use of Military Hospitals in Korea. *J Korean Med Sci*. Jul 19 2021;36(28):e204. doi:10.3346/jkms.2021.36.e204

23. Choi HG, Kong IG. Asthma, Allergic Rhinitis, and Atopic Dermatitis Incidence in Korean Adolescents before and after COVID-19. *J Clin Med*. Aug 3 2021;10(15)doi:10.3390/jcm10153446

24. Dayal AK, Sinha V. Trend of Allergic Rhinitis Post COVID-19 Pandemic: A Retrospective Observational Study. *Indian J Otolaryngol Head Neck Surg*. Oct 20 2020:1-3. doi:10.1007/s12070-020-02223-y

25. Gelardi M, Trecca E, Fortunato F, et al. COVID-19 lockdown and seasonal allergic rhinitis: our experience in 40 patients. *Acta Biomed*. May 12 2021;92(2):e2021215. doi:10.23750/abm.v92i2.10953

26. Sozener ZC, Ozturk BO, Aydin O, et al. Coincidence of pollen season and coronavirus disease 2019 pandemic: less time outdoors - lesser allergy symptoms in 2020. *Asia Pac Allergy*. Apr 2021;11(2):e16. doi:10.5415/apallergy.2021.11.e16

27. Zhang Y, Lan F, Zhang L. Advances and highlights in allergic rhinitis. *Allergy*. Nov 2021;76(11):3383-3389. doi:10.1111/all.15044

28. Yucel E, Suleyman A, Hizli Demirkale Z, Guler N, Tamay ZU, Ozdemir C. 'Stay at home': Is it good or not for house dust mite sensitized children with respiratory allergies? *Pediatr Allergy Immunol*. Jul 2021;32(5):963-970. doi:10.1111/pai.13477

29. Gallo O, Bruno C, Orlando P, Locatello LG. The impact of lockdown on allergic rhinitis: What is good and what is bad? *Laryngoscope Investig Otolaryngol*. Oct 2020;5(5):807-808. doi:10.1002/lio2.459

30. Dror AA, Eisenbach N, Marshak T, et al. Reduction of allergic rhinitis symptoms with face mask usage during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*. Nov - Dec 2020;8(10):3590-3593. doi:10.1016/j.jaip.2020.08.035

31. Mengi E, Kara CO, Alpturk U, Topuz B. The effect of face mask usage on the allergic rhinitis symptoms in patients with pollen allergy during the covid-19 pandemic. *Am J Otolaryngol*. Jan-Feb 2022;43(1):103206. doi:10.1016/j.amjoto.2021.103206

32. Patella V, Delfino G, Florio G, et al. Management of the patient with allergic and immunological disorders in the pandemic COVID-19 era. *Clin Mol Allergy*. 2020;18:18. doi:10.1186/s12948-020-00134-5

33. Wang Y, Shi C, Yang Y, et al. Anxiety and depression in allergic rhinitis patients during COVID-19 pandemic in Wuhan, China. *Asian Pac J Allergy Immunol*. Feb 21 2021;doi:10.12932/AP-140820-0941

34. Gonzalez-Diaz SN, Martin B, Villarreal-Gonzalez RV, et al. Psychological impact of the COVID-19 pandemic on patients with allergic diseases. *World Allergy Organ J*. Mar 2021;14(3):100510. doi:10.1016/j.waojou.2021.100510

35. Radulesco T, Verillaud B, Bequignon E, et al. COVID-19 and rhinology, from the consultation room to the operating theatre. *Eur Ann Otorhinolaryngol Head Neck Dis*. Sep 2020;137(4):309-314. doi:10.1016/j.anorl.2020.04.013

36. De Luca P, Scarpa A, Ralli M, et al. Nasal, pharyngeal and laryngeal endoscopy procedures during COVID-19 pandemic: available recommendations from national and international societies. *Eur Arch Otorhinolaryngol*. Jul 2020;277(7):2151-2153. doi:10.1007/s00405-020-06028-1

37. Klimek L, Jutel M, Bousquet J, et al. Management of patients with chronic rhinosinusitis during the COVID-19 pandemic-An EAACI position paper. *Allergy*. Mar 2021;76(3):677-688. doi:10.1111/all.14629

38. Zhang Y, Zhang L. Management Practice of Allergic Rhinitis in China During the COVID-19 Pandemic. *Allergy Asthma Immunol Res*. Jul 2020;12(4):738-742. doi:10.4168/aair.2020.12.4.738

39. Scadding GK, Hellings PW, Bachert C, et al. Allergic respiratory disease care in the COVID-19 era: A EUFOREA statement. *World Allergy Organ J*. May 2020;13(5):100124. doi:10.1016/j.waojou.2020.100124

40. McCarty EB, Soldatova L, Brant JA, Newman JG. Innovations in otorhinolaryngology in the age of COVID-19: a systematic literature review. *World J Otorhinolaryngol Head Neck Surg*. Jan 22 2021;doi:10.1016/j.wjorl.2021.01.001

41. Lee JH, Lee Y, Lee SY, et al. Management of Allergic Patients During the COVID-19 Pandemic in Asia. *Allergy Asthma Immunol Res*. Sep 2020;12(5):783-791. doi:10.4168/aair.2020.12.5.783

42. CDC - COVID-19 and Your Health - Centers for Disease Control and Prevention. Accessed November 13, 2021, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

43. Cianferoni A, Votto M. COVID-19 and allergy: How to take care of allergic patients during a pandemic? *Pediatr Allergy Immunol*. Nov 2020;31 Suppl 26:96-101. doi:10.1111/pai.13367

44. Klimek L, Pfaar O, Worm M, et al. Allergen immunotherapy in the current COVID-19 pandemic: A position paper of AeDA, ARIA, EAACI, DGAKI and GPA: Position paper of the German ARIA Group(A) in cooperation with the Austrian ARIA Group(B), the Swiss ARIA Group(C), German Society for Applied Allergology (AEDA)(D), German Society for Allergology and Clinical Immunology (DGAKI)(E), Society for Pediatric Allergology (GPA)(F) in cooperation with AG Clinical Immunology, Allergology and Environmental Medicine of the DGHNO-KHC(G) and the European Academy of Allergy and Clinical Immunology (EAACI)(H). *Allergol Select*. 2020;4:44-52. doi:10.5414/ALX02147E

45. Matos S, Sharma A, Crosby D. Objective Assessment of Aerosolization During Transnasal Endoscopy: A Systematic Review. *Otolaryngol Head Neck Surg*. Oct 12 2021:1945998211050632. doi:10.1177/01945998211050632

46. Thamboo A, Lea J, Sommer DD, et al. Clinical evidence based review and recommendations of aerosol generating medical procedures in otolaryngology - head and neck surgery during the COVID-19 pandemic. *J Otolaryngol Head Neck Surg*. May 6 2020;49(1):28. doi:10.1186/s40463-020-00425-6

47. Workman AD, Welling DB, Carter BS, et al. Endonasal instrumentation and aerosolization risk in the era of COVID-19: simulation, literature review, and proposed mitigation strategies. *Int Forum Allergy Rhinol*. Jul 2020;10(7):798-805. doi:10.1002/alr.22577

48. Sharma D, Rubel KE, Ye MJ, et al. Cadaveric Simulation of Endoscopic Endonasal Procedures: Analysis of Droplet Splatter Patterns During the COVID-19 Pandemic. *Otolaryngol Head Neck Surg*. Jul 2020;163(1):145-150. doi:10.1177/0194599820929274

49. Workman AD, Jafari A, Welling DB, et al. Airborne Aerosol Generation During Endonasal Procedures in the Era of COVID-19: Risks and Recommendations. *Otolaryngol Head Neck Surg*. Sep 2020;163(3):465-470. doi:10.1177/0194599820931805

50. Sharma D, Campiti VJ, Ye MJ, et al. Aerosol generation during routine rhinologic surgeries and in-office procedures. *Laryngoscope Investig Otolaryngol*. Feb 2021;6(1):49-57. doi:10.1002/lio2.520

51. Murr AT, Lenze NR, Gelpi MW, et al. Quantification of Aerosol Concentrations During Endonasal Instrumentation in the Clinic Setting. *Laryngoscope*. May 2021;131(5):E1415-E1421. doi:10.1002/lary.29122

52. Tan VYJ, Zhang EZY, Daniel D, et al. Respiratory droplet generation and dispersal during nasoendoscopy and upper respiratory swab testing. *Head Neck*. Oct 2020;42(10):2779-2781. doi:10.1002/hed.26347

53. Di Maio P, Traverso D, Iocca O, De Virgilio A, Spriano G, Giudice M. Endoscopic nasopharyngoscopy and ENT specialist safety in the COVID 19 era: the back endoscopy approach to the patient. *Eur Arch Otorhinolaryngol*. Sep 2020;277(9):2647-2648. doi:10.1007/s00405-020-06093-6

54. Olaguibel JM, Alobid I, Alvarez Puebla M, et al. Functional Examination of the Upper and Lower Airways in Asthma and Respiratory Allergic Diseases: Considerations in the Post-SARS-CoV-2 Era. *J Investig Allergol Clin Immunol*. Feb 17 2021;31(1):17-35. doi:10.18176/jiaci.0625

55. Suzaki I, Kobayashi H. Coronavirus Disease 2019 and Nasal Conditions: A Review of Current Evidence. *In Vivo*. May-Jun 2021;35(3):1409-1417. doi:10.21873/invivo.12393

56. Liu DT, Phillips KM, Speth MM, Besser G, Mueller CA, Sedaghat AR. Portable HEPA Purifiers to Eliminate Airborne SARS-CoV-2: A Systematic Review. *Otolaryngol Head Neck Surg*. Apr 2022;166(4):615-622. doi:10.1177/01945998211022636

57. Christopherson DA, Yao WC, Lu M, Vijayakumar R, Sedaghat AR. High-Efficiency Particulate Air Filters in the Era of COVID-19: Function and Efficacy. *Otolaryngol Head Neck Surg*. Dec 2020;163(6):1153-1155. doi:10.1177/0194599820941838

58. Bousquet J, Akdis CA, Jutel M, et al. Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: An ARIA-EAACI statement. *Allergy*. Oct 2020;75(10):2440-2444. doi:10.1111/all.14302

59. Klimek L, Pfaar O, Hamelmann E, et al. COVID-19 vaccination and allergen immunotherapy (AIT) - A position paper of the German Society for Applied Allergology (AeDA) and the German Society for Allergology and Clinical Immunology (DGAKI). *Allergol Select*. 2021;5:251-259. doi:10.5414/ALX02245E

60. Nittner-Marszalska M, Rosiek-Biegus M, Kopec A, et al. Pfizer-BioNTech COVID-19 Vaccine Tolerance in Allergic versus Non-Allergic Individuals. *Vaccines (Basel)*. May 25 2021;9(6)doi:10.3390/vaccines9060553

61. Ding M, Dong X, Sun YL, et al. Recent advances and developments in COVID-19 in the context of allergic diseases. *Clin Transl Allergy*. Sep 2021;11(7):e12065. doi:10.1002/clt2.12065

62. Gani F, Cottini M, Landi M, et al. Allergic rhinitis and COVID-19: friends or foes? *Eur Ann Allergy Clin Immunol*. Sep 10 2021;doi:10.23822/EurAnnACI.1764-1489.234

63. Adir Y, Humbert M, Saliba W. COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids: Nationwide real-world evidence. *J Allergy Clin Immunol*. Aug 2021;148(2):361-367 e13. doi:10.1016/j.jaci.2021.06.006

64. Strauss R, Jawhari N, Attaway AH, et al. Intranasal Corticosteroids Are Associated with Better Outcomes in Coronavirus Disease 2019. *J Allergy Clin Immunol Pract*. Nov 2021;9(11):3934-3940 e9. doi:10.1016/j.jaip.2021.08.007

65. Bozek A, Winterstein J. Montelukast's ability to fight COVID-19 infection. *J Asthma*. Oct 2021;58(10):1348-1349. doi:10.1080/02770903.2020.1786112

66. Larenas-Linnemann DE, Ortega-Martell JA, Blandon-Vijil MV, et al. Coronavirus disease 2019, allergic diseases, and allergen immunotherapy: Possible favorable mechanisms of interaction. *Allergy Asthma Proc*. May 1 2021;42(3):187-197. doi:10.2500/aap.2021.42.210013

67. Pfaar O, Agache I, Bonini M, et al. COVID-19 pandemic and allergen immunotherapy-an EAACI survey. *Allergy*. Nov 2021;76(11):3504-3516. doi:10.1111/all.14793

68. Koca Kalkan I, Ates H, Aksu K, et al. Real-life adherence to subcutaneous immunotherapy: What has changed in the era of the COVID-19 pandemic. *World Allergy Organ J*. Jul 2021;14(7):100558. doi:10.1016/j.waojou.2021.100558

69. Aytekin ES, Soyer O, Sekerel BE, Sahiner UM. Subcutaneous Allergen Immunotherapy in Children: Real Life Compliance and Effect of COVID-19 Pandemic on Compliance. *Int Arch Allergy Immunol*. 2021;182(7):631-636. doi:10.1159/000514587

70. Yegit OO, Demir S, Unal D, et al. Adherence to subcutaneous immunotherapy with aeroallergens in real-life practice during the COVID-19 pandemic. *Allergy*. Jan 2022;77(1):197-206. doi:10.1111/all.14876

71. Shaker MS, Mosnaim G, Oppenheimer J, Stukus D, Abrams EM, Greenhawt M. Health and Economic Outcomes of Home Maintenance Allergen Immunotherapy in Select Patients with High Health Literacy during the COVID-19 Pandemic: A Cost-Effectiveness Analysis During Exceptional Times. *J Allergy Clin Immunol Pract*. Jul - Aug 2020;8(7):2310-2321 e4. doi:10.1016/j.jaip.2020.05.007

72. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. Mar 17 2011;364(11):1005-15. doi:10.1056/NEJMoa1009705

73. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol*. Dec 2015;136(6):1476-1485. doi:10.1016/j.jaci.2015.09.008

74. Esquivel A, Busse WW, Calatroni A, et al. Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma. *Am J Respir Crit Care Med*. Oct 15 2017;196(8):985-992. doi:10.1164/rccm.201701-0120OC

75. Hammad H, Lambrecht BN. The basic immunology of asthma. *Cell*. Mar 18 2021;184(6):1469-1485. doi:10.1016/j.cell.2021.02.016

76. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med*. Feb 1 2017;195(3):302-313. doi:10.1164/rccm.201602-0419OC

77. Schroeder JT, Bieneman AP, Xiao H, et al. TLR9- and FcepsilonRI-mediated responses oppose one another in plasmacytoid dendritic cells by down-regulating receptor expression. *J Immunol*. Nov 1 2005;175(9):5724-31. doi:10.4049/jimmunol.175.9.5724

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.

REFERENCES

1. Aksoy C, Elsurer C, Artac H, Bozkurt MK. Evaluation of olfactory function in children with seasonal allergic rhinitis and its correlation with acoustic rhinometry. *Int J Pediatr Otorhinolaryngol*. Oct 2018;113:188-191. doi:10.1016/j.ijporl.2018.07.051

2. Liang C, Yang Z, Zou Q, Zhou M, Liu H, Fan J. Construction of an irreversible allergic rhinitis-induced olfactory loss mouse model. *Biochem Biophys Res Commun*. Jun 4 2019;513(3):635-641. doi:10.1016/j.bbrc.2019.03.110

3. Gupta N, Harit A, Taneja HC, Kumar R, Tripathi AK. Olfaction and Its Correlates in Allergic Rhinitis: A Case Control Study. *Indian J Otolaryngol Head Neck Surg*. Nov 2019;71(Suppl 3):1782-1786. doi:10.1007/s12070-017-1149-7

4. Bahri R, Custovic A, Korosec P, et al. Mast cell activation test in the diagnosis of allergic disease and anaphylaxis. *J Allergy Clin Immunol*. Aug 2018;142(2):485-496 e16. doi:10.1016/j.jaci.2018.01.043

5. Bahri R, Bulfone-Paus S. Mast Cell Activation Test (MAT). *Methods Mol Biol*. 2020;2163:227-238. doi:10.1007/978-1-0716-0696-4_19