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### International consensus statement on allergy and rhinology

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

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19

20

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24

25

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26

1 **ABSTRACT**

2

3 **Background:** In the 5 years that have passed since the publication of the 2018 International Consensus  
4 Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR-Allergic Rhinitis 2018), the literature has  
5 expanded substantially. The ICAR-Allergic Rhinitis 2023 update presents 144 individual topics on allergic  
6 rhinitis (AR), expanded by over 40 topics from the 2018 document. Originally presented topics from  
7 2018 have also been reviewed and updated. The executive summary highlights key evidence-based  
8 findings and recommendation from the full document.

9

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

14

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

20

21 **Conclusion:** The ICAR-Allergic Rhinitis 2023 update provides a comprehensive evaluation of AR and the  
22 currently available evidence. It is this evidence that contributes to our current knowledge base and  
23 recommendations for patient evaluation and treatment.

24

## 1 I. Executive summary

### 3 I.A. Introduction

4  
5 The International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis 2023 (ICAR-Allergic  
6 Rhinitis 2023) was developed as an update to the original ICAR-Allergic Rhinitis 2018<sup>1</sup> document. The  
7 goal of this document is to summarize and critically review the best evidence related to allergic rhinitis  
8 (AR). Through a systematic approach including literature review, semi-blinded stepwise iterative review  
9 process, and consensus and oversight by associate editors, all steps of document development have  
10 been rigorous and of high quality.

11  
12 ICAR-Allergic Rhinitis 2023 is not intended to be a clinical practice guideline, meta-analysis, or expert  
13 panel report. The ICAR authors have carefully reviewed all relevant literature and determined the  
14 strength of the available evidence. Based upon this evidence, where applicable, recommendations are  
15 made for various diagnostic and treatment options in the realm of AR. A secondary goal of this  
16 document is to identify updates in the field as compared to the previous ICAR-Allergic Rhinitis 2018  
17 document and highlight advances in our understanding of AR, as well as its diagnosis and treatment.  
18 Through this in-depth investigation, we are also able to identify areas in which further work is needed.

19  
20 Since the publication of ICAR-Allergic Rhinitis 2018, there are numerous new high-level publications in  
21 various aspects of AR. There have been updates in levels of evidence and recommendations. These  
22 findings, along with a comparison to the ICAR-Allergic Rhinitis 2018 available publications, and levels of  
23 evidence, are shown in the tables in this executive summary. Still, several important areas of future  
24 investigation remain.

### 26 I.B. Methods

27  
28 In the ICAR-Allergic Rhinitis 2023 update, there were a total of 144 individual topics assigned to 87  
29 primary authors. A multidisciplinary group of expert authors from around the world, often with a  
30 notable publication record in the field, were invited to contribute to both authorship and iterative peer  
31 review aspects of the ICAR process. Topics were assigned as literature reviews, evidence-based reviews  
32 without recommendations, or evidence-based reviews with recommendations, depending on the  
33 available literature, strength of evidence, and type of intervention. Topics that had sufficient evidence to

1 substantiate clinical recommendations were assigned as evidence-based reviews with  
2 recommendations, based on the work of Rudmik and Smith.<sup>2</sup>

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

11  
12 Each section then underwent a stepwise review in a semi-blinded fashion by two additional experts.  
13 Consensus was reached after each stage in the iterative review process. The review process was  
14 overseen by an associate editor to ensure adherence to the ICAR methodology and assist in resolution of  
15 any concerns. Following completion of all topics, the individual sections were collated into major  
16 content areas (e.g., Evaluation and Diagnosis, Management, Associated Conditions) and each major  
17 content area was reviewed by 3-5 associate editors. The final ICAR-Allergic Rhinitis 2023 document was  
18 then compiled and reviewed by all authors for consensus.

19  
20 The ICAR process aims to be systematic, consistent, and thorough; however, certain limitations exist.  
21 The literature search for each topic was performed by the individual invited author for that topic. This  
22 has the potential to introduce some variability in search results despite detailed literature search  
23 instructions. Also, for some topics, there is extensive high-quality literature available. This may allow an  
24 aggregate grade of evidence to be delineated without listing every published study on that topic. In  
25 these cases, an exhaustive list of lower-level studies may not be provided in the evidence tables.

## 26 I.C. Results

### 27 I.C.1. Definitions, classification, and differential diagnosis

28  
29  
30 AR is primarily driven by an IgE-mediated type 1 hypersensitivity response, due to an allergen exposure.  
31 Classically, seasonal AR was thought to be associated with outdoor allergens and perennial AR with  
32 indoor year-round exposure to allergens. However, climate change and polysensitization may make  
33 these classifications challenging. Intermittent AR is defined as symptoms for less than 4 days per week



1 or less than 4 consecutive weeks. Persistent AR is defined as symptoms for more than 4 days per week  
 2 for at least one month. Sensitization to allergens may be identified on skin or in vitro testing which  
 3 assesses the presence of allergen-specific IgE (sIgE). However, many people that are sensitized do not  
 4 exhibit allergy symptoms, so correlation with clinical symptoms upon allergen exposure is critical. Classic  
 5 AR symptoms include sneezing, rhinorrhea, and nasal congestion/obstruction. These symptoms are non-  
 6 specific, and the differential diagnosis of AR is broad. Section V. of the ICAR-Allergic Rhinitis 2023  
 7 document explores AR definition, classification, and differential diagnosis. [TABLE I.C.1.]

8

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

<b>Definition of allergic rhinitis</b>	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. <sup>5</sup>
<b>Differential diagnosis of allergic rhinitis</b>	<ul style="list-style-type: none"> <li>• Drug-induced rhinitis</li> <li>• Rhinitis medicamentosa</li> <li>• Occupational rhinitis</li> <li>• Chemical rhinitis</li> <li>• Smoke-induced rhinitis</li> <li>• Infectious rhinitis</li> <li>• Rhinitis of pregnancy</li> <li>• Hormonally induced rhinitis</li> <li>• Food and alcohol induced rhinitis</li> <li>• Non-allergic rhinitis with eosinophilia syndrome</li> <li>• Non-allergic rhinopathy and vasomotor rhinitis</li> <li>• Age-related rhinitis (i.e., elderly)</li> <li>• Empty nose syndrome</li> <li>• Atrophic rhinitis</li> <li>• Autoimmune, granulomatous, and vasculitic rhinitis</li> <li>• Rhinosinusitis</li> <li>• Non-rhinitis conditions (e.g., anatomical obstruction, neoplastic, cerebrospinal fluid rhinorrhea, foreign body, cystic fibrosis, primary ciliary dyskinesia, gastroesophageal reflux)</li> </ul>

10

11 **I.C.2. Pathophysiology and mechanisms**

12

13 Shortly after IgE receptor stimulation, mast cells secrete proteins due to stimulated gene transcription.

14 Multiple cytokines and chemokines are released, which recruit inflammatory cells such as eosinophils,  
15 basophils, neutrophils, macrophages, and T cells.

16

17 Various inflammatory processes occur at different stages of AR. These processes are driven by the type 2

18 immune response. Considering the pathophysiology of AR, the ICAR-Allergic Rhinitis 2023 document

1 explores local and systemic IgE mediated inflammation, cellular infiltrates, cytokines and soluble  
 2 mediators, neural mechanisms, histologic and epithelial changes, epithelial barrier alterations,  
 3 association with vitamin D, alterations in nitric oxide and the microbiome, as well as the unified airway  
 4 concept. Section VI. of the ICAR-Allergic Rhinitis 2023 document discusses AR pathophysiology and  
 5 mechanisms.

### 7 I.C.3. Epidemiology

8  
 9 The prevalence of AR has been reported from 5-50% worldwide. Prevalence reporting is dependent on  
 10 the method of diagnosis and age of participants studied, which may explain some of the variability in  
 11 reported AR prevalence. There have been increased attempts to provide more uniformity in the  
 12 terminology and diagnostic criteria for AR. The available literature suggests that AR had been previously  
 13 increasing across the globe. While recent evidence indicates this upward trend may have leveled off,  
 14 notable geographic differences exist. The rate of AR typically increases with age until young adulthood.  
 15 The effects of geographic influences on epidemiology of AR and the role of climate change are active  
 16 areas of research. Section VII. of the ICAR-Allergic Rhinitis 2023 document reviews the epidemiology of  
 17 AR.

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

20  
 21 Several risk factors for the development of AR have been investigated. There is conflicting data for many  
 22 of these potential risk factors, and this area of work remains a topic of active investigation. Section VIII.  
 23 of the ICAR-Allergic Rhinitis 2023 document explores risk factors and potential protective factors for the  
 24 development of AR. [TABLES I.C.4.-1 and I.C.4.-2]

25  
 26 **TABLE I.C.4.-1 Risk factors for the development of allergic rhinitis – comparison between 2018 and**  
 27 **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: <i>in utero</i> or early exposure	2023	7	C	Data inconclusive.
	2018	6	C	
Pollen: <i>in utero</i> or early exposure	2023	2	C	Data inconclusive.
	2018	2	C	
Animal dander: <i>in utero</i> or early exposure	2023	46	C	Data inconclusive.
	2018	39	C	

Fungal allergens: <i>in utero</i> or early exposure	2023	15	C	Data inconclusive.
	2018	13	C	
Restricted diet: <i>in utero</i> and early childhood	2023	18	A	Maternal diet restriction while child is <i>in utero</i> 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	

1 AR=allergic rhinitis; SES=socioeconomic status  
 2 \*Studies included in systematic reviews were not separately listed in tables  
 3

4 **TABLE I.C.4.-2 Protective factors for the development of allergic rhinitis – comparison of 2018 and**  
 5 **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	-----	

6 AR=allergic rhinitis  
 7 \*Studies included in systematic reviews were not separately listed in tables  
 8

9 **BREASTFEEDING – Aggregate grade of evidence: C** (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study)

10 **Benefit:** Benefits on general health of infant and possible protection against AR, especially in young  
 11 children.

12 **Harm:** None.

13 **Cost:** Low.

14 **Benefits-harm assessment:** Slight preponderance of benefit over harm for protection against AR. Large  
 15 preponderance of benefit over harm for breastfeeding for all infants, unless there is a contraindication.  
 16 The benefit of breastfeeding for all infants inextricably influences this recommendation.

17 **Value judgments:** Evidence suggests that breastfeeding may reduce the risk of AR without harm.

18 **Policy level:** Recommendation for breastfeeding due to various positive effects on general health and  
 19 possible protective effects on AR.

20 **Intervention:** Breastfeeding for at least 4-6 months should be encouraged unless contraindicated.  
 21

22 **CHILDHOOD EXPOSURE TO PETS – Aggregate grade of evidence: C** (Level 2: 1 study, level 3: 2 studies, le  
 23 vel 4: 2 studies)

24 **Benefit:** Exposure to pets at birth and in the first year of life has potential benefits of decreasing risk of A  
 25 R.

- 1 **Harm:** Pet keeping in childhood could have a negative effect, especially in Asians.
- 2 **Cost:** Various.
- 3 **Benefits-harm assessment:** Difficulty distinguishing between benefits and harm.
- 4 **Value judgment:** There is conflicting evidence that childhood pet exposure prevents the development of
- 5 AR.
- 6 **Policy level:** Option.
- 7 **Intervention:** Recommendation to expose or avoid pets for the prevention of AR in children cannot be
- 8 provided based on current evidence.
- 9

10 **I.C.5. Disease burden**

11  
 12 ICAR-Allergic Rhinitis 2023 reviewed the disease burden of AR as it relates to quality of life (QOL) and  
 13 sleep disturbance. Several new studies have been added in each of these categories since ICAR-Allergic  
 14 Rhinitis 2018. AR also has substantial impact at a societal level, which may be quantified in direct and  
 15 indirect costs, absenteeism or presenteeism, and other measures. Individual and societal burdens of AR  
 16 are significant and addressed further in the full ICAR-Allergic Rhinitis 2023 document. **[TABLE I.C.5.]**

17  
 18 **TABLE I.C.5. Allergic rhinitis disease burden – comparison between 2018 and 2023**

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

19 AR=allergic rhinitis; QOL=quality of life

- 20
- 21 **DISEASE BURDEN – QUALITY OF LIFE – Aggregate grade of evidence:** B (Level 1: 6 studies, level 2: 35 studies, level 3: 15 studies)
- 22
- 23 **Benefit:** Successful treatment of AR leads to improved overall and disease specific QOL.
- 24 **Harm:** Depending on the specific treatments for AR, there are variable levels of harm.
- 25 **Cost:** Treatments for AR have variable costs.
- 26 **Benefits-harm assessment:** The benefits of treating patients with AR to improve QOL likely outweigh risks of treatment.
- 27
- 28 **Value judgment:** Validated measures of QOL should be utilized in future studies of treatments for AR.
- 29 **Policy level:** Recommendation.
- 30 **Intervention:** Validated measures of QOL should be utilized in future studies of treatments for AR.
- 31

- 32 **DISEASE BURDEN – SLEEP DISTURBANCE – Aggregate grade of evidence:** B (Level 2: 5 studies, level 3: 8 studies, level 4: 50 studies)
- 33
- 34 **Benefit:** AR negatively impacts sleep quality. Successful management of AR leads to decreased sleep disturbance in adults and children.
- 35
- 36 **Harm:** Medical management of AR is generally low risk and medications have low side-effect profiles. AIT is associated with rare serious adverse events.
- 37
- 38 **Cost:** Associated costs consist of the direct costs of allergy testing and medical management, and

1 indirect cost of increased time and effort for allergen immunotherapy (AIT).  
 2 **Benefits-harm assessment:** The benefits of treating patients with AR may outweigh any associated risks.  
 3 **Value judgment:** In patients with AR, the successful control of symptoms with medical management or  
 4 AIT can lead to important improvements in sleep disturbance. The level of available evidence is stronger  
 5 for the adult population compared with the pediatric population.  
 6 **Policy level:** Treatment of AR to improve sleep disturbance -- Recommended in adults. Option in  
 7 children.  
 8 **Intervention:** Intranasal corticosteroids (INCS), oral antihistamines, montelukast, and AIT are  
 9 appropriate options, when medically indicated, to improve sleep disturbance in patients with AR.

10

### 11 I.C.6. Evaluation and diagnosis

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

16

17 **TABLE I.C.6. Diagnostic modalities for evaluation of allergic rhinitis – comparison between 2018 and**  
 18 **2023**

Diagnostic modality	Year	# of listed studies	Aggregate grade of evidence	Policy level	Interpretation
Clinical examination (history and physical)	2023	20	D	Recommendation	While there is low level evidence, guideline documents support the recommendation of combined history and physical.
	2018	9	D	Recommendation	
Nasal endoscopy	2023	10	C	Option	Nasal endoscopy may be considered a diagnostic adjunct.
	2018	5	D	Option	
Radiologic imaging	2023	8	D	Recommend against	Radiologic imaging is not recommended for the diagnosis of AR.
	2018	0	n/a	Recommend against	
Use of validated survey instruments	2023	22	B	Recommendation	Validated survey instruments can be used to screen for AR, follow treatment outcomes, and as an outcome measure for clinical trials.
	2018	10	A	Strong recommendation	
Skin prick testing	2023	12	B	Recommendation	Skin prick testing is recommended for AR diagnosis.
	2018	8	B	Recommendation	
Skin intradermal testing	2023	20	C	Option	Option for intradermal testing as a stand-alone test or confirmatory test.
	2018	17	B	Option	
Blended skin testing techniques	2023	7	D	Option	Modified quantitative testing is a technique that may be used to determine a safe starting dose for AIT.
	2018	5	D	Option	
Serum total IgE	2023	15	C	Option	Serum total IgE is an option to assess atopic status and guide therapy.
	2018	15	C	Option	
Serum allergen-specific IgE	2023	16	B	Recommendation	Serum sIgE testing is recommended for allergy testing.
	2018	7	B	Recommendation	
	2023	19	B	-----	

Correlation between skin and <i>in vitro</i> testing	2018	19	B	-----	Studies differ regarding the concordance of various allergy testing methods.
Nasal sIgE	2023	36	C	Option	Nasal sIgE is an option in patients with suspected AR.
	2018	24	C	Option	
Basophil activation test	2023	19	C	Option	BAT may be used for diagnosis when first-line tests are discordant, and for monitoring response to AIT.
	2018	12	B	Option	
Component resolved diagnostic testing	2023	18	C	Option	May improve selection of allergens for AIT, especially in polysensitized patients.
	2018	n/a	n/a	n/a	
Nasal provocation testing	2023	8	C	Option	Option for diagnostic testing for AR. Recommended for diagnosis of occupational rhinitis and local AR.
	2018	4	C	n/a	
Nasal cytology	2023	7	C	Option	May be considered with negative allergy testing results to assess for eosinophil levels.
	2018	4	C	n/a	
Nasal histology	2023	10	B	Recommend against	Nasal histology is used for research on the pathophysiology of AR but is not recommended for routine clinical use.
	2018	11	B	n/a	
Rhinomanometry	2023	19	B	Option	Option for use in AR diagnosis.
	2018	n/a	n/a	n/a	
Acoustic rhinometry	2023	11	C	Option	Acoustic rhinometry is most useful in a research setting.
	2018	n/a	n/a	n/a	
Peak nasal inspiratory flow	2023	8	B	Option	May be used with PROMs to improve utility.
	2018	n/a	n/a	n/a	
FeNO	2023	7	D	Recommend against	Should not be used routinely for the diagnosis of AR.
	2018	n/a	n/a	n/a	
nNO	2023	8	C	Recommend against	Should not be used routinely for the diagnosis of AR.
	2018	n/a	n/a	n/a	

1 AR=allergic rhinitis; AIT=allergen immunotherapy; IgE=immunoglobulin E; sIgE=allergen-specific immunoglobulin E;  
2 BAT=basophil activation test; n/a=not applicable (not considered in ICAR-Allergic Rhinitis 2018 document);  
3 PROM=patient reported outcome measure; FeNO=fraction of exhaled nitric oxide; nNO=nasal nitric oxide  
4

5 The section that follows includes the recommendation summaries for AR diagnostic modalities  
6 considered in the ICAR-Allergic Rhinitis 2023 document.  
7

8 **PATIENT HISTORY – Aggregate grade of evidence:** D (Level 4: 5 studies, level 5: 7 guidelines or expert  
9 recommendations)

10 **Benefit:** Improves accuracy of diagnosis, avoid unnecessary referrals, testing, or treatment.

11 **Harm:** Potential misdiagnosis or inappropriate treatment.

12 **Cost:** Minimal.

13 **Benefits-harm assessment:** Preponderance of benefit over harm.

14 **Value judgments:** Using history to make a presumptive diagnosis of AR is reasonable and would not  
15 delay treatment initiation. History should be combined with physical examination, which may not be  
16 possible in some scenarios such as telemedicine. Confirmation with diagnostic testing is required for  
17 progression to AIT or targeted avoidance therapy, or desirable with inadequate response to treatment.

- 1 **Policy level:** Recommendation.
- 2 **Intervention:** Despite low level evidence specifically addressing this area, history is essential in the  
3 diagnosis of AR.
- 4
- 5 **PHYSICAL EXAMINATION – Aggregate grade of evidence:** D (Level 4: 2 studies, level 5: 6 guidelines)
- 6 **Benefit:** Possible improved diagnosis of AR with physical examination findings, along with evaluation  
7 and/or exclusion of alternative diagnoses.
- 8 **Harm:** Possible patient discomfort from routine examination, not inclusive of endoscopy.
- 9 **Cost:** Minimal.
- 10 **Benefits-harm assessment:** Preponderance of benefit over harm, potential misdiagnosis and  
11 inappropriate treatment if used in isolation.
- 12 **Value judgments:** Telemedicine is a safe and useful tool in pandemic conditions but does limit what can  
13 be gleaned from physical examination. Without the use of nasal endoscopy, it is possible some physical  
14 examination findings may be missed.
- 15 **Policy level:** Recommendation.
- 16 **Intervention:** When possible, physical examination should be performed with appropriate personal  
17 protective equipment to aid in the diagnosis of AR and exclusion of other conditions. When combined  
18 with patient history, it increases diagnostic accuracy and may exclude alternative causes of symptoms.
- 19
- 20 **NASAL ENDOSCOPY – Aggregate grade of evidence:** C (Level 2: 2 studies, level 3: 1 study, level 4: 7  
21 studies)
- 22 **Benefit:** Possible improved diagnosis with visualization of middle or inferior turbinate edema, contact  
23 and pale/bluish discoloration or isolated central compartment polypoid changes and/or edema, which  
24 have been associated with AR.
- 25 **Harm:** Possible patient discomfort.
- 26 **Cost:** Moderate equipment and processing costs, as well as procedural charges.
- 27 **Benefits-harm assessment:** Balance of benefit and harm.
- 28 **Value judgments:** Nasal endoscopy may increase diagnostic sensitivity among children and adults with  
29 allergic rhinitis.
- 30 **Policy level:** Option.
- 31 **Intervention:** Nasal endoscopy may be considered as a diagnostic adjunct in the evaluation of patients  
32 with suspected AR.
- 33
- 34 **RADIOLOGIC STUDIES – Aggregate grade of evidence:** D (level 3: 1 study, level 4: 7 studies)
- 35 **Benefit:** Some radiologic findings, particularly those associated with central compartment  
36 edema/polyposis, may alert the clinician to the possibility of an associated allergic etiology.
- 37 **Harm:** Unnecessary radiation exposure, unnecessary cost.
- 38 **Cost:** High equipment and processing costs. Additional costs for interpretation of studies by radiologist.
- 39 **Benefits-harm assessment:** Preponderance of harm over benefit.
- 40 **Value judgments:** Long-term risks of ionizing radiation outweigh potential benefit.
- 41 **Policy level:** Recommendation against.
- 42 **Intervention:** Routine use of imaging is not recommended for the diagnosis of AR.
- 43
- 44 **USE OF VALIDATED SUBJECTIVE INSTRUMENTS – Aggregate grade of evidence:** B (Level 1: 2 studies,  
45 level 2: 2 studies, level 3: 5 studies, level 4: 13 studies)
- 46 **Benefit:** Validated surveys offer a simple point-of-care option for screening and tracking symptoms,  
47 QOL, and control of allergic disease.

- 1 **Harm:** Minimal. Time to complete survey. Potential risk of misdiagnosis when based on survey data  
2 alone.
- 3 **Cost:** No financial burden to patients. Some fees associated with validated tests used for clinical  
4 research.
- 5 **Benefits-harm assessment:** Preponderance of benefit over harm. Risk of misdiagnoses leading to  
6 unnecessary additional testing. Likewise, there is a risk that false negative responses may lead to delay  
7 in testing and further management.
- 8 **Value judgments:** Validated surveys may be used as a screening tool and primary or secondary outcome  
9 measure.
- 10 **Policy level:** Recommendation.
- 11 **Intervention:** Validated surveys may be used to screen for AR, follow treatment outcomes and as a  
12 primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathological  
13 scenarios.
- 14
- 15 **SKIN PRICK TESTING – Aggregate grade of evidence:** B (Level 1: 1 study, level 3: 2 studies, level 4: 7  
16 studies, level 5: 2 studies)
- 17 **Benefit:** Confirm AR diagnosis and direct appropriate pharmacological therapy, initiation of AIT, as well  
18 as avoidance measures. See **TABLE II.C.** in full ICAR document.
- 19 **Harm:** Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma  
20 symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results.
- 21 **Cost:** Moderate cost of testing procedure.
- 22 **Benefits-harm assessment:** Preponderance of benefit over harm.
- 23 **Value judgments:** Patients can benefit from identification of their specific sensitivities. Skin prick testing  
24 (SPT) is a quick and relatively comfortable way to test several antigens with accuracy similar to other  
25 available methods of testing.
- 26 **Policy level:** Recommendation.
- 27 **Intervention:** Regular use of the same SPT device type will allow clinicians to familiarize themselves with  
28 it and interpretation of results may therefore be more consistent. The use of standardized allergen  
29 extracts can further improve consistency of interpretation.
- 30
- 31 **SKIN INTRADERMAL TESTING – Aggregate grade of evidence:** C (Level 3: 7 studies, level 4: 13 studies)
- 32 **Benefit:** May improve identification of allergic sensitization in patients with low-level skin sensitivity or  
33 with non-standardized allergens.
- 34 **Harm:** Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma  
35 symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. See **TABLE II.C.** in full  
36 ICAR document.
- 37 **Cost:** Moderate cost of testing procedure.
- 38 **Benefits-harm assessment:** Benefit over harm when used as a stand-alone diagnostic test, when used to  
39 confirm the results of SPT, and as a quantitative diagnostic test.
- 40 **Value judgments:** Intradermal skin tests may not perform as well as SPT in most clinical situations.
- 41 **Policy level:** : Option for using intradermal testing as a stand-alone diagnostic test for individuals with  
42 suspected AR. Option for using intradermal testing as a confirmatory test following negative SPT for  
43 non-standardized allergens.
- 44 **Intervention:** Intradermal testing may be used to determine aeroallergen sensitization in individuals  
45 suspected of having AR.
- 46
- 47 **BLENDED SKIN TESTING TECHNIQUES – Aggregate grade of evidence:** D (Level 4: 7 studies)



1 **Benefit:** Ability to establish an endpoint in less time than intradermal dilutional testing, potential to  
2 determine allergen sensitization after negative SPT.

3 **Harm:** Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma  
4 symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. Additional time and  
5 discomfort versus SPT alone. See **TABLE II.C.** in full ICAR document.

6 **Cost:** Moderate cost of testing procedure.

7 **Benefits-harm assessment:** Preponderance of benefit over harm.

8 **Value judgments:** While AIT can be based off SPT results alone, endpoint-based immunotherapy may  
9 have possible benefits of decreased time to therapeutic dosage.

10 **Policy level:** Option

11 **Intervention:** Blended skin testing techniques, such as modified quantitative testing, are methods that  
12 can be used to determine a starting point for AIT or confirm allergic sensitization.

### 13 **ISSUES THAT MAY AFFECT THE PERFORMANCE AND INTERPRETATION OF SKIN TESTS – MEDICATIONS:**

- 14 • **H<sub>1</sub> antihistamines** – Aggregate Grade of Evidence: A (Level 2: 3 studies, level 3: 3 studies, level 4:  
15 1 study). Should be discontinued 2-7 days prior to testing.
- 16 • **H<sub>2</sub> antihistamines** – Aggregate Grade of Evidence: A (Level 2: 2 studies, level 3: 1 study, level 4:  
17 1 study). Ranitidine may suppress skin whealing response, leading to false negative results.  
18 Should be discontinued 2 days prior to testing.
- 19 • **Topical antihistamines** – Aggregate Grade of Evidence: Unable to determine from one Level 2  
20 study. Should be discontinued 2 days prior to testing.
- 21 • **Anti-IgE (omalizumab)** – Aggregate Grade of Evidence: A (Level 2: 1 study, level 3: 1 study).  
22 Results in negative allergy skin test results. May suppress skin whealing response for 4-6  
23 months.
- 24 • **Leukotriene modifying agents** – Aggregate Grade of Evidence: A (Level 2: 2 studies, level 3: 1  
25 study). May be continued during testing.
- 26 • **Tricyclic antidepressants** – Aggregate Grade of Evidence: B (Level 2: 1 study, level 4: 1 study).  
27 Antidepressants with antihistaminic properties suppress allergy skin test responses. Should be  
28 discontinued 7-14 days prior to testing.
- 29 • **Topical (cutaneous) corticosteroids** – Aggregate Grade of Evidence: A (Level 2: 3 studies, level 3:  
30 1 study). Skin tests should not be placed at sites of chronic topical steroid treatment.
- 31 • **Systemic corticosteroids** – Aggregate Grade of Evidence: C (Level 2: 1 study, level 3: 1 study,  
32 level 4: 2 studies; conflicting results). Systemic corticosteroid treatment does not significantly  
33 impair skin test responses.
- 34 • **Selective serotonin reuptake inhibitors** – Aggregate Grade of Evidence: C (Level 3: 1 study, level  
35 4: 1 study). Do not suppress allergy skin test responses.
- 36 • **Benzodiazepines** – Aggregate Grade of Evidence: C (Level 4: 2 studies). May suppress skin test  
37 responses. Should be discontinued 7 days prior to testing.
- 38 • **Topical calcineurin Inhibitors (tacrolimus, picrolimus)** – Aggregate Grade of Evidence: C (Level  
39 2: 2 studies; conflicting results). Conflicting results regarding skin test suppression.

### 40 **ISSUES THAT MAY AFFECT THE PERFORMANCE AND INTERPRETATION OF SKIN TESTS – SKIN**

41 **CONDITIONS:** Common sense dictates that allergy skin tests should not be performed at sites of active  
42 dermatitis, but clinical studies to investigate this phenomenon are lacking. There are insufficient studies  
43 published on this topic, and an Aggregate Grade of Evidence could not be assigned.  
44  
45  
46

- 1 **SERUM TOTAL IMMUNOGLOBULIN E (IgE) – Aggregate grade of evidence:** C (Level 2: 4 studies, level 3:  
2 11 studies)
- 3 **Benefit:** Possibility to suspect allergy or atopy in a wide screening.  
4 **Harm:** Cost of test, undergoing of venipuncture, low level does not exclude AR.  
5 **Cost:** Low, dependent on country and local healthcare environment.  
6 **Benefits-harm assessment:** Slight preponderance of benefit over harm. In addition, the ratio of total to  
7 allergen-specific IgE (sIgE) may be useful to interpret the real value of specific IgE production and predict  
8 treatment outcomes with AIT.  
9 **Value judgments:** The evidence does not support a routine use.  
10 **Policy level:** Option.  
11 **Intervention:** Assessment of tIgE may be useful to assess overall atopic status; furthermore, in selected  
12 cases it might help guide therapy (i.e., predict outcome of AIT).  
13
- 14 **SERUM ALLERGEN SPECIFIC IMMUNOGLOBULIN E – Aggregate grade of evidence:** B (Level 1: 1 study,  
15 level 2: 2 studies, level 3: 6 studies, level 4: 6 studies, level 5: 1 study)  
16 **Benefit:** Confirms diagnosis and directs appropriate pharmacological therapy while possibly avoiding  
17 unnecessary/ineffective treatment, guides avoidance, directs AIT.  
18 **Harm:** Adverse events from testing including discomfort from blood draw, inaccurate test results, false  
19 positive test results, misinterpreted test results.  
20 **Cost:** Moderate cost of testing.  
21 **Benefits-harm assessment:** Preponderance of benefit over harm.  
22 **Value judgments:** Patients can benefit from identification of their specific sensitivities. Further, in some  
23 patients who cannot undergo SPT, serum sIgE testing is a safe and effective alternative.  
24 **Policy level:** Recommendation.  
25 **Intervention:** Serum sIgE testing may be used in patients who cannot undergo allergy skin testing. Use  
26 of highly purified allergen or recombinants can increase the sensitivity, specificity, and diagnostic  
27 accuracy of sIgE tests. Rigorous proficiency testing on the part of laboratories may also improve  
28 accuracy.  
29
- 30 **NASAL ALLERGEN SPECIFIC IMMUNOGLOBULIN E – Aggregate grade of evidence:** C (Level 1: 1 study,  
31 level 2: 21 studies, level 3: 3 studies, level 4: 11 studies)  
32 **Benefit:** Patients with non-allergic rhinitis found to have nasal sIgE may have local AR and could benefit  
33 from avoidance or AIT.  
34 **Harm:** Measurement of nasal sIgE is minimally invasive. No significant adverse effects have been  
35 reported. Possible discomfort from sample collection.  
36 **Cost:** Associated costs include the direct costs of testing and indirect cost of increased time and effort  
37 for performing nasal sIgE diagnostic test.  
38 **Benefits-harm assessment:** The benefits of identifying patients with an allergic component to their  
39 rhinitis may outweigh associated risks.  
40 **Value judgments:** In patients with non-allergic rhinitis who also have risk factors for atopic disease and  
41 have inadequate response to pharmacotherapy, testing for nasal sIgE may be helpful in confirming a  
42 diagnosis of local AR and allowing for treatment with AIT. There is no consensus for levels of nasal sIgE  
43 that indicate sensitivity.  
44 **Policy level:** Option.  
45 **Intervention:** Measurement of nasal sIgE is an option in patients with non-allergic rhinitis suspected of  
46 having local AR to support this diagnosis and guide AIT if pharmacologic therapies are inadequate.  
47 Consensus for levels of nasal sIgE indicating AR need to be established.  
48

- 1 **BASOPHIL ACTIVATION TEST – Aggregate grade of evidence:** C (Level 2: 5 studies, level 3: 13 studies,  
2 level 4: 1 study)
- 3 **Benefit:** May help diagnose AR in specific cases where common approaches are not possible or show  
4 conflicting results.
- 5 **Harm:** Discomfort of venipuncture.
- 6 **Cost:** Moderate cost of performing the test, plus venipuncture. Depending on the local situation and  
7 availability.
- 8 **Benefits-harm assessment:** Balance of benefit and harm.
- 9 **Value judgments:** The evidence does not support routine use for the diagnosis of AR or for following AIT  
10 response.
- 11 **Policy level:** Option.
- 12 **Intervention:** Application of basophil activation test in specific situations where other diagnostic  
13 procedures for AR are not possible or conflicting. Potentially useful for monitoring AIT if other methods  
14 fail or show conflicting results.
- 15
- 16 **COMPONENT RESOLVED DIAGNOSTIC TESTING – Aggregate grade of evidence:** C (Level 2: 4 studies,  
17 level 3: 2 studies, level 4: 11 studies, level 5: 1 study)
- 18 **Benefit:** Reliable. May help in identification and selection of suitable allergens for AIT, as well as possibly  
19 improving safety of AIT.
- 20 **Harm:** Discomfort of venipuncture.
- 21 **Cost:** Moderate cost of testing, minimal cost of venipuncture; depends in local availability.
- 22 **Benefits-harm assessment:** Balance of benefit and harm.
- 23 **Value judgments:** Molecular diagnosis may be a useful tool for diagnosis of AR in some scenarios,  
24 especially in polysensitized patients.
- 25 **Policy level:** Option.
- 26 **Intervention:** Molecular diagnosis is an option for diagnosis of AR by specialists.
- 27
- 28 **NASAL PROVOCATION TESTING – Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 7 studies)
- 29 **Benefit:** May assist in confirming diagnosis of AR in specific cases when immunological tests are  
30 unavailable or unreliable. Nasal provocation testing is crucial in diagnosing occupational rhinitis and  
31 local AR.
- 32 **Harm:** Not necessary if first- and second- line tests are indicative for AR diagnosis.
- 33 **Cost:** Depending on the local situation and availability of equipment and staff, costs may be high.
- 34 **Benefits-harm assessment:** Balance of benefit and harm.
- 35 **Value judgments:** The evidence does not support routine use for diagnosis of AR, but provocation  
36 testing is useful for diagnosis of occupational rhinitis and local AR.
- 37 **Policy level:** Option for diagnosis of AR when skin or in vitro tests are equivocal or unreliable.  
38 Recommendation for diagnosis of local AR and occupational rhinitis.
- 39 **Intervention:** Application of nasal provocation testing is useful in local AR and to confirm occupational  
40 rhinitis.
- 41
- 42 **NASAL CYTOLOGY – Aggregate grade of evidence:** C (Level 1: 1 study, level 3: 3 studies, level 4: 3  
43 studies)
- 44 **Benefit:** Low costs and low invasiveness. Could help to detect eosinophils in non-allergic rhinitis and to  
45 diagnose a mixed rhinitis.
- 46 **Harm:** Nasal cytology is minimally invasive and minimal adverse effects have been reported.
- 47 **Cost:** Associated costs include the direct cost of nasal cytology and indirect cost of increased time and  
48 effort for performing nasal cytology.

1 **Benefits-harm assessment:** Preponderance of benefit over harm.

2 **Value judgments:** The evidence does not support routine clinical use.

3 **Policy level:** Option.

4 **Intervention:** Nasal cytology could help in cases of non-allergic rhinitis to suspect local AR or in cases of  
5 AR to diagnose a mixed rhinitis. It could be considered an option in cases of negative SPT and/or serum  
6 sIgE to evaluate the presence of mucosal eosinophils and consideration of local AR or type 2  
7 inflammation. The cut-off values for determining non-allergic rhinitis with eosinophilia syndrome  
8 (NARES) are not yet clear.

9

10 **NASAL HISTOLOGY – Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 7 studies, level 4: 2  
11 studies)

12 **Benefit:** May assist in evaluation of tissue eosinophilia and expression of mediators. May be useful in  
13 clinical research.

14 **Harm:** Small risk of complications (e.g., bleeding, infection).

15 **Cost:** Associated costs consist of the direct cost of nasal histology and indirect cost of increased time and  
16 effort for performing nasal histology.

17 **Benefits-harm assessment:** Preponderance of benefit over harm.

18 **Value judgments:** The evidence does not support routine clinical use.

19 **Policy level:** Recommendation against.

20 **Intervention:** Nasal histology may be helpful in clinical research or selected cases (e.g., evaluation of  
21 tissue eosinophils during surgery). Recommendation against in routine clinical practice for AR evaluation  
22 due to invasive nature of obtaining a specimen.

23

24 **RHINOMANOMETRY – Aggregate grade of evidence:** B (Level 1: 2 studies, level 2: 2 studies, level 3: 5  
25 studies, level 4: 4 studies, level 5: 6 studies)

26 **Benefit:** Rhinomanometry is useful to improve patient selection for surgery, distinguish between  
27 structural and functional causes of nasal obstruction, diagnose nasal valve collapse, clarify conflicting  
28 symptoms and exam findings, use as a medicolegal tool and in nasal allergen challenges. Four-phase  
29 rhinomanometry correlates with subjective scores.

30 **Harm:** Low. Rhinomanometry has limited effectiveness in patients with complete nasal obstruction or  
31 septal perforation. The equipment is not portable and therefore requires a clinic visit and trained staff.  
32 The procedure may be considered time consuming.

33 **Cost:** High.

34 **Benefits-harm assessment:** Benefits outweigh harm.

35 **Value judgments:** For some patients, it may be important to avoid unnecessary costs in the diagnosis of  
36 AR; therefore, this procedure is less preferred.

37 **Policy level:** Option.

38 **Intervention:** Rhinomanometry is useful in distinguishing between structural and soft tissue causes of  
39 obstruction, when history and examination findings are not congruent, as well as a research tool. Better  
40 with individual nasal cavity assessment and four-phase rhinomanometry.

41

42 **ACOUSTIC RHINOMETRY – Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 5 studies, level 4: 3  
43 studies, level 5: 2 studies)

44 **Benefit:** Improves patient selection for surgery, helps distinguish between structural and functional  
45 causes of nasal obstruction, evaluates a response in nasal allergen challenges, and functions as a  
46 medicolegal tool to demonstrate objective evidence of effectiveness of an intervention.

47 **Harm:** Low. Equipment is not portable therefore, requires a clinic visit and trained staff. Time-  
48 consuming. Leakage into sinuses may provide inaccurate results and lead to inappropriate treatment.

1 **Cost:** High.  
 2 **Benefits-harm assessment:** Benefits outweigh harm as harm is low.  
 3 **Value judgments:** For some patients, it may be important to avoid unnecessary cost in the diagnosis of  
 4 AR, and thus acoustic rhinometry is less preferred.  
 5 **Policy level:** Option.  
 6 **Intervention:** Acoustic rhinometry is most useful in research setting as opposed to as a clinical  
 7 diagnostic tool.

8  
 9 **PEAK NASAL INSPIRATORY FLOW – Aggregate grade of evidence:** B (Level 2: 2 studies, level 3: 4 studies,  
 10 level 4: 1 study, level 5: 1 study)

11 **Benefit:** Can improve patient selection for surgery, can evaluate a response in nasal allergen challenges,  
 12 and can be used as a medicolegal tool to demonstrate objective evidence of effectiveness of an  
 13 intervention.

14 **Harm:** Low. Risk of missing valve collapse and septal deviation as causes of obstruction.

15 **Cost:** Low.

16 **Benefits-harm assessment:** Benefits likely to outweigh harm as harm is low.

17 **Value judgments:** Relies on patient effort and does not assess individual nasal cavities. Unable to  
 18 evaluate nasal valve collapse.

19 **Policy level:** Option.

20 **Intervention:** Use in conjunction with patient reported outcome measures to improve utility.

21  
 22 **NITRIC OXIDE MEASUREMENTS – Aggregate grade of evidence:**

23 - Fractional exhaled nitric oxide (FeNO): D (Level 4: 7 studies)

24 - Nasal nitric oxide (nNO): C (Level 2: 2 studies, level 4: 6 studies)

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

27 **Harm:** No studies have shown harm with either exam.

28 **Cost:**

29 - FeNO: Relatively high. FeNO analyzers are approximately \$7000-10000 US, but testing is covered by  
 30 some insurance plans.

31 - nNO: High. Chemiluminescence NO analyzers are approximately \$30,000-50,000 US, and clinical  
 32 testing is not covered by insurance in the US.

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

35 **Benefits-harm assessment:** Preponderance of benefit over harm.

36 **Value judgments:** There is inconsistent evidence in the ability of FeNO or nNO to differentiate adults  
 37 and children with AR and non-allergic rhinitis. Most studies were of low evidence or small impact. There  
 38 is no agreed upon cut-off value when performing FeNO or nNO for the diagnosis of AR.

39 **Policy level:**

40 - FeNO: Recommend against for routine diagnosis of AR.

41 - nNO: Recommend against for routine diagnosis of AR.

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

## 45 46 I.C.7. Management

### 47 I.C.7.a. Avoidance measures and environmental controls

48

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

8  
 9 **TABLE I.C.7.a. Avoidance measures and environmental controls for the treatment of allergic rhinitis –**  
 10 **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	

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

13  
 14 The section that follows includes recommendation summaries for allergen avoidance and environmental  
 15 controls that are included in the ICAR-Allergic Rhinitis 2023 document.

16  
 17 **AVOIDANCE – HOUSE DUST MITE (HDM) – Aggregate grade of evidence:** B (Level 1: 2 studies, level 2:  
 18 12 studies)

19 **Benefit:** Potential improvement in AR symptoms and QOL with reduced concentration of environmental  
 20 HDM antigens.

21 **Harm:** None.

22 **Cost:** Mild to moderate. However, cost-effectiveness was not evaluated.

23 **Benefits-harm assessment:** Benefit outweighs harm.

24 **Value judgments:** There is supporting evidence for the use of acaricides in reducing HDM concentration  
 25 in children who have AR coexistent with asthma. In adults and children without concomitant asthma,  
 26 the use of acaricides with/without bedroom-based control programs for reducing HDM concentration  
 27 are promising, but further, high-quality studies are needed to evaluate clinical outcomes.

28 **Policy level:** Option.

1 **Intervention:** Acaricides used independently or alongside environmental control measures such as air  
2 filtration devices, could be considered as options in the management AR.

3  
4 **AVOIDANCE – COCKROACH – Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 8 studies, level  
5 3: 2 studies, level 4: 1 study)

6 **Benefit:** Reduction in cockroach count but allergen concentrations (Bla g 1 & Bla g 2) often above  
7 acceptable levels for clinical benefits. No studies included clinical endpoints related to AR.

8 **Harm:** None noted.

9 **Cost:** Direct costs include multiple treatment applications or multi-interventional approaches. Indirect  
10 costs include potential time off work for interventions in home and substantial labor of cleaning  
11 measures to eradicate allergens.

12 **Benefits-harm assessment:** Balance of benefits and harms since lack of clear clinical benefits.

13 **Value judgments:** Control of cockroach populations especially in densely populated multi-family  
14 dwellings is important to control cockroach allergen levels.

15 **Policy level:** Option.

16 **Intervention:** Combination of physical measures (e.g., insecticide bait traps, house cleaning) and  
17 education-based methods seem to have the greatest efficacy. Additional research on single intervention  
18 approaches is needed with cost analysis, as well as investigation of clinical outcomes related to AR.

19  
20 **AVOIDANCE – PETS – Aggregate grade of evidence:** C (Level 2: 2 studies, level 3: 2 studies, level 4: 1  
21 study)

22 **Benefit:** Decreased environmental antigen exposure with possible reduction in symptoms and  
23 secondary prevention of asthma.

24 **Harm:** Emotional distress caused by removal of household pets. Financial and time costs of potentially  
25 ineffective intervention.

26 **Cost:** Low to moderate.

27 **Benefits-harm assessment:** Equivocal.

28 **Value judgments:** While several studies have demonstrated an association between environmental  
29 controls and reductions in environmental antigens, only a single, multi-modality randomized controlled  
30 trial has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity.  
31 The secondary prevention and treatment of asthma in sensitized individuals must also be considered.

32 **Policy level:** Option.

33 **Intervention:** Pet avoidance and environmental control strategies, particularly multi-modality  
34 environmental controls among patients with diagnosed Fel d 1 sensitivity, may be presented as an  
35 option for the treatment of AR.

36  
37 **AVOIDANCE – RODENTS – Aggregate grade of evidence:** C (Level 2: 5 studies, level 3: 5 studies, level 4:  
38 4 studies, level 5: 1 study)

39 **Benefit:** Reduces rodent allergen levels (specifically mouse allergen) but no information on AR  
40 outcomes.

41 **Harm:** Reduction in patient QOL due to removal of pet rodent to whom patient is emotionally attached.  
42 Change in job position or role if primary rodent exposure is work-related.

43 **Cost:** Direct costs include the cost of interventions such as extermination and mitigating causal factors  
44 or loss of income if a job change occurs. Indirect costs include time off work for pest control  
45 appointments.

46 **Benefits-harm assessment:** Balance of benefit and harm.

47 **Value judgments:** Careful patient selection based on exposure history. Heterogeneity of integrated pest  
48 management protocols makes quantification of benefit difficult.

1 **Policy level:** Option.

2 **Intervention:** Avoidance likely improves rodent-specific allergen exposure, especially when the  
3 interaction can be eliminated such as when it is work-related or with a pet rodent. Integrated pest  
4 management should be considered in select patients, such as pediatric inner-city patients that suffer  
5 from asthma and are mouse sensitized.

6  
7 **AVOIDANCE – POLLEN – Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 3 studies)

8 **Benefit:** Decreased symptoms and medication use with potential for improved QOL.

9 **Harm:** Interventions may vary in cost and efficacy of each may be inadequately defined.

10 **Cost:** Generally low monetary cost depending on strategy.

11 **Benefits-harm assessment:** Equivocal, most interventions with lower harm but not well-defined  
12 benefits.

13 **Value judgments:** Most pollen avoidance measures are based on clinical and expert opinion although  
14 trial-based evidence is available for some interventions.

15 **Policy level:** Option.

16 **Intervention:** Pollen avoidance strategies are generally well tolerated and lower cost, non-medication-  
17 based interventions that may have benefit with minimal harm to the patient, but further randomized  
18 controlled trials with larger populations would be needed to better characterize efficacy.

19  
20 **AVOIDANCE – OCCUPATIONAL – Aggregate grade of evidence:** C (Level 3: 5 studies)

21 **Benefit:** Decreased allergen exposure may lead to reduction in symptoms, improvement in QOL and  
22 possible reduced likelihood of developing occupational asthma.

23 **Harm:** Potential for socioeconomic harm with loss of wages or requiring changes in occupation.

24 **Cost:** Individually may vary if avoidance results in loss of income; for employers, potentially high cost  
25 depending on interventions or environmental controls required.

26 **Benefits-harm assessment:** Where possible from a patient-centered perspective, in occupational rhinitis  
27 complete avoidance is likely beneficial in improving health quality compared to ongoing exposures.

28 **Value judgments:** Based primarily on observational studies, allergen avoidance or decreasing exposure  
29 is recommended for all patients but can be nuanced depending on the resulting socioeconomic impact.

30 **Policy level:** Recommendation.

31 **Intervention:** Patients should be counseled to avoid or decrease exposure to inciting agents in  
32 occupational respiratory disease.

33

34

### 35 I.C.7.b. Pharmacotherapy and procedural options

36

37 Pharmacologic treatments are frequently employed to control AR symptoms. Depending on the specific  
38 therapy and geographic region, these may be available by prescription or over the counter. The  
39 evidence for pharmacologic options for AR has been reviewed with evidence-based recommendations  
40 below. [TABLE I.C.7.b.]

41

42 **TABLE I.C.7.b. Pharmacotherapy options for the treatment of allergic rhinitis – comparison between**  
43 **2018 and 2023**

Medication	Year	# of listed studies	Aggregate grade of evidence	Policy level	Interpretation
------------	------	---------------------	-----------------------------	--------------	----------------



Oral H <sub>1</sub> antihistamines	2023	24	A	Strong recommendation	Newer-generation oral H <sub>1</sub> antihistamines are strongly recommended for AR treatment.
	2018	21	A	Strong recommendation	
Oral H <sub>2</sub> 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 <sub>1</sub> 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	

1 AR=allergic rhinitis; INCS=intranasal corticosteroids; n/a=not applicable (not considered in ICAR-Allergic Rhinitis  
2 2018 document); LTRA=leukotriene receptor antagonists; DSCG=disodium cromoglycate; IPB=ipratropium  
3 bromide; US=United States; FDA=Food and Drug Administration  
4 \*Studies included in systematic reviews were not separately listed in tables

5  
6 The section that follows includes recommendation summaries for pharmacotherapies and procedural  
7 interventions that are included in the ICAR-Allergic Rhinitis 2023 document. A standard listing of side  
8 effect and adverse effects of most AR management options may be found in **TABLE II.C.** within the full  
9 ICAR-Allergic Rhinitis 2023 document.

10  
11 **ORAL H<sub>1</sub> ANTIHISTAMINES – Aggregate grade of evidence:** A (Level 1: 19 studies, level 4: 5 studies)  
12 **Benefit:** Reduction in symptoms of AR.  
13 **Harm:** Compared to first-generation oral antihistamines, newer-generation antihistamines have fewer  
14 central nervous system and anticholinergic side effects. The side effects of first-generation  
15 antihistamines can be more pronounced in the elderly. See **TABLE II.C.** in full ICAR document.  
16 **Cost:** Inexpensive. Given their improved side effect profile, newer-generation oral antihistamines also  
17 have lower indirect costs than first generation oral H<sub>1</sub> antihistamines.

- 1 **Benefits-harm assessment:** The benefits outweigh harm for use of newer-generation H<sub>1</sub> oral  
2 antihistamines for AR.
- 3 **Value judgments:** First-generation oral antihistamines are not recommended for the treatment of AR  
4 because of their central nervous system and anticholinergic side effects.
- 5 **Policy level:** Strong recommendation for the use of newer-generation oral antihistamines for AR.
- 6 **Intervention:** Newer-generation oral antihistamines can be considered in the treatment of AR.  
7
- 8 **ORAL H<sub>2</sub> ANTIHISTAMINES – Aggregate grade of evidence:** B (Level 2: 7 studies)
- 9 **Benefit:** Decreased objective nasal resistance, and improved symptom control in 4 studies when used in  
10 combination with H<sub>1</sub> antagonists.
- 11 **Harm:** Drug-drug interaction (p450 inhibition, inhibited gastric secretion and absorption).
- 12 **Cost:** Increased cost associated with H<sub>2</sub> antagonist over H<sub>1</sub> antagonist alone.
- 13 **Benefits-harm assessment:** Unclear benefit and possible harm.
- 14 **Value judgments:** No studies evaluating efficacy of H<sub>2</sub> antihistamines in context of INCS. There were 2  
15 studies that showed no benefit for H<sub>2</sub> antagonist when used alone or as an additive to H<sub>1</sub> antagonist  
16 therapy.
- 17 **Policy level:** No recommendation. Available does not adequately address the benefit of H<sub>2</sub>  
18 antihistamines in AR.
- 19 **Intervention:** Addition of an oral H<sub>2</sub> antagonist to an oral H<sub>1</sub> antagonist may improve symptom control in  
20 AR, but data is limited.  
21
- 22 **INTRANASAL ANTIHISTAMINES – Aggregate grade of evidence:** A (Level 2: 44 studies)
- 23 **Benefit:** Rapid onset; more effective for nasal congestion than oral antihistamines; more effective for  
24 ocular symptoms than INCS; consistent reduction in symptoms and improvement in QOL in randomized  
25 controlled trials compared to placebo.
- 26 **Harm:** Patient tolerance, typically related to taste aversion; less effective for congestion than INCS. See  
27 **TABLE II.C.** in full ICAR document.
- 28 **Cost:** Low-to-moderate financial burden; available as prescription or nonprescription product.
- 29 **Benefits-harm assessment:** Preponderance of benefit over harm. Intranasal antihistamine as  
30 monotherapy is consistently more effective than placebo. Most studies show intranasal antihistamines  
31 superior to INCS for sneezing, itching, rhinorrhea, and ocular symptoms. Adverse effects are minor and  
32 infrequent. Generic prescription and over-the-counter formulations now available.
- 33 **Value judgments:** Extensive high-level evidence comparing intranasal antihistamine monotherapy to  
34 active and placebo controls demonstrates overall effectiveness and safety.
- 35 **Policy level:** Strong recommendation.
- 36 **Intervention:** Intranasal antihistamines may be used as first- or second-line therapy in the treatment of  
37 AR.  
38
- 39 **ORAL CORTICOSTEROIDS – Aggregate grade of evidence:** B (Level 2: 6 studies, level 3: 1 study, level 4: 3  
40 studies)
- 41 **Benefit:** Oral corticosteroids can attenuate symptoms of AR and ongoing allergen induced inflammation.
- 42 **Harm:** Oral corticosteroids have multiple potential adverse effects, including hypothalamic-pituitary axis  
43 suppression. Prolonged use may lead to growth retardation in pediatric populations. See **TABLE II.C.** in  
44 full ICAR document.
- 45 **Cost:** Low.
- 46 **Benefits-harm assessment:** The risks of oral corticosteroids outweigh the benefits, given similar  
47 symptomatic improvement observed with the use of safer INCS.

1 **Value judgments:** In the presence of effective symptom control using INCS, the risk of adverse effects  
2 from using oral corticosteroids for AR outweighs potential benefits.

3 **Policy level:** Strong recommendation against routine use.

4 **Intervention:** Although not recommended for routine use in AR, certain clinical scenarios may warrant  
5 the use of short courses of systemic corticosteroids, following a discussion of the risks and benefits with  
6 the patient. For example, oral steroids could be considered in select patients with significant nasal  
7 obstruction that precludes adequate penetration of intranasal agents (corticosteroids or  
8 antihistamines). In these cases, a short course of systemic corticosteroids may improve congestion and  
9 facilitate access of topical medications. No evidence supports this suggestion, and thus careful clinical  
10 judgment and risk discussion are advocated.

11  
12 **INTRANASAL CORTICOSTEROID SPRAYS – Aggregate grade of evidence:** A (Level 1: 18 studies, level 2:  
13 29 studies, level 3: 3 studies)

14 **Benefit:** INCS sprays are effective in reducing nasal and ocular symptoms of AR. Studies have  
15 demonstrated superior efficacy compared to oral antihistamines and leukotriene receptor antagonists  
16 (LTRAs).

17 **Harm:** INCS sprays have known undesirable local adverse effects such as epistaxis with some increased  
18 frequency compared to placebo in prolonged administration studies. There are no apparent negative  
19 effects on the hypothalamic-pituitary axis. There might be some negative effects on short-term growth  
20 in children, but it is unclear whether these effects translate into long-term growth suppression. See

21 **TABLE II.C.** in full ICAR document.

22 **Cost:** Low.

23 **Benefits-harm assessment:** The benefits of using INCS sprays outweigh the risks when used to treat  
24 seasonal or perennial AR.

25 **Value judgments:** INCS sprays are first line therapy for the treatment of AR by virtue of their superior  
26 efficacy in controlling nasal symptoms. Subjects with seasonal AR should start prophylactic treatment  
27 with INCS sprays several days before the pollen season with an evaluation of the patient's response a  
28 few weeks after initiation, including a nasal exam to evaluate for local irritation or mechanical trauma.  
29 Children receiving INCS sprays should be on the lowest effective dose to avoid negative growth effects.

30 **Policy level:** Strong recommendation.

31 **Intervention:** The demonstrated efficacy of INCS sprays, as well as their superiority over other agents,  
32 make them first line therapy in the treatment of AR.

33  
34 **INTRANASAL STEROIDS: NON-TRADITIONAL APPLICATION – Aggregate grade of evidence:** B (Level 2: 4  
35 studies, level 3: 1 study)

36 **Benefit:** Nebulized steroids or those used via irrigation show some benefit in the treatment of AR in  
37 limited studies. Furthermore, steroids inhaled or exhaled through the nose in patients with asthma and  
38 rhinitis also show some benefit for rhinitis. Nasal steroid drops are not approved for treatment of  
39 rhinitis but are used in certain countries.

40 **Harm:** Nasal steroid drops have significant systemic side effects. See **TABLE II.C.** in full ICAR document.

41 **Cost:** Low.

42 **Benefits-harm assessment:** The risks of using corticosteroid nasal drops for AR outweigh the benefits.  
43 Limited evidence suggests that nasal steroid irrigations for rhinitis lead to significant improvement of  
44 symptoms. Scarce evidence does not support routine recommendation for this route of therapy.

45 **Value judgments:** In the presence of effective symptom control using traditional spray administration  
46 for INCS, there is no solid data to support other routes of administration.

47 **Policy level:** Recommendation against routine use.

1 **Intervention:** There is some evidence that inhaled steroids, when exhaled through the nose might  
 2 improve AR symptoms. Similar benefit is seen when steroids are inhaled by first passing through the  
 3 nose. These routes might be useful in patients with both rhinitis and asthma.

4  
 5 **INJECTABLE CORTICOSTEROIDS – Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 11 studies,  
 6 level 4: 2 studies)

7 **Benefit:** Injectable corticosteroids improved symptoms of AR in clinical studies.

8 **Harm:** Injectable corticosteroids have known undesirable adverse effects on the hypothalamic-pituitary  
 9 axis, growth, osteoporosis, glycemic control, and other systemic adverse effects, for varied periods of  
 10 time after injection. Intraturbinate corticosteroids have a small but potentially serious risk of ocular side  
 11 effects including decline or loss of vision. See **TABLE II.C.** in full ICAR document.

12 **Cost:** Low.

13 **Benefits-harm assessment:** In routine management of AR, the risk of serious adverse effects outweighs  
 14 the demonstrated clinical benefit.

15 **Value judgments:** Injectable corticosteroids are effective for the treatment of AR. However, given the  
 16 risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of  
 17 effective alternatives (e.g., INCS sprays), injectable corticosteroids are not recommended for the routine  
 18 treatment of AR.

19 **Policy level:** Recommendation against.

20 **Intervention:** None.

21

22 **ORAL DECONGESTANTS – Aggregate grade of evidence:** A (Level 2: 12 studies)

23 **Benefit:** Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.

24 **Harm:** Oral decongestants have known undesirable adverse effects. See **TABLE II.C.** in full ICAR  
 25 document.

26 **Cost:** Low.

27 **Benefits-harm assessment:** Balance of benefit and harm for pseudoephedrine. Possible harm for  
 28 phenylephrine.

29 **Value judgments:** Little evidence for benefit in controlling symptoms other than nasal congestion.

30 **Policy level:** Strong recommendation against for routine use in AR. In certain cases, combination therapy  
 31 with an oral antihistamine may be beneficial to alleviate severe nasal congestion in short courses.

32 **Intervention:** Although not recommended for routine use in AR, pseudoephedrine can be effective in  
 33 reducing nasal congestion in patients with AR; however, it should only be used as short-term/rescue  
 34 therapy after a discussion of the risks and benefits with the patient (comorbidities) and consideration of  
 35 alternative intranasal therapy options.

36

37 **INTRANASAL DECONGESTANTS – Aggregate grade of evidence:** B (Level 2: 10 studies, level 3: 2 studies)  
 38 Limitation -- only 3 studies included subjects with AR.

39 **Benefit:** Reduction in symptoms of nasal congestion/blockage and corresponding objective markers with  
 40 intranasal decongestants compared to placebo.

41 **Harm:** Side effects include nasal discomfort/burning, dependency, dryness, hypertension, anxiety, and  
 42 tremors. Potential for rebound congestion with long-term use. See **TABLE II.C.** in full ICAR document.

43 **Cost:** Low.

44 **Benefits-harm assessment:** Harm likely outweighs benefit if used long-term, with adverse effects  
 45 appearing as early as 3 days.

46 **Value judgments:** Intranasal decongestants can be helpful for short-term relief of nasal congestion.

47 **Policy level:** Option for short-term use.

1 **Intervention:** Intranasal decongestants can provide effective short-term relief of nasal congestion in  
 2 patients with AR during an acute flare but recommend against chronic use due to risk of rhinitis  
 3 medicamentosa.

4  
 5 **LEUKOTRIENE RECEPTOR ANTAGONIST (LTRA) – Aggregate grade of evidence:** A (Level 1: 13 studies;  
 6 level 2: 21 studies)

7 **Benefit:** Consistent reduction in symptoms and improvement in QOL compared to placebo.

8 **Harm:** United States Food and Drug Administration (FDA) boxed warning regarding neuropsychiatric side  
 9 effects, including suicidal ideation. Consistently inferior compared to INCS at symptom reduction and  
 10 improvement in QOL. Equivalent or inferior effect compared to oral antihistamines in symptom  
 11 reduction and improvement of QOL. See **TABLE II.C.** in full ICAR document.

12 **Cost:** Moderate.

13 **Benefits-harm assessment:** LTRAs are effective as monotherapy compared to placebo. However, there  
 14 is a consistently inferior or equivalent effect to other, less expensive agents used as monotherapy. The  
 15 FDA boxed warning is associated with LTRAs as well.

16 **Value judgments:** LTRAs are more effective than placebo at controlling both asthma and AR symptoms  
 17 in patients with both conditions. However, in the light of significant concerns over its safety profile and  
 18 the availability of effective alternatives such as INCS and oral antihistamines, evidence is lacking to  
 19 recommend LTRAs as monotherapy in the management of AR.

20 **Policy level:** Recommendation against LTRAs as first-line monotherapy for patients with AR. Option for  
 21 LTRA as monotherapy in patients with contraindications to other preferred treatments.

22 **Intervention:** LTRAs should not be used as monotherapy in the treatment of AR but can be considered in  
 23 select situations where patients have contraindications to alternative treatments.

24

25 **INTRANASAL CROMOLYN – Aggregate grade of evidence:** A (Level 2: 25 studies)

26 **Benefit:** Disodium cromoglycate (DSCG) is effective in reducing sneezing, rhinorrhea, and nasal  
 27 congestion.

28 **Harm:** Rare local side effects.

29 **Cost:** Low.

30 **Benefits-harm assessment:** Preponderance of mild to moderate benefit over harm. Less effective than  
 31 INCS and intranasal antihistamines.

32 **Value judgments:** DSCG is useful for preventative short-term use in adult-patients, children (2 years and  
 33 older), and pregnant patients with known exposure risks.

34 **Policy level:** Recommendation as a second-line treatment in AR.

35 **Intervention:** DSCG may be used as a second line treatment for AR in patients who fail INCS or intranasal  
 36 antihistamines, or for short-term preventative benefit prior to allergen exposures.

37

38 **INTRANASAL ANTICHOLINERGICS (IPRATROPIUM BROMIDE) – Aggregate grade of evidence:** A (Level 2:  
 39 10 studies, level 3: 2 studies)

40 **Benefit:** Reduction of rhinorrhea with topical anticholinergics.

41 **Harm:** Care should be taken to avoid overdose leading to systemic side effects. See **TABLE II.C.** in full  
 42 ICAR document.

43 **Cost:** Low.

44 **Benefits-harm assessment:** Preponderance of benefit over harm in AR patients with rhinorrhea.

45 **Value judgments:** Benefits limited to controlling rhinorrhea. Can be used as add on treatment for AR  
 46 patients with persistent rhinorrhea despite first line medical management.

47 **Policy level:** Option.

1 **Intervention:** Ipratropium bromide nasal spray may be used as an adjunct medication to INCS in AR  
2 patients with persistent rhinorrhea.

3  
4 **BIOLOGIC THERAPIES – Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 8 studies, level 3: 2  
5 studies)

6 **Benefit:** Omalizumab treatment resulted in improvement of symptoms, rescue medication and QOL as a  
7 monotherapy. Dupilumab data is less robust and needs further investigation.

8 **Harm:** Local reaction at injection site and risk of anaphylaxis.

9 **Cost:** High.

10 **Benefits-harm assessment:** Benefit outweighs harm.

11 **Value judgments:** Biologic therapies show promise as a treatment option for AR; however, no biologic  
12 therapies have been approved by the US FDA for this indication.

13 **Policy level:** Option based upon published evidence, although not currently approved for this indication.

14 **Intervention:** Monoclonal antibody (biologic) therapies are not currently approved for the treatment of  
15 AR.

16  
17 **INTRANASAL SALINE – Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 17 studies)

18 **Benefit:** Improved nasal symptoms and QOL, reduction in oral antihistamine use, and improved  
19 mucociliary clearance. Well-tolerated with excellent safety profile.

20 **Harm:** Nasal irritation, sneezing, cough, and ear fullness. See **TABLE II.C.** in full ICAR document.

21 **Cost:** Minimal.

22 **Benefits-harm assessment:** Preponderance of benefit over harm.

23 **Value judgments:** Nasal saline can and should be used as a first line treatment in patients with AR,  
24 either alone or combined with other pharmacologic treatments as evidence supports an additive effect.  
25 Hypertonic saline may be more effective in children. Data is otherwise inconclusive on optimal salinity,  
26 buffering, and frequency and volume of administration.

27 **Policy level:** Strong recommendation.

28 **Intervention:** Nasal saline is strongly recommended as part of the treatment strategy for AR.

29  
30 **PROBIOTICS – Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 5 studies)

31 **Benefit:** Improved nasal/ocular symptoms or QOL in most studies.

32 **Harm:** Mild gastrointestinal side-effects.

33 **Cost:** Low.

34 **Benefits-harm assessment:** Balance of benefit and harm.

35 **Value judgments:** Minimal harm associated with probiotics. Heterogeneity across studies makes  
36 magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific  
37 recommendation for treatment.

38 **Policy level:** Option.

39 **Intervention:** Consider adjuvant use of probiotics for patients with symptomatic seasonal or perennial  
40 AR.

41  
42 **COMBINATION ORAL ANTIHISTAMINE AND ORAL DECONGESTANT – Aggregate grade of evidence:** A  
43 (Level 2: 30 studies)

44 **Benefit:** Improved nasal congestion and total symptom scores with combination oral antihistamine-oral  
45 decongestants.

46 **Harm:** Oral decongestants can cause adverse events in patients with cardiac conditions, hypertension,  
47 or benign prostatic hypertrophy and are not indicated in patients under age 12 or pregnant patients.

1 Oral antihistamines are not indicated in patients under two years of age, and caution should be  
 2 exercised in patients aged 2-5 years old. See **TABLE II.C.** in full ICAR document.

3 **Cost:** Low.

4 **Benefits-harm assessment:** Combination oral antihistamine-oral decongestant medications carry  
 5 relatively low risks of adverse events when used as needed for episodic AR symptoms in well-selected  
 6 patients. Risk may be higher if used daily or in patients with certain comorbidities. There is not a  
 7 preponderance of benefit or harm when used appropriately as a treatment option.

8 **Value judgments:** Oral antihistamine-oral decongestants may be an effective option for acute AR  
 9 symptoms such as nasal congestion and sneezing. Caution should be exercised with more long-term use.

10 **Policy level:** Option for episodic or acute AR symptoms.

11 **Intervention:** Combination oral antihistamine-oral decongestant medications may provide effective  
 12 relief of nasal symptoms of AR on an episodic basis. Caution should be exercised in chronic or long-term  
 13 use as the adverse effect profile of oral decongestants is greater for chronic use.

14

15 **COMBINATION ORAL ANTIHISTAMINE AND INTRANASAL CORTICOSTEROID – Aggregate grade of**  
 16 **evidence:** A (Level 1: 1 study, level 2: 12 studies)

17 **Benefit:** The addition of oral antihistamine to INCS has not consistently demonstrated a benefit over  
 18 INCS alone for symptoms of AR.

19 **Harm:** Oral antihistamines generally not recommended in patients under 2 years old, and attention to  
 20 dosing is necessary in patients 2-12 years old. See **TABLE II.C.** in full ICAR document.

21 **Cost:** Low.

22 **Benefits-harm assessment:** Benefit likely outweighs potential harms in patients with significant nasal  
 23 congestion symptoms in addition to symptoms such as sneezing and ocular itching. Addition of an INCS  
 24 may be limited benefit versus potential harm in patients without significant nasal congestion symptoms.

25 **Value judgments:** Adding oral antihistamine to INCS spray has not been demonstrated to confer  
 26 additional benefit over INCS spray alone. INCS improves congestion with or without oral antihistamine.

27 **Policy level:** Option.

28 **Intervention:** Current evidence is mixed to support antihistamines as an additive therapy to INCS, as  
 29 several randomized trials have not demonstrated a benefit over INCS alone for symptoms of AR.

30

31 **COMBINATION ORAL ANTIHISTAMINE AND LEUKOTRIENE RECEPTOR ANTAGONIST – Aggregate grade**  
 32 **of evidence:** A (Level 1: 4 studies, level 2: 13 studies)

33 **Benefit:** Combination LTRA and oral antihistamine were superior in symptom reduction and QOL  
 34 improvement compared to placebo, and to either agent as monotherapy.

35 **Harm:** FDA boxed warning due to risks of mental health side effects limiting use for AR. See **TABLE II.C.**  
 36 in full ICAR document.

37 **Cost:** Generic montelukast added to generic loratadine or cetirizine is more expensive per month than  
 38 generic fluticasone furoate nasal sprays, according to National Average Drug Acquisition Cost data  
 39 provided by the Centers for Medicare and Medicaid Services.

40 **Benefits-harm assessment:** Combination LTRA and oral antihistamine is superior to placebo, and  
 41 superior to either agent as monotherapy. However, there is an inferior effect versus INCS, which is also  
 42 less costly. In addition, there is a boxed warning associated with montelukast.

43 **Value judgments:** Combination therapy of LTRA and oral antihistamines is effective, but in light of  
 44 concerns over the safety profile of montelukast, and the availability of effective alternatives such as  
 45 INCS, evidence is lacking to recommend combination therapy in the management of AR.

46 **Policy level:** Recommendation against as first line therapy.



1 **Intervention:** Combination LTRA and oral antihistamines should not be used as first line therapy for AR  
 2 but can be considered in patients with contraindications to other alternatives. This combination should  
 3 be used judiciously after carefully weighing potential risks and benefits.

4  
 5 **COMBINATION INTRANASAL CORTICOSTEROID AND INTRANASAL ANTIHISTAMINE – Aggregate grade**  
 6 **of evidence:** A (Level 1: 2 studies, level 2: 18 studies, level 4: 3 studies)

7 **Benefit:** Rapid onset; more effective for relief of multiple symptoms than either INCS or intranasal  
 8 antihistamine alone.

9 **Harm:** Patient tolerance, especially due to taste. See **TABLE II.C.** in full ICAR document.

10 **Cost:** Moderate financial burden for combined formulation. Concurrent use of individual intranasal  
 11 antihistamine and corticosteroid sprays is likely a more economical option.

12 **Benefits-harm assessment:** Preponderance of benefit over harm. Combination therapy with intranasal  
 13 antihistamine and INCS is consistently more effective than placebo or monotherapy. Low risk of non-  
 14 serious adverse effects.

15 **Value judgments:** High-level evidence demonstrates that combination spray therapy with INCS plus  
 16 intranasal antihistamine is more effective than monotherapy or placebo, as well as more effective than  
 17 combination of INCS plus oral antihistamine. The increased financial cost and need for prescription limit  
 18 the value of combination therapy as a routine first-line treatment for AR. When a combined formulation  
 19 is financially prohibitive, the concurrent use of two separate formulations (antihistamine and  
 20 corticosteroid) is an alternative option.

21 **Policy level:** Strong recommendation for the treatment of AR when monotherapy fails to control  
 22 symptoms.

23 **Intervention:** Combination therapy with INCS and intranasal antihistamine may be used as second-line  
 24 therapy in the treatment of AR when initial monotherapy with either INCS or antihistamine does not  
 25 provide adequate control.

26  
 27 **COMBINATION INTRANASAL CORTICOSTEROID AND LEUKOTRIENE RECEPTOR ANTAGONIST –**

28 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 8 studies)

29 **Benefit:** Some studies demonstrate improvement of symptoms and QOL with combination therapy. One  
 30 meta-analysis did not show benefit with the exception of ocular itching.

31 **Harm:** Boxed warning due to risks of serious neuropsychiatric events for LTRA limiting use for AR. See  
 32 **TABLE II.C.** in full ICAR document.

33 **Cost:** Low.

34 **Benefits-harm assessment:** Boxed warning for AR limits use. If comorbid asthma and AR, treatment is an  
 35 option with consideration of mental health risks.

36 **Value judgments:** Possibly useful for symptom control, especially in patients with comorbid asthma,  
 37 however, boxed warning limits use in AR without asthma.

38 **Policy level:** Option as combination therapy if co-morbid asthma present and mental health risks are  
 39 considered. Not recommended for AR alone.

40 **Intervention:** Consider use in patients with AR and asthma, after weighing therapeutic benefits against  
 41 risks of mental health adverse effects.

42  
 43 **COMBINATION INTRANASAL CORTICOSTEROID AND INTRANASAL DECONGESTANT – Aggregate grade**  
 44 **of evidence:** B (Level 1: 1 study, level 2: 5 studies, level 3: 1 study)

45 **Benefit:** Some evidence in randomized studies of benefit from addition of intranasal decongestant to  
 46 INCS therapy in refractory AR patients. The evidence regarding the magnitude of effect is unclear, and a  
 47 meta-analysis that tried to estimate this effect was significantly limited by study heterogeneity and low  
 48 sample size (2 trials).

- 1 **Harm:** See **TABLE II.C.** in full ICAR document.
- 2 **Cost:** Low.
- 3 **Benefits-harm assessment:** Balance of benefit and harm with current evidence base.
- 4 **Value judgments:** While combination therapy of intranasal decongestant and INCS is superior to INCS  
5 therapy alone with low risk of tachyphylaxis in patients with refractory AR, the magnitude of effect is  
6 still unclear. There may be a role in patients with AR refractory to INCS and intranasal antihistamine  
7 combination therapy prior to consideration of surgery or in patients uninterested in surgery.
- 8 **Policy level:** Option.
- 9 **Intervention:** Short-term combination therapy with INCS and intranasal decongestant may be  
10 considered in patients with AR refractory to combination therapy with INCS and intranasal antihistamine  
11 prior to consideration of inferior turbinate reduction or in patients declining surgery.
- 12
- 13 **COMBINATION INTRANASAL CORTICOSTEROID AND INTRANASAL IPRATROPIUM BROMIDE (IPB) –**
- 14 **Aggregate grade of evidence:** Unable to determine based on one study. (Level 2: 1 study)
- 15 **Benefit:** Reduction of rhinorrhea in INCS-treatment refractory AR.
- 16 **Harm:** Usually, no systemic anticholinergic activity if administered intranasally in the recommended  
17 doses. See **TABLE II.C.** in full ICAR document.
- 18 **Cost:** Low.
- 19 **Benefits-harm assessment:** Benefit for combined INCS and IPB therapy in patients with treatment  
20 refractory AR and the main symptom of rhinorrhea.
- 21 **Value judgments:** No evidence for benefits in controlling symptoms other than rhinorrhea. Evidence is  
22 limited, but results are encouraging for patients with persistent rhinorrhea.
- 23 **Policy level:** Option.
- 24 **Intervention:** Combining IPB with beclomethasone dipropionate can be more effective than either agent  
25 alone for the treatment of rhinorrhea in refractory AR in children and adults. Although multiple  
26 consensus guidelines have recommended, and there is evidence to support this recommendation, it is  
27 important to note that there has only been one RCT to study the efficacy of combined INCS and IPB  
28 therapy compared to either agent alone, and this study was performed in a combined population of  
29 patients with AR and non-allergic rhinitis.
- 30
- 31 **ACUPUNCTURE – Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 1 study)
- 32 **Benefit:** Improvement of QOL and symptoms. Fairly well tolerated with no systemic adverse effects.
- 33 **Harm:** Needle sticks associated with minor adverse events including skin irritation, erythema,  
34 subcutaneous hemorrhage, pruritus, numbness, fainting, and headache. Electroacupuncture can  
35 interfere with pacemakers and other implantable devices. Caution is recommended in pregnant patients  
36 as some acupoints can theoretically induce labor. Need for multiple treatments and possible on-going  
37 treatment to maintain any benefit gained. Relatively long treatment period.
- 38 **Cost:** Moderate-high. Cost and time associated with acupuncture treatment; multiple treatments  
39 required.
- 40 **Benefits-harm assessment:** Balance of benefit and harm.
- 41 **Value judgments:** The evidence is generally supportive of acupuncture. Acupuncture may be  
42 appropriate for some patients to consider as an adjunct/alternative therapy.
- 43 **Policy level:** Option.
- 44 **Intervention:** In patients who are interested in avoiding medications, acupuncture can be suggested as a  
45 possible therapeutic adjunct.
- 46
- 47 **HONEY – Aggregate grade of evidence:** D (Level 2: 3 studies, conflicting evidence)

- 1 **Benefit:** Unclear as studies have shown differing results and include different preparations of honey in  
 2 the trials. Local honey may be able to modulate symptoms and decrease need for antihistamines.
- 3 **Harm:** Potential compliance issues with patients not tolerating the level of sweetness. Potential risk of  
 4 allergic reaction and rarely anaphylaxis. Caution should be exercised in in pre-diabetics and diabetics for  
 5 concern of elevated blood glucose levels.
- 6 **Cost:** Cost of honey and associated healthcare costs with increased consumption.
- 7 **Benefits-harm assessment:** Balance of benefit and harm.
- 8 **Value judgments:** More studies are required before honey intake can be widely recommended.
- 9 **Policy level:** No recommendation.
- 10 **Intervention:** None.
- 11
- 12 **HERBAL THERAPIES – Aggregate grade of evidence:** Uncertain.
- 13 **Benefit:** Unclear, but some herbs may be able to provide symptomatic relief.
- 14 **Harm:** Some herbs are associated with mild side effects. Also, the safety, quality and standardization of  
 15 herbal remedies and supplements are unclear.
- 16 **Cost:** Cost of herbal supplements.
- 17 **Benefits-harm assessment:** Unknown.
- 18 **Value judgments:** There is a lack of sufficient evidence to recommend the use of herbal supplements in  
 19 AR.
- 20 **Policy level:** No recommendation.
- 21 **Intervention:** None.
- 22
- 23 **SEPTOPLASTY/SEPTORHINOPLASTY – Aggregate grade of evidence:** C (Level 3: 1 study, level 4: 3  
 24 studies, level 5: 11 studies)
- 25 **Benefit:** Improved postoperative symptoms and nasal airway.
- 26 **Harm:** Risk of complications (e.g., septal hematoma or perforation, nasal dryness, cerebrospinal fluid  
 27 leak, epistaxis, unfavorable aesthetic change); persistent obstruction.
- 28 **Cost:** Surgical/procedural costs, time off from work.
- 29 **Benefits-harm assessment:** Potential benefit must be weighed against low risk of harm and cost of  
 30 procedure.
- 31 **Value judgments:** Properly selected patients with septal deviation impacting their nasal patency can  
 32 experience improved nasal obstruction symptoms.
- 33 **Policy level:** Option for those with obstructive septal deviation.
- 34 **Intervention:** Septoplasty/septorhinoplasty may be considered in AR patients that have failed medical  
 35 management and who have anatomic, obstructive features that may benefit from this intervention.
- 36
- 37 **INFERIOR TURBINATE (IT) SURGERY – Aggregate grade of evidence:** B (Level 1: 4 studies, level 2: 13  
 38 studies, level 3: 18 studies, level 4: 50 studies)
- 39 **Benefit:** Improvement in rhinitis symptoms including nasal breathing, congestion, sneezing, and itching.  
 40 Improved nasal cavity area via objective measures, as well as increased QOL via subjective measures.
- 41 **Harm:** Risk of complications (e.g., swelling, crusting, empty nose syndrome, epistaxis).
- 42 **Cost:** Surgical/procedural costs, potential time off from work.
- 43 **Benefits-harm assessment:** Potential benefit outweighs low risk of harm.
- 44 **Value judgments:** Current evidence suggests that patients with AR who suffer from IT hypertrophy will  
 45 likely experience improvement in symptoms, nasal patency, and QOL.
- 46 **Policy level:** Recommendation in patients with medically refractory nasal obstruction.
- 47 **Intervention:** In AR patients with IT hypertrophy that have failed medical management, IT reduction is a  
 48 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	

1 SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; n/a=not applicable (not considered in ICAR-  
2 Allergic Rhinitis 2018 document); ICAR=International Consensus Statement on Allergy and Rhinology; AR=allergic  
3 rhinitis; ILIT=intralymphatic immunotherapy  
4

5 **CONVENTIONAL SUBCUTANEOUS IMMUNOTHERAPY (SCIT) – Aggregate grade of evidence:** A (Level 1:  
6 2 studies, level 2: 46 studies, level 3: 29 studies)

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

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

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

15 **Benefits-harm assessment:** For patients with symptoms lasting longer than a few weeks per year and  
16 for those who cannot obtain adequate relief with symptomatic treatment or who prefer an  
17 immunomodulation option, benefits of SCIT outweigh harm. The potential benefit of secondary disease-  
18 modifying effects, especially in children and adolescents, should be considered.

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

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

9 Strong recommendation for SCIT over no therapy for the treatment of AR.  
10 Option for SCIT over sublingual immunotherapy (SLIT) for the treatment of AR.

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

15

16 **RUSH SUBCUTANEOUS IMMUNOTHERAPY – Aggregate grade of evidence:** B (Level 2: 12 studies, level  
17 3: 4 studies, level 4: 4 studies)

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

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

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

26 **Benefits-harm assessment:** Balance of benefit and harm.

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

29 **Policy level:** Option.

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

34

35 **CLUSTER SUBCUTANEOUS IMMUNOTHERAPY – Aggregate grade of evidence:** B (Level 1: 1 study, level  
36 2: 12 studies, level 4: 2 studies)

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

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

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

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

1 **Value judgments:** Careful patient selection and shared decision making would reduce risks.  
 2 Heterogeneity of protocols, extract types and dosing across studies makes risk quantification difficult.  
 3 **Policy level:** Option.  
 4 **Intervention:** Cluster SCIT can be safely implemented in clinical practice and offered to those patients  
 5 eligible for SCIT that may prefer this protocol compared to conventional build-up protocols due to  
 6 convenience. Premedication should be strongly considered.

7  
 8 **SUBLINGUAL IMMUNOTHERAPY (SLIT): GENERAL CONSIDERATIONS – Aggregate grade of evidence:** A  
 9 (Level 1: 17 studies, level 2: 12 studies, level 4: 1 study)

10 Due to heterogeneity of SLIT study reporting, it is difficult to separate out overall vs aqueous SLIT vs  
 11 tablet SLIT.

12 **Benefit:** SLIT improves patient symptom scores, even as add-on treatment with rescue medication. SLIT  
 13 reduces medication use. The effect of SLIT lasts for at least 2 years after a 3-year course of therapy. In  
 14 AR patients, there is some evidence that SLIT reduces the frequency of onset of asthma and the  
 15 development of new sensitizations up to 2 years after treatment termination. Benefit is generally higher  
 16 than with single-drug pharmacotherapy, however, it may be less than with SCIT (low quality evidence).

17 **Harm:** Minimal harm with very frequent, but mild local adverse events, and very rare systemic adverse  
 18 events. SLIT seems to be safer than SCIT.

19 **Cost:** Intermediate. SLIT becomes cost-effective compared to pharmacotherapy after several years of  
 20 administration. Total costs seem to be lower than with SCIT.

21 **Benefits-harm assessment:** Benefit of treatment over placebo is small but tangible and occurs in  
 22 addition to improvement with medication. There is a lasting effect at least 2 years off treatment.  
 23 Minimal harm with SLIT, greater risk for SCIT.

24 **Value judgments:** SLIT improved patient symptoms with low risk for adverse events.

25 **Policy level:** Strong recommendation for use of SLIT grass pollen tablet, ragweed tablet, HDM tablet,  
 26 and tree pollen aqueous solution. Recommendation for SLIT for *Alternaria* allergy. Option for SLIT for  
 27 animal allergy. Recommendation for dual-therapy SLIT in bi-allergic patients.

28 **Intervention:** Recommend tablet or aqueous SLIT in patients (adults and children) with seasonal and/or  
 29 perennial AR who wish to reduce their symptoms and medication use, as well as possibly reduce the  
 30 propensity to develop asthma or new allergen sensitizations.

31  
 32 **SUBLINGUAL IMMUNOTHERAPY TABLETS – Aggregate grade of evidence:** A (Level 1: 11 studies, level 2:  
 33 4 studies)

34 **Benefit:** Improvement of symptoms, rescue medication and QOL.

35 **Harm:** Local reaction at oral administration site and low risk of anaphylaxis.

36 **Cost:** Intermediate. More expensive than standard pharmacotherapy, but persistent benefit may result  
 37 in cost-saving in the long-term.

38 **Benefits-harm assessment:** Benefit outweighs harm.

39 **Value judgments:** Useful for patients with severe or refractory symptoms of AR.

40 **Policy level:** Strong recommendation.

41 **Intervention:** SLIT tablets are recommended for patients with severe or refractory AR. Epinephrine auto-  
 42 injector is recommended in the FDA labeling for approved tablets due to the rare but serious risk of  
 43 anaphylaxis. Tablets for select antigens are available in various countries.

44  
 45 **AQUEOUS SUBLINGUAL IMMUNOTHERAPY – Aggregate grade of evidence:** B (Level 1: 7 studies, level  
 46 2: 5 studies, level 4: 1 study)

- 1 **Benefit:** Aqueous SLIT improves patient symptom scores and decreases rescue medication use. There is  
 2 some indication of less benefit from aqueous versus tablet SLIT, but the lack of standardized dosing  
 3 across multiple trials does not allow for adequate comparison.
- 4 **Harm:** Common mild to moderate local adverse events. Very rare cases of systemic adverse events. No  
 5 reported cases of life-threatening reactions
- 6 **Cost:** Intermediate. More expensive than standard pharmacotherapy, but there are indications of lasting  
 7 benefit and cost-saving in the long-term.
- 8 **Benefits-harm assessment:** Appreciable benefit in patient symptoms and minimal harm.
- 9 **Value judgments:** Aqueous SLIT improves patient symptoms and rescue medication usage with minimal  
 10 risk of serious adverse events but common local mild adverse events. Single allergen therapy has been  
 11 extensively tested. Multiallergen AIT requires future studies to validate its use.
- 12 **Policy level:** Recommendation.
- 13 **Intervention:** High-dose aqueous SLIT is recommended for those patients who wish to reduce their  
 14 symptoms and rescue medication use.
- 15
- 16 **EPICUTANEOUS/TRANSCUTANEOUS IMMUNOTHERAPY – Aggregate grade of evidence:** B (Level 2: 5  
 17 studies)
- 18 **Benefit:** Epicutaneous AIT to grass pollen resulted in limited and variable improvement in symptoms,  
 19 medication use, and allergen provocation tests in patients with AR or conjunctivitis.
- 20 **Harm:** Epicutaneous AIT resulted in systemic and local reactions, with a relative risk of 4.65 and 2.29  
 21 respectively. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous AIT.
- 22 **Cost:** Unknown.
- 23 **Benefits-harm assessment:** There is limited and inconsistent data on benefit of the treatment, while  
 24 there is a concerning rate of adverse effects. Three out of 4 studies on this topic were published by the  
 25 same investigators from 2009-2015.
- 26 **Value judgments:** Epicutaneous AIT could offer a potential alternative to SCIT and SLIT, but further  
 27 research is needed.
- 28 **Policy level:** Recommendation against.
- 29 **Intervention:** While epicutaneous AIT may potentially have a future clinical application in the treatment  
 30 of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a  
 31 significant rate of adverse reactions. Given the above and the availability of alternative treatments,  
 32 epicutaneous AIT is not recommended at this time.
- 33
- 34 **INTRALYMPHATIC IMMUNOTHERAPY – Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 11  
 35 studies, level 4: 3 studies)
- 36 **Benefit:** Shorter treatment period, decreased number of injections, smaller amount of allergen, lower  
 37 risk of adverse events versus SCIT.
- 38 **Harm:** Local reaction at injection site and risk of anaphylaxis.
- 39 **Cost:** Cost savings due to shorter treatment duration and fewer injections. Additional cost for training  
 40 required.
- 41 **Benefits-harm assessment:** Benefit outweighs harm.
- 42 **Value judgments:** Apparent short-term favorable effect, but long-term effect is lacking.
- 43 **Policy level:** Option.
- 44 **Intervention:** More studies are essential to establish the long-term effects of ILIT.
- 45
- 46 **COMBINATION SUBCUTANEOUS IMMUNOTHERAPY AND BIOLOGICS – Aggregate grade of evidence:** B  
 47 (Level 2: 5 studies)



1 **Benefit:** Improved safety of accelerated cluster and rush SCIT protocols, with decreased symptom and  
2 rescue medication scores among a carefully selected population.

3 **Harm:** Financial cost and low risk of anaphylactic reactions to omalizumab.

4 **Cost:** Moderate to high.

5 **Benefits-harm assessment:** Preponderance of benefit over harm.

6 **Value judgments:** Combination therapy increases the safety of SCIT, with decreased systemic reactions  
7 following cluster and rush protocols. Associated treatment cost benefits must be considered. While two  
8 high-quality RCTs have demonstrated improved symptom control with combination therapy over SCIT or  
9 anti-IgE alone, not all patients will require this approach. Rather, an individualized approach to patient  
10 management must be considered, with evaluation of alternative causes for persistent symptoms, such  
11 as unidentified allergen sensitivity. Also, the studies did not compare optimal medical treatment of AR  
12 (INCS + antihistamine with allergen avoidance measures) to combination therapy versus SCIT alone. The  
13 current evidence does not support the utilization of combination therapy for all patients failing to  
14 benefit from SCIT alone.

15 **Policy level:** Option.

16 **Intervention:** Current evidence supports that anti-IgE may be beneficial as a premedication prior to  
17 induction of cluster or rush SCIT protocols, and combination therapy may be advantageous as an option  
18 for carefully selected patients with persistent symptomatic AR following AIT. However, at the time of  
19 this writing, biologic therapies are not approved by the US FDA for AR alone. An individualized approach  
20 to patient management must be considered.

### 23 I.C.8. Pediatric considerations

25 The pediatric section is a new addition for ICAR-Allergic Rhinitis 2023 and encompasses several literature  
26 reviews. AR takes a few years to develop in children. A family history of AR, atopy or asthma is  
27 important to discuss as children may be at an increased risk of developing AR or other allergic diseases.

28 The “allergic march,” described as a specific sequence of atopic disorders, should be considered in  
29 children with clinical suspicion. Diagnosis may be challenging in the pediatric population, and some  
30 diagnostic clues include chapped lips from mouth breathing, fatigue, irritability, poor appetite, and  
31 attention issues. Physical exam findings include posterior pharyngeal cobblestoning, clear drainage, and  
32 enlarged/boggy inferior turbinates, “allergic” or “adenoid” facies, the allergic salute, allergic crease,  
33 allergic shiners, or Dennie-Morgan lines. The diagnosis of AR in children should be based on both clinical  
34 history and testing. SPT is generally accepted as the preferred method of testing in children. Treatment  
35 options for children under age 2 are limited. For older children, treatment options are similar to the  
36 adult population. AIT is also an option for children with persistent symptoms. AIT may reduce the risk of  
37 development of asthma in pediatric patients with AR.

### 39 I.C.9. Associated conditions

- 1 There is evidence for the association of several comorbid conditions with AR, which are listed below.  
 2 Several additional conditions have been added since ICAR-Allergic Rhinitis 2018. [TABLE I.C.9.]

3

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

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

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

1 AR=allergic rhinitis; AIT=allergen immunotherapy; SCIT=subcutaneous immunotherapy; SLIT=sublingual  
2 immunotherapy; AFRS=allergic fungal rhinosinusitis; CCAD=central compartment atopic disease; AERD=aspirin  
3 exacerbated respiratory disease; PFAS=pollen food allergy syndrome; OSA=obstructive sleep apnea  
4 \*Studies included in systematic reviews were not separately listed in tables  
5

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

7  
8 COVID-19 (coronavirus disease 2019) case rates have changed practice strategies. AR has not been  
9 identified as a risk factor for severe COVID-19. However, there have been challenges with overlapping  
10 symptoms of AR and COVID-19. Telemedicine visits have been helpful for initial evaluation, however  
11 many diagnostic techniques for AR require face-to-face encounters. Recommendations have continued  
12 to evolve during the pandemic. Standard therapies for AR were not shown to increase the risk of severe  
13 COVID-19. Of note, anti-IgE therapy has also not increased susceptibility or severity of COVID-19  
14 infection.

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

16  
17  
18 See **FIGURE I.C.11** for summary diagnosis and management options for AR, based upon current  
19 evidence.

# ALLERGIC RHINITIS SUMMARY RECOMMENDATIONS

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

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

### I.C.12. Knowledge gaps

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

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

Major content area	Knowledge gaps and future research needs
Epidemiology and risk factors	<ul style="list-style-type: none"> <li>• Improved understanding of the incidence of AR based on geographic location</li> <li>• Evaluation of climate change effects on incidence and severity of AR</li> <li>• Improved understanding of the relationship between genetics and environmental factors in the development of AR</li> <li>• High quality longitudinal studies evaluating risk factors for development of AR</li> </ul>
Evaluation and diagnosis	<ul style="list-style-type: none"> <li>• Increased understanding of hyposmia as a symptom of AR or a marker of its severity</li> <li>• Further evaluation and validation of nasal sIgE testing for AR diagnosis</li> <li>• 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</li> <li>• Improvement of low-cost diagnostic tools</li> </ul>
Pediatrics	<ul style="list-style-type: none"> <li>• Improved treatment options for young children</li> <li>• Improved interpretation of skin testing results in young children</li> <li>• Optimizing treatment strategies for children who are polysensitized</li> <li>• Further work developing allergen immunotherapy delivery routes appropriate and safe for children</li> </ul>
Management	<ul style="list-style-type: none"> <li>• Continued investigation of combination therapy options, including topical therapies</li> <li>• Studies of comparative effectiveness and cost-effectiveness for AR treatments</li> <li>• Further work directly comparing SCIT to SLIT in large-scale RCTs</li> <li>• Standardization of rush and cluster SCIT protocols for aeroallergen immunotherapy</li> </ul>
Associated conditions	<ul style="list-style-type: none"> <li>• Improved understanding of treatment effects of AR on specific comorbid CRSwNP subtypes/endotypes</li> <li>• Continued work to determine the relationship of AR to ear disease</li> <li>• Investigation of treatment effect of AR on cough</li> </ul>
COVID-19	<ul style="list-style-type: none"> <li>• Improved understanding of the aerosolization risk during nasal endoscopy</li> <li>• Improved understanding of the risks of AR treatment, including allergen immunotherapy, during COVID infection</li> </ul>

- |  |   |
|--|---|
|  | <ul style="list-style-type: none"> <li>• A deeper understanding of the long-term effects of COVID on allergic diseases and their development</li> </ul> |
|--|---|

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

## I.D. Discussion

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

## I.E. Lay summary

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

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

### **What is allergic rhinitis?**

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

### **How common is allergic rhinitis?**

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

### **How severe is allergic rhinitis?**

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

### **How is allergic rhinitis treated?**

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

### **What disorders are associated with allergic rhinitis?**

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

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45	AAO-HNSF	American Academy of Otolaryngology-Head and Neck Surgery Foundation
46	AAP	American Academy of Pediatrics
47	AC	allergic conjunctivitis
48	ACC	allergen challenge chamber

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

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

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



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

1	TRP	transient receptor potential
2	TSLP	thymic stromal lymphopoietin
3	TSS	total symptom score
4	UK	United Kingdom
5	US	Unites States
6	VAS	visual analog scale
7	VCAM	vascular cell adhesion molecule
8	VCOS	validated clinical outcome survey
9	VD3	vitamin D
10	VDR	vitamin D receptor
11	VHI	voice handicap index
12	WAO	World Allergy Organization
13	WHO	World Health Organization
14	ZO	zonula occludens

15

16

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

18

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

26

27 **TABLE II.C. Possible side effects and adverse effects of common allergic rhinitis diagnostic modalities**  
 28 **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 <i>For high volume nasal irrigations:</i> 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

<b>Oral decongestants</b>	Irritability, anxiety, restlessness, sleep disturbance, hypertension, tachycardia, heart palpitations, drug-drug interactions, tremors <i>In young children:</i> tachycardia, seizures, loss of consciousness, death
<b>Intranasal decongestants</b>	Discomfort/burning, dependency, dryness, increased congestion, rhinitis medicamentosa, hypertension, anxiety, tremors
<b>Oral H<sub>1</sub> antihistamines</b>	Drowsiness, headache, dry mucous membranes, restlessness, anxiety, insomnia, tachyphylaxis, urinary retention
<b>Intranasal H<sub>1</sub> antihistamines</b>	Discomfort/burning, drowsiness, dizziness, epistaxis, dryness, crusting, foul taste, headache, sore throat, sneezing, nausea
<b>Intranasal ipratropium</b>	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
<b>Leukotriene antagonists</b>	Behavior/mood alterations, agitation, depression, irritability, hallucinations, tremor, suicidal thoughts and behavior <i>For zileuton:</i> hepatotoxicity
<b>Subcutaneous allergen immunotherapy</b>	Redness/swelling at injection site, large local injection site reactions, sneezing, cough, throat swelling, wheezing, chest tightness, nausea, dizziness, anaphylaxis
<b>Sublingual allergen immunotherapy</b>	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

1 \*May not include all possible risks of listed interventions

### 1 III. Introduction

2

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

15

16 When evaluating a scientific publication, it is important to critically assess the study methods and  
17 presentation of results, as these contribute to the evidence levels and ultimate recommendations for  
18 patient care. ICAR-Allergic Rhinitis 2023 aims to incorporate new high-level evidence into an updated  
19 document and utilizes this evidence, along with assessment of benefit, harm, and cost to determine  
20 recommendations for AR diagnostic and management strategies, where appropriate. ICAR-Allergic  
21 Rhinitis 2023 follows previously developed methodology that has produced multiple evidence-based  
22 reviews with recommendations (EBRR)<sup>2</sup> in the *International Forum of Allergy and Rhinology*, as well as  
23 several ICAR documents, including those covering topics of AR, rhinosinusitis, endoscopic skull base  
24 surgery, and olfaction.<sup>1,3-6</sup>

25

26 ICAR-Allergic Rhinitis 2023 was created by conducting systematic literature searches on 144 individual  
27 AR topics, by 87 primary authors and 40 additional consultant authors. Over 40 new topics have been  
28 added for this ICAR-Allergic Rhinitis update, and the number of cited references has expanded by over  
29 1400. Like previous ICAR documents, structured grading of evidence was performed, recommendations  
30 were created where appropriate, and each section underwent stepwise semi-blinded iterative review  
31 (blinded for initial peer review then un-blinded to reach consensus). Finally, a panel of editors critiqued  
32 each major content area, and the collated manuscript was reviewed by all authors. The EBRR and ICAR

1 methodology appears to be effective and robust and continues to be used regularly in evaluation of the  
2 rhinology and allergy literature.

3  
4 Throughout the ICAR-Allergic Rhinitis 2023 document, it is evident that many AR topics have grown in  
5 literature citations compared to 2018. This may be noted by a simple increase in the number of  
6 publications; however, the reader will also recognize that many topic areas contain new systematic  
7 reviews and meta-analyses (SRMA) that have been published since ICAR-Allergic Rhinitis 2018. This is an  
8 exciting development, as SRMAs represent the highest level of evidence and, when performed with  
9 robust methodology, collate the available evidence into a single report that should be easily understood  
10 by the reader. Still, while some areas of AR have very strong evidence, others are lacking in high-level  
11 evidence.

12  
13 It is important to recognize the limitations of ICAR-Allergic Rhinitis 2023. Recommendations in this  
14 document are based on the available evidence. Each recommendation is only as strong as the evidence  
15 that supports it and the population/sample included in the studies. Practicing evidence-based medicine  
16 takes into account the available evidence, along with clinical expertise and the patient's values and  
17 expectations.<sup>7</sup> ICAR-Allergic Rhinitis 2023 presents evidence-based recommendations, but it is not a  
18 manual, flowchart, or algorithm for care of an individual AR patient. The clinician should continue to  
19 evaluate and treat each AR patient individually, using an evidence-based foundation combined with  
20 clinical acumen/expertise and consideration of patient values and principles. Recommendations in ICAR-  
21 Allergic Rhinitis 2023, as in previous ICAR documents, do not define the standard of care or medical  
22 necessity, nor do they dictate the care of individual patients.

23  
24 Through the ICAR-Allergic Rhinitis 2023 process, several gaps in knowledge have been identified and  
25 may encourage further research in AR. Additionally, some evidence grades have changed since 2018,  
26 and we anticipate that we will continue to see evidence grow and evolve in the future. Ultimately,  
27 improved patient outcomes should result as we continue to evaluate the growing body of AR literature.

28  
29

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## 1 IV. Methods

### 2 IV.A. Topic development

3

4 The methods of ICAR-Allergic Rhinitis 2023 largely follow previous ICAR documents,<sup>1-3</sup> with utmost  
5 reliance on published evidence and minimal influence of expert opinion and other biases. The 2011  
6 EBRR method described by Rudmik and Smith<sup>4</sup> is the foundation of ICAR and aims to evaluate existing  
7 literature on each AR topic, grade the evidence, and provide literature-based recommendations where  
8 appropriate.

9

10 To complete ICAR-Allergic Rhinitis 2023, the subject of AR was initially divided into 144 individual topics,  
11 representing 41 additional topics compared to ICAR-Allergic Rhinitis 2018. A primary author who is a  
12 recognized expert in allergy, rhinology, or the assigned topic was assigned to evaluate each topic.

13 Authors were initially selected via online literature searches for each ICAR-Allergic Rhinitis 2023 topic.

14 Authors of high-quality publications in each topic area were invited as ICAR contributors. Other invited  
15 authors included experts in the EBRR process, experts in education on specific AR topic areas, and those  
16 with knowledge of the systematic review process. The invited primary author was able to choose a  
17 secondary/consultant author for each section if desired.

18

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

27

28 Creation of the content for each individual AR topic area began with a literature search. Authors  
29 received specific instructions to perform a systematic review of the literature for each topic area using  
30 the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) standardized  
31 guidelines.<sup>5</sup> Ovid MEDLINE® (1947-2021), EMBASE (1974-2021) and Cochrane Review databases were  
32 included. The search began by identifying any previously published systematic reviews or guidelines  
33 pertaining to the assigned topic. Since clinical recommendations are best supported by high quality

1 evidence, the search focused on identifying randomized controlled trials (RCT) and meta-analyses of  
2 RCTs to provide the highest level of evidence (LOE). Reference lists of all identified studies were  
3 examined to ensure all relevant studies were captured. If the authors felt that a non-English study  
4 should be included in the review, it was instructed that the paper be appropriately translated to  
5 minimize the risk of missing important data during the development of recommendations.<sup>5</sup>

6  
7 To optimize transparency of the evidence, all included studies in EBR and EBRR topic sections are  
8 presented in a standardized table format and the quality of each study was evaluated to receive a level  
9 based on the Oxford LOEs (level 1 to 5, **TABLE IV.A.-1**).<sup>6</sup> Adjustments were made to the LOE due the  
10 quality of each study based on accepted standards, with specific changes often highlighted in the text or  
11 evidence tables.<sup>7</sup> At the completion of the systematic review and research quality evaluation for each  
12 EBR or EBRR topic, an aggregate grade of evidence (A to D) was produced for the topic based on the  
13 guidelines from the American Academy of Pediatrics (AAP) Steering Committee on Quality Improvement  
14 and Management.<sup>8</sup> **[TABLE IV.A.-2]** For AR topics that addressed a diagnostic or therapeutic intervention  
15 and contained evidence to appropriately support formulation of a recommendation, the AAP guidelines  
16 for recommendation development were followed, thus completing the EBRR process.<sup>8</sup> **[TABLE IV.A.-3]**  
17 Each evidence-based recommendation was formulated with consideration of the aggregate grade of  
18 evidence, benefit, harm, and cost. A summary of the EBRR topic development process is provided in  
19 **Figure IV.A.**

20  
21 It is important to note that assignment of LOE for each publication is not always straightforward. In  
22 some instances, individual studies do not fit neatly into one of the Oxford LOE categories. Also, Oxford  
23 LOE grading has changed over time, adding complexity to the evidence grading when undertaking  
24 updates such as this one. This becomes even more difficult when evaluating certain documents that  
25 employ advanced systematic evidence searches to formulate guidelines, practice parameters, position  
26 papers and recommendation documents (e.g., Clinical Practice Guidelines, ICAR statements, European  
27 Position Statements on Sinusitis). In these instances, even methodological experts may disagree on  
28 evidence levels – some seeing the document as a systematic review with a high evidence level, while  
29 others would assign a lower level of evidence typical of a consensus statement, guideline, or expert  
30 opinion. Furthermore, these documents often contain multiple subsections that vary in the amount and  
31 quality of available evidence. Therefore, when these types of documents are included in individual topic  
32 areas, the assigned LOEs may differ.



1

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

8

#### 9 IV.B. Iterative review

10

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

22

#### 23 IV.C. ICAR-Allergic Rhinitis statement development

24

25 After the content of each of topic was reviewed and consensus reached amongst the initial author and  
26 two iterative reviewers, the principal editor (SKW) compiled associated topics into major content areas.  
27 The first draft of each major content area (i.e., Evaluation and Diagnosis, Pharmacotherapy,  
28 Immunotherapy, etc.) then underwent additional reviews for consistency and flow by a group of 3-5  
29 ICAR associate editors. Finally, the full draft of ICAR-Allergic Rhinitis 2023 was compiled and circulated to  
30 all authors. The final ICAR-Allergic Rhinitis 2023 manuscript was produced when all authors agreed upon  
31 the literature and final recommendations. **[FIGURE IV.C.]**

32

#### 33 IV.D. Limitations of methods and data presentation

1  
2 It is important to note that each topic author individually performed the literature search for his/her  
3 assigned topic. Therefore, search results may contain some inherent variability despite specific and  
4 detailed search instructions. Furthermore, while aiming to be as comprehensive as possible, this  
5 document may not present every study published on every topic. For certain topics, the literature is  
6 extensive and only high-quality studies or systematic reviews are listed. If the aggregate evidence on a  
7 topic reached a high evidence grade with only high-level studies, an exhaustive list of lower-level studies  
8 (or all studies ever performed) is not provided.

9  
10 **TABLE IV.A.-1 Levels of evidence<sup>6</sup>**

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 <i>n</i> -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

11 \*Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency  
12 between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very  
13 large effect size or if a significant dose-response relationship is demonstrated.

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

15  
16 **TABLE IV.A.-2 Aggregate grade of evidence<sup>8</sup>**

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

17 RCT=randomized controlled trial

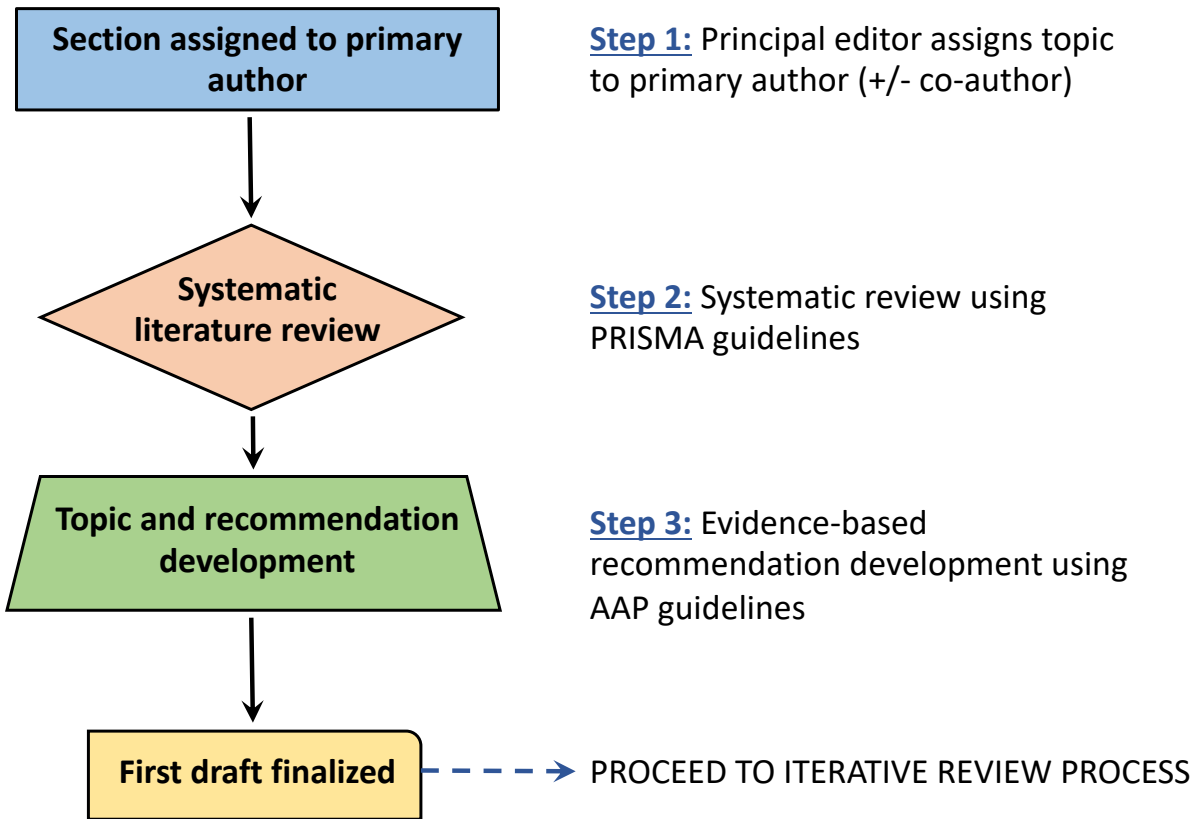
18  
19  
20 **TABLE IV.A.-3 American Academy of Pediatrics defined strategy for recommendation development<sup>8</sup>**

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

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

1 RCT=randomized controlled trial  
 2

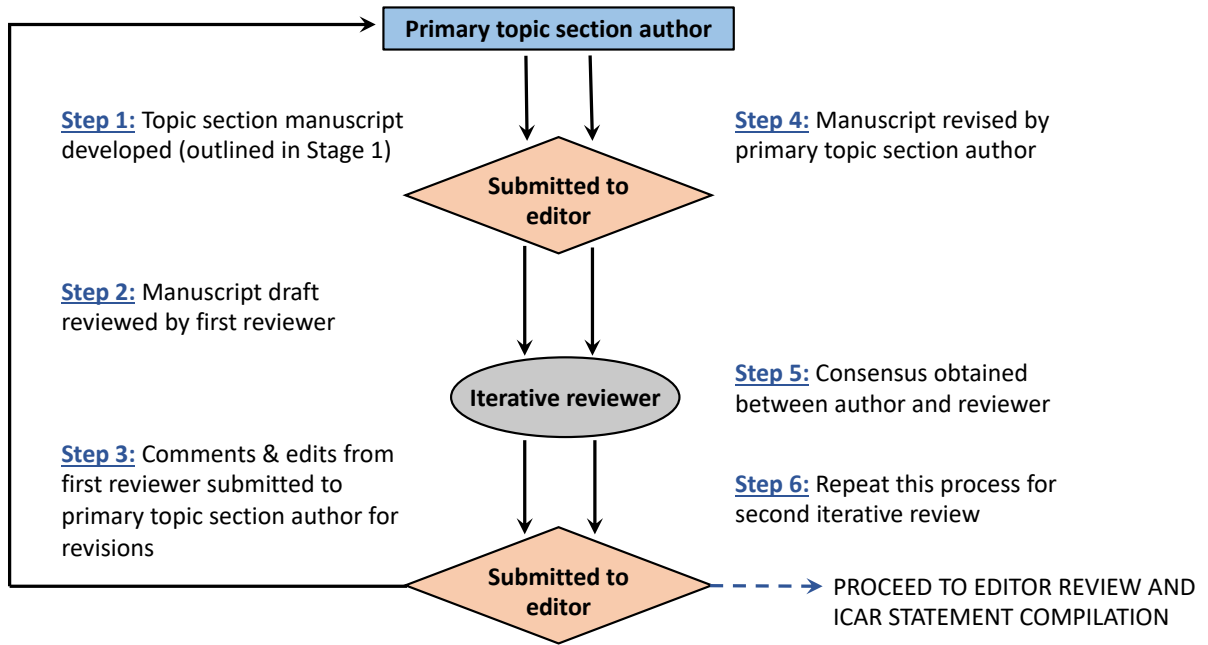
1 **FIGURE IV.A. Topic development (Stage 1)**



2  
3  
4  
5  
6  
7

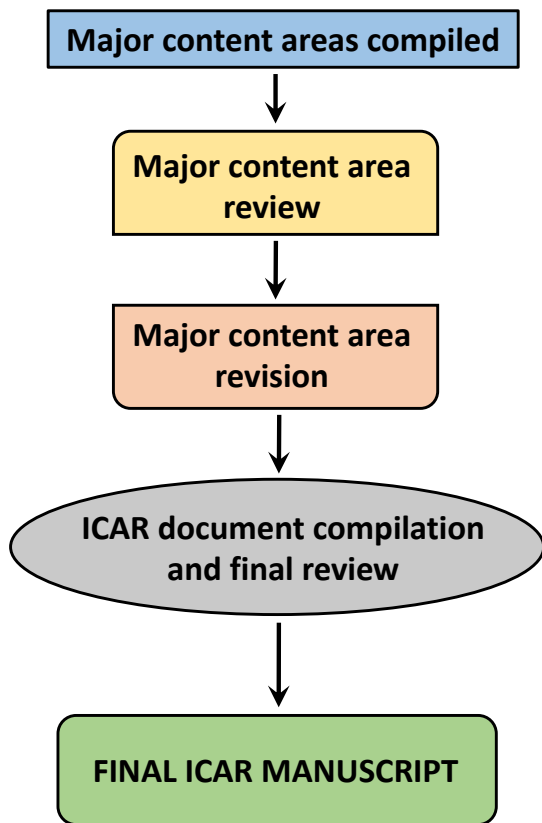
PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AAP=American Academy of Pediatrics

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



2  
3  
4

1 **Figure IV.C. ICAR-Allergic Rhinitis 2023 statement development (Stage 3)**  
 2



**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

3  
 4  
 5 ICAR=International Consensus Statement on Allergy and Rhinology

6  
 7  
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- 9

## 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.<sup>1</sup> Symptomatically, it is characterized by anterior or posterior rhinorrhea, nasal congestion/blockage, nasal pruritis, and sneezing.<sup>2</sup> AR is widely prevalent and can result in significant physical sequelae and recurrent or persistent morbidities.<sup>1</sup> Additionally, it is strongly associated with asthma, supporting the unified airway theory which postulates that upper and lower airway inflammation share common pathophysiologic mechanisms.<sup>3</sup> (*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.<sup>4</sup> 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.<sup>5</sup> 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



1 occurs during seasons with high pollen counts.<sup>1</sup> *Perennial AR* is typically associated with indoor  
2 allergens, such as house dust mites (HDM), insects, and animal dander, and has been considered to  
3 occur consistently throughout the year.<sup>1</sup> Mold exposure may occur indoors or outdoors depending on  
4 the specific environmental situation.

5  
6 Of note, the classification of seasonal vs perennial AR can potentially be in conflict. For example,  
7 seasonal AR may persist for longer periods secondary to the effects of climate change, with resultant  
8 prolonged elevations in pollen counts. Seasonal AR may also continue across multiple seasons secondary  
9 to polysensitization. Furthermore, manifestations of perennial allergy may not occur throughout the  
10 entire year. This is particularly the case for patients allergic to HDM, who may demonstrate mild or  
11 moderate/severe intermittent AR.<sup>6-9</sup>

12  
13 Because of the priming effect on the nasal mucosa introduced by low levels of pollen exposure,<sup>10-15</sup> and  
14 minimal but persistent nasal inflammation in patients with “symptom-free rhinitis”,<sup>8,16,17</sup> symptoms may  
15 not occur entirely in conjunction with allergen exposure. This may result in non-specific exacerbations.  
16 Additionally, air pollution may also contribute to variations in allergen sensitivity, resulting in fluctuating  
17 symptom severity depending on location/air quality.<sup>18</sup> (See Section VII.D. Risk Factors for Allergic Rhinitis  
18 - Pollution for additional information on this topic.)

19  
20 Subsequently, ARIA proposed a new method of classification based on the length and persistence of  
21 symptoms.<sup>19</sup> *Intermittent AR* is characterized by symptoms for less than 4 days per week or less than 4  
22 consecutive weeks. *Persistent AR* is characterized by symptoms occurring more than 4 days per week for  
23 at least 4 consecutive weeks.<sup>20</sup> Additionally, it was demonstrated that the previous categories of  
24 seasonal and perennial AR cannot be used along with the new classification of intermittent/persistent  
25 AR, as they do not represent the same stratification of the disease state. As such, intermittent AR and  
26 persistent AR are not synonymous with seasonal and perennial classifications.<sup>21-24</sup>

27  
28 The ARIA guidelines have likewise proposed another stratification of severity (mild and moderate-  
29 severe) with respect to these disabilities.<sup>7</sup> AR can result in problematic symptoms, including sleep  
30 disturbance; impairment of daily, leisure, or sport activities; impairment of school or work; or  
31 troublesome symptoms. AR is considered mild if none of the these occur. If one or more of these  
32 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.<sup>25,26</sup> Currently used taxonomy is largely organ-based and does not fully take into account the mechanisms leading to symptoms.<sup>27</sup> 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.<sup>28</sup> Interestingly, most patients hospitalized with severe asthma attack did not have a diagnosis of asthma. They did have a diagnosis of AR<sup>29</sup> and allergen-specific immunotherapy (AIT) appeared to offer protection.<sup>30</sup> 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).<sup>31</sup>

Although patients with AR and allergic asthma are by definition sensitized, many individuals with allergic sensitization do not have symptoms of allergic disease,<sup>32</sup> and in a proportion of patients with AR and allergic asthma, sensitization is not related to the presence or severity of symptoms.<sup>27</sup> Furthermore, the reliability of skin testing depends greatly on allergen extracts and methods used.<sup>33</sup> 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.<sup>31</sup> (*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.<sup>34-37</sup> However, the problem of false-positive test results remains.<sup>37</sup> 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%.<sup>38,39</sup> 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.

1

2 We can now assess sensitization in greater detail using component-resolved diagnostics (CRD), which  
3 measures sIgE to multiple allergenic molecules and may be more informative than standard tests.<sup>40-44</sup>  
4 Recent novel analyses of CRD data demonstrated that the pattern of interaction between allergen  
5 component-specific IgEs predicts asthma<sup>45</sup> and that networks of interactions between sIgE to multiple  
6 components are predictors of asthma severity across the lifespan.<sup>46</sup> These findings offer clues about  
7 mechanisms contributing to presence and severity of allergic airway disease and suggest that it may be  
8 possible to develop biomarkers/prediction tools based on CRD to help in diagnosis,<sup>45</sup> severity  
9 assessment,<sup>46</sup> prediction of future risk,<sup>41</sup> and ultimately, the prediction of response to treatment.<sup>47</sup>

10

11

## 12 V.B. Differential diagnosis

### 13 V.B.1. Drug induced rhinitis

14

15 Rhinitis secondary to systemic medications can be classified into local inflammatory, neurogenic, and  
16 idiopathic types.<sup>48-50</sup> The local inflammatory type occurs when usage of a drug causes a direct change in  
17 inflammatory mediators within the nasal mucosa. The neurogenic type occurs after use of a drug that  
18 systemically modulates neural stimulation, leading to downstream changes in the nasal mucosa. The  
19 idiopathic classification is applied when a well-defined mechanism has not been elucidated. Rhinitis  
20 medicamentosa and hormone-induced rhinitis are discussed in later sections. [TABLE V.B.1.]

21

22 **Local inflammatory type.** Systemic ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) in  
23 specific patients can cause respiratory symptoms and may be associated with nasal polyposis and  
24 asthma due to abnormal arachidonic acid metabolism.<sup>51</sup> NSAIDs inhibit cyclooxygenase (COX)-1, leading  
25 to decreased prostaglandin (PG) E<sub>2</sub> and increased leukotriene production due to an imbalance towards  
26 the lipoxygenase pathway. Reduction in PGE<sub>2</sub>, and increased leukotriene C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> production  
27 contributes to eosinophilic and mast cell inflammation within the upper and lower respiratory  
28 tracts.<sup>48,52-54</sup>

29

30 **Neurogenic type.** Neurogenic-type non-allergic rhinitis is caused by drug-induced modulation of the  
31 autonomic nervous system. Antihypertensives and vasodilators are among the many classes of drugs  
32 that cause neurogenic drug-induced non-allergic rhinitis. Other nonspecific drugs, such as psychotropics  
33 and immunosuppressants, have unknown direct mechanisms and are categorized as idiopathic type, but

1 can also cause neuromodulatory effects. Modulation of the autonomic nervous system leads to  
2 downstream changes in the nasal mucosa, blood vessels, and secretory glands.<sup>55</sup>

3

4 ***Alpha- and beta-adrenergic modulators.*** Alpha and  $\beta$ -adrenergic receptor modulators are indicated for  
5 various cardiovascular and respiratory diseases. The nasal mucosa is replete with sympathetic and  
6 parasympathetic end-units that influence nasal physiology during systemic drug use. Alpha and  $\beta$ -  
7 adrenergic antagonists, and presynaptic  $\alpha$ -agonists cause decreased sympathetic tone and unopposed  
8 parasympathetic stimulation producing mucosal engorgement, nasal congestion, and rhinorrhea.<sup>56-58</sup>

9

10 ***Phosphodiesterase inhibitors.*** Phosphodiesterase (PDE) inhibitors prevent enzymatic breakdown of  
11 cyclic nucleotides. This inhibition has diverse effects including smooth muscle relaxation, vasodilation,  
12 and bronchodilation, making PDE inhibitors useful for numerous disease processes. PDE-3 and PDE-5  
13 inhibitors are commonly used to treat intermittent claudication, heart failure, pulmonary hypertension,  
14 lower urinary tract symptoms, and erectile dysfunction.<sup>59,60</sup> PDE-3 and nonselective PDE inhibitors  
15 inhibit cyclic adenosine monophosphate (cAMP) hydrolysis, which ultimately prevents platelet aggregation  
16 and encourages vasodilation with increased extremity blood flow. PDE-5-specific inhibitors encourage  
17 smooth muscle relaxation through inhibition of nitric oxide-generated cyclic guanosine monophosphate  
18 (cGMP), causing vasodilation of the corpus cavernosum and pulmonary vasculature as well as changes in  
19 the lower urinary tract. Nitric oxide/cyclic nucleotide mediated vasodilation occurs in the nasal mucosa  
20 causing nasal mucosal engorgement and edema.<sup>61-65</sup> **[TABLE V.B.1.]**

21

22 ***Angiotensin converting enzyme inhibitors.*** Angiotensin converting enzyme inhibitors (ACEI) inhibit the  
23 conversion of angiotensin I to angiotensin II in the lungs and are commonly used for cardiac and renal  
24 diseases. ACEI upregulate the formation of bradykinin, an inflammatory peptide that causes vasodilation  
25 and smooth muscle contraction.<sup>66</sup> Bradykinin B1 and B2 receptors have been demonstrated in nasal  
26 mucosa,<sup>67</sup> and bradykinin application to nasal mucosa has resulted in increased sneezing.<sup>63,68</sup> In addition  
27 to cough, rhinorrhea and nasal obstruction have been associated with ACEI.<sup>66</sup>

28

29 ***Illicit drug use.*** The nose provides a unique portal for illicit drug use due to well vascularized and easily  
30 accessible nasal mucosa. Applying a crushed solid, liquid, or aerosolized form of a drug to the nasal  
31 cavity avoids invasive intravascular or intramuscular administration. For some drugs, nasal

1 administration increases bioavailability and shortens time to onset when compared to oral ingestion.<sup>69,70</sup>  
 2 In contrast to oral agents, intranasal administration bypasses portal filtration.

3  
 4 Cocaine is most commonly associated with nasal illicit drug use and exerts its effect by modulating  
 5 dopamine transporters to inhibit synaptic reuptake, increasing dopamine for post-synaptic stimulation.<sup>71</sup>  
 6 After application to nasal mucosa, cocaine is quickly metabolized by native mucosal esterases into its  
 7 bioactive metabolite, which then passively diffuses across the nasal mucosa and the olfactory bulb,  
 8 leading to elevated systemic and brain concentrations resulting in a psychotropic euphoria.<sup>72</sup> Cocaine-  
 9 induced rhinitis is a result of vasoconstrictive events, which can be followed by rebound nasal mucosal  
 10 edema and mucus production, similar to rhinitis medicamentosa.<sup>73-76</sup> In the repeat user,  
 11 vasoconstriction, direct trauma compounded by anesthetic effects, and/or injury secondary to  
 12 contaminants may result in tissue necrosis.<sup>77-80</sup> Similarly, prescription narcotics,<sup>81</sup> antidepressants,<sup>67</sup>  
 13 anticholinergics, and psychostimulants can be abused by intranasal administration.<sup>67,81</sup> Tissue necrosis  
 14 has also been associated with intranasal opioid and acetaminophen abuse.<sup>82-84</sup> Possible mechanisms of  
 15 injury include hyperosmotic conditions, vasculitic-like inflammation, or direct injury secondary to  
 16 talc.<sup>84,85</sup>

17  
 18 Drug-induced rhinitis is a subtype of non-allergic rhinitis that can cause mucosal edema, vasodilation,  
 19 and inflammatory mediator production. Vasoconstriction and mucosal injury often accompany illicit  
 20 drug use. Drug-induced rhinitis differs from AR as it is not allergen-induced nor dependent on IgE  
 21 mechanisms, although symptomatology may be similar.

22  
 23 **TABLE V.B.1. Drug-induced rhinitis medication list**<sup>48,50,62</sup>

<p><b>Local inflammatory type</b></p>			<p>-NSAIDs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, naproxen, piroxicam, sulindac)                      -Aspirin                      -Ketolorac (if administered via nasolacrimal duct)</p>
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<b>Neurogenic type</b>	<b>Alpha and <math>\beta</math>-adrenergic receptor modulators</b>	Alpha antagonists	-Alfuzosin ( $\alpha$ -1) -Doxazosin ( $\alpha$ -1) -Indoramin ( $\alpha$ -1) -Phentolamine ( $\alpha$ -1, $\alpha$ -2) -Prazosin ( $\alpha$ -1) -Silodosin ( $\alpha$ -1) -Tamulosin ( $\alpha$ -1)
		Presynaptic $\alpha$ -2 agonists	-Clonidine -Guanfacine -Methyldopa -Piribedil
		Beta-antagonists	-Atenolol ( $\beta$ -1) -Bisoprolol ( $\beta$ -1) -Carvedilol ( $\beta$ -1, $\beta$ -2, $\alpha$ -1) -Labetolol ( $\beta$ -1, $\beta$ -2, $\alpha$ -1) -Metoprolol ( $\beta$ -1) -Pindolol ( $\beta$ -1, $\beta$ -2) -Propranolol ( $\beta$ -1, $\beta$ -2)
		Presynaptic depletion of norepinephrine stores	-Guanethidine
	<b>Phosphodiesterase inhibitors</b>	Phosphodiesterase-3 specific	-Amrinone -Anagrelide -Cilostazol -Dipyridamole -Milrinone
		Phosphodiesterase-5 specific	-Avanafil -Sildenafil -Tadalafil -Vardenafil
		Non-selective phosphodiesterase	-Pentoxifylline -Theophylline
	<b>Angiotensin Converting Enzyme Inhibitor</b>		-Benazepril -Captopril -Enalapril -Lisinopril -Quinapril -Ramipril
<b>Idiopathic type</b>		Psychotropics	-Alprazolam -Amitriptyline -Chlorpromazine -Mianserin -Reserpine -Risperidone -Thioridazine
		Immunomodulators	-Cyclosporine

		Hormones	-Estrogen -Oral contraceptives
		Antihypertensives	-Amiloride -Chlorothiazide -Hydralazine -Hydrochlorothiazide
		Other	-Gabapentin -Gingko biloba

1

2

3

4 **V.B.2. Rhinitis medicamentosa**

5

6 Rhinitis medicamentosa is a drug-induced rhinitis resulting from prolonged topical intranasal

7 decongestant (INDC) use.<sup>20,86</sup> Topical INDCs are readily available without a prescription and often lack

8 appropriate warnings of prolonged use, potentially resulting in overuse and dependence. Although no

9 consensus diagnostic criteria exist, rhinitis medicamentosa was originally associated with the triad of

10 prolonged INDC use, persistent nasal obstruction, and rebound swelling of the nasal mucosa.<sup>86</sup> Patients

11 present with nasal congestion, often lack rhinorrhea or sneezing, and may note reduced efficacy, or

12 tachyphylaxis, with further use of INDCs.<sup>76,87,88</sup> Physical examination is variable, but often reveals nasal13 mucosal edema, erythema, and hyperemia. **[TABLE V.B.2.]**

14

15 ***Nasal anatomy and physiology.*** Vasculature within the nasal mucosa consists of resistance vessels16 (arterioles), whose sympathetic innervation is predominated by  $\alpha$ -2 adrenergic receptors, and17 capacitance vessels (venous sinusoids), that are innervated by  $\alpha$ -1 and  $\alpha$ -2 receptors. Stimulation of

18 these receptors results in vasoconstriction with resultant decongestion due to decreased blood flow and

19 increased sinusoid emptying.<sup>86,89</sup> The two classes of nasal decongestants are imidazolines and20 sympathomimetic amines. Imidazolines are  $\alpha$ -2 receptor agonists, while sympathomimetic amines21 encourage presynaptic norepinephrine release. Norepinephrine stimulates  $\alpha$ -adrenergic receptors and22 weakly stimulates  $\beta$ -adrenergic receptors. Both medication classes have a rapid onset, are potent, and23 are long-acting.<sup>86,90</sup>

24

25 The exact pathophysiologic mechanism causing rhinitis medicamentosa is unclear, although several

26 hypotheses exist: (1) chronic vasoconstriction causes recurrent nasal tissue hypoxia and ischemia, which

1 may cause interstitial edema; (2) changes in endothelial permeability may result in increased edema;  
2 and (3) continuous INDC use may decrease endogenous norepinephrine and downregulate  $\alpha$ -receptors,  
3 through negative neural feedback, causing decreased adrenergic responsiveness.<sup>75,76,86,89-91</sup>  
4 Inflammatory cells, local inflammatory mediators, uninhibited parasympathetic stimulation, and  
5 increased mucin production also contribute to symptomatology.

6  
7 Histologic changes within the mucosa after prolonged INDC use include ciliary damage and ciliary loss,  
8 epithelial cell injury, epithelial metaplasia and hyperplasia, dilated intercellular spaces, goblet cell  
9 hyperplasia, and edema.<sup>92-94</sup> Benzalkonium chloride, an antimicrobial preservative used in many nasal  
10 sprays, has been implicated in the mechanism of rhinitis medicamentosa. Studies have demonstrated  
11 that benzalkonium chloride is toxic to nasal epithelium and induces mucosal edema, propagating rhinitis  
12 medicamentosa, although the data are inconclusive.<sup>95-99</sup> Neither duration, nor cumulative dose of INDC  
13 needed to initiate rhinitis medicamentosa is known. Rebound congestion has developed after three to  
14 ten days of medication use,<sup>76,93</sup> but may not occur until after 30 days.<sup>100,101</sup> Other studies have  
15 demonstrated a lack of rebound congestion after eight weeks of continuous use.<sup>100-103</sup> Furthermore,  
16 doubling the dose of intranasal imidazoline did not increase the extent of rebound edema.<sup>100</sup> Although  
17 inconclusive, studies suggest that INDC use should be discontinued after three days to avoid rebound  
18 congestion.<sup>87,104,105</sup>

19  
20 ***Treatment of rhinitis medicamentosa.*** Despite the lack of formal treatment guidelines for rhinitis  
21 medicamentosa, discontinuation of INDCs is paramount. Patients should be educated regarding  
22 common over-the-counter products containing decongestants as labeling may be inadequate. Various  
23 treatments have been trialed including nasal cromolyn, nasal saline spray, oral/intranasal  
24 antihistamines, turbinate steroid injections, and oral/intranasal corticosteroids.<sup>87,89,106-111</sup> Intranasal  
25 corticosteroids (INCS) are the most common treatment for rhinitis medicamentosa. Many initiate INCSs  
26 while weaning INDCs.<sup>90,94,109-112</sup> Often there is an underlying undiagnosed rhinitis and/or anatomic issue  
27 that initiated decongestant use, and this should be addressed to relieve the drive to use INDCs. For  
28 refractory cases, oral steroids and inferior turbinate reduction have been considered.<sup>111</sup>

29  
30 Rhinitis medicamentosa is typically associated with repeated exposure to INDCs, with increasing  
31 symptoms when the medication is withheld. In contrast, AR is classically associated with an allergic  
32 trigger with similar symptoms increasing upon allergen exposure and is dependent upon IgE-mediated



1 inflammation. It is possible that both may coexist, and a careful history should be obtained regarding  
2 these triggers to obtain an accurate diagnosis and provide appropriate treatment.

3  
4 **TABLE V.B.2. Intranasal decongestants associated with rhinitis medicamentosa<sup>20,86</sup>**

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

5 OTC=over the counter

### 6 7 8 **V.B.3. Occupational rhinitis**

9  
10 Occupational rhinitis is an inflammatory disease of the nose, characterized by intermittent or persistent  
11 symptoms of nasal congestion, sneezing, rhinorrhea, itching, and/or variable nasal airflow obstruction  
12 due to causes and conditions attributable to a particular work environment.<sup>113,114</sup> While many social  
13 activities or hobbies can result in overlapping symptoms, stimuli that are encountered outside the  
14 workplace are not considered occupationally related.<sup>115</sup>

15  
16 The pathophysiological mechanisms of occupational rhinitis are the same as other forms of chronic  
17 rhinitis although symptoms may be intimately tied to work exposure.<sup>113,115,116</sup> Occupational rhinitis may  
18 be classified as allergic, resulting from an immunological exposure to a sensitizing high molecular weight  
19 protein (HMW > 5kD) or non-allergic, mediated by non-immunological low molecular weight chemical  
20 irritant (LMW < 5kD).<sup>117,118</sup> Non-allergic occupational rhinitis is sometimes subdivided into annoyance  
21 (e.g., perfumes), irritant-induced (e.g., formaldehyde or smoke), or corrosive rhinitis (e.g., ammonia or  
22 acids), the latter of which may include permanent inflammation of the nasal mucosa, ulcerations, and  
23 perforation of the nasal septum.<sup>113,116</sup>

24  
25 Cross sectional studies of various workers show a wide range of occupational rhinitis prevalence rates  
26 (3-87%),<sup>113,115,119</sup> although rates are higher for HMW agents compared to lower for LMW agents.<sup>115</sup>

1 Occupations and commonly implicated agents are reported in **Table V.B.3.**<sup>120-125</sup> Pre-existing AR or  
2 allergic asthma, baseline total IgE >150 kIU/L, or occupations with frequent exposure to animals have  
3 been shown to be risk factors for occupational rhinitis.<sup>126,127</sup>

4  
5 Occupational rhinitis tends to be three times more prevalent than occupational asthma,<sup>119</sup> but the two  
6 disorders are often associated (up to 92% of cases).<sup>115</sup> In most cases, work-related nasal symptoms  
7 develop 5-6 months before the onset of bronchial symptoms.<sup>113,128</sup> Consequently, occupational rhinitis  
8 may be considered a marker of the likelihood of developing occupational asthma. Previous practice  
9 parameters and consensus documents suggest that workers in certain high-risk occupations be  
10 periodically monitored by survey and/or skin prick testing (SPT) so that risk mitigation strategies can  
11 reduce sensitization, and potentially limit progression of occupational rhinitis or the development of  
12 occupational asthma.<sup>116,129,130</sup>

13  
14 The clinical presentation of occupational rhinitis does not differ from those of non-occupational chronic  
15 rhinitis. Diagnostic assessment must include a thorough clinical and occupational history, aimed to  
16 investigate the type of symptoms and work-related temporality, and to collect information on specific  
17 occupational exposures. Documentation of noxious compounds in the workplace should include  
18 examination of available Material Safety Data Sheets.<sup>113</sup> The presence of a latency period between  
19 beginning of occupational exposure and symptom onset (months or even years) suggests an  
20 immunologic mechanism. This contrasts to non-allergic irritant occupational rhinitis which may occur  
21 immediately upon first exposure.

22  
23 Nasal endoscopy, assessing nasal patency, inflammation and secretions minimize patient  
24 misclassification.<sup>116,131,132</sup> Sensitization to a suspected HMW agent by SPT may be preferred over serum  
25 sIgE assessment as skin testing has been reported to be more sensitive and specific in various reports.<sup>133-</sup>  
26 <sup>136</sup> However, the reliability of sIgE testing depends on the equipment, materials, and technique  
27 employed; therefore, a standardized approach and validated extracts are required, which are often not  
28 available especially for LMW agents.<sup>33,115,136-138</sup> A truly definitive diagnosis can only be established by  
29 objective demonstration of the causal relationship between rhinitis and the work environment through  
30 nasal provocation test (NPT) with the suspected agent(s). However, irritant triggers, LMW agents, and  
31 delayed type reactions are often not easily identified by NPT.<sup>38,113,136,139,140</sup> **[FIGURE V.B.3.]** Validated  
32 clinical assessment tools such as the Total Nasal Symptom Score (TNSS) or and/or sneeze counts

1 administered pre-and-post exposure may aid in quantifying the severity of the response. At some  
2 institutions, rhinomanometry is also available to obtain additional quantitative data.

3  
4 If NPT is negative, further evaluation of work-related changes in nasal parameters at the workplace is  
5 recommended, especially in the presence of a highly suggestive clinical history.<sup>141</sup> When possible, a  
6 formal site visit may allow the technician to directly observe the workplace environment,  
7 symptomatology and Material Safety Data Sheets, and suggest specific workplace modifications. Due to  
8 the strict relationships between upper and lower airways, spirometry and exhaled NO assessment  
9 should be performed in patients with occupational rhinitis.<sup>115,116</sup>

10

11 The primary treatment of allergic occupational rhinitis is avoidance or reduction of culprit exposures.<sup>115</sup>  
12 Pharmacologic treatment does not differ from that of non-occupational rhinitis, although medications  
13 alone may be insufficient given the intensity and frequency of many workplace exposures.<sup>142</sup> In allergic  
14 occupational rhinitis due to HMW sensitizers, AIT may be considered when validated extracts are  
15 available.<sup>143</sup> However, AIT may have limitations in those individuals with continued high workplace  
16 exposure; therefore, simultaneous mitigation and avoidance strategies are essential.

17

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

23

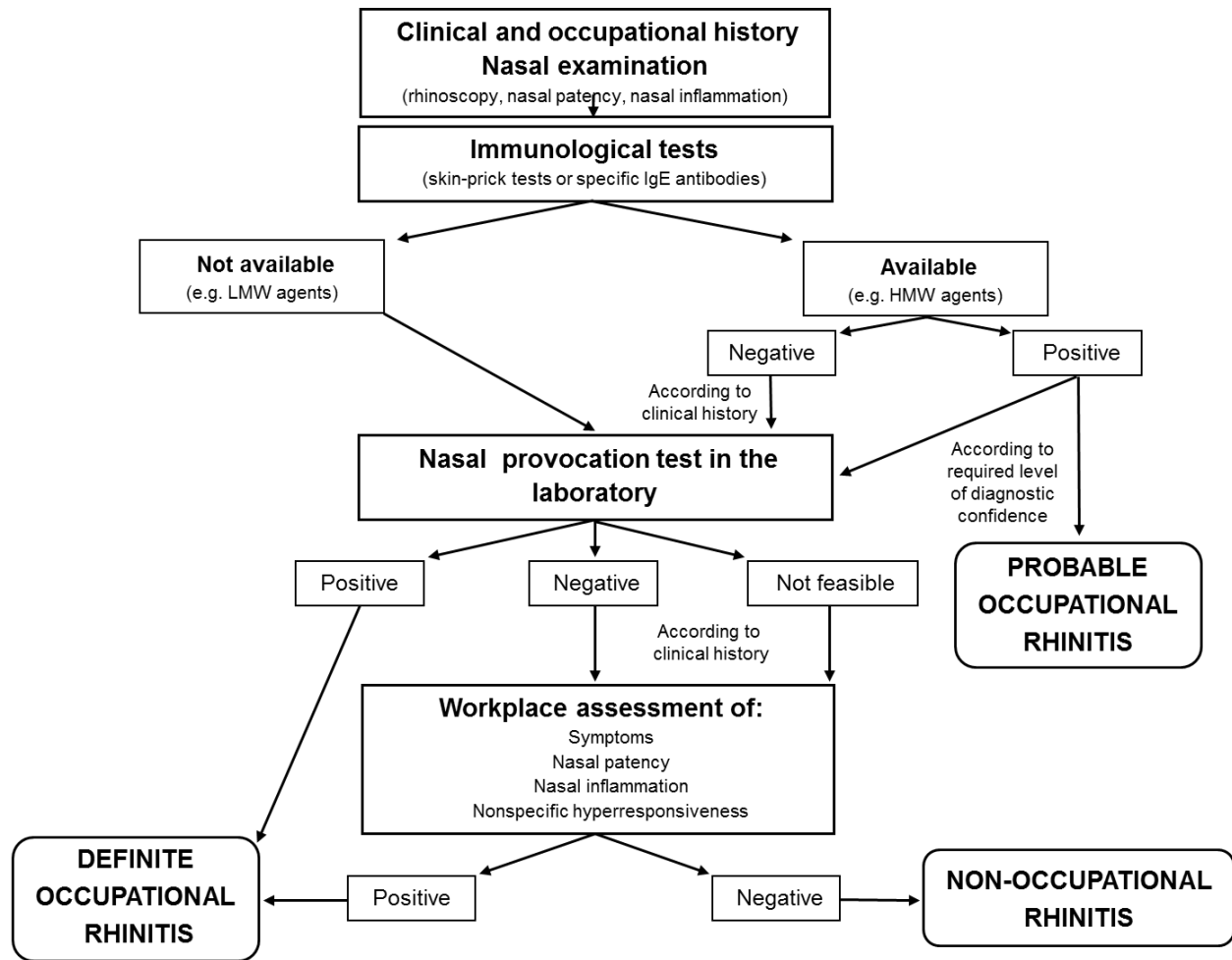
24 **TABLE V.B.3. High risk occupations and causal agents for occupational rhinitis<sup>120-125</sup>**

Agents	Occupation
<b>Allergic agents (high molecular weight)</b>	
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
<b>Non-allergic agents (low molecular weight)</b>	
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

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



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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.<sup>115</sup> 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.

1 Volatile organic compounds such as benzene, toluene, and the secondary production of formaldehyde  
2 can be found in cleaning products, furniture, plastics, flooring and can cause barrier dysfunction and  
3 inflammation in both the upper and lower airway.<sup>124,147,148</sup> Larger chemical particles greater than 10  
4 microns in diameter are generally deposited in the upper airway and agents such as ammonia,  
5 formaldehyde, nitrogen dioxide, or sulfur dioxide among others may readily disrupt the epithelial  
6 barrier.<sup>113</sup>

7  
8 In general, inquiring about exposures to vapors, fumes, smoke, and dust can be helpful to determine if a  
9 patient has an element of chemical rhinitis. These responses are often non-IgE mediated by a reflex  
10 response which is often termed neurogenic inflammation.<sup>149</sup> A subset of these individuals involved in  
11 single exposure incidents may develop persistent and chronic symptoms. This phenomenon has been  
12 described as reactive upper airways dysfunction syndrome when only rhinitis symptoms are present,  
13 and reactive airways dysfunction syndrome when asthma-like symptoms are present.<sup>150,151</sup>

14  
15 Chemicals known to cause respiratory inflammation and in some cases, allergic sensitization include  
16 diisocyanates, acid anhydrides, some platinum salts, reactive dyes, and many cleaning products that are  
17 used in hospitals and in the pandemic era including glutaraldehyde, quaternary ammonium compounds,  
18 and chloramine.<sup>124,152-154</sup> There is still debate concerning the exact mechanism behind sensitization to  
19 these chemicals. However, smaller chemical compounds must associate with larger protein molecules in  
20 order to induce an immune response. As a result, evaluation of sensitization through skin testing and/or  
21 evaluation of sIgE can be helpful and in the future, immunoassays based on cellular responses may serve  
22 as better biomarkers of exposure to chemicals.<sup>155,156</sup>

23  
24

#### 25 V.B.5. Smoke induced rhinitis

26

27 Tobacco smoke exposure is associated with chronic rhinitis and CRS.<sup>157-159</sup> Other smoke exposure  
28 sources besides conventional cigarettes, cigars, and pipes include electronic cigarettes, vaping, and  
29 cannabis. Although there is limited research on these other methods of smoke exposure, initial studies  
30 support that there may be an increased risk of rhinitis with some of these products and these exposures  
31 should be considered in the differential diagnosis.<sup>160,161</sup> Symptoms common to both AR and smoke-  
32 induced rhinitis include rhinorrhea and congestion, but smoke-induced rhinitis is not driven by IgE-  
33 mediated hypersensitivity which tends to also exhibit sneezing on exposure to a specific allergen.<sup>162-165</sup>

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

One of the mechanisms to explain nasal irritation resulting from smoke exposure may be related to capsaicin-sensitive neurons in the nasal mucosa.<sup>169</sup> 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.<sup>170</sup>

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.<sup>168</sup> 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).<sup>171</sup> 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.<sup>168</sup> 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.<sup>20,172</sup>

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.<sup>173</sup> (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.<sup>20</sup> The incidence of acute viral rhinosinusitis is expected to be as high as 98%.<sup>174,175</sup> Common organisms are rhinovirus, adenovirus, influenza virus, and parainfluenza virus.<sup>109</sup> 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.<sup>176</sup> 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.<sup>177-179</sup> The increased expression of ICAM-1 was demonstrated in both upper and lower allergic airway diseases compared with healthy controls.<sup>180-182</sup> This enhances the susceptibility of airway epithelial cells to viral infection.



1 In some cases, viral rhinitis episodes are secondarily infected by bacterial organisms such as  
2 *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis*.<sup>174,175</sup> This occurs in 0.5-  
3 2.0% of all viral infections.<sup>173,174</sup> Clinical presentation distinguishing viral from bacterial  
4 rhinitis/rhinosinusitis is often impossible.<sup>183-186</sup> Inappropriate prescribing of antibiotics and diagnostic  
5 tools is often secondary to misdiagnosis of the symptoms and signs of viral and bacterial origin with up  
6 to 60% starting a course of antibiotics at first symptom presentation.<sup>187-189</sup>

7

8 The possibility of bacterial infection increases if there is deterioration in symptoms after day 5.<sup>176</sup>  
9 Predicting criteria for bacterial infection has been suggested using clinical characteristics, the pattern of  
10 symptoms and laboratory reports.<sup>173,190,191</sup> However, the maximum sensitivity and specificity only reach  
11 69% and 81%, respectively, among various criteria.<sup>189,192</sup> Additionally, a collection of factors contribute  
12 to developing an infection of bacterial origin. These factors include dental infection or procedure,  
13 previous sinus surgery/nasogastric tube insertion/nasal packing, underlying immunodeficiency,  
14 structural nasal problems, and evidence of underlying nasal mucosa edema such as AR.<sup>176</sup>

15

16

### 17 V.B.7. Rhinitis of pregnancy and hormonally induced rhinitis

18

19 **Rhinitis of pregnancy.** Pregnancy-induced rhinitis describes nasal symptoms that occur during  
20 pregnancy, are independent of other etiologies for rhinitis, and remit after delivery.<sup>193-195</sup> Symptoms  
21 include rhinorrhea, sneezing, hyposmia, and nasal itching.<sup>196</sup> In a multicenter study of 599 previously  
22 asymptomatic women, prevalence of rhinitis of pregnancy was 22%.<sup>197</sup> A history of AR and smoking  
23 increase risk for its development.<sup>193-195</sup>

24

25 Quantifying the impact of pregnancy-induced rhinitis has been done objectively and subjectively.  
26 Acoustic rhinometry, rhinomanometry, peak nasal airflow measurements, and saccharin testing confirm  
27 that changes to nasal airway patency occur.<sup>195,196,198</sup> Electron microscopy demonstrates glandular  
28 hyperactivity, increased phagocytotic activity, and increased amounts of acid mucopolysaccharides in  
29 the ground substance.<sup>199</sup> Studies using validated patient reported outcome measures (e.g., Nasal  
30 Obstruction Symptom Evaluation [NOSE] scale, Rhinitis Quality of Life Questionnaire [RQLQ])<sup>198,200</sup>  
31 confirm the subjective component of pregnancy-induced rhinitis.<sup>195,196,198</sup>

32

1 The precise pathophysiology of pregnancy-induced rhinitis remains unknown.<sup>196,201,202</sup> Estrogen,  
2 progesterone, and placental growth hormonal have all been implicated.<sup>193-195,198</sup> Increased expression of  
3 histamine receptors secondary to  $\beta$ -estradiol and progesterone in nasal epithelial and endothelial cells  
4 has been demonstrated and is proposed as a potential mechanism of nasal hyperreactivity in pregnancy-  
5 induced rhinitis.<sup>203</sup> Additionally, serum levels of placental growth hormone were significantly higher in  
6 patients with pregnancy-induced rhinitis throughout their pregnancy.<sup>204</sup>

7

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

15

16 Treatment is conservative and relies on education. Reassurance regarding the temporary nature of  
17 pregnancy-induced rhinitis is beneficial. Regular use of nasal saline lavage is safe and provides  
18 symptomatic relief.<sup>172,201,202</sup> Counseling against the routine use of oral and topical decongestants is  
19 critical due to the risk for congenital gastroschisis, pyloric stenosis, endocardial cushion defects, renal  
20 anomalies, and limb defects. These risks are greater in the first trimester, but caution should be  
21 maintained throughout the pregnancy.<sup>172,201,202</sup> INCS are generally considered safe for use during  
22 pregnancy; however, triamcinolone is associated with congenital respiratory defects.<sup>172</sup> A treatment  
23 option under investigation is topical hyaluronate, which facilitates mucociliary clearance and hydration.  
24 In a 2019 pilot study of pregnancy-induced rhinitis, sodium hyaluronate use decreased snoring, mucosa  
25 congestion, and nasal secretions and had no adverse events.<sup>206</sup> More studies are needed before  
26 recommending its routine use during pregnancy.

27

28 **Hormonally induced rhinitis.** Cytological changes and cell turnover of the nasal epithelium during the  
29 phases of the menstrual cycle have been demonstrated. In general, estrogens are thought to cause nasal  
30 vascular engorgement, resulting in obstruction and rhinorrhea. As with pregnancy-induced rhinitis, the  
31 mechanism of these changes remains unclear.<sup>172,207-209</sup> The expression of histamine H<sub>1</sub>-receptors within

1 the nasal epithelium and microvascular endothelial cells are increased in response to  $\beta$ -estradiol and  
2 progesterone. These hormones may also induce eosinophil migration and/or degranulation.<sup>207</sup>

3  
4 Rhinitis can also occur in patients with endocrine pathologies. Hypothyroidism can cause hypertrophy of  
5 mucous glands, increased submucosal connective tissue, and resultant nasal obstruction and  
6 rhinorrhea.<sup>207,208,210</sup> These patients may also have prolonged mucociliary clearance time.<sup>211</sup> Rhinitis with  
7 sinonasal mucosal hypertrophy and polyp formation can also be seen in acromegaly, though it is unclear  
8 if elevated serum levels of growth hormone are the cause.<sup>212</sup>

9

10

### 11 V.B.8. Food and alcohol induced rhinitis

12

13 **Food-induced rhinitis.** Gustatory rhinitis is characterized by watery, unilateral and/or bilateral  
14 rhinorrhea within a few minutes after the ingestion of food, usually hot and spicy foods such as tabasco  
15 sauce, hot chili peppers, horseradish, red cayenne or black pepper and other foods that contain  
16 capsaicin. The rhinorrhea lasts as long as the food is ingested.<sup>172,213-216</sup> Gustatory rhinitis can be confused  
17 with IgE-mediated food allergy, but there is no sneezing, pruritus, or facial pain and the time course of  
18 the rhinorrhea is self-limited.<sup>213</sup> There is also no associated disturbance of smell or taste.<sup>217</sup> Gustatory  
19 rhinitis occurs more often in patients with AR and patients who have a history of smoking, but not those  
20 with asthma or food allergies.<sup>215</sup>

21

22 The pathophysiology has been confirmed through pharmacologic observations and immunohistology  
23 studies to occur through a neural reflex arc initiated upon the stimulation of afferent sensory nerves.  
24 This leads to the stimulation of the parasympathetic efferent nerve supply to the submucosal glands in  
25 the nasal mucosa.<sup>214,216</sup> It is additionally possible that interactions between the sympathetic and  
26 parasympathetic nervous system could lead to uninhibited activity of the parasympathetic system with  
27 resultant rhinorrhea.<sup>216</sup> For example, the chemical capsaicin is known to cause gustatory rhinitis. The  
28 capsaicin receptor is a transient receptor potential vanilloid subtype 1 (TRPV1) receptor and exists in  
29 neuronal as well as non-neuronal cells along the nasal mucosa and oral epithelium.<sup>218</sup> A direct effect on  
30 goblet cell secretion may be triggered when capsaicin is ingested.<sup>217</sup> A well-known culprit of gustatory  
31 rhinitis is chili peppers, which contain capsaicin.<sup>217</sup> A variety of other foods are associated with gustatory  
32 rhinitis including horseradish, wasabi, black pepper, hot mustard and vinegar.<sup>215,216</sup>

33

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

5  
6 **Alcohol-induced rhinitis.** Exacerbation of respiratory symptoms after ingestion of alcohol occurs in  
7 approximately 3-4% of the general population. Among the nasal symptoms that occur, blockage is the  
8 most common and may be accompanied by rhinorrhea, sneezing and lower airway symptoms. This is  
9 reportedly more common in patients with AR, asthma, chronic obstructive pulmonary disease (COPD),  
10 emphysema.<sup>220</sup> Up to 75% of aspirin-exacerbated respiratory disease (AERD) patients suffer  
11 exacerbations of respiratory symptoms when they consume alcohol.<sup>221-223</sup> Symptom exacerbations occur  
12 relatively soon after alcohol ingestion, are often associated with the ingestion of small volumes, and  
13 seem to correlate with peak blood alcohol levels.<sup>223</sup> Such symptoms can arise regardless of the type of  
14 alcohol ingested.<sup>220,222</sup> These reactions to alcohol consumption are more prevalent in chronic  
15 rhinosinusitis with nasal polyp (CRSwNP) patients who suffer with severe and recurrent disease and are  
16 related to the severity of upper airway inflammation.<sup>223</sup>

17  
18 In AERD patients, the severity of aspirin-induced respiratory symptoms is positively correlated with the  
19 severity of alcohol-induced reactions.<sup>223</sup> Exacerbations of respiratory symptoms in response to alcohol  
20 has been shown to be decreased after aspirin-desensitization in patients with AERD.<sup>221</sup> Patients with  
21 AERD have elevated baseline cysteinyl leukotriene levels, which are proposed to mediate the upper and  
22 lower airway reactions to aspirin.<sup>221,222</sup> Cardet et al<sup>222</sup> propose that cysteinyl leukotrienes also mediate  
23 the response to alcohol in these patients as well, though the pathway for such a mechanism is unknown.

24  
25 High alcohol consumption is 'observationally and genetically' associated with high serum IgE levels,  
26 though not with allergic disease. Two possible mechanisms have been proposed as the etiology for this  
27 observation: (1) alcohol changes the balance of the Th1 and Th2 responses toward a Th2 immune  
28 response with a direct effect on B cells, or 2) alcohol induces increased uptake of endotoxins from the  
29 gut resulting in elevated IgE levels.<sup>224</sup>

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

1 Non-allergic rhinitis with eosinophilia syndrome (NARES) is a clinical disorder comprising symptoms  
2 consistent with perennial AR in which there is an absence of atopy but presence of local eosinophilia  
3 found on nasal cytology.<sup>225</sup> The pathophysiology of NARES is not well understood, but a key component  
4 involves chronic local eosinophilic, self-perpetuating inflammation, with non-specific histamine release.  
5 It is one of the most common type of inflammatory nonallergic rhinitis that was first described by Jacobs  
6 and colleagues in 1981.<sup>226</sup>

7

8 NARES patients report symptoms that are similar to those of perennial AR: nasal congestion, profuse  
9 aqueous rhinorrhea, sneezing, and nasal and ocular pruritis. A prominent feature of NARES is olfactory  
10 dysfunction. NARES patients demonstrate significantly higher thresholds on olfactory testing than  
11 seasonal and perennial AR patients.<sup>227</sup> NARES is diagnosed by obtaining a careful history, findings on  
12 physical exam, not unlike those found in perennial AR patients (pale, boggy turbinates), and negative  
13 skin or in vitro allergy testing. Cytologic examination in NARES reveals the presence of prominent  
14 eosinophilia, usually 10-20% on nasal smear, with a diagnostic criterion of 25% or more  
15 eosinophils.<sup>225,228</sup> In addition, nasal biopsies from these patients commonly show increased numbers of  
16 mast cells with prominent degranulation.<sup>229,230</sup>

17

18 Research has supported the role of chronic inflammation in the development of NARES. Though there is  
19 still a lack of understanding as to the exact pathophysiology, studies have shown an increased  
20 transendothelial migration of eosinophils in nasal lavage fluid, which are attracted and activated by  
21 chemokines and cytokines.<sup>231,232</sup> Specifically, NARES is characterized by elevated nasal fluid levels of  
22 tryptase (which is also seen in perennial AR) and eosinophilic cationic protein.<sup>233</sup> Elevated levels of  
23 interleukin (IL)-1 $\beta$ , IL-17, interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , monocyte chemoattractant  
24 protein (MCP)-1 and RANTES (regulated upon activation, normal T cell expressed and presumably  
25 secreted) in nasal fluid were found in NARES compared to controls.<sup>234,235</sup>

26

27 A correlation between the concentration of RANTES with nasal symptoms and eosinophil counts in  
28 perennial AR patients has been shown.<sup>236</sup> However, levels of MCP-1 and RANTES were significantly  
29 higher in the nasal fluid of NARES compared to perennial AR subjects. Elevation of these cytokines  
30 correlated with the ratio of nasal symptom scores/percentage of eosinophils in NARES patients, where  
31 nasal symptoms of nasal obstruction, rhinorrhea, hyposmia, sneezing, and itching were each measured  
32 using a 3-point scale.<sup>236</sup> Several studies from European cohorts have found a lack of nasal mucosal IgE in

1 NARES patients.<sup>237,238</sup> More recent studies of Chinese cohorts of NARES patients have found increased  
2 expression of Charcot Leyden Crystals which correlated with severity of symptoms and degree of  
3 eosinophilia.<sup>239</sup> Elevated cysteine protease inhibitor cystatin SN was also observed with greater loss of  
4 sense of smell.<sup>240</sup> Neuropeptide mediated eosinophil chemotaxis, including substance P, calcitonin gene-  
5 related peptide and cholecystokinin octapeptide, has also been described as a contributing factor to the  
6 symptomatology in NARES patients.<sup>241</sup>

7  
8 NARES may occur in isolation, but it can be associated with (and may be a precursor for) AERD.<sup>225</sup> NARES  
9 has also been identified as a risk factor for the induction or exacerbation of obstructive sleep apnea<sup>242</sup>  
10 and has been associated with increased tendency for lower airway hyperresponsiveness.<sup>243</sup>

11  
12 The treatment of non-allergic rhinitis centers on its underlying cause. NARES is primarily treated with  
13 INCS, which decrease neutrophil and eosinophil chemotaxis, reduce mast cell and basophil mediator  
14 release, and result in decreased mucosal edema and local inflammation.<sup>244,245</sup> A combined analysis of  
15 three double-blind, randomized, prospective, placebo-controlled studies of 983 patients (309 of whom  
16 were classified as NARES) demonstrated a positive treatment effect using INCS with improvement in  
17 symptoms of nasal obstruction, postnasal drip, and rhinorrhea.<sup>246</sup> Additionally, the intranasal  
18 antihistamine azelastine and leukotriene receptor antagonists (LTRA) have been shown to reduce  
19 symptoms of rhinitis, including postnasal drainage, sneezing, rhinorrhea, and congestion.<sup>142,247-249</sup>

20  
21

## 22 V.B.10. Non-allergic rhinopathy

23  
24 Non-allergic rhinopathy/rhinitis is a chronic rhinitis made by a diagnosis of exclusion of other etiological  
25 factors. These include CRSwNP, NARES, AERD, infectious rhinitis, anatomical abnormalities, rhinitis  
26 medicamentosa, drug side effects, cerebrospinal fluid (CSF) rhinorrhea, and rhinitis of pregnancy.

27 Clinical characteristics of non-allergic rhinopathy/rhinitis include primary symptoms of nasal congestion  
28 and rhinorrhea, postnasal drip in the absence of acid reflux, throat clearing, cough, Eustachian tube  
29 dysfunction (ETD), sneezing, hyposmia and facial pressure/headache.<sup>56</sup> These symptoms may be  
30 perennial, persistent, or seasonal, and are typically elicited by defined triggers, such as cold air, climate  
31 changes (e.g., temperature, humidity, barometric pressure), strong smells, tobacco smoke, changes in  
32 sexual hormone levels, environmental pollutants, physical exercise, and alcohol. Notably, the lack of a  
33 defined trigger does not preclude the diagnosis of non-allergic rhinopathy.

1

2 The prevalence of non-allergic rhinopathy, the second most common form of rhinitis, is between 7-9.6%  
3 in the adult population in the United States (US) and Europe.<sup>23,49</sup> Vasomotor rhinitis is the most common  
4 cause of non-allergic rhinitis, and is found in 71% of cases.<sup>250-252</sup> Non-allergic rhinopathy occurs with a  
5 female-to-male ratio of 2:1 to 3:1<sup>56</sup> and is typically seen after the age of 20.<sup>253</sup> It is defined by the  
6 absence of an IgE-mediated immune response.<sup>142</sup> The term “non-allergic rhinopathy” has been  
7 suggested to replace vasomotor rhinitis, as allergic inflammation is absent in the pathogenesis, although  
8 vasomotor causes may not account for the entirety of non-allergic rhinopathy/rhinitis cases.

9

10 The nasal mucosa of patients with non-allergic rhinopathy displays erythema and clear rhinorrhea.  
11 Allergy testing can be used to differentiate between non-allergic rhinopathy and AR. Vasomotor rhinitis,  
12 the most common subtype of non-allergic rhinopathy, has been linked to autonomic dysfunction and  
13 has been attributed to an imbalance between the parasympathetic and sympathetic systems.<sup>254</sup>

14

15 Local allergic rhinitis (LAR) is a distinct rhinitis that presents with features in between AR and non-  
16 allergic rhinopathy.<sup>255</sup> Patients with LAR demonstrate entopy or local IgE production in the nasal mucosa  
17 but lack skin test positivity. Individuals with LAR suffer from typical allergic symptoms upon allergen  
18 exposure but display a lack of systemic IgE sensitization. Local provocation is necessary to definitively  
19 exclude this diagnosis.<sup>255,256</sup> The prevalence of LAR among non-allergic rhinopathy has been reported to  
20 be 26.5%.<sup>257</sup> (*See Section VI.A.3. Local IgE Production for additional information on this topic.*) Additional  
21 forms of nonallergic rhinopathy include food-induced rhinorrhea and age-related rhinitis. (*See Section*  
22 *V.B.8. Food and Alcohol Induced Rhinitis and Section V.B.11. Age-related Rhinitis for additional*  
23 *information on this topic.*)

24

25 Neurosensory abnormalities are thought to play an important role the development of non-allergic  
26 rhinopathy.<sup>56</sup> In previous evaluation of central responses to olfactory stimuli, subjects with non-allergic  
27 rhinopathy underwent functional magnetic resonance imaging following exposure to different odors  
28 (vanilla and hickory smoke). Findings included increased blood flow to the olfactory cortex, leading to  
29 the hypothesis of an altered neurologic response.<sup>258,259</sup>

30

31 Medical management of non-allergic rhinopathy includes topical nasal sprays that have variable  
32 responses which have been used alone or in combination: INCS,<sup>246,260</sup> topical azelastine,<sup>261</sup> and

1 ipratropium bromide (IPB).<sup>262</sup> In addition adjunctive treatments include nasal saline sprays or lavage,  
2 especially with tenacious post nasal drip.<sup>254</sup>

3

4 For severely symptomatic patients refractory to medical therapy, surgical approaches targeting the  
5 vidian nerve and its branches have been shown to result in symptom control.<sup>219,263</sup> These include

6 botulinum toxin injection which result in temporary symptom improvement, endoscopic vidian

7 neurectomy, endoscopic posterior nasal neurectomy, and cryoablation of the posterior nasal nerve.

8 Posterior nasal neurectomy is purported to result in lower rate of complication of dry eyes than vidian

9 neurectomy.<sup>264</sup> Recent studies show that office based cryotherapy can achieve improvement in

10 rhinorrhea and congestion for up to 1 year.<sup>265,266</sup>

11

12

### 13 V.B.11. Age-related rhinitis

14

15 As the percentage of the adult population aged 65 years and older continues to increase, so does the

16 prevalence of diseases associated with aging. Specific to rhinologic disease, the physiological process of

17 aging results in neural, hormonal, mucosal, and histologic alterations that cause morphological and

18 functional changes in the nasal cavity.<sup>267,268</sup> This, in turn, can result in symptoms of rhinorrhea, nasal

19 congestion, postnasal drip, dry nose, intranasal crusting, and decreased olfaction in the elderly

20 population.<sup>269,270</sup>

21

22 **Rhinorrhea.** A questionnaire distributed to a cohort of adults in Pittsburgh demonstrated that 33% of

23 the younger age group respondents (n=76, mean age 19 years) regularly reported clear anterior nasal

24 drainage as compared to 74% of the older age group respondents (n=82, mean age 86 years).<sup>271</sup> It is

25 known that autonomic function declines with age as  $\alpha$ - and  $\beta$ -receptors become less sensitive.

26 Therefore, an imbalance of this system with decreased sympathetic tone and unopposed

27 parasympathetic stimulation could result in a rise in glandular activity in the nasal cavity, leading to

28 increased nasal drainage.<sup>271-274</sup> This mechanism is similar to the process classically termed “vasomotor

29 rhinitis”, where the autonomic response to certain stimulants causes the nasal mucosal blood vessels to

30 vasodilate and the mucus glands to become overactive, resulting in hypersecretion and excessive

31 drainage.<sup>275</sup> Vasomotor rhinitis is the most common type of nonallergic rhinopathy/rhinitis, and the

32 highest prevalence of non-allergic rhinopathy is seen in the elderly,<sup>250,270,276,277</sup> supporting an autonomic

33 nervous system mechanism as the physiologic reason for increased rhinorrhea in this population.



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**Nasal obstruction and congestion.** Other changes that occur in the aging nose include thicker mucus secondary to a decrease in body water content,<sup>278-280</sup> loss of nasal cartilage elasticity and tip support,<sup>268,270,280</sup> mucus stasis secondary to a less effective mucociliary clearance system,<sup>270,279,281</sup> and age-related central nervous system changes that affect the physiologic nasal cycle,<sup>278,282</sup> 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.<sup>283</sup> This, in turn, results in intranasal volume increase due to nasal mucosal atrophy.<sup>269</sup> Schrodter et al<sup>284</sup> 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.<sup>270</sup>

**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,<sup>268</sup> with the prevalence estimated to be around 5-10%.<sup>280,285</sup> 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,<sup>286,287</sup> 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,<sup>280,288</sup> and AIT.<sup>289</sup> For age-related/nonallergic rhinitis rhinorrhea, saline lavage and topical anticholinergics may be therapeutic.<sup>267</sup> 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.<sup>290,291</sup> It is characterized by

1 progressive atrophy of the nasal mucosa and bone, leading to anatomically wider nasal airways, albeit  
2 many patients paradoxically complain about the symptom of nasal obstruction. Upon removing crusts,  
3 the nasal cavity appears enlarged, with significant atrophy of the nasal turbinates. Atrophic rhinitis can  
4 be classified into primary or if occurring as a sequela of a causative factor, secondary.<sup>292</sup> Both primary  
5 and secondary atrophic rhinitis are significantly different in their clinical presentation and underlying  
6 pathophysiology compared to AR.<sup>172</sup>

7  
8 The prevalence of primary atrophic rhinitis varies across regions worldwide, with a higher prevalence in  
9 tropical countries such as India or Thailand compared to Europe or the US.<sup>293-297</sup> It is also more  
10 commonly found in young to middle-aged adults, with a predominance of females.<sup>293</sup> Primary atrophic  
11 rhinitis has also been linked to environmental and socioeconomic factors. For example, it has been more  
12 commonly found in industrial workers, those with lower socioeconomic status (SES), and those in rural  
13 areas.<sup>293</sup> While there are no universally accepted guidelines for diagnosing primary atrophic rhinitis, it  
14 usually consists of a structured medical history and physical examination, including nasal  
15 endoscopy.<sup>296,298</sup>

16  
17 The differentiation with secondary atrophic rhinitis includes the exclusion of potential causative  
18 etiologies related to secondary atrophic rhinitis, such as excessive nasal surgery, chronic granulomatous  
19 infections (e.g., tuberculosis, syphilis, leprosy), autoimmune/inflammatory disorders (e.g.,  
20 granulomatosis with polyangiitis [GPA] or sarcoidosis), and excessive drug use (nasal sprays and  
21 cocaine).<sup>299</sup> Studies in the US on atrophic rhinitis patients revealed that secondary atrophic rhinitis  
22 accounted for more than 80% of atrophic rhinitis cases and was most commonly found in middle-aged  
23 adults.<sup>294</sup> Compared to the diagnosis of primary atrophic rhinitis, which mainly consists of excluding  
24 potential causative etiologies related to secondary atrophic rhinitis, a complete medical history to  
25 evaluate for causative factors represents the most critical step for correct diagnosing secondary atrophic  
26 rhinitis.<sup>290</sup>

27  
28 To work up atrophic rhinitis, accurate and comprehensive medical history is important. Nasal  
29 endoscopy, cultures and histopathology can also help clarify the diagnosis. Ly et al<sup>300</sup> identified seven  
30 key symptoms that can be used to establish the diagnosis of atrophic rhinitis: purulence, nasal  
31 obstruction, history of nasal/sinus surgeries (at least two), crusting, recurrent epistaxis, smell loss, and  
32 chronic inflammatory disease of the upper airway. While more symptoms are associated with a higher

1 sensitivity to diagnose atrophic rhinitis, the authors proposed that the presence of at least two  
2 symptoms (excluding nasal obstruction) enhances the sensitivity and specificity to 95% and 77%,  
3 respectively, to support the diagnosis of atrophic rhinitis.<sup>300</sup> Endoscopic findings usually include nasal  
4 crusting and enlarged lateral sidewalls.<sup>294</sup>

5  
6 The underlying etiology and pathophysiology of primary atrophic rhinitis are still unknown, although  
7 persistent bacterial infection is commonly believed to be the causative agent. Microbiological cultures  
8 from the middle meatus can aid in the diagnosis.<sup>301</sup> The most common bacteria found in affected  
9 individuals is *Klebsiella ozaenae*,<sup>293,294,302,303</sup> albeit many other bacteria such as *Staphylococcus aureus* or  
10 *Pseudomonas aeruginosa* have also been isolated from nasal cultures.<sup>293,296</sup> Histopathological changes in  
11 both primary and secondary atrophic rhinitis may include partial or total squamous metaplasia,  
12 granulation tissue, atrophy, reduction of the seromucous glands, and vascular changes (e.g., reduced  
13 vascularity, dilated blood vessels and in some cases endarteritis).<sup>299</sup> Interestingly, there have also been  
14 case reports which suggest primary atrophic rhinitis may have a genetic inheritance pattern.<sup>304</sup>

### 15 16 17 V.B.13. Empty nose syndrome

18  
19 Empty nose syndrome (ENS) is a rare and complex acquired upper airway disease. ‘ENS’ was coined  
20 nearly 3 decades ago to describe the ‘empty’ or ‘wide open’ nasal cavity examination and imaging in  
21 patients following turbinoplasty with excess loss of turbinate tissue or contour.<sup>294,305-309</sup> Clinically, it is  
22 characterized by a spectrum of debilitating symptoms like nasal burning, dryness, and crusting,  
23 accompanied by symptoms quite unique to ENS like severe suffocation, paradoxical sensation of nasal  
24 obstruction, or excessive nasal airflow (i.e., “nose feels too open”).<sup>294,310,311</sup>

25  
26 ENS is linked to several inferior turbinate (IT) reduction approaches, such as total turbinectomy, IT  
27 trimming, and radiofrequency ablation.<sup>311,312</sup> Presentation can be immediate or delayed, secondary to  
28 over-aggressive IT reduction or suboptimal post-surgical healing and scarring, respectively.<sup>306,313,314</sup>

29 While ENS is mostly associated with inferior turbinoplasty (ENS-IT), ENS from MT tissue loss (ENS-MT)  
30 has been reported.<sup>307</sup>

31  
32 The physiologic basis for perceiving reduced and/or unpleasant nasal breathing may be related to  
33 altered signaling through trigeminal sensory receptors, specifically TRPM8. Resultant aberrant

1 thermosensation and neurosensory deprivation manifest as muted airflow sensation.<sup>315-320</sup> Damage to,  
2 and/or delayed recovery of, the trigeminal sensory nerve has also been implicated in the development  
3 of ENS in a minority of patients.<sup>321</sup> Additionally, objective shifts in nasal airflow support a novel ‘aberrant  
4 airflow’ hypothesis.<sup>322-324</sup> Computational fluid dynamics modeling of nasal airflow demonstrates  
5 abnormally high velocity airflow to the middle meatus and dampened airflow vectors to the inferior  
6 meatus in ENS.

7  
8 There has been welcome progress in the diagnosis and treatment of ENS in the past decade. In addition  
9 to a history of nasal surgery and abnormally expansive unilateral/bilateral nasal airway with  
10 concomitant IT tissue loss, thickened central nasal septum mucosa has been shown to be present in  
11 longstanding ENS.<sup>313</sup> The validated patient reported outcome measure Empty Nose Syndrome 6-item  
12 Questionnaire (ENS6Q) can be used to quantify the severity of six cardinal ENS symptoms on a 5-point  
13 Likert scale. A score  $\geq 11$  indicates ENS.<sup>310</sup> Placement of a cotton plug in the inferior meatus to simulate  
14 turbinate bulk (the cotton test) has been validated as an office-based tool to assess/alleviate ENS  
15 symptoms.<sup>325</sup> A positive blinded cotton test both confirms the ENS diagnosis and informs candidacy for  
16 possible treatment interventions.<sup>325</sup>

17  
18 ENS has historically been a challenging disease to effectively treat due to debilitating nasal symptoms  
19 and, in a minority of patients, concerning psychiatric overtones.<sup>326-330</sup> Past therapies were confined to  
20 reducing the daily burden of ENS symptoms via nasal maintenance strategies including moisturizers and  
21 emollients, increasing nasal airflow (supplemental oxygen, CPAP [continuous positive airway pressure]  
22 use), and psychiatric interventions like cognitive behavioral therapy.<sup>331,332</sup>

23  
24 Current published interventions focus on restoring tissue volume to the truncated ITs or the adjacent  
25 inferior meatus. Submucosal injection of slow-resorbing gel fillers can be trialed for the effect of  
26 ‘transient turbinate augmentation’ lasting 1-3 months.<sup>333</sup> A wide variety of biomaterials – including  
27 acellular dermis, implants, and xenografts – have been published as bulking options to sites of inferior  
28 meatus and IT tissue loss.<sup>334-339</sup> Importantly, a procedure originally reported by Houser,<sup>308</sup> now termed  
29 the inferior meatus augmentation procedure (IMAP), where missing turbinate contour is replaced with  
30 fashioned rounded rib grafts placed in the anterolateral nasal airway, has accumulated strong evidence  
31 for effectively treating ENS.<sup>340</sup> IMAP has yielded statistically significant short<sup>341</sup> and long<sup>342</sup> term  
32 reductions in the ENS6Q and the Sinonasal Outcome Test (SNOT)-22. Mechanistically, comparing

1 computational fluid dynamics airflow modeling pre/post-surgery, the cotton test and IMAP procedures  
2 both normalize disordered vectors of ENS airflow,<sup>343</sup> highlighting a novel function of the turbinates in  
3 guiding and/or enhancing nasal airflow. Future ENS research will determine anatomic versus physiologic  
4 prognostic factors to identify 'at risk' subpopulations for developing ENS<sup>326,327</sup> and design more nuanced  
5 airflow metrics for upper airway function in health and disease.

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#### 8 V.B.14. Autoimmune, granulomatous, and vasculitic rhinitis

9

10 **Differential diagnosis.** Vasculitic, granulomatous, and autoimmune diseases may cause non-specific  
11 sinonasal symptoms (e.g., nasal obstruction, rhinorrhea, facial pain, and loss of smell) often mimicking  
12 AR. Therefore, broadening the differential diagnosis to consider systemic etiologies when evaluating  
13 these sinonasal symptoms is crucial. Crusting, recurrent epistaxis, or negative skin and/or blood allergy  
14 tests are among the signs that should heighten one's suspicion of alternative systemic diseases.<sup>344,345</sup>

15

16 **Granulomatosis with polyangiitis (GPA).** This an uncommon disease with highest prevalence amongst  
17 people of Northern European descent, with men and women equally affected and incidence peaking in  
18 the seventh decade of life.<sup>346</sup> It is a chronic, relapsing, and idiopathic disease characterized by  
19 necrotizing and granulomatous inflammation affecting predominantly small to medium sized blood  
20 vessels.<sup>347</sup> Potential triggers include *Staphylococcus aureus* as well as other infectious, environmental,  
21 chemical, or pharmacologic agents.

22

23 Sinonasal manifestations (e.g., nasal obstruction, crusting, epistaxis, anosmia, cacosmia and paranasal  
24 sinus inflammation) are the presenting symptoms of GPA in about 73% of patients.<sup>348</sup> Recurrent serous  
25 otitis, mastoiditis causing hearing loss, and lower respiratory tract symptoms (e.g., cough,  
26 breathlessness, stridor, wheeze) occur in 80-90% of patients.<sup>344,349</sup> Additionally, renal (75% of patients),  
27 ocular (50% of patients), and systemic manifestations (e.g., fever, arthritis, weight loss) are also  
28 possible.<sup>350</sup>

29

30 Diagnosis is often dependent on a multidisciplinary approach and based on a combination of suggestive  
31 local and systemic clinical manifestations, positive ANCA (anti-neutrophil cytoplasmic antibody)  
32 serology, and histological evidence of necrotizing vasculitis or glomerulonephritis by a positive organ  
33 biopsy (skin, lung, or kidney).<sup>351,352</sup>

1

2 Before the introduction of effective therapy, GPA was a potentially life-threatening disease. Treatment  
3 includes corticosteroids and immunosuppressive agents to induce remission. Cyclophosphamide and  
4 rituximab are often used for induction and maintenance. Patients can be transitioned to other  
5 immunosuppressive agents (e.g., azathioprine, mycophenolate, or methotrexate) with fewer potential  
6 side effects when disease remission is obtained.<sup>353</sup>

7

8 ***Eosinophilic granulomatosis with polyangiitis (EGPA)***. EGPA (formerly Churg-Strauss syndrome) is a  
9 small-vessel vasculitis. Defining features include eosinophil-rich, necrotizing granulomatous  
10 inflammation involving the respiratory tract. It is associated with asthma, eosinophilia, and CRSwNP. It is  
11 a rare disease with a prevalence of 10-15 people per million in Europe and appears in patients 40-60  
12 years old.<sup>354</sup> EGPA has different triggers and frequently progresses through three stages gradually  
13 appearing over years. An initial phase with rhinitis (75%), asthma, and CRSwNP, is often followed by  
14 peripheral eosinophilia and additional organ involvement, and finally diffuse clinical manifestations  
15 secondary to small vessel vasculitis.<sup>355</sup> Diagnosis should be suspected in patients with asthma, increased  
16 peripheral-blood eosinophil count (>10%) and pulmonary infiltrates.<sup>355</sup> CRSwNP is present in  
17 approximately 50% of patients. Nasal crusting, purulent or bloody discharge can be present, but is less  
18 common than in GPA.<sup>356</sup> Treatment includes high doses of corticosteroids with rituximab in specific  
19 cases. Mepolizumab, an anti-IL-5 antibody, has shown efficacy in the eosinophilic inflammation and was  
20 approved for the treatment of EGPA in 2017 by the Food and Drug Administration (FDA).<sup>345,357</sup>

21

22 ***Sarcoidosis***. This is chronic multisystem disorder characterized by bilateral hilar lymphadenopathy and  
23 pulmonary infiltrates. Ocular and skin lesions are more common in young and middle-aged adults.<sup>358</sup>  
24 Sinonasal involvement occurs in 1-4% of cases and symptoms are non-specific: chronic crusting (70-  
25 90%), nasal obstruction (80-90%), anosmia (70%), and epistaxis (2%).<sup>345,347,359</sup> Aggressive non-caseating  
26 granulomas can cause hard or soft palate erosions as well as a saddle-nose deformity. Intranasal findings  
27 include erythematous, edematous, and friable mucosa, as well as submucosal yellow nodules  
28 (representative of intramucosal granulomas).<sup>360</sup> Diagnosis is usually made by a lung (transbronchial),  
29 skin, minor salivary gland, or lymph node biopsy.<sup>358</sup>

30

31 Sinonasal sarcoidosis treatment depends on its location, extension, and severity going from topical to  
32 systemic therapy (when nasal obstruction is severe). Endoscopic sinus surgery can be effective when

1 medical treatment has failed, particularly in cases of sinus drainage blockage. Sinus surgery improves  
2 quality of life (QOL) but does not eradicate the disease nor prevent recurrence.<sup>361</sup> Biological therapy  
3 with anti-TNF agents has improved the therapeutic options in refractory organ-threatening  
4 sarcoidosis.<sup>361</sup>

5  
6 **Systemic lupus erythematosus.** This is an autoimmune disease that predominantly affects women (10:1)  
7 with an incidence of 5.6 per 100,000 people.<sup>362</sup> Oral, nasal (nasal skin or vestibule), and pharyngeal  
8 mucosal lesions are seen in 9-18% of cases.<sup>347,362</sup> Diagnosis requires a detailed medical history, physical  
9 examination, and laboratory tests (ANA [antinuclear antibody] or anti-dsDNA [double stranded  
10 DNA]).<sup>344,363</sup>

11  
12 Therapy with corticosteroids, immunomodulators (e.g., prasterone, vitamin D, hydroxychloroquine), or  
13 immunosuppressants (e.g., azathioprine, cyclophosphamide, mycophenolate) are used for symptom  
14 control. Belimumab, an anti-BAFF [B cell activating factor] monoclonal antibody, is the only therapy  
15 currently utilized for extrarenal disease due to its modest effect on lupus activity.<sup>364</sup> Anifrolumab, an  
16 IFN-type 1 monoclonal antibody, has substantial evidence in effectively and safely treating moderate to  
17 severe active lupus.<sup>365</sup>

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19

## 20 V.B.15. Rhinosinusitis

21

22 The symptoms of AR may overlap with those of rhinosinusitis.<sup>366,367</sup> Rhinosinusitis is a broad term that  
23 includes the diagnosis of acute rhinosinusitis (ARS), RARS, and CRS. Symptomatically, these conditions  
24 are characterized by nasal obstruction, nasal congestion, facial pressure or pain, anterior or posterior  
25 nasal discharge and anosmia/hyposmia.<sup>173,366</sup> AR and rhinosinusitis have several overlapping symptoms,  
26 namely rhinorrhea and nasal congestion, which can make it challenging to differentiate these  
27 conditions.<sup>366,368,369</sup> It is important to differentiate between AR and rhinosinusitis to ensure the correct  
28 diagnosis and subsequent treatment.

29

30 ARS is defined as the sudden onset of sinonasal symptoms outlined above with associated sinonasal  
31 inflammation that lasts less than 4 weeks – it may be viral or bacterial in nature.<sup>173,174,191,366,370</sup> In ARS,  
32 nasal discharge is often unilateral and purulent.<sup>173,191</sup> Associated facial pressure and pain is described as  
33 moderate to severe.<sup>191</sup> Viral ARS is typically present for less than 10 days, whereas a longer duration of

1 illness suggests bacterial ARS.<sup>173,191</sup> Progressive worsening over a short period of time (i.e. 5 days) is also  
2 suggestive of bacterial ARS.<sup>173,191</sup> RARS is defined as at least 4 episodes of ARS per year.<sup>173,191,370,371</sup> CRS is  
3 an inflammatory condition of the sinonasal cavity, defined as sinonasal inflammation persisting for more  
4 than 12 weeks with at least two of the sinonasal symptoms outlined above.<sup>173,174,191,366,370</sup> In addition,  
5 patients must have objective evidence of sinonasal inflammation on either nasal endoscopy (polyps,  
6 edema, mucopurulent rhinorrhea) or on computed tomography (CT) scan of the sinuses.<sup>173,174,191,370</sup>

7  
8 Comparatively, AR is characterized by nasal obstruction, nasal congestion, clear watery rhinorrhea  
9 (anterior or posterior) and allergic symptoms such as nasal itching, sneezing, and allergic  
10 conjunctivitis.<sup>368,369</sup> AR is not typically associated with purulent or unilateral nasal discharge. Moderate  
11 to severe facial pain is also atypical and may indicate an episode of ARS or an acute exacerbation of  
12 CRS.<sup>173,191,366</sup> AR symptoms are variable in duration and tend to have daily and/or local environmental  
13 fluctuations.<sup>173,191,366</sup> As a result, AR symptoms have been classified by duration (intermittent vs.  
14 persistent) and severity. AR symptoms, in general, present for at least 1 hour on most days; however,  
15 patients may have symptom-free intervals.<sup>368,369</sup> AR symptoms are also exacerbated by exposure to  
16 allergens in a time-dependent fashion.<sup>368</sup> The early reaction occurs immediately after exposure, lasting  
17 approximately 30 minutes (sneezing, nasal/ocular itching, rhinorrhea), while the late reaction occurs up  
18 to 6 hours after exposure (nasal obstruction and congestion).<sup>368</sup> Superimposed late reactions from  
19 multiple exposures may blunt the manifestation of acute phase symptoms and make the diagnosis of AR  
20 less obvious.

21  
22 When attempting to determine whether a patient has AR, ARS, RARS or CRS, it is important to elicit the  
23 onset and duration of symptoms. A history of allergic symptoms or allergen exposure-related symptoms  
24 is more consistent with AR.<sup>368,369</sup> The development of acute, unilateral, moderate to severe symptoms,  
25 and nasal purulence may be consistent with ARS or RARS.<sup>173,191,366</sup> A prolonged duration of symptoms  
26 (greater than 12 weeks) as well as presence of smell loss, which is not as common in AR, should raise  
27 suspicion for CRS and prompt further investigation.<sup>173,191,366</sup> Of note, these conditions are not mutually  
28 exclusive. It is possible to have concurrent AR and rhinosinusitis, and this should be considered when  
29 patient symptomatology or response to treatment does not fit a single diagnosis.<sup>173,366,367</sup> (*See Section*  
30 *XIII.B. Associated Conditions – Chronic Rhinosinusitis for additional information on this topic.*) Careful  
31 consideration of these symptoms and environmental triggers may help guide clinicians to the correct  
32 diagnoses.



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### 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.<sup>372</sup> Septal deviations often have an asymmetry in airflow, with one side being more obstructed than the other.<sup>373-375</sup> Nasal valve collapse is often associated with obstruction on inspiration or during exercise.<sup>372,373,376</sup> 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.<sup>377</sup> The majority of these structural conditions should be evident on a physical examination including nasal endoscopy.

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

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.<sup>385</sup> Unlike AR, CSF rhinorrhea is most commonly unilateral and often reproducible with positional maneuvers.<sup>385</sup> While many CSF leaks are spontaneous, a history of significant head trauma or previous sinonasal surgery

1 preceding the onset of symptoms should raise suspicion for a CSF leak over AR.<sup>279,386</sup> Retained foreign  
 2 bodies or rhinolithiasis can also cause nasal obstruction and rhinorrhea, though these are usually  
 3 associated with unilateral symptoms and purulent nasal drainage.<sup>279,387,388</sup> Disorders which affect  
 4 mucociliary clearance, including primary ciliary dyskinesia or cystic fibrosis can also lead to nasal  
 5 obstruction and rhinorrhea.<sup>389,390</sup> These persistent rhinitis symptoms without allergic variation, with  
 6 viscous secretions and systemic organ dysfunction are not consistent with AR and should raise suspicion  
 7 for alternative diagnoses.<sup>373,389</sup>

8  
 9 There is increasing evidence suggesting an association between reflux disease and sinonasal  
 10 symptoms.<sup>391</sup> Reflux disease (gastroesophageal, laryngopharyngeal) has been associated with nasal  
 11 congestion and postnasal drip.<sup>392,393</sup> Congestion and inflammation of the nasal mucosa may result from  
 12 acidic content directly affecting the mucosa or from esophageal-nasal reflexes triggered by the vagal  
 13 nerve.<sup>391,393</sup> Reflux symptoms may warrant treatment but whether this improves sinonasal symptoms or  
 14 not is unclear.<sup>391</sup>

15  
 16 While many of these non-rhinitis conditions have symptoms that overlap with AR, a careful assessment  
 17 of the laterality, timing and associated symptoms can help differentiate these conditions from AR.  
 18 Similarly, a careful physical examination and nasal endoscopy will aid in identifying the correct diagnosis.  
 19 A high degree of clinical suspicion will help clinicians accurately diagnose AR versus alternative  
 20 diagnoses.

21  
 22 **TABLE V.B.16. Allergic rhinitis differential diagnosis: non-rhinitis conditions**

Category	Examples	Potential differentiating symptoms
<b>Anatomical</b>	Septal deviation Turbinate hypertrophy Nasal valve collapse Piriform aperture stenosis Choanal atresia	Asymmetric airflow Obstruction on inspiration or during exercise
<b>Neoplastic</b>	Papillomas Hemangiomas Encephaloceles Osseous lesions (osteoma, fibrous dysplasia, ossifying fibroma) Congenital masses (dermoid, dacryocystocele) Carcinomas Melanomas Lymphomas	Unilateral nasal obstruction Unilateral rhinorrhea Mucopurulent rhinorrhea Progressive worsening of symptoms Epistaxis Hypoesthesia Visual changes Epiphora Trismus Dental changes

<b>Other</b>	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
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21

## 1 VI. Pathophysiology and mechanisms

### 2 VI.A. IgE-mediated allergic rhinitis

#### 3 VI.A.1. IgE/IgE-receptor cascade

4  
5  
6 In the last several years, much has been learned about the immunologic cascade that follows antigen  
7 cross-linking of IgE bound to cellular receptors. Three different IgE receptors have been described. The  
8 type I high-affinity IgE receptor (FcεRI) is found on mast cells and basophils through which it mediates  
9 cellular degranulation and cytokine production.<sup>1</sup> It is also found on dendritic cells and macrophages  
10 where it mediates the internalization of IgE-bound antigens for processing and presentation, and  
11 facilitates production of cytokines promoting the Th2 immune response.<sup>1</sup> The low affinity (cluster of  
12 differentiation (CD)23/FcεRII receptor is found on macrophages and epithelial cells and mediates the  
13 uptake of IgE-antigen complexes.<sup>2</sup> FcεRIII is expressed by B cells and regulates IgE production and  
14 facilitates antigen processing and presentation.<sup>3</sup> This section will focus on the cascade that follows  
15 activation of the high-affinity receptor FcεRI.

16  
17 FcεRI consists of an α chain which is a transmembrane protein that binds the IgE FC portion, a β chain  
18 which is a receptor-stabilizing and signal-amplifying subunit with four transmembrane domains, and  
19 disulfide-linked dimeric γ chains which act as signal-triggering subunits.<sup>4</sup> Secreted IgE binds to FcεRI on  
20 mast cells or basophils. When an antigen binds or cross-links two IgE/FcεRI complexes, activation of  
21 mast cells and basophils is triggered and degranulation occurs causing the release of histamine,  
22 tryptase, cysteinyl leukotrienes, and platelet activating factors among others.<sup>3,5</sup> This process is known as  
23 the early allergic response and is associated with vasodilation, edema, and bronchoconstriction.<sup>3,5</sup>

24  
25 Within the β and γ subunits of the FcεRI receptor is the immunoreceptor tyrosine-based activation motif  
26 (ITAM). Following receptor stimulation, ITAM on the β and γ subunits undergo phosphorylation by Src  
27 family protein tyrosine kinases and recruitment of another tyrosine kinase Syk.<sup>6</sup> Through conformational  
28 changes and tyrosine phosphorylation, Syk is activated.<sup>7</sup> Syk is critical for most activation events within  
29 the mast cell which lead to degranulation as well as the de novo synthesis and production of  
30 chemokines, cytokines, and lipid mediators.<sup>8,9</sup>

31  
32 Within a few hours of IgE receptor stimulation by IgE cross-linking, activated mast cells secrete a large  
33 amount of newly synthesized proteins, a result of de novo gene transcription prompted by receptor

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

6  
7 Cross-linking of the FcεRI receptors by antigen bound IgE leads to the activation of several transcription  
8 factors. These signal dependent transcription factors including signal transducer and activator of  
9 transcription (STAT)-5, nuclear factor of activated T cells (NFAT), activator protein (AP)-1, nuclear factor  
10 (NF)-κB, and early growth response (EGR)-2 function in FcεR1 upregulated gene expression.<sup>14</sup> Ultimately,  
11 this complex process of de novo gene transcription, and upregulation/down regulation of genes results  
12 in the production and release of cytokines and chemokines.<sup>15</sup> This includes IL-3, IL-4, IL-5, IL-13, C-C  
13 chemokine ligand-5 (CCL5), and granulocyte-macrophage colony stimulating factor (GM-CSF).<sup>16-18</sup> The  
14 effect of these cytokines and chemokines is the recruitment of inflammatory cells including eosinophils,  
15 basophils, neutrophils, macrophages, and T cells.<sup>16-18</sup> This is referred to as the late allergic response  
16 characterized by airway inflammation, hyperresponsiveness, airway remodeling, and mucus  
17 hypersecretion.<sup>5</sup>

18  
19

## 20 VI.A.2. Systemic mechanisms and manifestations of allergic rhinitis

21

22 Allergic diseases such as asthma, atopic dermatitis (AD), and AR share a common inflammatory pathway  
23 involving the adaptive immune system mediated by sIgE. The adaptive immune system can generally be  
24 categorized into Th1, Th2, and Th17 responses, named after the Th cells that orchestrate the  
25 corresponding immune responses. The Th1 response provides defense against intracellular pathogens,  
26 and has interferon IFN-γ as its canonical cytokine.<sup>19</sup> The Th17 response also provides defense against  
27 pathogens, such as bacteria and fungi, and is characterized by neutrophilic inflammation and its  
28 canonical cytokine, IL-17. The Th2 response provides defense against parasites and is marked by the  
29 expression of IL-4, -5 and -13.<sup>19,20</sup> These ILs represent integral mediators responsible for driving IgE- and  
30 eosinophil-associated inflammation that often characterizes atopic disease.<sup>19</sup> Type 2 innate lymphoid  
31 cells (ILC2s) are a newly characterized group of effector cells of the innate immune response that also  
32 have the capacity to produce large quantities of the type 2 cytokines, especially IL-4, IL-5 and IL-13,

1 playing a critical early role in the initiation of Th2 responses to aero-allergens during allergic  
2 inflammation.<sup>21-23</sup>

3  
4 In AR, aeroallergens are inhaled onto the nasal mucosa. When mucosal epithelial integrity is disrupted,  
5 epithelial cells release alarmins and other damage-associated molecular patterns (DAMPs).<sup>24,25</sup> These  
6 mediators possess pro-inflammatory properties and have been shown to assist in initiating and  
7 maintaining a Th2 immune response.<sup>26,27</sup> For example, thymic stromal lymphopoietin (TSLP) is an  
8 important alarmin which can promote the recruitment of inflammatory cells (i.e. eosinophils, basophils  
9 and mast cells) and the maturation of dendritic cells into Th2-promoting subtypes, further enhancing  
10 Th2 polarization.<sup>28-31</sup> It is theorized that in AR, this pathway is similarly activated and there are  
11 aeroallergens (e.g., dust mite allergens), that directly compromise the mucosa through protease activity  
12 or by activating pattern recognition receptors of which the Toll-like receptor family is the most well-  
13 known.<sup>32</sup>

14  
15 On first exposure to an allergen, dendritic cells in the nasal mucosa process the allergen and then  
16 migrate to present it on MHC class II to naive helper T (Th0) cells in secondary lymphoid organs.<sup>20</sup> Once  
17 exposed to antigen/allergen in the appropriate costimulatory environment, Th0 cells become activated  
18 and differentiate into allergen-specific Th2 cells. Th2 differentiation requires co-stimulation via the  
19 interaction of CD28 on T cells with CD80 and CD86 on antigen presenting cells and the presence of IL-  
20 4.<sup>33,34</sup> IL-4 binds STAT-6 on Th0 cells which activates the master switch GATA-3 (GATA-binding protein  
21 3).<sup>28</sup> As a result, Th2 cells release cytokines such as IL-4, IL-5 and IL-13 which activate B cells and initiate  
22 IgE class switching.<sup>20,32</sup> Class switching occurs via up-regulation of  $\epsilon$ -germline gene transcription and  
23 clonal expansion, as well as the interaction between surface CD40 ligand on T cells with surface CD40 on  
24 B cells. This process allows B cells to differentiate into plasma cells that produce allergen-specific IgE  
25 (sIgE).<sup>33</sup> The end result is the creation of a pool of memory Th2 and B cells.<sup>32</sup> sIgE is released into  
26 circulation and binds to high-affinity Fc $\epsilon$ RI IgE receptors on the surface of effector cells such as mast  
27 cells and basophils.<sup>32</sup> During IgE-mediated reactions, PGD<sub>2</sub> which is mainly synthesized by mast cells has  
28 recently been shown to exert an important role in recruitment and activation of ILC2s, in addition to  
29 leukotrienes, and innate cytokines.<sup>35,36</sup> Crosslinking of IgE on the surface of these effector cells causes  
30 degranulation and the release of inflammatory mediators such as histamine and leukotrienes, resulting  
31 in classic symptoms of AR.

32

1 AR has traditionally been thought of as resulting from an immune response leading to systemic IgE  
2 production.<sup>37,38</sup> The classic example of systemic reactivity in AR is the cutaneous reaction elicited during  
3 traditional skin testing.<sup>39</sup> The concept of LAR is discussed in the section that follows.

4  
5

### 6 VI.A.3. Local IgE production

7

8 When systemic allergen sensitization is present, sIgE is detected via serum in vitro testing or allergy skin  
9 testing. However, systemic allergy testing methods do not provide direct information regarding the  
10 target-organ immunological response.<sup>40-43</sup> Studies in recent decades support the concept of local IgE  
11 production. LAR is characterized by allergic nasal symptoms in patients with negative systemic allergy  
12 testing. However, in these patients, positive nasal provocation test NPT and/or detection of nasal sIgE  
13 and/or positive basophil activation test (BAT) demonstrate a localized allergic response.<sup>41,43-48</sup>

14

15 Local IgE production has been demonstrated in patients with AR<sup>49-52</sup> and LAR.<sup>53-62</sup> In LAR, sIgE in nasal  
16 secretions has been confirmed after natural exposure,<sup>54,55</sup> after controlled exposure to aeroallergens by  
17 NPT,<sup>55,57-59,63</sup> and also during periods of non-exposure to aeroallergens.<sup>54,55</sup> It is theorized that in LAR  
18 individuals, sIgE produced at the mucosal level can be enough to sensitize nasal effector cells, but not to  
19 reach skin mast cells or to be detected in the free state in serum.<sup>64</sup>

20

21 The immunopathology of local sIgE production in LAR is not completely understood. Flow cytometry of  
22 nasal lavage confirms a nasal IgE-mediated inflammatory response in LAR patients, with increased  
23 eosinophils, basophils, mast cells, CD3+ and CD4+ T cells, and local sIgE, along with characteristic pro-  
24 inflammatory mediators such as tryptase and eosinophil cationic protein (ECP) during natural exposure  
25 to aeroallergens.<sup>42,53-65</sup>

26

27 NPT studies to assess potential mechanisms of local sIgE production have revealed characteristic  
28 immediate/early and late phases of the allergic response in LAR. In these patients, nasal mucosal  
29 reaction to administered allergen is immediate and occurs mostly by stimulation of IgE-coated mast cells  
30 and basophils. This results in the secretion of tryptase, histamine, cys-leukotriene, and PGD<sub>2</sub>, which  
31 then stimulate the local sensory nerve and vascular receptors in nasal mucosa. Mast cells secrete  
32 chemotactic agents and platelet activating factor, contributing to the development of inflammation with  
33 local production of sIgE and eosinophil activation.<sup>61</sup> As a result, serum IL-5 levels increase and IL-5 is

1 transported into the pulmonary circulation, causing increased exhaled nitric oxide and bronchial  
2 hyperreactivity.<sup>60,62</sup> Finally, in a study by Campo et al,<sup>66</sup> following NPT with nOle e 1 (the most significant  
3 allergen of *Olea europaea*), 83% of LAR *Olea europaea* sensitized subjects responded. Further, ECP levels  
4 in nasal lavage significantly increased after NPT in LAR patients indicating that secretion of ECP following  
5 NPT could potentially act as a confirmatory biomarker.

6

7 Additional studies have shown that sIgE produced in the nasal mucosa of patients with LAR sensitized to  
8 HDM and pollens has the capability of binding to the FcεRI high-affinity receptor on basophils.<sup>49,67</sup>  
9 Furthermore, the sIgE-related mechanism of basophil activation in LAR has been demonstrated by  
10 performing BAT with wortmannin pretreatment, showing reversal of positive results when wortmannin  
11 was added to the assay.<sup>67</sup> These findings suggest that after local IgE production, basophils might be the  
12 first target cells for sIgE produced in the target organ transported from the site of inflammation (nasal  
13 mucosa) to the general circulation.<sup>68</sup>

14

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

21

22

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

24

25 AR is thought of as mainly an IgE-driven response.<sup>79</sup> Nonetheless, our awareness and comprehension of  
26 the important contributions of the nasal innate immune response to the pathogenesis of AR has grown  
27 immensely in recent years.<sup>80</sup>

28

29 The pathophysiological mechanisms of inflammatory airway diseases are associated with large biological  
30 networks involving the environment and the host.<sup>81</sup> The nasal epithelium first encounters aeroallergens  
31 in the host. Disruption of epithelial barrier function by proteolytic mechanisms, lipid-binding activity,  
32 and interactions with polysaccharides and polysaccharide molecular recognition systems of allergens  
33 may allow allergen to penetrate into local tissues, perpetuating chronic and ongoing inflammatory



1 processes.<sup>82,83</sup> This may also occur with irritants like chlorine<sup>84</sup> and air pollution.<sup>85</sup> Epithelial barrier  
2 dysfunction has been shown to contribute to the development of inflammatory diseases including AR.<sup>86</sup>  
3 However, additional research is needed to determine the extent to which primary (genetic) versus  
4 secondary (inflammatory) mechanisms drive barrier dysfunction.<sup>87</sup> (*see Section VI.G. Epithelial Barrier*  
5 *Alterations for additional information on this topic.*)

6  
7 Epithelial cells act as a physical barrier toward inhaled allergens and actively contribute to airway  
8 inflammation by detecting and responding to environmental factors. Nasal epithelial cells bear pattern  
9 recognition receptors called toll-like receptors (TLRs).<sup>81,88,89</sup> Exposure of the nasal epithelium to  
10 molecules such as allergens and pathogens results in stimulation of TLRs and the production of alarmins:  
11 IL-25, IL-33 and TSLP, which in turn activate dendritic cells, T cells and type 2 ILCs. ILCs are key players in  
12 the pathogenesis of Th2 type diseases like AR, CRSwNP, and asthma.<sup>90-92</sup> Three major subsets have been  
13 defined based on their phenotype and functional similarities to Th1 (ILC1), Th2 (ILC2), and Th17 (ILC3)  
14 cells. The release of the cytokines IL-25, IL-33, and TSLP by epithelial cells directly activate ILC2s, then  
15 they produce the prototypical type 2 cytokines IL-5 and IL-13.<sup>93</sup>

16  
17 Allergen challenge in AR subjects induces increased numbers of peripheral blood ILC2s<sup>94,95</sup> and results in  
18 and influx of ILC2 in the nasal mucosa.<sup>96</sup> Pre-treatment with INCS attenuates allergen-induced increases  
19 in ILC2s in the nasal mucosa of AR patients.<sup>97</sup> ILC2s also contribute to epithelial barrier leakiness through  
20 IL-13.<sup>98</sup> Treatment with anti-IL13 has shown significant reduction of AR symptoms,<sup>99</sup> pointing to the  
21 important role of the innate immune system in the development of symptoms and signs of disease. AIT  
22 reduces ILC2's and increases IL-10-producing ILCs in the peripheral blood of AR patients.<sup>100</sup> Moreover,  
23 the frequency of IL-10-producing ILCs correlated with improvement in clinical parameters. More novel  
24 therapies directed toward the innate immune system are in development for treatment of AR.<sup>81</sup>

25  
26

### 27 VI.C. Cellular inflammatory infiltrates

28

29 Various types of inflammation are involved at different AR stages, including sensitization, exacerbations,  
30 remodelling and remission. Different mediators orchestrate a type 2 immune response.<sup>101</sup> Most  
31 commonly a type 2 inflammatory environment is observed with Th2 cells, M2 macrophages, eosinophils  
32 and type 2 ILCs playing important roles.<sup>102</sup> Other patterns with mixed type 2 and type 3, or even type 1  
33 may arise depending on the allergen protease activity and the microbial and inorganic

1 environments.<sup>103,104</sup> As it is virtually impossible to define one inflammatory pattern, endotyping in AR  
2 seems highly important to drive personalized medicine.<sup>105</sup>

3  
4 Cellular interactions are important, including the role of a defective barrier and the release of epithelial  
5 alarmins. IL-33 acts on Type 2 ILCs and promotes mast cell degranulation through inhibition of  
6 autophagy.<sup>106</sup> In the induction of a type 2 response, IL-25 acts on Th2 cells and ILC2s while TSLP mainly  
7 activates dendritic cells.<sup>101</sup>

8  
9 Allergen-specific CD4+ T cells regulate multiple facets of allergen-specific responses: IgE production in B  
10 cells, regulation of eosinophilia by IL-5, and enhancement of type 2 inflammation by IL-9. Antigen-  
11 presenting cells, such as dendritic cells are increased in frequency, higher in maturation markers CD40<sup>107</sup>  
12 and loaded with sIgE contributing to atopy, while elimination of dendritic cells suppresses AR.<sup>108</sup>  
13 Dendritic cells are crucial in the initiation of a Th2 response, while basophils will merely amplify it.<sup>109</sup>  
14 Myeloid dendritic cells may activate ILC2s and plasmacytoid dendritic cells play important roles in AR  
15 through IL-2 and IL-6 pathway alterations.<sup>110</sup>

16  
17 Innate and effector mechanisms affect allergic disease.<sup>111</sup> A skew towards Th2 with GATA-3  
18 overexpression are hallmark findings in AR mucosa.<sup>112,113</sup> Tissue  $\gamma/\delta$ -T cells and CD4+ memory T cells are  
19 increased.<sup>114</sup> Different type 2 cytokines orchestrate the production of sIgE, eosinophilia, mucus, tissue  
20 migration of Th2 cells and regulation of tight junctions (TJ) and barrier integrity.<sup>101,115-118</sup>

21  
22 Distinct phenotypes of regulatory T cells (Treg) subsets include CD4<sup>+</sup>CD25<sup>+</sup> Forkhead-box P3 (FOXP3)+  
23 Tregs and type 1 Tregs.<sup>119-121</sup> Allergen-specific Tregs suppress other T cells, IgE, eosinophils and dendritic  
24 cell maturation to control AR development. They increase in the mucosa after AIT correlating with  
25 clinical remission.<sup>122-124</sup> The ratio between effector and regulatory cell-types determines whether an  
26 allergic response is triggered. Regulatory B cells and Th17 cells may play important roles in intolerance  
27 and AR.<sup>125,126</sup> Increased levels of CD4+T cells were identified in AR patients' blood with reduced CXCR3  
28 expression.<sup>127</sup>

29  
30 ILCs, introduced and described in prior sections, lack rearranged antigen receptor or lineage markers. In  
31 addition to their contribution to type 2 inflammation, ILC1s increase in local sinonasal infections and  
32 ILC3s increase more in remodeling. ILC2s closely interact with epithelial cells and others leading to a

1 type 2 favoring cytokine environment.<sup>128</sup> They particularly open epithelial barriers and make the tissues  
2 prone to environmental insults.

3  
4 IgE-producing B cells reside in the lymphoid follicles of the Waldeyer's ring where antibodies are  
5 transferred to the mucosa.<sup>129</sup> However, B cells and plasma cells also produce IgE locally which is  
6 becoming a hallmark finding of AR.<sup>130</sup> In AR, numbers of circulating memory B cells were found to be  
7 increased.<sup>131</sup>

8  
9 Major basic protein (MBP) positive and activated eosinophils can increase locally during the pollen  
10 season. This increase is not observed in the T lymphocyte subsets, neutrophils, and macrophages. Yet,  
11 mast cells seem to infiltrate the mucosa and the submucosal layer similarly to eosinophils.<sup>132</sup>

12  
13 Both mast cell and basophil granulocyte degranulation are relevant components of the early and late  
14 phases of a type I hypersensitivity reaction after an allergen is encountered and crosslinking of IgE  
15 occurs.<sup>133,134</sup> Basophils accumulate within one hour after allergen provocation in the lamina propria.<sup>135</sup>

16  
17 Adhesion molecules are upregulated and chemoattractants facilitate the influx of inflammatory cells  
18 during the late phase.<sup>136</sup> This allows for further accumulation of cells promoting remodelling with  
19 upregulation of matrix metalloproteinases and angiogenic factors.<sup>137</sup>

20  
21

## 22 VI.D. Cytokine network and soluble mediators

23  
24 The pathophysiology of AR involves IgE-mediated inflammation which is a type 2 immune response. IgE  
25 crosslinking results in mast cell activation and release of inflammatory cytokines such as IL-4, IL-5, IL-6,  
26 IL-13, IL-25, and IL-33 as well as preformed bioactive mediators and newly formed mediators including  
27 histamine, leukotrienes, prostaglandins, and kinins. These cytokines regulate the allergic inflammatory  
28 cascade through induction of IgE synthesis, upregulation of IgE production, and production of other  
29 cytokines and chemokines from epithelial cells which results in the mucosal recruitment of inflammatory  
30 cells.<sup>138-140</sup> Numerous cell types act as sources for type 2 cytokines including T cells, nasal epithelial cells,  
31 ILC2s, mast cells, and eosinophils.

32

1 Nasal epithelial cells secrete inflammatory cytokines including TSLP, IL-25, and IL-33.<sup>141</sup> TSLP is a critical  
2 upstream cytokine for ILC2s, mast cells, dendritic cells, T cells, and basophils.<sup>142-144</sup> IL-25, IL-33, and TSLP  
3 secreted by epithelial cells act on surrounding cells resulting in the release of IL-4, IL-5, and IL-13 which  
4 recruit additional inflammatory cells leading to a type 2 response.<sup>145</sup> Nasal epithelial cells are also a  
5 source for IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)- $\alpha$ , and through these signals, play a role in the  
6 migration and activation of eosinophils, basophils, and Th2 cells.<sup>146</sup>

7  
8 ILC2s are tissue resident cells that can be stimulated to secrete IL-4, IL-5, and IL-13 by the alarmins TSLP,  
9 IL-25, and IL-33 (which are secreted by epithelial cells or myeloid dendritic cells) via the IL-33/ST2  
10 pathway.<sup>110,145,147</sup> Survival factors or co-stimulators including IL-2, IL-4, IL-7, IL-9, TNF-like cytokine 1A  
11 (TL1A) and glucocorticoid-induced TNF receptor ligand (GITRL) serve to maintain basic functionality of  
12 ILC2s.<sup>102</sup> Both TL1A and GITRL are responsible for ILC2 proliferation and the release of type 2 cytokines  
13 from these cells.<sup>148</sup> IL-2, IL-7, and IL-9 are regulatory factors necessary for the development,  
14 maintenance, and survival of ILC2s.<sup>148</sup> IL-2 activates ILC2s and induces them to secrete IL-9, which is also  
15 critical for maintaining the activity and survival of ILC2s.<sup>90,149,150</sup>

16  
17 Airway mast cells are a source of type 2 cytokines, proinflammatory cytokines, chemokines and  
18 TSLP.<sup>138,151-153</sup> IL-13 from mast cells plays a role in mast cell-induced local IgE synthesis by B cells, which  
19 in turn upregulate Fc $\epsilon$ RI expression on mast cells.<sup>154</sup> Along with IL-4 and IL-13, TNF- $\alpha$ , a proinflammatory  
20 cytokine produced by mast cells, enhances the production of thymus and activation-regulated  
21 chemokine (TARC), TSLP, and eotaxin from epithelial cells.<sup>139</sup> This suggests a crucial interplay between  
22 mast cells and epithelial cells in promoting and regulating the allergic inflammatory cascade.

23  
24 Both mast cells and epithelial cells directly produce or up-regulate eosinophil chemoattractants  
25 including eotaxin, macrophage/monocyte chemotactic protein 4, RANTES (regulated upon activation,  
26 normal T cell expressed and presumably secreted) , and cysteinyl leukotrienes.<sup>155-157</sup> Eosinophils are a  
27 key factor in type 2 inflammation and are regulated by IL-4, IL-5, and IL-13. These cells are also a major  
28 source of inflammatory cytokines including macrophage migration inhibitory factor, eosinophil  
29 peroxidase, and nerve growth factor.<sup>158,159</sup>

30  
31 Finally, Th17 cells may play an important role in AR. The major cytokine of Th17 cells is IL-17. Six  
32 isoforms of IL-17 exist denoted as IL-17a-IL-17f.<sup>160</sup> Currently, it is understood that IL-17a and IL-17f play

1 roles in allergic-type inflammation.<sup>160</sup> Studies have shown that the production of IL-1, IL-6, IL-8, matrix  
2 metalloproteinases, and TNF- $\alpha$  can be induced via IL-17 receptors on different cell types.<sup>126</sup> A recent  
3 systematic review by Hofmann et al<sup>126</sup> evaluated 10 studies looking at IL-17 levels in either serum or  
4 nasal fluid in patients with AR. In all studies, elevated IL-17 levels in either serum or nasal fluid were  
5 observed in patients with AR compared to controls. These findings could indicate that Th-17 cells and  
6 associated type 3 inflammation play a role in the pathophysiology of AR, but the exact role remains  
7 unclear.

8  
9

## 10 VI.E. Neural mechanisms

11

12 The pathophysiology of AR is heavily influenced by sensory neurons, axonal reflexes, and  
13 neurotransmitters.<sup>161</sup> The trigeminal sensory, sympathetic, and parasympathetic nervous systems work  
14 in concert to form a protective barrier in the upper airway mucosa and regulate epithelial, glandular,  
15 and vascular processes.<sup>162</sup> Branches of the trigeminal nerve innervate blood vessels and mucous  
16 membranes in the nasal cavity. The trigeminal nerve has nociceptive A $\delta$  and C fibers that are stimulated  
17 by physical and chemical ligands as well as products of allergic reactions.<sup>163</sup> Inflammatory mediators  
18 (e.g. bradykinin, histamine, acetylcholine, capsaicin) are capable of activating sensory neurons in the  
19 trigeminal nerve, largely through transient receptor potential (TRP) ion channels.<sup>164-167</sup> Through  
20 repeated depolarization, lasting changes develop in TRP channels as demonstrated for the TRP cation  
21 channel subfamily V member 1 (TRPV1) and subfamily A member 1 (TRPA1). This leads to  
22 hyperexcitability of neurons in AR patients through changes in stimulation threshold and membrane  
23 potentials<sup>166,168</sup> Studies investigating treatment with intranasal capsaicin, the prototypic ligand for  
24 TRPV1, have demonstrated significant improvement in nasal congestion, sinus pressure, pain and  
25 headache within five minutes after administration in patients with non-allergic and mixed rhinitis but  
26 not clearly in AR.<sup>169</sup> Furthermore, treatment with azelastine nose spray, approved by the FDA for  
27 treatment of AR and non-allergic rhinitis, has been shown to downregulate TRP receptors.<sup>164,165</sup>

28

29 Depolarization of these nociceptive channels on sensory nerves leads to the release of neuropeptides  
30 including substance P, calcitonin gene-related peptide (CGRP), and neurokinin-A.<sup>165</sup> Substance P  
31 receptors are located on nasal epithelium, glands, and arterial and venous vessels, and sinusoidal vessels  
32 which leads to glandular secretion, increased vessel permeability, edema, vasodilation, and further  
33 activation of inflammatory cells.<sup>163,167,168</sup> Substance P has been recognized as a short acting vasodilator

1 while CGRP is a long-acting arterial vasodilator found in increased concentrations in AR patients  
2 compared to controls.<sup>168,170,171</sup> Substance P and CGRP also activate mast cells to release more  
3 inflammatory mediators, such as histamine, that further propagate the hypersensitivity reaction.<sup>166</sup>  
4 Neurokinin A, a tachykinin that acts similarly to substance P, causes increased vascular permeability,  
5 vasodilation, bronchial smooth muscle contraction, mucus secretion, mast cell degranulation, as well as  
6 leukocyte chemotaxis and activation.<sup>163,165,168</sup> Understanding these biologic pathways has led to  
7 investigation of novel therapies including bradykinin antagonists and TRP receptor calcium ion channel  
8 blockers.<sup>168</sup>

9  
10 Parasympathetic and sympathetic nerves also play a central role in the neural response to allergens.  
11 Acetylcholine and vasoactive intestinal peptide are released during the parasympathetic response  
12 leading to mucous cell secretion, vasodilation, and epithelial cell activation via muscarinic receptors  
13 found on the nasal epithelium, submucosal glands, and blood vessels.<sup>167,168</sup> Sympathetic nerves respond  
14 to neurokinin Y leading to vasoconstriction and nasal decongestion.<sup>168</sup> A widely accepted mechanism of  
15 non-allergic rhinitis has been an imbalance between the sympathetic and parasympathetic response  
16 leading to parasympathetic overactivity and manifests as nasal congestion, rhinorrhea, and postnasal  
17 drainage.<sup>172</sup>

18  
19 The neuropeptides previously discussed are significantly increased in nasal lavage of AR patients  
20 compared to controls.<sup>170,173</sup> Upregulation of these inflammatory mediators and neuropeptides leads to  
21 peripheral sensitization of nerve fibers which can subsequently cause central sensitization or a lowered  
22 threshold for a given stimulus.<sup>170</sup> Neural growth factor (NGF) is a neurotrophin that leads to survival and  
23 growth of neurons that express an NGF receptor. Sources of NGF, such as mast cells and eosinophils, are  
24 chronically activated in AR patients and may account in part for the nasal hyper-responsiveness,  
25 increased sensory nerve concentration, and increase in neuropeptides that further propagate this  
26 inflammatory response.<sup>173-176</sup> Unfortunately, clinical trials investigating neuropeptide and TRP  
27 antagonists in seasonal AR have been unsuccessful this far.<sup>177-179</sup>

28  
29

## 30 VI.F. Histologic and epithelial changes

31

32 The nasal mucosa warms, conditions, and humidifies air entering the respiratory tract. It is also the first  
33 line of defense against pathogens, through both the innate and acquired immunity.<sup>180-182</sup> The structure

1 of the nasal mucosa is well adapted to carry out these roles. The normal sinonasal epithelium forms a  
2 physical barrier, comprised of pseudostratified columnar ciliated and non-ciliated cells, goblet cells and  
3 basal cells. The epithelial cells are linked by apical junctional complexes.<sup>117</sup> At the superior nasal septum  
4 and superior turbinate, olfactory epithelium is also present, which consists of bipolar olfactory receptor  
5 neurons, sustentacular (supporting) cells, basal cells and Bowman glands.<sup>183</sup> Overlying the sinonasal  
6 epithelium is a mucus blanket, which consists of water, mucin glycoproteins and antimicrobial peptides  
7 such as lactoferrin, lysozyme and defensins.<sup>184</sup> The mucus blanket forms a double layer, consisting of an  
8 inner serous (sol or periciliary) layer and an outer viscous (gel) layer. The basement membrane  
9 separates the epithelium from the submucosa, or lamina propria.

10

11 In the presence of conditions that impair mucosal integrity, the epithelium releases alarmins and other  
12 DAMPs or pathogen-associated molecular patterns (PAMPs) that initiate repair mechanisms and induce  
13 protective inflammation.<sup>32,185</sup> The epithelial inflammatory response to allergens is a key feature of AR.  
14 The histological characteristics of airway inflammation are commonly goblet cell hyperplasia, mucus  
15 hypersecretion, basal membrane thickening and airway smooth muscle hyperplasia.<sup>186</sup> This  
16 inflammatory response translates into mucosal edema, increased mucosal secretions and hyper-  
17 responsiveness common in AR. Allergens (e.g., *Alternaria* and HDM) are shown to enhance the chemical  
18 mediator production from nasal epithelial cells, and these allergens may induce not only a type 2  
19 inflammatory response but also other, for example type 1, inflammatory responses in the nasal  
20 mucosa.<sup>187</sup> Nasal epithelial cells of AR patients showed increased expression of pro-inflammatory and IL-  
21 1 family cytokines at baseline and under stimulation, which could contribute to a micromilieu which is  
22 favorable for type 2 of inflammation.<sup>188</sup> Whether robust type 2 inflammation contributes to the  
23 development of airway remodeling in AR remains controversial. One study demonstrated that after  
24 repeated nasal allergen challenge, no differences were observed in epithelial integrity, reticular  
25 basement membrane thickness, glandular area, expression of markers of activation of airway  
26 remodeling including  $\alpha$ -smooth muscle actin (SMA), heat shock protein (HSP-47), extracellular matrix  
27 (matrix metalloproteinase [MMP]-7, MMP-9 and TIMP [metallopeptidase inhibitor]-1), angiogenesis and  
28 lymphangiogenesis for AR patients compared with healthy controls.<sup>189</sup>

29

30 The nasal lavage samples from patients with ongoing grass pollen AR showed distinct gene expression  
31 profiles and functional gene pathways which reflect their anatomical and functional origins.<sup>190</sup> Mucin  
32 production, regulated by the mucin genes MUC5AC and MUC5B in particular, is upregulated by

1 allergens.<sup>191</sup> Goblet cell hyperplasia in allergic airway inflammation is partially due to high expression of  
2 CD44v3, a surface marker for intermediate progenitor cells from basal cells.<sup>192</sup> AR may be associated  
3 with increased epithelial permeability or defective epithelial barriers as a result of decreased expression  
4 of the TJ proteins occludin and zonula occludens (ZO)-1.<sup>86</sup> Impairment of ZO proteins are observed in AR  
5 patients and dysfunction of ZOs allows allergens to pass into the subepithelium.<sup>193</sup> This may also be  
6 mediated by various factors such as histone deacetylase activity<sup>194</sup> and deficiency of the MUC1 gene.<sup>195</sup>  
7 Some allergens, such as Der p 1 in HDM, have protease activity and can directly compromise the  
8 epithelial barrier.<sup>25</sup> Dysfunction of the epithelial barrier and allergen entry into the submucosa may  
9 trigger the inflammatory cascade observed in AR. (*see Section VI.G. Epithelial Barrier Alterations for*  
10 *additional information on this topic.*)

11

## 12 VI.G. Epithelial barrier alterations

13

14 The epithelial barrier consists of different layers that defend against airborne pollutants, allergens, and  
15 pathogens, while maintaining homeostasis within the subepithelial compartment. Over 40 years ago,  
16 epithelial barrier leakiness was described in AR.<sup>196</sup> A defective epithelial barrier may facilitate allergens  
17 and pathogens entering the mucosa, thus perpetuating inflammation.

18

19 Within the supra-epithelial layer different proteins and peptides (including mucins) are found, mainly  
20 protecting against pathogens, but also against allergens. Furthermore, a large part of the nasal  
21 microbiome is found within this layer. However, improperly cleared bacteria and fungi may lead to  
22 colonization and activation of the adaptive immune system, accentuating the cycle of inflammation.  
23 Proinflammatory cytokines produced during allergic inflammation, in particular IL-13, are known to  
24 affect mucin expression (i.e., MUC5AC), and leading to viscous secretions and impairment of  
25 mucocilliary clearance.<sup>197</sup> Microbial derived short chain fatty acids also impact the epithelial barrier.  
26 Sodium butyrate leads to blocking of histone deacetylase, restoring defective TJs.<sup>198</sup> Synthetic histone  
27 deacetylase inhibitors show strong antiallergic effects in a HDM-sensitized mouse model.<sup>194</sup>

28

29 The epithelium itself creates the main barrier. Intercellular junctions are prerequisites of an intact  
30 barrier. TJs, adherens junctions, (hemi-)desmosomes and gap junctions with their connecting proteins  
31 are the main determinants of an intact epithelial barrier. They also polarize the epithelium into an apical  
32 and basolateral compartment. TJs are defective in both AR and rhinosinusitis patients.<sup>86,115</sup> Disruption of



1 different parts of the TJs in AR have been demonstrated microscopically and in functional analyses  
 2 comparing diseased mucosa with healthy controls. Type 2 cytokines like IL-4 and IL-13 can disrupt the  
 3 epithelial barrier leading to leakiness as shown by fluorescently labelled small molecule (fluorescein  
 4 isothiocyanate [FITC])-dextran assays. Pollen peptidases and Der p 1 were shown to actively disrupt the  
 5 epithelial barrier specifically at the level of TJs.<sup>199,200</sup> Interestingly, fluticasone treatment of air-liquid  
 6 interfaces in IL-4 exposed primary nasal epithelial cells could restore TJs even in the absence of  
 7 inflammatory cells. INCS are also effective ex-vivo in restoring the barrier in HDM-sensitive AR patients'  
 8 derived mucosa.

9  
 10 AR derived nasal secretions and histamine are strong disruptors of the epithelial barrier function.<sup>201</sup> Very  
 11 recently, high mobility group box-1 (HMGB1), which is increased by transforming growth factor (TGF)- $\beta$ 1  
 12 in AR, was shown to disrupt the epithelial barrier by decreasing angulin-1/LSR (lipolysis-stimulated  
 13 lipoprotein receptor) in vitro in human nasal epithelial cell cultures.<sup>202</sup> Even particulate matter (PM)-2.5,  
 14 a very fine particle found in air pollution, affects the epithelial barrier in an AR mouse model by reducing  
 15 ZO-1 expression.<sup>203</sup> TSLP seems to play an important role in AR; interestingly it increases TJ proteins thus  
 16 preserving the epithelial barrier.<sup>204</sup> Finally, epithelial to mesenchymal transition has been shown to  
 17 occur in type 2 CRS affecting the barrier function of the epithelium.<sup>205</sup> Similar findings are expected to  
 18 occur in AR.<sup>206</sup>

19  
 20 There are several features of the epithelial barrier that seem impaired in AR and can contribute to the  
 21 cycle of inflammation at different levels of the epithelium. This may contribute to the recently observed  
 22 increase in allergies worldwide.<sup>206</sup> The cause and consequence of a defective epithelial barrier in AR  
 23 remains open for additional research.

24

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

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

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

1 IL=interleukin; TJ=tight junction; ZO=zonula occludens; HDAC=histone deacetylase; AR=allergic rhinitis; HMGB-1=  
2 high mobility group box-1; LSR=lipolysis-stimulated lipoprotein receptor; HDM=house dust mite; JAM=junction  
3 adhesion molecule; TSLP=thymic stromal lymphopoietin  
4

## 6 VI.H. Vitamin D

7  
8 Vitamin D (VD3) circulates in its inactive form (25-VD3) and is converted to its active form (1,25-VD3) by  
9 1-alpha hydroxylase. VD3 is obtained from two distinct sources, diet and ultraviolet-mediated synthesis  
10 in the epidermal layer of the skin.<sup>209</sup> In the skin, ultraviolet rays promote biochemical reactions  
11 converting 25-VD3 to 1,25-VD3. The liver and kidneys also play important roles in 1,25-VD3 synthesis.  
12 The active form of VD3 binds to vitamin D receptors (VDR), ultimately modulating gene transcription and  
13 expression.<sup>210</sup> VDRs are present in several organ systems including bone, skin, intestines, kidneys, brain,  
14 eyes, heart, pancreas and immune cells.<sup>211</sup> VD3 is an important immune mediator influencing T cell  
15 activation, cytokine production, and B lymphocyte inhibition. VD3's role in AR has been a focus of  
16 investigation and the discovery of VDR on immune cells has led to research aiming to elucidate the  
17 immunomodulatory action of 1,25-VD3.  
18

19 Many immune cells, including macrophages and dendritic cells, are capable of synthesizing 1,25-VD3  
20 potentially shaping adaptive immune responses.<sup>209</sup> While conflicting data exists, most studies suggest  
21 that type 1 inflammatory cytokines (e.g. IFN- $\gamma$ , IL-2, TNF- $\alpha$ , IL-12) are suppressed by exposure to 1,25-  
22 VD3 while type 2 cytokines are upregulated.<sup>212</sup> The impact of VD3 on the Th1/Th2 balance has been a  
23 focus of research as it may potentially explain, in part, the role of VD3 in allergic diseases. In recent  
24 studies Th17 and Treg cells have been implicated in the development of AR as well, and among the  
25 various T cells, elevated VDR expression is found on differentiated Th17 cells.<sup>213-215</sup>  
26

1 Increasing numbers of epidemiological studies have linked VD3 levels with allergic disorders, especially  
2 asthma. Recent systematic reviews have demonstrated some support for VD3 in reducing asthma  
3 exacerbations, but further well-designed studies are required.<sup>216,217</sup> This has led to more recent  
4 investigations into the relationship between VD3 and AR.

5  
6 Clinical studies investigating an association between VD3 and AR are conflicting. A recent clinical study  
7 investigating the relationship between VD3 levels and allergen sensitization to 59 aeroallergens in adults  
8 demonstrated no significant association after controlling for confounders (sex, age, and winter  
9 season).<sup>218</sup> A separate cross-sectional study looking at a pediatric population (<16 years old) found a  
10 high prevalence of vitamin D deficiency in children with asthma and AR.<sup>219</sup> A recent systematic review  
11 investigating VD3 levels in AR found that prior VD3 levels were not predictive of developing AR, but  
12 lower VD3 levels were associated with higher AR prevalence in children.<sup>220</sup> The precise relationship  
13 between VD3 and AR, however, is still a subject of investigation.

14  
15 Similarly, the data on VD3 supplementation for AR is inconclusive. Multiple RCTs looking specifically at  
16 children with AR have demonstrated symptom improvement following VD3 supplementation.<sup>221,222</sup>  
17 However, a recent systematic review concluded that there is insufficient evidence to support VD3  
18 supplementation for AR prevention.<sup>220</sup> Given the widespread prevalence of VD3 deficiency and its  
19 impact upon a spectrum of health aspects, physicians should consider evaluating VD3 levels, especially  
20 in children.

21  
22 In summary, VD3 has critical immunomodulatory effects and has been implicated in other allergic  
23 disease processes such as asthma. There appears to be a stronger association between VD3 and AR in  
24 the pediatric population and assessing VD3 levels is a low-risk intervention that may provide useful  
25 information in the management of AR, as well as other aspects of health. Further research is needed to  
26 elucidate the relationship between AR and VD3.

27  
28

## 29 VI.I. Nitric oxide

30

31 The nose and paranasal sinuses are a major site of intrinsic nitric oxide (NO) production in human  
32 airways, and AR is characterized by increased release of NO.<sup>223-228</sup> NO plays several important roles in  
33 the maintenance of physiological homeostasis and regulation of airway inflammation<sup>229,230</sup> through the

1 expression of three isoforms: neuronal NO synthase (nNOS), endothelial NO synthase (eNOS), and  
2 inducible NO synthase (iNOS).<sup>231</sup>

3

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

14

15 NO also causes disruption of Treg cell-mediated tolerance. Accordingly, NO derived from iNOS and eNOS  
16 affects the differentiation of helper T cells and the effector functions of T lymphocytes.<sup>254,255</sup> The  
17 function of T cell mediated immunity can be regulated by endogenous NO at various concentrations.<sup>256-</sup>  
18 <sup>258</sup> NO secreted by activated dendritic cells plays a complicated role in restricting T cell activity, by  
19 inducing dendritic cell stimulatory capacity on T cells.<sup>259-264</sup> Therefore, NO might have potential impact in  
20 the regulation of inflammatory responses through its interaction with Treg cells.

21

22 NO further links innate and adaptive immunity, regulates the adaptive immune response<sup>265-269</sup> and is  
23 believed to participate in both type 1 and type 2 immune responses, which may depend on the  
24 concentration of NO. Type 1 inflammation is triggered by low NO concentrations and inhibited by high  
25 concentrations,<sup>270-272</sup> whereas type 2 cell proliferation can be induced by higher NO  
26 concentrations.<sup>256,273-276</sup> Moreover, NO is involved in T cell differentiation at the transcriptional level, and  
27 high levels of NO may activate Th2 transcription factors, upregulating IL-4-mediated Th2 cell  
28 differentiation.<sup>270,271</sup> In this sense, NO is a key molecule in maintaining the Th1/Th2 balance that  
29 regulates the evolution of airway inflammation.

30

31 NO is also presumably involved in the regulation of various signaling pathways related to transcription  
32 factor activation and gene expression, as well as posttranslational regulation. NF- $\kappa$ B is a key mediator

1 regulated by NO in the airway epithelial inflammatory response, which is either increased or decreased  
2 after NO exposure, dependent on the NO concentration and the time of exposure.<sup>277</sup> NO increases IL-8  
3 expression in airway epithelial cells, which may be important to initiate an inflammatory response in the  
4 airway epithelium.<sup>278,279</sup> In addition, the IL-33–ST2 axis is believed to control Th2 and Th17 immune  
5 responses in allergic airway diseases,<sup>280</sup> and the balance between oxidative stress and antioxidant  
6 responses plays a key role in controlling IL-33 release in airway epithelium.<sup>281</sup>

7

8 Therefore, expression of NO and NOS in innate and adaptive immune cells reveals new functions and  
9 modes of NO action. These are particularly notable in the control and escape of microbes, T lymphocyte  
10 differentiation, interaction with NO reaction partners, and regulation of NOS by micromilieu factors,  
11 micro RNAs, and ‘unexpected’ cytokines. However, we only understand the ‘tip of the iceberg’ regarding  
12 NO and its role in nasal mucosal physiopathology. (*See Section X.G. Evaluation and Diagnosis – Nitric  
13 Oxide for additional information on this topic.*)

14

15

## 16 VI.J. Microbiome

17

18 Humans are colonized by an estimated 100 trillion microorganisms.<sup>282</sup> The aggregate of these  
19 microorganisms that live on or within human tissue and fluids is termed the human microbiome. The  
20 microbiome is extraordinarily diverse – both within an individual at various anatomic sites and between  
21 individuals.<sup>283-286</sup> With modern technology we can use culture-independent high throughput sequencing  
22 techniques to gain insight into the composition of the microbiome among organs and individuals to try  
23 and understand its role in health and disease.

24

25 ICAR-Allergic Rhinitis 2018 presented a number of studies that linked the gut microbiome to the  
26 development of allergic disease, specifically in children.<sup>287-292</sup> However, differing methodologies, sample  
27 sizes, and culture techniques used in each study made it difficult to interpret results and draw  
28 conclusions.<sup>293</sup> In the years since then, the role of the microbiome in the development of AR has been  
29 further investigated.

30

31 In an analysis of gut microbial composition of adults with AR compared to healthy controls, Watts et  
32 al<sup>294</sup> concluded that the AR cohort had reduced overall microbial diversity, with more abundant  
33 *Bacteroidetes* and decreased *Firmicutes* phyla. Similar results were reported by Zhou et al<sup>295</sup> in a smaller

1 patient series and by Hua et al<sup>296</sup> in an evaluation of the association of the gut microbiome and self-  
2 reported allergy utilizing data from the American Gut Project. The *Firmicutes* phyla is associated with  
3 butyrate production, which is an important regulator of the intestinal barrier via TJ modulation. It is  
4 hypothesized that decreased butyrate may lead to increased pro-inflammatory molecular activity in the  
5 submucosa.<sup>294</sup> In a mouse model studying the effect of intranasal sodium butyrate in AR, Wang et al<sup>198</sup>  
6 demonstrate that nasal mucosal epithelial morphology improved and levels of pro-inflammatory  
7 markers corrected, supporting this proposed mechanism.

8  
9 Although the gut is the most well studied microbiome, the nasal microbiome may also influence  
10 pathologic states, including allergic inflammation.<sup>297</sup> In a study comparing the nasal microbiome of  
11 patients with AR, CRS, and a control group, Gan et al<sup>298</sup> did not find a significant difference in  
12 microorganism richness or diversity between the groups. Similarly, in a study evaluating the role of AIT  
13 on the nasal microbiome of patients with AR, Bender et al<sup>299</sup> showed no difference in the nasal microbial  
14 richness between patients with AR and controls, although they did conclude that AR patients have more  
15 similar microbiomes to each other than to controls. Gan et al<sup>298</sup> identified an association between  
16 *Spirochaetae* and AR, a higher abundance of *Pseudomonas* and *Peptostreptococcaceae* in AR, and lower  
17 abundance of *Lactobacillus* in AR. These findings may suggest a possible role of microbial dysbiosis as  
18 the pathogenesis of local mucosal inflammation. However, a mechanism for this is not yet elucidated  
19 and the validation of these results remains uncertain.

20  
21 Interestingly, the differentially detected microorganism species in the adult population studied by Watts  
22 et al<sup>294</sup> were not always consistent with those found in reports with children.<sup>300</sup> The reason for this is  
23 unclear. Nonetheless, the microbes present in infancy cannot be extrapolated to adults. However, there  
24 is evidence that altered DNA methylation patterns in upper airway mucosal cells during infancy  
25 contributes to the development of AR into childhood.<sup>301</sup> Longitudinal studies to understand shifts in the  
26 microbiome of AR patients over time will be required.

27  
28 While it seems apparent that microbiome biodiversity is associated with microbiome fitness and  
29 alterations are associated with disease states, including AR, there are studies that contradict this  
30 assertion.<sup>302</sup> Specific mechanisms of the microbe-host relationship are not well understood. Future  
31 research should provide a more complete understanding of the dynamic human microbiome during all

1 ages and at all anatomic sites and its impact on AR. (See Section VIII.G. Hygiene Hypothesis and Section  
2 XI.B.9. Management – Probiotics for additional information on this topic.)

3  
4

#### 5 VI.K. Unified airway

6

7 The upper and lower airways are linked anatomically, histologically, and immunologically, to form a  
8 united airway system.<sup>303</sup> Inflammation in either the upper or lower airway influences the other, giving  
9 rise to the concept of united airway disease.<sup>303,304</sup> As the development of biological treatments options  
10 progresses, understanding the unified airway system has been recently underscored.<sup>305,306</sup>

11

12 The upper and lower airways share several histological features, such as in the mucosa, which is  
13 composed of columnar pseudo-stratified epithelium and ciliated cells on a basement membrane.

14 Likewise, the submucosa of both airway portions consists of mucus glands, fibroblasts, and  
15 inflammatory cells. Differences in histology lie in the absence of smooth muscles in the upper airways,  
16 while the lower airways lack extensive sub-epithelial capillaries, arterial systems, and venous cavernous  
17 sinusoids, all of which are instrumental in oxygen exchange.

18

19 In the allergy realm, the concept of unified airway disease has arisen with the observation that upper  
20 and lower airway allergic diseases often coexist.<sup>307</sup> Indeed, evidence has uncovered the association  
21 between AR and asthma, as well as between CRS and asthma.<sup>307-309</sup> Moreover, both AR and non-allergic  
22 rhinitis have been suggested to be risk factors for asthma onset and asthma persistence, while CRSwNP  
23 has been suggested to share a common pathogenic mechanism.<sup>303</sup> Interestingly, both AR and asthma  
24 have similar hyperreactivity, further solidifying the concept a unified response between the upper and  
25 lower airways.<sup>310-312</sup>

26

27 Similarities between the upper and lower airways extend to endotypes, such as in type 2 immune  
28 responses. Type 2 inflammation is a prominent endotype in allergic diseases and can involve Th2 cells,  
29 type 2 B cells, IL-4 producing natural killer (NK)/T cells, basophils, eosinophils, mast cells, ILC2, IL-4, IL-5,  
30 IL-13, IL-25, IL-31, IL-33.<sup>79,93,313-315</sup> In general, the type 2 profile in AR and asthma is related to a good  
31 response to corticosteroids.<sup>316</sup> However, systemic corticosteroids carry serious adverse effects and side  
32 effects which generally outweigh the benefits especially in the upper airways.<sup>317,318</sup> Alternative type 2  
33 inflammation-targeted treatments include anti-IgE antibodies, anti-IL5 (mepolizumab), and anti-IL4/13

1 (dupulimab), which have been used to treat asthma - a lower airway disease - with greater efficacy.<sup>305</sup>  
2 These drugs have also been shown to be effective in the treatment of upper airway disease such as  
3 CRSwNP, due to the similarities in endotype response between upper and lower airway inflammatory  
4 diseases.<sup>319,320</sup>

5  
6 Shared characteristics between the upper and lower airways extend from acquired immune response to  
7 the role of innate immunity like epithelial barrier function and innate lymphoid cells.<sup>321-325</sup> (*See Section*  
8 *VI.B. Non-IgE-mediated Inflammation in Allergic Rhinitis for additional information on this topic.*)

9 Mechanisms proposed for the interaction between upper and lower airway dysfunction include altered  
10 breathing patterns, nasal-bronchial reflex, and uptake of inflammatory mediators in the systemic  
11 circulation.<sup>326</sup> Most convincingly, AR may result in nasal blockage and the preference for oral breathing,  
12 which is associated with asthma.<sup>327</sup> Additionally, small molecules such as molds and cat dander -- which  
13 may pass through the upper airway into the lower airway -- are associated with an increased risk for  
14 asthma; larger molecules such as tree and grass pollen, are primarily associated with upper airway  
15 symptoms.<sup>328</sup> The evidence supporting other hypotheses are weak. Although a clear relationship exists  
16 between postnasal drip and cough, the relationship between nasal secretions and its contact with  
17 bronchial mucosa remains unclear, since radio-labelled allergen deposited in the upper airway it is not  
18 detected in the lower airway.<sup>329</sup> Instead, stimulation of pharyngolaryngeal receptors has been suggested  
19 as the more likely cause of a postnasal drip-related cough.<sup>328</sup> Likewise, evidence supporting nasal-  
20 bronchial reflex as an important contributor to the unified airways is lacking. Nasal allergen challenge  
21 could be blocked with a vasoconstrictor but not with lidocaine, and the lower airway responses after  
22 allergen challenge were generally more delayed than would be expected following a nasal-bronchial  
23 reflex.<sup>328</sup>

24  
25 Allergen provocation studies have provided a greater understanding of the nasal-bronchial interaction in  
26 allergic airway disease. In patients with AR, segmental bronchial provocation, as well as nasal  
27 provocation, induced allergic inflammation in both the nasal and bronchial mucosa.<sup>330-332</sup> Presumably,  
28 absorption of inflammatory mediators (e.g., IL-5 and eotaxin) from sites of inflammation into the  
29 systemic circulation results in the release of eosinophils, basophils, and their progenitor cells from the  
30 bone marrow.<sup>333</sup> The systemic allergic response is further characterized by increased expression of  
31 adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and E-selectin, on nasal and  
32 bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue.<sup>332</sup> Increases



1 in CD34+ cells capable of eosinophil differentiation, as well as other circulatory mediators (IL-5, eotaxin,  
 2 and cysteinyl leukotrienes), are associated with impaired lung function parameters and enhanced  
 3 mucosal inflammation in asthmatic patients<sup>333</sup> and can be inhibited by local corticosteroids in rhinitis  
 4 patients.<sup>334</sup> Supporting evidence suggests that treatment with biologics against type 2 inflammation has  
 5 been shown to be effective in both asthma and eosinophilic upper airway disease.<sup>305,335</sup> Overall, these  
 6 studies demonstrate that AR is not a local disease but that the entire respiratory tract is involved, even  
 7 in the absence of clinical asthma. Systemic factors, such as the number of blood eosinophils and atopy  
 8 severity, are indicative of a more extensive airway disease.

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## 1 VII. Epidemiology of allergic rhinitis

### 2 3 VII.A. Epidemiology of allergic rhinitis in adults

4  
5 To assist in concretely defining the prevalence of AR in adults, recent literature has attempted to  
6 provide more uniformity in the terminology and diagnostic criteria used to identify it. The International  
7 Study of Asthma and Allergies in Childhood (ISAAC), ARIA, the European Community Respiratory Health  
8 Survey (ECHRS), and International Classification of Diseases (ICD), have all recognized and adopted a  
9 more standardized definition and methodology for diagnosing AR in a given population.<sup>1-3</sup> As such, there  
10 has been more consistency in the response data obtained from study subjects and clarity in the criteria  
11 used in identifying AR. Nonetheless, the prevalence estimates of AR still differ widely across studies,  
12 with an approximate range of 5-50%.<sup>4,5</sup>

13  
14 As noted in ICAR-Allergic Rhinitis 2018,<sup>6</sup> differing AR definitions affect prevalence estimates. Incidence of  
15 physician-diagnosed AR, which entails the precondition of being diagnosed or informed of AR affliction,  
16 potentially underestimates AR, as reflected in the South Korean National Health and Nutrition  
17 Examination Survey (KNHANES) data from 2008-2012 (35.02% according to questionnaire responses and  
18 ARIA guidelines; 14.89% when “diagnosed with AR by a medical doctor”).<sup>7</sup> Likewise, the inclusion of at  
19 least one allergen test reaction (e.g., positive reaction to SPT) resulted in a lower prevalence estimates  
20 for AR in a Danish study in 2010 (AR, 39.0%; AR with SPT reaction, 25.9%), a Chinese study in 2018 (AR,  
21 32.4%; AR with SPT reaction, 18.5%), and KNHANES data from 2008-2012 (current AR, 35.02%; AR based  
22 on allergy tests: 17.56%).<sup>7-9</sup> Identification of AR according to ICD codes from databases generally yielded  
23 lower estimates for AR (German AOK Saxony database study, 6.2%).<sup>10</sup> Conversely, estimates for lifetime  
24 AR were slightly higher than that of current AR, which was often defined as occurring within 12 months;  
25 this was observed in the Tromsø Study Fit Future 2 study, an expansion of the Tromsø Study (current AR,  
26 26.0%; ever AR, 28.9%).<sup>11-13</sup>

27  
28 Additionally, age ranges of given study samples may also capture subjects at different stages of the  
29 putative atopic march.<sup>14</sup> KNHANES identified a falling AR prevalence from 21.1% in 20- to 29-year-olds,  
30 to 5.4% in over 60-year-olds.<sup>15</sup> Considering all age ranges, AR prevalence in a Swedish study of 18- to 65-  
31 year-olds was 24%, and 27.2% in an Iranian study of 20- to 65-year-olds.<sup>16,17</sup> Although time of year and  
32 study location may potentially affect the presence of allergens and manifestations of AR, this  
33 discrepancy can often be obviated by including the temporal range of any time “in the last 12 months.”



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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.<sup>18</sup> 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;<sup>19</sup> 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%.<sup>20</sup> In contrast, in Brazil the prevalence of ever having hay fever in adults decreased from 52.0% in 2011 to 43.3% in 2018.<sup>5</sup>

10 Overall, the AR prevalence in Asia ranges approximately 5-35%, depending on the method of diagnosis.  
11 In Europe, the most recent estimates put AR prevalence at around 25%. Variations in the prevalence  
12 were likely due to differences in participants' age, and thus the corresponding stage of the atopic march.  
13 Regardless, considering the data available, the worldwide prevalence of AR likely ranges between 5-  
14 50%.

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## VII.B. Epidemiology of allergic rhinitis in children

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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.<sup>21</sup> 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%.<sup>22</sup> Kulig et al,<sup>23</sup> 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.<sup>24</sup>

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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.<sup>25-28</sup> 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.<sup>25</sup> In the 6-7-year age group, a lower current symptom prevalence was observed in the Indian subcontinent (4.2%) and highest in Latin

1 America (12.7%). In the 13-14-year age group, the lowest prevalence was in Northern and Eastern  
2 Europe (9.2%), and the highest regional prevalence rates were recorded in Africa (18%) and Latin  
3 America (17.3%). Several follow up studies of similar design have been performed on smaller scales in  
4 several countries across the world. For instance, such survey-based epidemiologic studies have been  
5 performed in children from Costa Rica (42.6% prevalence), Japan (18.7% in 6-8-year-olds, 26.7% in 13-  
6 15-year-olds), United Arab Emirates (46.5% in 6-7-year-olds, 51.3% in 13-14-year-olds), Nigeria (19.4% in  
7 6-17-year-olds), Brazil (range of 45.3% to 35.4% in children over 10 years of age), and Ecuador (48% in 3-  
8 5-year-olds).<sup>29-34</sup> These studies also indicate an overall increase in AR prevalence with age into young  
9 adulthood. Recent Chinese studies have estimated an AR prevalence averaging 28.6% in 6-12-year-olds  
10 in Wuhan, and 28.9% in 5-18-year-olds in Zhongshan.<sup>35,36</sup>

11  
12 The regional variations in reported AR prevalence highlight some limitations in questionnaire-based,  
13 “open” studies of AR prevalence.<sup>37</sup> Many of these studies might be over- or underestimating prevalence  
14 of AR because of disparities in responder education and researcher definitions of AR.<sup>38</sup> Also, one must  
15 consider differences accounted for by measuring point prevalence and lifetime prevalence of AR. Pols et  
16 al<sup>39</sup> investigated AR prevalence by using physician-diagnosed and treated atopic disease in a primary  
17 care database consisting of 478,076 children and found the peak point-prevalence of AR to be 5.7% at  
18 18 years. The lifetime cumulative incidence in this study was much higher at 16-22.5%. A separate study  
19 conducted by Kurukulaaratchy et al<sup>40</sup> in the Isle of Wright birth cohort (1456 participants) performed  
20 SPT to define AR and observed prevalence from 5.4% at 4 years to 27.3% at 18 years. In a separate  
21 longitudinal study comprising 5471 children from birth to 10 years, de Jong et al<sup>41</sup> estimated a  
22 prevalence of allergic sensitization to be 32.2% when using skin testing results and 12.4% when using  
23 physician diagnosis.

24  
25 Taken together, the available evidence indicates that the prevalence of AR in children increases with age  
26 into young adulthood. Moreover, the prevalence of AR has previously been reported to be increasing  
27 across the globe. It should be noted, however, that recently published data indicate that this trend of  
28 increasing AR prevalence may not persist into the future, although substantial geographic differences  
29 exist.<sup>42</sup> The underlying factors that determine prevalence are complex, multifactorial, and reviewed in  
30 detail in the sections that follow.

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

1  
2 The prevalence of AR varies significantly based on geographic location. However, other factors such as  
3 population density (urban vs rural) can further alter AR rates within the same locale. One important  
4 challenge in meaningfully comparing AR rates between locations is the variability created by differences  
5 in study subject recruitment and method of diagnosing AR. For example, Bauchau et al,<sup>43</sup> who diagnosed  
6 patients via serological IgE testing after a positive telephone screen, reported that Belgium had an AR  
7 prevalence of 28.5% (the highest of the European countries he evaluated). On the other hand, Bousquet  
8 et al,<sup>44</sup> who skin tested randomly sampled subjects, reported a rate in Belgium of 16.4%, one of the  
9 lowest of 15 countries examined.

10  
11 Given the difficulty in standardizing AR prevalence studies across different locations, there have been  
12 major international efforts to examine national prevalence rates of AR using standardized methods (i.e.,  
13 ECRHS and ISAAC). These studies show marked geographic variation with a higher prevalence of AR in  
14 'English speaking' countries (i.e., United Kingdom [UK], Australia, New Zealand), a higher rate in Western  
15 Europe than in Eastern Europe, and a higher prevalence in countries with higher rates of asthma and  
16 sensitization to seasonal allergens.<sup>45,46</sup> However, these studies have evaluated national rates from only  
17 one or a few centers within each country, and substantial intra-country variation may occur. For  
18 example, the prevalence of AR varies from 9.6% to 23.9% in 18 major cities in China.<sup>47</sup>

19  
20 Geographic variation in AR prevalence may also be impacted by climate change, which has an  
21 association with lengthening pollen seasons, increasing pollen counts, and broadening/altering the  
22 typical vegetative species for a location.<sup>48</sup> Climate change has been estimated to be associated with  
23 increased seasonal pollen exposures, and as a result, sensitizations are anticipated to be more than  
24 double in the next few decades, particularly in colder climates that previously were spared from higher  
25 rates of seasonal AR.<sup>49</sup> Additionally, this increased environmental exposure has been shown to be  
26 associated with an increased risk of AR as well as patient symptoms of atopic nasal diseases.<sup>50,51</sup>

27  
28 When assessing geographic variations associated with AR, differentiating between seasonal and  
29 perennial AR is also an important consideration not examined in the ECRHS or ISAAC studies. Smaller  
30 studies over more limited geographic regions which have examined perennial AR suggest increased  
31 sensitivity rates in urban settings and colder climates.<sup>52-55</sup> Li et al<sup>53</sup> theorized that urban dwellers  
32 participate in more indoor activities compared to their rural counterparts, amplifying their exposure to

1 dust mites and possibly leading to increased sensitization to these perennial allergens. Additionally,  
2 some reports suggest exposure to urban pollutants may be associated with increased AR in children.<sup>52</sup>

3  
4 Latitude plays a more questionable role with regards to perennial AR. For example, the prevalence of  
5 persistent AR was found to be higher in both Northern Europe and Northern China compared to their  
6 southern counterparts.<sup>43,53</sup> This may occur because those in colder climates spend more time indoors,  
7 increasing their exposure to dust mites and other perennial allergens. However, it has also been  
8 reported that peak months for AR outpatient visits were the same in most regions of China, regardless  
9 of the latitude.<sup>56</sup> Latitude may also be an important determinant of seasonal AR. Allergenic plants are  
10 often characteristic for certain locations and the pollen concentrations of various species depend on the  
11 climate of a specific region.<sup>48</sup>

12  
13 Overall, improved knowledge of the geographic influences, seasonal variations, and the role of climate  
14 change on AR prevalence, is important in that it allows patients to anticipate and better self-manage  
15 their symptoms through avoidance techniques and preemptive use of pharmacologic therapies.<sup>51,57</sup>

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20



## 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.<sup>1</sup> Studies on twins have shown that genetic factors account for up to 70-80% of interindividual variability in susceptibility to development of AR.<sup>2,3</sup> 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,<sup>4-8</sup> as well as with asthma,<sup>5,9</sup> eczema,<sup>6,10</sup> and other allergy-related co-morbidities.<sup>4,9,11</sup> *LRRC32* is known to regulate T cell proliferation, cytokine secretion and TGF- $\beta$  activation.<sup>12</sup> These associations support the concept of shared genetic mechanisms for AR and other allergy-related diseases. This concept is further supported by a GWAS on self-reported cat, dust mite, and pollen sensitization (as well as AR), which revealed 16 shared susceptibility loci with strong association ( $p < 5 \times 10^{-8}$ ; *TLR*-locus top hit).<sup>5</sup> Strong overlap between top loci for sensitization and self-reported allergies also are found in two of the larger GWASs.<sup>5,13</sup> 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.<sup>14</sup> In a follow-up study, additional novel loci for comorbid allergic disease were identified by applying a gene-based test of association.<sup>15</sup> 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.<sup>16</sup>

1 As expected, larger studies with better power allow for improved ability to accurately detect novel loci  
2 and potentially novel AR-related disease mechanisms. Recently, very large GWASs were able to confirm  
3 many of the previously identified susceptibility loci for AR, with top hits *HLA-DQB1/DQA1*, *IL1RL1*,  
4 *TLR1/10*, *WDR36* and *LRRC32*.<sup>7,8</sup> A recent multi-institutional study comprising over 50,000 cases of AR  
5 identified the novel loci *IL7R*, which encodes the receptor for IL-7 (and TSLP) involved in  
6 immunoregulation, and *CXCR5*, a chemokine receptor involved in B cell migration.<sup>8</sup>

7  
8 **Candidate gene studies.** The candidate gene approach for selecting disease-relevant genes is based on  
9 known molecular biology or gene function relevant to disease pathophysiology. Such studies in AR have  
10 identified several well-replicated genes, as summarized previously.<sup>17-19</sup> Notably, results from many  
11 candidate gene studies often overlap with GWASs results. For example, SNPs in genes involved in  
12 antigen presentation (e.g., *HLA-DQA1*), pathogen recognition (e.g., *TLR2,7,8*), IL signaling and pro-  
13 inflammatory signaling (e.g., *IL13*, *IL18*, *TSLP*) have been highlighted.<sup>17-23</sup> However, many of the  
14 candidate gene study findings have not been well-replicated across studies and populations.<sup>24,25</sup> This  
15 could be due to lack of power from small sample sizes, inconsistent phenotype definition, or lack of true  
16 disease association.

### 18 **Gene-environment interactions and epigenetic effects**

19 Epigenetic mechanisms, defined as changes in phenotype or gene expression caused by mechanisms  
20 (e.g., methylation) other than changes in the underlying DNA sequence, have been proposed to  
21 constitute a link between genetic and environmental factors. Recent studies show that DNA methylation  
22 in children is very strongly influenced by well-known risk factors for allergic diseases, such as tobacco  
23 smoking / maternal smoking during pregnancy,<sup>26</sup> air pollution exposure,<sup>27</sup> and length of pregnancy.<sup>28</sup>  
24 However, it is not currently known if these methylation changes are part of a causal pathway in the  
25 development of AR (and asthma), or if these epigenetic biomarkers are simply markers of exposure. Still,  
26 several studies have convincingly linked methylation profiles to AR<sup>29-31</sup> and IgE-related outcomes.<sup>32,33</sup>  
27 Recently, methylation signatures in nasal epithelial brushes were shown to be strongly associated with  
28 AR (and also asthma).<sup>34</sup> Also, epigenetic studies have highlighted shared molecular mechanisms  
29 underlying asthma, eczema and AR pathophysiology.<sup>35</sup>

30  
31 In summary, a family history of AR remains one of the strongest risk factors for disease development,  
32 and strong associations with genes involved in antigen presentation (e.g., *HLA* genes), T cell activation

1 (e.g., *LRRC32*) and innate immunity (e.g., *TLRs*) have been identified. Shared genetic mechanisms for AR  
2 and other allergy-related diseases clearly exist. These novel findings lend insight into mechanisms  
3 underlying the pathogenesis of AR, as well as comorbid atopic conditions, and may aid drug discovery  
4 efforts for novel disease targets. With increasing evidence for the role of epigenetics in AR, future  
5 research should also focus on investigating mechanisms, thereby providing a functional explanation for  
6 the link between genetics variants, environmental exposures, and disease development.

7

8 **Aggregate grade of evidence:** C (Level 3: 8 GWASs and 1 exome sequencing study. Candidate gene  
9 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 <sup>36</sup>	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) <i>MRPL4</i> 2) <i>BCAP (PIK3AP1)</i>	1) Protein synthesis within the mitochondrion 2) Protein tyrosine kinase	3
Ramasamy et al <sup>6</sup>	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) <i>LRR32</i> or <i>C11orf30</i> 2) <i>TMEM232</i> or <i>SLCA25A46</i> 3) <i>ENTPD6</i>	1) LRR32: T cell regulation, TGF- $\beta$ activity. C11orf30: regulation of viral immunity and interferon pathways 2) Transmembrane protein 3) Catabolism of extracellular nucleotides	3
Hinds et al <sup>5</sup>	2013	Private company data (23andMe)	46,646 total (look-up association for AR of GWAS top hits for self-reported allergy)	>97% European ancestry	1) rs1438673 2) rs2101521 3) rs10189629	1) 3.7E-19 2) 6.0E-17 3) 9.9E-15	1) <i>WDR36</i> 2) <i>TLR1-TLR6 - TLR10</i> 3) <i>IL1RL2 -IL1RL1</i>	1) Cellular processes and T cell activation 2) Pathogen recognition and activation of innate immunity 3) Pro-inflammatory effects, T helper cell function	3
Ferreira et al <sup>4</sup>	2014	Meta-analysis of four cohorts/data sets	16,513 hay fever cases 17,256 controls	European ancestry	1) rs4833095 2) rs2155219 3) rs10197862	1) 4E-12 2) 7E-10 3) 2E-09	1) <i>TLR1</i> 2) <i>LRR32</i> or <i>C11orf30</i> 3) <i>IL1RL1</i>	1) Pathogen recognition and activation of innate immunity 2) See above 3) Pro-inflammatory effects, T helper cell function	3
Bunyavanich et al <sup>37</sup>	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) <i>AKR1E2</i> 2) <i>DLG1</i> 3) <i>FERD3L</i>	1) NAD(P)H-dependent oxidation-reduction 2) Scaffolding protein involved in cell metabolism 3) Transcription factor	3
Waage et al <sup>8</sup>	2018	Meta-analyses	59,762 AR cases 152,358 controls	European ancestry	Top 5 SNPs in previously known loci (21 in total): 1) rs34004019 2) rs950881 3) rs5743618 4) rs1438673 5) rs7936323  Top 5 SNPs in novel loci (20)	Known loci: 1) $1.00 \times 10^{-30}$ 2) $1.74 \times 10^{-30}$ 3) $4.38 \times 10^{-27}$ 4) $3.15 \times 10^{-26}$ 5) $6.53 \times 10^{-24}$  Novel loci:	Known loci: 1) <i>HLA-DQB1</i> , <i>HLA-DQA1</i> 2) <i>IL1RL1</i> 3) <i>TLR1</i> , <i>TLR10</i> 4) <i>CAMK4</i> , <i>WDR36</i> 5) <i>LRR32</i> , <i>C11orf30</i>  Novel loci: 1) <i>CAPSL</i> , <i>IL7R</i>	Known loci: 1) Antigen presentation 2) See above 3) See above 4) See above 5) See above  Novel loci: 1) <i>CAPSL</i> : Calcium ion binding involved in adipogenesis, <i>IL7R</i> : Receptor for IL-7 (and TSLP); immunoregulation	3

					in total): 1) rs7717955 2) rs63406760 3) rs28361986 4) rs2070902 5) rs1504215	1) $3.78 \times 10^{-32}$ 2) $2.54 \times 10^{-24}$ 3) $2.32 \times 10^{-23}$ 4) $6.19 \times 10^{-19}$ 5) $1.54 \times 10^{-18}$	2) <i>CDK2AP1</i> , <i>C12orf65</i> 3) <i>CXCR5</i> , <i>DDX6</i> 4) <i>AL590714.1</i> , <i>FCER1G</i> 5) <i>BACH2</i> , <i>GJA10</i>	2) CDK2AP1: cell-cycle kinase inhibitor 3) CXCR5: Involved in B-cell migration, DDX6: Involved in RNA metabolism 4) FCER1G: Component of the high-affinity IgE receptor 5) BACH2: Transcriptional regulator, GJA10: Gap junction protein	
Johansson et al <sup>7</sup>	2019	UK biobank	18 915 hay fever cases 327,630 controls	European ancestry	Top 5 SNPs in previously known loci (27 in total): 1) rs11236797 2) rs7728912 3) rs66819621 4) rs72823641 5) rs7744020  Novel locus (1 in total): 1) rs12920150	Known loci: 1) 4.97E-32 2) 4.50E-26 3) 2.20E-25 4) 2.35E-25 5) 3.80E-25  Novel locus: 1) $1.02 \times 10^{-9}$	Known loci: 1) <i>LRR32</i> , <i>EMSY</i> 2) <i>WDR36</i> 3) <i>TLR1</i> 4) <i>IL1RL1</i> <i>IL18R1</i> 5) <i>HLA-DQB1</i>  Novel locus: 1) <i>CBLN1</i>	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 <sup>38</sup>	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) <i>CD207</i> 2) <i>HLA-B</i> 3) <i>HLA-DQB1</i> 4) <i>RORA</i>	1) Antigen presentation 2) Antigen presentation 3) See above 4) Key regulator of embryonic development, cellular differentiation	3
Backman et al <sup>16</sup>	2021	UK Biobank (exome sequencing project)	73,313 seasonal AR cases 280,381 controls	European ancestry	9:6255967:G:C	9.52E-27	<i>IL33</i>	Maturation and activation of immune cells, including Th2 cells.	3

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

## 1 VIII.B. Risk factors

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

## 3 VIII.B.1.a. Mites

4

5 While there have not been any major new studies published on this topic since 2016, three older  
6 prospective birth cohorts (not included in ICAR-Allergic Rhinitis 2018<sup>39</sup>) concur with the conclusion that  
7 there is no established association of early mite exposure and the development of AR.<sup>40-42</sup> Studies  
8 showing that early life dust mite exposure results in early sensitization (e.g., positive skin tests without  
9 symptoms) and AR later in childhood are often limited in that they fail to measure and account for dust  
10 mite allergen concentrations in the home.<sup>43</sup> Likewise, other studies implement dust mite reduction  
11 interventions without pre and post dust mite allergen measurements and/or combine environmental  
12 changes with dietary changes.<sup>44-46</sup> [TABLE VIII.B.1.a.]

13

14 It has been suggested that the effect of dust mite exposure on sensitization may follow a bell-shaped  
15 dose response curve, with both very low and very high exposure being protective.<sup>47-51</sup> Exposure levels  
16 that are less than 2mg dust mite allergen/gram of house dust may be a “safe” level for atopic children  
17 for primary allergic disease prevention.<sup>52,53</sup> The risk of allergic disease in childhood may also depend  
18 upon mono- vs polysensitization at age 1 or 2.<sup>54</sup>

19

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

21

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions*
Schoos et al <sup>55</sup>	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 <sup>56</sup>	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 <sup>42</sup>	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 <sup>40</sup>	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 <sup>57</sup>	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 <sup>41</sup>	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 <sup>58</sup>	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)

1 LOE=level of evidence; COPSAC=Copenhagen Prospective Study on Asthma in Childhood; AR=allergic rhinitis;  
2 OR=odds ratio; CI=confidence interval; PAULA=Perinatal Asthma and Environment Long-term Allergy;  
3 PIAMA=Prevention and Incidence of Asthma and Mite Allergy; MAAS = Manchester Asthma and Allergy Study;  
4 CRC=chronic rhinitis conjunctivitis; RR=relative risk  
5 \*ORs are unadjusted and reported with 95% CI  
6  
7

### 8 VIII.B.1.b. Pollen

9  
10 Since ICAR-Allergic Rhinitis 2018,<sup>39</sup> no new studies were identified that addressed the impact of early  
11 pollen exposure on the development of AR; furthermore, the two previous studies were  
12 inconclusive.<sup>59,60</sup> While very few studies longitudinally track pollen counts and the subsequent  
13 development of AR, several studies have demonstrated that the development of pollen sensitization in  
14 early life is associated with AR in later childhood.<sup>61,62</sup> In fact, following initial pollen sensitization in  
15 children, there is a progressive increase in both the level and number of pollen sensitizations.<sup>63</sup> While  
16 seasonal AR symptoms are rare before age 3, between 3 and 12 years, the percentage of new cases



1 increases at a rate of approximately 2% per year.<sup>61,64,65</sup> With the environmental changes associated with  
 2 global warming, such as increased length of pollination season, we are starting to see higher rates of  
 3 pollen sensitization in young children which will likely lead to increased AR in adolescence and  
 4 adulthood.<sup>66</sup> [TABLE VIII.B.1.b.]

5  
 6 Focusing on early life sensitization rather than pollen exposure may be a more productive research  
 7 pathway. Sensitization to one or more allergenic molecules (e.g., Phl p 1) at age 4, has been shown to  
 8 be a better predictor of AR at age 16, than a positive test to Timothy extract.<sup>67</sup> Likewise, higher levels of  
 9 Bet v 1 or finding multiple pathogenesis-related class 10 allergens at age 4, helped to predict AR to birch  
 10 in adolescence.<sup>68</sup> With the difficulty of conducting longitudinal pollen studies and the inability to control  
 11 the year-to-year variation in pollen counts or the young child's level of exposure, the use of component  
 12 resolved diagnosis in early childhood may prove to be the best tool for predicting pollen-induced AR in  
 13 adolescence and adulthood.

14

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

16

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

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

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

20 CI=confidence interval

21 \*ORs are adjusted and reported with 95% CI

<sup>a</sup>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,<sup>39</sup> high quality studies have found that early life exposure to animal dander may be protective from the development of AR,<sup>69-71</sup> while two lower quality studies concluded that it was a risk factor.<sup>72,73</sup> A 2020 systematic review and pooled analysis of 5 cohort studies found a protective effect for early life exposure to cats and dogs.<sup>69</sup> Two additional prospective birth cohorts found a similar protective effect.<sup>70,71</sup> Animal exposure during the first two years of life offers the best possibility for protection.<sup>54,70,71,74</sup> 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).<sup>75</sup> 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.<sup>76</sup> 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. <sup>77-82</sup> )						
Gao et al <sup>69</sup>	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 <sup>70</sup>	2020	3	Prospective birth cohort	3782 children (5 years old)	Exposure at home to cats or dog or visit to building housing farm	-Dogs: protective factor for AR (OR 0.72; 95% CI 0.53-0.97) -Exposure to cats and farm animals non-significant

					animals during first year of life	
Al-Tamprouri et al <sup>71</sup>	2019	3	Prospective birth cohort	834 children (13 years old)	Exposure at home to cats or dogs during 1 <sup>st</sup> 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 <sup>54</sup>	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 <sup>74</sup>	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 <sup>83</sup>	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 <sup>84</sup> §	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 <sup>85</sup> §	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. <sup>72,73,82,86-94</sup> )						
Early exposure to animal dander is not associated with AR (Level 3 studies listed. Level 4 studies referenced. <sup>86,88,90,95-101</sup> )						
Schoos et al <sup>55</sup>	2016	3	Prospective birth cohort	399 children (13 years old) from COPSAC study	-Prenatal (3rd trimester of pregnancy) and perinatal (at 1 year) cat exposure, and Fel d 1 in dust	-Cat: no association with AR at 13 years old (OR prenatal 1.2; 95% CI 0.44-3.82); (OR perinatal 1.33; 95% CI 0.53-3.42); (OR Fel d 1 1.10; 95% CI 1.2-4.96) -Dog: no association with

					samples (at 1 year) -Prenatal (at 3rd trimester of pregnancy) and perinatal (at 1 year) dog exposure and Can f 1 in dust samples (at 1 year)	AR at 13 years old (OR prenatal 0.95; 95% CI 0.21-4.3); (OR perinatal 0.86; 95% CI 0.19-3.89); (OR Can f 1 1.0: 95% CI 0.87-1.16)
Illi et al <sup>56</sup>	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 <sup>102</sup>	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 <sup>103</sup>	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 <sup>83</sup>	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 <sup>76</sup>	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 <sup>104</sup> §	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 <sup>105</sup>	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 <sup>57 §</sup>	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 Fel 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 <sup>58</sup>	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)

1 LOE=level of evidence; AR=allergic rhinitis; RR=relative risk; CI=confidence interval; OR=odds ratio;  
2 aOR=adjusted odds ratio; COPSAC=Copenhagen Prospective Study on Asthma in Childhood; PAULA=Perinatal  
3 Asthma and Environment Long-term Allergy; GINI=German Infant Nutritional Intervention; LISA=Lifestyle-  
4 Immune-System-Allergy; MAAS=Manchester Asthma and Allergy Study; SAR=seasonal allergic rhinitis  
5 § Part of GAO meta-analysis  
6 \*All ORs are adjusted unless differently specified and are reported with 95% CI  
7  
8

### 9 VIII.B.1.d. Fungal allergens

10  
11 Further supporting the ICAR-Allergic Rhinitis 2018<sup>39</sup> conclusions, all newly reviewed studies, many  
12 having a higher evidence level, concluded that early life exposure to fungal allergens or dampness is a  
13 risk factor for AR.<sup>106-108</sup> Unfortunately, existing studies have not been able to establish a dose-response  
14 relationship for mold exposure and the subsequent development of AR nor have they been able to  
15 define a threshold below which no effect of mold exposure on the health of the general or high-risk

1 population would be expected.<sup>109,110</sup> It may be that the presence of fungal diversity alone or in  
 2 combination with microbial diversity could play an even greater role than levels of indoor mold.<sup>109</sup> The  
 3 role of outdoor fungal spores, which can vary widely by geographical location, has rarely been  
 4 considered. While most studies adjust for demographic characteristics, the co-exposure levels or  
 5 symptoms produced by other allergens (e.g., HDM, pollen, pet dander) are rarely studied. Consistent  
 6 results from well-designed longitudinal studies are needed before one can determine the causal effect  
 7 of early life exposure to fungal components on the future development of AR. [TABLE VIII.B.1.d.]

8  
 9 **Aggregate grade of evidence:** C (Level 3: 3 studies, level 4: 12 studies; TABLE VIII.B.1.d.)

10  
 11  
 12

**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 <sup>107</sup>	2015	3	Birth cohort	406 children (12-13 years old) asthmatic/allergic parents from metropolitan Boston, Massachusetts	Exposure to high levels of culturable <i>Aspergillus</i> 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 <i>Cladosporium</i> 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 <sup>106</sup>	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 <sup>108</sup>	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 <sup>111</sup>	2016	4	Cross-sectional	2598 children (3-6 years old) attending kindergarten	Prenatal (whole pregnancy) or postnatal (from birth)	Risk factors for rhinitis-like current symptoms: prenatal

					to current) exposure to indoor mold/dampness	(OR 1.5; 95% CI 1.2-1.9); postnatal (OR 2.1; 95% CI 1.6-2.8)
Lin et al <sup>112</sup>	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 <sup>100</sup>	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 <sup>99</sup>	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 <sup>88</sup>	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 <sup>89</sup>	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 <sup>113</sup>	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 <sup>114</sup>	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 <sup>115</sup>	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 <sup>111</sup>	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 <sup>93</sup>	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 <sup>116</sup>	2006	4	Cross-sectional	585 infants (1-year old) born to families with at least 1 parent with positive SPT	-High mold exposure (mold in 1 room $\geq 0.2$ m <sup>2</sup> or a combined area of visible mold and water damage on	No association with AR at low (OR 1.2; 95% CI 0.6-2.5) or high levels (OR 3.2; 95% CI 0.7-14.8)

					<p>the same surface <math>\geq 0.2</math> m<sup>2</sup>) during early infancy (average 7.5 months)</p> <p>-Low mold exposure (mold in one room <math>&lt; 0.2</math> m<sup>2</sup> or a combined area of visible mold and water damage on the same surface <math>&lt; 0.2</math> m<sup>2</sup>) during early infancy (average 7.5 months)</p>	
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1 LOE=level of evidence; AR=allergic rhinitis; HR=hazard ratio; CI=confidence interval; OR=odds ratio; CCHH=China  
 2 Child Health and Home study; SD=standard deviation; SIDRIA-2=Studi Italiani sui Disturbi Respiratori del l’Infanzia  
 3 el Ambiente; BAMSE=Barn/Child Allergy Milieu Stockholm Epidemiology; NAR=non-allergic rhinitis; SPT=skin prick  
 4 test.

5 \*ORs are adjusted unless otherwise specified

6  
 7 **Summary for the effect of inhaled allergens (in utero and early childhood exposure) as a risk factor**

8 **for the development of AR.** The impact of early inhaled allergen exposure (HDM, pollen, animal dander,  
 9 fungal allergens) on the development of AR remains ambiguous. Early life allergen exposures identified  
 10 as significant risk factors for AR at age 6 are often found to be insignificant by age 12 or later. Despite  
 11 several in-depth reviews and a growing body of literature,<sup>69,109,117,118</sup> no definitive conclusions may be  
 12 drawn regarding risk-benefit of early inhaled allergen exposure, and further research is welcomed to  
 13 address this unmet need.

14

15 **VIII.B.2. Food allergens**

16

17 Historically, there has been concern that highly allergenic foods in the maternal as well as the infant’s  
 18 diet would lead to the development of food allergy and subsequently to other atopic diseases, such as  
 19 AR. Since ICAR-Allergic Rhinitis 2018,<sup>39</sup> six publications have looked at the effect of early introduction of  
 20 specific foods (e.g., fish and peanut) and diverse foods into the infant’s diet and the subsequent  
 21 development of AR.<sup>119-124</sup> Older publications (not part of ICAR-Allergic Rhinitis 2018) have looked at the  
 22 effect of fish and tree nuts in the maternal diet<sup>125-127</sup> and early introduction of specific or diverse foods  
 23 into the infant’s diet.<sup>128-131</sup> **[TABLE VIII.B.2.]**

24

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



1

2 Early sensitization to food has been linked to the development of AR in childhood.<sup>58,136,137</sup> A meta-  
3 analysis of high-risk infants found that food sensitization at age less than 24 months increased the risk of  
4 AR during childhood.<sup>136</sup> In a prospective birth cohort, food allergy at 4-10 years old, however, had no  
5 association with AR at age 18 or 26; whereas food sensitization (independent of symptoms) increased  
6 the risk of AR at both age 18 and 26.<sup>121</sup> Additional cohort studies have found that food sensitization at  
7 age less than 24 months, especially when combined with inhalant sensitization, increases the risk of AR  
8 in childhood.<sup>137-141</sup>

9

10 Multiple studies have evaluated the effect of early introduction of highly allergenic foods into the  
11 infant's diet. In a prospective RCT, cow's milk, egg, and peanut were avoided during the last trimester of  
12 pregnancy and during lactation and infants avoided milk, egg, peanut, and fish for 1, 2, 3, and 3 years  
13 respectively. By age 7, the food avoidance group had no reduced rates of AR.<sup>132</sup> In an open label RCT,  
14 there was no association of avoiding or consuming peanuts from 4-11 months on the risk of developing  
15 AR at age 5 years.<sup>120</sup>

16

17 In a subgroup meta-analysis of observational studies, the introduction of fish into the infant's diet  
18 before 6-12 months was associated with a reduced risk for AR at 4 and 14 years.<sup>119</sup> Three additional  
19 prospective birth cohort studies support this conclusion.<sup>123,130,131</sup> One prospective birth cohort found  
20 that introduction of rye, oat, and barley before 5-5.5 months and egg before 11 months reduced the risk  
21 of AR at 5 years old.<sup>130</sup> However, there are conflicting conclusions regarding the timing of introduction of  
22 complementary foods and risk for AR.<sup>142,143</sup>

23

24 While guidelines have recommended that all infants have a diverse diet, the evidence is both limited  
25 and conflicting on whether this reduces the risk of AR.<sup>144</sup> Food diversity has been reported to increase,<sup>124</sup>  
26 decrease,<sup>128</sup> decrease if there are concurrent skin symptoms,<sup>124</sup> or have no effect<sup>129</sup> on the risk of  
27 developing AR in childhood.

28

29 Current guidelines as well as a Cochrane systematic review recommend an unrestricted maternal diet  
30 during pregnancy as avoidance of highly allergenic foods is unlikely to substantially reduce the risk of  
31 atopic disease including AR, in the offspring.<sup>145-148</sup> Furthermore, it is recommended that complementary  
32 foods be introduced into the diet of all infants, regardless of atopic risk, at 4-6 months of age as

1 avoidance or delayed introduction has not been shown to reduce atopic disease.<sup>145</sup> Guidelines have not  
 2 made recommendation on the early introduction into the infant's diet of any specific foods to prevent  
 3 the development of AR.

4

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

6

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
du Toit et al <sup>120</sup>	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 <sup>136</sup>	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 <sup>119</sup>	2016	2	SRMA of observational studies, subgroup analysis (GRADE)	10,313 children (4 years or younger); 3112 children (5-14 years old)	Introduction of dietary fish before 6-12 months old	-Reduced risk for AR at age $\leq 4$ years (OR 0.59; 95% CI 0.40-0.87; high heterogeneity [I <sup>2</sup> =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 $\leq 4$ was not significant
Zeiger & Heller <sup>132</sup>	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 <sup>133</sup>	1989	2	RCT	163 infants (18 months old) of high-risk mothers -79 mothers with egg and	Maternal diet very low in egg and milk during last 3 months of pregnancy	No association with the development of AR at 18 months

				milk restricted diet -83 daily ingestion of one egg and 11 oz milk		
Falsh-Magnusson & Kjellman <sup>134</sup>	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 <sup>143</sup>	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 <sup>121</sup>	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 <sup>123</sup>	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 <sup>124</sup>	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 (3 <sup>rd</sup> vs. lowest quartile for foods introduced: OR 2.12; 95% CI 1.04-4.29)
Nwaru et al <sup>128</sup>	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 <sup>129</sup>	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 <sup>126</sup>	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 <sup>130</sup>	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 <sup>119</sup> 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 <sup>125</sup>	2012	3	Population-based birth cohort	38,389 children (7 years old)	Maternal diet to include ≥1 serving tree nuts/week or to have ≥1 serving of	-Maternal tree nut ingestion associated with reduced risk for self-reported AR at age

					peanuts/pistachios/week from mid-pregnancy to delivery	7 (OR 0.80; 95% CI 0.64-1.01) -Maternal ingestion of peanuts/pistachios had no association with self-reported AR at age 7
Virtanen et al <sup>131</sup>	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 $\leq$ 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 <sup>142</sup>	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 <sup>135</sup>	2007	3	Longitudinal birth cohort	1253 children (5 years old)	Maternal intake of oily fish $\geq$ 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)

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

### 6 VIII.B.3. Pollution

7  
8 According to the World Health Organization (WHO), air pollution is defined as “contamination of the  
9 indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural  
10 characteristics of the atmosphere”.<sup>149</sup> Pollutants, produced through traffic-related combustion and  
11 industrial activity, generally include NO and nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), carbon  
12 monoxide and dioxide (CO and CO<sub>2</sub>), as well as PM <10 microns (PM<sub>10</sub>) and PM <2.5 microns (PM<sub>2.5</sub>). The  
13 effect of air pollution on human morbidity is well-known, though the relationship with AR is  
14 complex.<sup>39,150,151</sup> It is thought that through oxidative stress pathways, pollutants may stimulate the  
15 expression of antioxidant genes and recruitment of inflammatory cells to the nasal mucosa, though the  
16 mechanisms remain unclear.<sup>152,153</sup>

17  
18 At the time of ICAR-Allergic Rhinitis 2018,<sup>39</sup> the strongest evidence in the literature suggested minimal or  
19 no significant associations between air pollutants and AR development.<sup>154-159</sup> Kim et al<sup>160</sup> found that the  
20 incidence of AR was not significantly associated with exposure to air pollutants, while Codispoti et al<sup>161</sup>

1 reported that diesel exhaust particle exposure at age 1 was associated with allergen sensitization at ages  
2 2 and 3, though not to a significant degree. In a pooled prospective cohort, air pollution was reported to  
3 not be associated with adverse effects on rhinoconjunctivitis.<sup>162</sup>

4  
5 In more recent years, the interest in understanding a potential relationship between air pollution and AR  
6 has further increased. Li et al<sup>163</sup> reported a positive association between air pollution and AR while Burte  
7 et al<sup>164</sup> found that individuals with AR living in highly polluted areas were more likely to experience more  
8 severe nasal symptoms. Evaluating environmental air pollutants from 2013 to 2015, Teng et al<sup>165</sup>  
9 reported that levels of PM are strongly associated with the prevalence of AR. In another study, ozone  
10 and NO<sub>2</sub>, oxidant air pollutants, were associated with an 8% increased risk of AR.<sup>166</sup> A meta-analysis by  
11 Zou et al<sup>167</sup> reported increased AR prevalence in children with exposure to high levels of NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>10</sub>,  
12 and PM<sub>2.5</sub>. This was further supported by a SRMA by Lin et al<sup>168</sup> who reported that PM<sub>2.5</sub> exposure may  
13 be correlated with childhood AR. Hao et al<sup>169</sup> studied children aged 2-4 years and found that those with  
14 family stress and boys compared to girls were particularly vulnerable to increased risk of AR with early  
15 exposure to traffic-related air pollution. **[TABLE VIII.B.3.]**

16  
17 Co-exposure of diesel exhaust and indoor or outdoor inhalant allergens were found to induce changes in  
18 lung protein concentrations, alter DNA methylation patterns of bronchial epithelial cells, and result in  
19 lung function impairment.<sup>170-172</sup> In a controlled allergen challenge facility study by Ellis et al,<sup>173</sup>  
20 participants with ragweed-induced AR aggravated by exposure to diesel exhaust particle were  
21 effectively treated with fexofenadine hydrochloride, resulting in reduced AR symptoms, compared to  
22 placebo.

23  
24 The evidence demonstrating the role of air pollution on AR severity has certainly advanced. In 2018, the  
25 European Institute of Innovation and Technology launched the “Impact of air POLLution on sleep,  
26 Asthma and Rhinitis” (POLLAR) project, in efforts to use machine learning to better evaluate the  
27 relationship between sleep disorders, air pollution, and AR across 6 European countries.<sup>174</sup> The  
28 recognition of the impact of pollution on AR is highlighted by the 2020 consensus paper published in the  
29 *World Allergy Organization Journal* which summarizes strategies to manage pollution-induced AR  
30 symptoms.<sup>175</sup>

31

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

4

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

6

7 **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 <sup>163*</sup>	2022	3	SRMA, cross-sectional & cohort studies	Exposure to air pollutants (PM <sub>2.5</sub> , PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> and CO) on the prevalence of AR across ages	Diagnosis of AR	Air pollution positively associated with AR prevalence
Lin et al <sup>168**</sup>	2021	3	SRMA, cross-sectional & cohort studies	Exposure to PM <sub>2.5</sub> and PM <sub>10</sub> : -High exposure -Low exposure	Diagnosis of AR among children	Particulate matter exposure may increase prevalence of childhood AR, with PM <sub>2.5</sub> having greater effect
To et al <sup>166</sup>	2020	3	Prospective cohort	Exposure to oxidant air pollutants: -High exposure -Low exposure	Diagnosis AR, birth through adolescence	Oxidant air pollutants, specifically O <sub>3</sub> and NO <sub>2</sub> , associated with an 8% increased risk of AR
Zou et al <sup>167***</sup>	2018	3	Meta-analysis, cross-sectional & cohort studies	Exposure to NO <sub>2</sub> , SO <sub>2</sub> , PM <sub>10</sub> , or PM <sub>2.5</sub> : -High exposure -Low exposure	Self-reported diagnosis of AR	Air pollution (specifically NO <sub>2</sub> , SO <sub>2</sub> , PM <sub>10</sub> and PM <sub>2.5</sub> ) increase the risk of AR in children
Teng et al <sup>165</sup>	2017	3	Time-series study	Exposure to PM <sub>2.5</sub> and PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> and O <sub>3</sub> : -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 <sup>161</sup>	2015	3	Prospective cohort	-High DEP exposure (≥66 <sup>th</sup> percentile) -Low DEP exposure (<66 <sup>th</sup> percentile)	Development of AR from age 1 to 4	DEP exposure at age 1 associated with allergen sensitization at ages 2 and 3, though not significantly
Gehring et al <sup>162</sup>	2015	3	Prospective birth cohort	Exposure to NO <sub>2</sub> , PM <sub>2.5</sub> , and PM <sub>10</sub> : -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 <sup>160</sup>	2011	3	Prospective pediatric cohort	Exposure to NO <sub>2</sub> , O <sub>3</sub> , SO <sub>2</sub> , CO, PM <sub>10</sub> : -Metropolitan cities -Industrial areas	AR sensitization during 2-year timespan	Exposure to ozone in industrial areas associated with AR
Hao et al <sup>169</sup>	2021	4	Case-control	Exposure to PM <sub>10</sub> and NO <sub>2</sub> in	Diagnosis or parent-	Early exposure to PM <sub>10</sub> and NO <sub>2</sub> among

				males with or without family stress: -High exposure -Low exposure	reported symptoms of AR at age 2-4 years	young boys with family stress may increase risk of AR
Singh et al <sup>156</sup>	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 <sup>155</sup>	2016	4	Case-control	Exposure to SO <sub>2</sub> : -High exposure -Low exposure	AR diagnosis in children 11-14 years old	Children exposed to higher levels of SO <sub>2</sub> had significantly higher incidence of AR
Kim et al <sup>159</sup>	2016	4	Cross-sectional	Daily concentrations of SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> , CO, and PM <sub>10</sub> : -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 <sup>157</sup>	2015	4	Cross-sectional	Traffic-related air pollution exposure within 200m home area: -Distance from main road (<75, 75-150, 150-225, or >225 m) -Length of main road (0, 1-165, 165-254, and >254 m) -Proportion of the main road area (0, 0.1-1.94, 1.94-3.58, and >3.58%)	Measurements of pulmonary functions and allergic sensitization in children 6-14 years old	Positive association between distance to and the length of main road with the prevalence of AR
Shirinde et al <sup>158</sup>	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 <sup>154</sup>	2010	4	Cross-sectional	Exposure to PM <sub>10</sub> : -High exposure -Low exposure	Prevalence of rhinoconjunctivitis in age groups 6-7 and 13-14 years	Positive association between PM <sub>10</sub> and hay fever in the 6-7-year age group and rhinoconjunctivitis/atopy in the 13-14-year age group

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; PM=particulate matter; AR=allergic rhinitis;

2 DEP=diesel exhaust particles



1  
2 \*The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Kim et al,<sup>160</sup> Chung et  
3 al,<sup>176</sup> Deng et al,<sup>111</sup> Liu et al,<sup>177</sup> Wang et al.<sup>178</sup>

4 \*\*The following individual studies from ICAR-Allergic Rhinitis 2018 are included in this SRMA: Chung et al,<sup>176</sup> Deng  
5 et al,<sup>111</sup> Liu et al,<sup>177</sup> Kim et al.<sup>179</sup>

6 \*\*\*The following individual studies from ICAR 2018 are included in this meta-analysis: Chung et al,<sup>176</sup> Deng et al,<sup>111</sup>  
7 Liu et al,<sup>177</sup> Wang et al,<sup>178</sup> Kim et al.<sup>179</sup>

#### 8 9 10 VIII.B.4. Tobacco smoke

11  
12 Most prospective cohort studies and systematic reviews presented in ICAR-Allergic Rhinitis 2018<sup>39</sup> have  
13 found no correlation between active or passive tobacco smoke and AR.<sup>180-183</sup> One study suggested that  
14 tobacco smoke may have a protective effect against the development of AR.<sup>184</sup> Similarly,  
15 pathophysiology studies examining this relationship have contradictory findings. It has been shown that  
16 tobacco smoke negatively impacts the barrier function of the bronchial epithelium leading to increased  
17 allergen penetration.<sup>185</sup> A recent study in an AR mouse model showed that intranasal exposure to a  
18 tobacco smoke solution exacerbated the allergic response and increased eosinophil levels and IL-5  
19 expression in the respiratory epithelium.<sup>186</sup> Conversely, nicotine has been shown to suppress type 2  
20 responses to allergens, effectively acting as an immunosuppressant.<sup>187</sup>

21  
22 Since the last ICAR-Allergic Rhinitis 2018,<sup>39</sup> two large meta-analyses have investigated the impact of  
23 tobacco smoke on AR.<sup>188,189</sup> Skaaby et al<sup>188</sup> performed a Mendelian randomization meta-analysis of data  
24 from 22 studies in the Causal Analysis Research in Tobacco and Alcohol (CARTA) consortium and the UK  
25 Biobank. The smoking-increasing allele of rs1051730/rs16969968 was associated with a lower odds ratio  
26 of AR in current smokers. They saw similar results in their observational analysis; current smokers had a  
27 lower risk of hay fever than never smokers, and, accordingly, they saw an inverse dose-response  
28 relationship between smoking heaviness and hay fever. These results suggest that smoking may  
29 decrease the risk of AR. Zhou et al<sup>189</sup> also systematically reviewed 16 studies in a meta-analysis of  
30 maternal tobacco smoke exposure during pregnancy and AR. This study found that maternal passive  
31 smoking during pregnancy but not maternal active smoking during pregnancy increases the risk of their  
32 offspring developing AR. **[TABLE VIII.B.4.]**

33  
34 Recent birth cohort and prospective cohort studies have contributed to our understanding of tobacco's  
35 effect on AR development. A meta-analysis was performed on the Mechanisms of the Development of  
36 ALLergy consortium,<sup>190</sup> including 5 European birth cohort studies and 10,080 participants followed from

1 pregnancy to 14 to 16 years of age. In this cohort, maternal smoking was not associated with a  
 2 significant increase in rhinoconjunctivitis during childhood and adolescence. However, in children who  
 3 developed AR, maternal smoking of 10 or more cigarettes per day during pregnancy was associated with  
 4 persistent, rather than transient, rhinoconjunctivitis. Abramson et al<sup>191</sup> performed an analysis of  
 5 questionnaire and sIgE data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in  
 6 Adults (SAPALDIA) to assess secondhand smoking's impact on AR risk. They found that while those with  
 7 AR were significantly less likely to be current or former smokers, there were no significant associations  
 8 between secondhand smoking and AR.

9  
 10 It is known that AR represents a risk factor for asthma onset or worsening. A cross-sectional study by  
 11 Ciprandi et al<sup>192</sup> reported a clustering analysis to identify the subset of patients with AR at a higher risk  
 12 of asthma development. This subset of patients had characteristics that included longer AR history and  
 13 smoking, among others that also represent risk factors for evolving asthma. These results suggest that  
 14 smoking may be a possible risk factor for asthma development in people with AR.

15  
 16 Another area of interest is electronic cigarettes and heated tobacco products and their impact on AR. In  
 17 2020, a survey study of Korean youth reported that current smokers of conventional tobacco cigarettes  
 18 had a higher risk of AR than those using heated tobacco products and electronic cigarettes. However,  
 19 the use of heated tobacco products and electronic cigarettes among conventional tobacco smokers  
 20 increases the apparent risk of AR and asthma.<sup>193</sup> Future research should focus on understanding the  
 21 effects of these new products on a mechanistic level.

22  
 23 In summary, there have been few large prospective cohort studies or systematic reviews examining the  
 24 effect of tobacco smoke exposure on the development of AR since ICAR-Allergic Rhinitis 2018. The  
 25 studies presented herein predominantly found no correlation between active or passive tobacco smoke  
 26 and AR. However, some studies suggest that tobacco may decrease AR risk, a finding that warrants  
 27 further investigation.

28  
 29 **Aggregate grade of evidence:** C (Level 2: 3 studies, level 3: 1 study, level 4: 2 studies; **TABLE VIII.B.4.**)

30  
 31 **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 <sup>189</sup>	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 <sup>190</sup>	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 $\geq 10$ cigarettes/day during pregnancy associated with children developing persistent rhinoconjunctivitis
Skaaby et al <sup>188</sup>	2017	2	Meta-analysis, population-based studies	-Never smokers -Former smokers -Current smokers -Ever smokers	Association between smoking-associated SNPs and disease outcomes (hay fever, asthma, and allergic sensitization)	-Current smokers had lower risk of hay fever and allergic sensitization than never smokers -Current smokers had lower risks of hay fever and allergic sensitization per smoking-increasing allele
Abramson et al <sup>191</sup>	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 <sup>193</sup>	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 <sup>192</sup>	2018	4	Cross-sectional	Patients with AR	Asthma risk	-Cluster including smoking, among other factors, is associated with asthma risk

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

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

4

5

6

### 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.<sup>194</sup> 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).<sup>195</sup> (See Section VIII.G.3. Hygiene Hypothesis for additional information on this topic.) As an example, Wee et al<sup>196</sup> 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.<sup>197-200</sup> 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).<sup>199</sup>

Chen et al<sup>201</sup> 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<sup>202</sup> 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<sup>203</sup> 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).

1 Studies of SES and its impact on risk of AR highlight the role that study participant education may play  
 2 on the reporting of AR symptoms, or its diagnosis. This is illustrated by a study performed by Mercer et  
 3 al,<sup>204</sup> who evaluated 4947 children aged 13-14 in South Africa and found that residents living in low SES,  
 4 but attending high SES schools, showed significantly higher prevalence of rhinitis symptoms than  
 5 children in low SES schools. This suggests that education and access to medical care may affect  
 6 differences in reporting in survey-based, cross-sectional studies.

7  
 8 Not all studies have demonstrated a positive relationship of AR with higher SES. A cross-sectional study  
 9 performed in Bolu, Turkey including 1403 subjects observed that poor living conditions and income was  
 10 associated with a greater risk of self-reported AR.<sup>205</sup> Similarly, Lewis et al<sup>206</sup> examined allergen  
 11 sensitization patterns in 458 adult women and found that lower SES was associated with increases in  
 12 tIgE, number of allergen sensitizations, and sIgE levels. In a separate prospective cohort study  
 13 performed in 4089 families in Sweden, Almqvist et al<sup>207</sup> found increased SES (using parent occupation as  
 14 a measure of SES) to be associated with lower risk of AR at age 4. Similarly, a prospective cohort  
 15 performed by Grabenhenrich et al<sup>65</sup> among 941 children up to age 20 in Germany showed no association  
 16 between SES and AR development. And finally, using IgE-based sensitivity testing (in addition to  
 17 symptom-based testing), Ahn et al<sup>208</sup> found that only high income (and not education or occupation)  
 18 was associated with symptom-based AR, but not IgE-based AR.

19  
 20 Thus, while most of the available evidence indicates that higher SES is associated with increased risk of  
 21 AR, the data is not uniform. SES is related to a myriad of factors, many of which play an important role in  
 22 the development of AR.

23

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

25

26 **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 <sup>196</sup>	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 <sup>208</sup>	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 <sup>209</sup>	2016	2	Cross-sectional	Children (n=75,643), South Korea	Prevalence of AR	Greater affluence and education increased risk of AR
Li et al <sup>202</sup>	2011	2	Cross-sectional	Children (n=23,791), China	Prevalence of AR	Parental education, income predicts increased AR prevalence
Braback et al <sup>210</sup>	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 <sup>204</sup>	2004	2	Cross-sectional	Children (n=4947)	Prevalence of AR symptoms	Education associated with AR
Chen et al <sup>201</sup>	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 <sup>65</sup>	2016	3	Prospective cohort	Children (n=941), Germany	Prevalence of AR	Parental income and education had no association with AR development
Penaranda et al <sup>211</sup>	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 <sup>203</sup>	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 <sup>199</sup>	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 <sup>207</sup>	2005	3	Prospective cohort	Children (n=4089 families), Sweden	Prevalence of AR at 4 years	Higher SES decreases risk of AR
Lewis et al <sup>206</sup>	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 <sup>212</sup>	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 <sup>213</sup>	1998	3	Prospective cohort	Children (n=6000), British Isles	Prevalence of AR symptoms	Social advantage independently predicts risk of AR
Goh et al <sup>214</sup>	1996	3	Cross-sectional	Children (n=6238), Singapore	Prevalence of AR	Higher SES associated with better housing and higher household income
Talay et al <sup>205</sup>	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
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1 LOE=level of evidence; AR=allergic rhinitis; IgE=immunoglobulin E; SES=socioeconomic status; US=United States

## 2 3 4 VIII.C. Protective factors

### 5 VIII.C.1. Breastfeeding

6  
7 Breastfeeding is considered to have several benefits for mothers and infants. WHO guidelines  
8 recommend breastfeeding for 6 months and European Academy of Allergy and Clinical Immunology  
9 (EAACI) guidelines advise exclusive breastfeeding for 4-6 months.<sup>215,216</sup> ICAR-Allergic Rhinitis 2018 also  
10 documented that breastfeeding has been strongly recommended due to its multiple benefits in general;  
11 the policy level was “option” for the specific purpose of AR prevention.<sup>39</sup> Several mechanisms have been  
12 suggested to explain how breastfeeding might prevent allergic disease. Breast milk contains  
13 immunomodulatory factors that stimulate host defense mechanisms and immune response.<sup>217,218</sup>  
14 Although the association of breastfeeding with the development of allergic disease has been  
15 investigated in many studies, there is no consensus on whether breastfeeding is effective in preventing  
16 AR.

17  
18 A recent SRMA revealed that exclusive or non-exclusive breastfeeding for 6 or more months may have  
19 protective effects on the development of AR up to 18 years of age.<sup>219</sup> A 2019 systematic review that  
20 included one cluster RCT and five prospective cohort studies examined the relationship between shorter  
21 versus longer durations of any human milk feeding (whether or not it was fed at the breast) and AR in  
22 childhood.<sup>220</sup> The only statistically significant association was found by Codispoti et al,<sup>221</sup> noting that  
23 longer duration of breastfeeding was associated with a lower risk of AR in 3-year-old African Americans  
24 (OR 0.8; 95% CI 0.6-0.9). The authors stated that published data are insufficient to determine whether  
25 the duration of any human milk feeding was associated with AR.<sup>220</sup> **[TABLE VIII.C.1.]**

26  
27 The results from a questionnaire-based cross-sectional study of 4-6-year-old Shanghai children  
28 suggested that exclusive breastfeeding for greater than 6 months reduced the risk of hay fever (odds  
29 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  
30 never breastfed.<sup>222</sup> Food Allergy and Intolerance Research (FAIR) birth cohort in the Isle of Wight, UK,  
31 also showed exclusive breastfeeding for greater than 4 months reduced the risk of rhinitis (OR 0.36; 95%  
32 CI 0.18-0.71) from birth up to 10 years of age.<sup>215</sup> A recent cohort study of children with AR compared to

1 non-AR in Korea showed that breastfeeding for 12 or more months had a significantly lower prevalence  
 2 of AR compared with breastfeeding for less than 6 months, and the association was still valid,  
 3 accounting for age, sex, mode of delivery, number of siblings, parental atopy history, and living area (OR  
 4 0.54; 95% CI 0.34-0.88).<sup>223</sup> However, in one study using a large population-based cohort (336,364  
 5 participants) from the UK, researchers found that breastfeeding increased the risk of hay fever when  
 6 adjusted for body mass index, birth weight, SES, home area, and year of birth (OR 1.11; 95% CI 1.06-  
 7 1.16).<sup>224</sup>

8  
 9 These inconsistencies in studies, which are mainly observational surveys, can possibly be influenced by  
 10 demographic, socioeconomic, educational, ethnic, cultural, psychological status, and study  
 11 design.<sup>223,225,226</sup> In addition, since it is difficult to distinguish between AR and viral respiratory infection at  
 12 a young age, the protective effect of breastfeeding against viral infection has possibly been confused as  
 13 a protective effect on AR.<sup>227</sup> Furthermore, differences in methodological factors such as duration of  
 14 breastfeeding, any or exclusive breastfeeding, diagnostic criteria of AR, comorbid allergic disease, and  
 15 the follow-up period may account for discrepancies in assessing the association between breastfeeding  
 16 and AR.

17  
 18 Overall, considering the literature review on the association between breastfeeding and AR,  
 19 breastfeeding should be recommended due to various positive effects on general health and possible  
 20 protective effects on AR.

21  
 22 **Aggregate grade of evidence:** C (Level 2: 2 studies, level 3: 4 studies, level 4: 1 study; **TABLE VIII.C.1.**)

23 **Benefit:** Benefits on general health of infant and possible protection against AR, especially in young  
 24 children.

25 **Harm:** None.

26 **Cost:** Low.

27 **Benefits-harm assessment:** Slight preponderance of benefit over harm for protection against AR. Large  
 28 preponderance of benefit over harm for breastfeeding for all infants, unless there is a contraindication.  
 29 The benefit of breastfeeding for all infants inextricably influences this recommendation.

30 **Value judgments:** Evidence suggests that breastfeeding may reduce the risk of AR without harm.

31 **Policy level:** Recommendation for breastfeeding due to various positive effects on general health and  
 32 possible protective effects on AR.

33 **Intervention:** Breastfeeding for at least 4-6 months should be encouraged unless contraindicated.

34

35

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



Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hoang et al <sup>219</sup>	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 <sup>220</sup>	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 <sup>143</sup>	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 <sup>223</sup>	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 <sup>224</sup>	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 <sup>215</sup>	2016	3	Prospective birth cohort	-loW cohort: 1456 subjects at the ages of 1 or 2, 4, 10 and 18 -FAIR cohort: 988 subjects at the ages of 1, 2, 3 and 10	Effects of breastfeeding on long-term outcome for rhinitis	Protective effect of breastfeeding on long-term allergic outcomes is inconsistent, but exclusive breastfeeding for >4 months protects against repeated rhinitis in the FAIR cohort
Huang et al <sup>222</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized  
2 controlled trial; PACT = Prevention of Allergy among Children in Trondheim; ARCO= Allergic Rhinitis Cohort;  
3 loW=Isle of Wight; FAIR=Food Allergy and Intolerance Research; CCHH= China, Children, Homes, Health  
4 \*The systematic reviews in this table are appropriately inclusive of previously published studies on this topic.  
5  
6  
7  
8

### VIII.C.2. Childhood exposure to pets

1 Pet-keeping families are concerned about the effects of pets on their children with regard to allergic  
2 diseases; however, the recommendation of guidelines for AR in relation to childhood pet exposure  
3 remains conflicting.<sup>39,228,229</sup> ICAR-Allergic Rhinitis 2018 stated that early pet exposure may reduce the  
4 development of AR and its protective effect is stronger in non-allergic families with dog exposure.<sup>39</sup>

5  
6 A recent SRMA investigating the association between pet exposure and the risk of AR revealed the  
7 protective effect of early cat exposure (RR 0.60; 95% CI 0.33-0.86) or dog exposure (RR 0.68; 95% CI  
8 0.44-0.90) on the development of AR.<sup>69</sup> Furthermore, early cat ownership in the first 2 years of life has  
9 been associated with a significantly lower risk of AR compared to non-ownership (OR 0.51; 95% CI 0.28-  
10 0.92).<sup>77</sup> **[TABLE VIII.C.2.]**

11  
12 A prospective birth cohort study in Finland revealed that having a dog in the house in the first year of life  
13 seemed to protect against AR (OR 0.72; 95% CI 0.53-0.97) by the age of 5 years compared to those  
14 without.<sup>70</sup> Additional studies support the finding that exposure to pets during childhood reduces the risk  
15 of AR.<sup>230,231</sup> Nevertheless, these studies did not make a firm conclusion about the protective effect of pet  
16 exposure on the development of AR. Heterogeneous factors such as the timing of exposure, duration of  
17 exposure, animal species, dose of exposure (number of household pets, environmental exposure vs.  
18 ownership), and avoidance behavior may be the reason.<sup>69,232</sup>

19  
20 Furthermore, some studies have shown conflicting results. A cross-sectional survey conducted in first  
21 graders (6-8 years old) in Taiwan demonstrated that having a cat in the first year of life was associated  
22 with an increased risk of AR.<sup>73</sup> In addition, one study in Chinese children aged 0-8 years old showed a  
23 negative effect of pet keeping (aOR 3.60; 95% CI 2.07-6.27) for AR after adjustment for avoidance  
24 behavior.<sup>233</sup> However, these results should be interpreted with caution because of ethnic differences,  
25 family inheritance, and other environmental risk factors that may confound of the association between  
26 pet keeping and AR. Although the exact mechanism of the effects of pet exposure on allergic disease  
27 remains unclear, it has been suggested that environmental exposure may increase or decrease the risk  
28 of AR according to the stage of immune system development.<sup>69,234-236</sup>

29  
30 Overall, the causal relationship between pet exposure in childhood and the protective effect of AR is  
31 inconsistent; thus, no strong advice can be provided regarding childhood exposure to pets.  
32 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 development of AR.

**Policy level:** Option.

**Intervention:** Recommendation to expose or avoid pets for the prevention of AR in children cannot be provided based on current evidence.

**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 <sup>236</sup>	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 <sup>69</sup>	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 <sup>70</sup>	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 <sup>73</sup>	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 <sup>233</sup>	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

1  
2 The *hygiene hypothesis* originated from the observation that frequent and recurrent infections in early  
3 childhood appear to protect against the development of AR later in life.<sup>237</sup> Over time, the *hygiene*  
4 *hypothesis* evolved to the *biodiversity hypothesis*, which expands the scope from the protective effect of  
5 infection from single microbes to the protective effect of microbial variety during development.<sup>238</sup> The  
6 *microbiota hypothesis* was later proposed to confine the causative microbes specifically to those living in  
7 or on the human body and their impact on our immune system.<sup>239,240</sup>

8  
9 A SRMA was conducted to determine the effect of the number of siblings on AR development; this  
10 analysis assessed 53 studies with 300,062 participants.<sup>241</sup> They saw a strong inverse association between  
11 many siblings (three or more) and the development of AR. Similarly, a large international cohort study  
12 based on questionnaire data for children aged 6-7 years and 13-14 years also saw an inverse association  
13 between the number of siblings and AR but only in affluent countries.<sup>242</sup> **[TABLE VIII.C.3.]**

14  
15 It has also been observed in several studies that exposure to early-life farming may protect against  
16 childhood allergic diseases particularly, exposure to farm animals and stables.<sup>243-253</sup> In a recent meta-  
17 analysis by Campbell et al,<sup>243</sup> the risk of sensitization measured by sIgE or SPT in childhood or adulthood,  
18 was 40% lower among children who had lived on a farm during the first year of life. Further, a 2017 US  
19 case-control study showed farm exposure in utero provides even greater protection against sensitization  
20 in adulthood.<sup>244</sup> While an isolated exposure to bacterial endotoxin was claimed to have a similar  
21 protective effect, the results thus far have been inconclusive.<sup>254,255</sup>

22  
23 Increased diversity in the gut and skin microbiome has been associated with a protective effect on  
24 atopy.<sup>239,256-261</sup> Recently, three large cohort studies have reported that reduced bacterial diversity in the  
25 infant's intestinal flora within the first 6 years of life predisposes them to a higher risk of developing  
26 AR.<sup>239,262,263</sup> Notwithstanding this, a meta-analysis of 29 trials did not find supplementation of probiotics  
27 to pregnant mothers or infants beneficial in preventing atopy.<sup>264</sup> A publicly available American Gut  
28 Project questionnaire and database was used in a study to determine the fecal microbiota richness and  
29 composition in adults with AR.<sup>259</sup> They found an imbalance (dysbiosis) of gut flora with higher  
30 *Bacteroides* and reduced *Clostridia* taxa in this population. In addition, the role of *Helicobacter pylori* has  
31 been investigated, with inconsistent findings.<sup>265-267</sup> Interestingly, in a meta-analysis of 21 studies  
32 assessing the association between *H. pylori* infection and allergic diseases, a significant inverse

1 association was found between *H. pylori* infection with atopy from the case-control studies while an  
 2 association was seen between allergic disease and *H. pylori* infection from the cross-sectional studies.<sup>267</sup>

3  
 4 Lower biodiversity on the skin and in the home living environment is associated with an increased risk of  
 5 atopy.<sup>260</sup> Ruokolainen et al<sup>268</sup> performed a comparative study of the microbiota of skin and nose in  
 6 randomly selected school children from urban and rural areas. They saw that rural school children had  
 7 increased microbial diversity on their skin and in their noses and this was associated with lower allergy  
 8 prevalence compared urban school children.

9  
 10 In summary, there is some evidence of the protective effect of the hygiene hypothesis on AR from  
 11 epidemiological studies but more studies that evaluate causality are needed. (See Section VI.J.

12 *Microbiome and Section XI.B.9. Probiotics for additional information on this topic.*)

13  
 14 **Aggregate grade of evidence:** B (Level 1: 4 studies, level 3: 12 studies, level 4: 3 studies, level 5: 2 studies;  
 15 **TABLE VIII.C.3.)**

16  
 17 **TABLE VIII.C.3. Literature summary – Protective factors against development of allergic rhinitis:**  
 18 **hygiene hypothesis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Campbell et al <sup>243</sup>	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 <sup>264</sup>	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 <sup>267</sup>	2014	1	SRMA	21 studies: 11 case-control, 10 cross-sectional	Relationship between <i>H. pylori</i> and atopy/allergic diseases	-Some evidence of inverse association between atopy/allergic diseases and <i>H. pylori</i> infection -Inconsistent pooled results from case-control and cross-sectional studies require further investigation

Karmaus & Botezan <sup>241</sup>	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 <sup>244</sup>	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 <sup>268</sup>	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 - <i>Acinetobacter lwoffii</i> oligotype profile differed in Finnish sensitized subjects -Causal relationship not proven
Fujimura et al <sup>258</sup>	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 <i>Bifidobacteria</i> , <i>Lactobacillus</i> , <i>Faecalibacterium</i> , <i>Akkermansia</i> and <i>Malazzesia</i> during the neonatal period may influence the risk of multi-sensitization predictive for asthma
Hua et al <sup>259</sup>	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 <sup>257</sup>	2015	3	Nested case-control	319 children followed from	Association of sensitization and wheezing at 1 year	Suggests that reduced colonization of <i>Faecalibacterium</i> ,

				birth until 5 years of age	with fecal microbiota at age 3 months and 1 year	<i>Lachnospira</i> , <i>Veillonella</i> and <i>Rothia</i> during the first 3 months of life may increase the risk of atopic asthma
Strachan et al <sup>242</sup>	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 <sup>269</sup>	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 <sup>265</sup>	2012	3	Prospective cohort	545 Dutch children	Association between <i>H. pylori</i> and AR	No association between <i>H. pylori</i> and AR
Bisgaard et al <sup>239</sup>	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 <sup>270</sup>	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 <sup>255</sup>	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 <sup>271</sup>	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 <sup>266</sup>	2020	4	Cross-sectional	274 children and adults	Association between <i>H. pylori</i> infection and allergy	Positive correlation between <i>H. pylori</i> infection and AR
Abrahamsson et al <sup>256</sup>	2014	4	Case-control	47 infants (20 with IgE-associated eczema and 27 healthy)	Association of sensitization, asthma, and AR with fecal diversity in infancy	-Low microbial diversity associated with asthma later in childhood -No association with sensitization or rhinitis

				controls) followed until 7 years of age		
Sjogren et al <sup>262</sup>	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 <sup>254</sup>	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 <sup>263</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; AR=allergic  
2 rhinitis; GABRIELA=Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the  
3 European Community Advanced Study; PARSIFAL= Prevention of Allergy-Risk Factors for Sensitization in Children  
4 Related to Farming and Anthroposophic Lifestyle; IgE=immunoglobulin E  
5  
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## 1 IX. Allergic rhinitis disease burden

### 2 IX.A. Individual burden

#### 3 IX.A.1. Quality of life

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5  
6 High quality evidence evaluating the impact of AR on QOL continues to show AR patients suffer from  
7 decreased general and disease-specific QOL due to impacts on physical and mental health.<sup>1-6</sup> These  
8 studies also show that treatment of AR with INCS, oral antihistamines, and AIT leads to improved QOL.  
9 Validation of QOL metrics in AR continues. There has been a trend toward use of disease specific QOL  
10 metrics, especially the RQLQ.<sup>7</sup> As this has become more accepted, use of general health related QOL  
11 metrics such as Short Form 12 and 36 (SF-12/36) has decreased.<sup>8,9</sup> A measure of QOL used in CRS, the  
12 SNOT-22, has now been studied in AR.<sup>10</sup> This study showed SNOT-22 was able to assess QOL and  
13 response to treatment in AR. Olfaction, an objective measure of QOL also typically used in CRS, has also  
14 been studied in AR recently. Olfactory dysfunction was identified in 44% of patients with AR.<sup>11</sup> The use  
15 of SNOT-22 and objective measures of olfaction could simplify implementation of QOL monitoring for  
16 both diseases from a clinical standpoint. **[TABLE IX.A.1.]**

17  
18 Despite the availability of disease specific QOL instruments, many studies continue to rely on  
19 unvalidated methods to assess QOL. This leads to difficulty comparing outcomes between some studies.  
20 A recent SRMA evaluated the outcomes of medical therapy with INCS, oral antihistamines, or AIT for AR.  
21 Treatment with oral antihistamines and AIT had a statistically significant impact on QOL. Despite near  
22 universal acceptance of INCS for the treatment of AR, meta-analysis of the impact of INCS on QOL could  
23 not be performed due to a lack of available data.<sup>2</sup> There are numerous individual RCTs evaluating the  
24 effect of INCS,<sup>12</sup> oral antihistamines,<sup>13-16</sup> and AIT.<sup>17-20</sup> The overarching findings in these individual RCTs is  
25 that these treatments improve QOL.

26  
27 While numerous studies exist comparing changes in symptoms with treatment for AR,<sup>21</sup> direct, head-to-  
28 head comparisons of changes in QOL with different treatments for AR are lacking. There is only one  
29 study comparing the impact of monotherapy with INCS (mometasone) to combination therapy with INCS  
30 and oral antihistamine (mometasone + levocetirizine) or INCS and leukotriene D<sub>4</sub>-receptor  
31 antagonist (mometasone + montelukast) on QOL as measured with the 14-question mini-RQLQ. This  
32 study found that polytherapy with mometasone and levocetirizine or montelukast improved QOL more  
33 than mometasone alone; no difference was seen between montelukast or levocetirizine when added to  
34 mometasone.<sup>22</sup>

1  
 2 New evidence evaluating the impact of AR on QOL in children and in the parents of children with AR is  
 3 emerging. As expected, these studies show impacts on QOL in this population. More surprisingly, they  
 4 show impacts on parental QOL as well.<sup>23-26</sup> In one study, parents overestimate their children's QOL.<sup>27</sup>  
 5 This focus on assessing QOL in children and adolescents with AR was built on prior work measuring  
 6 general QOL in children with instruments such as KINDL®.<sup>28</sup> Disease-specific instruments (Pediatric  
 7 Rhinoconjunctivitis Quality of Life Questionnaire [PRQLQ] and RhinAsthma Patient Perspective [RAPP]-  
 8 children) have now been developed to measure the impact of AR on QOL in pediatric and adolescent  
 9 populations.<sup>23,29</sup> In children and adolescents with persistent AR, those with nasal obstruction secondary  
 10 to septal deviation or turbinate hypertrophy have the worst QOL.<sup>26</sup> Nasal endoscopy should be  
 11 considered in patients in this population not responding to therapy to ensure nasal obstruction is not  
 12 contributing.

13  
 14 Variations in QOL in AR patients have not been prospectively studied over time. Most studies are either  
 15 cross-sectional or have short follow-up periods with few time points at which QOL is assessed. Control  
 16 groups from RCTs and meta-analyses of RCTs can provide insight into long-term variation in QOL in AR,  
 17 however. Two RCTs have studied the effect of oral antihistamines with a follow up period of at least 6  
 18 months.<sup>15,16</sup> These RCTs show that both the placebo and treatment groups experience clinically and  
 19 statistically significantly improvements in generic and disease specific QOL, but the improvement is  
 20 greater in the treatment arm. A more recent meta-analysis of a combination INCS and intranasal  
 21 antihistamine showed short-term but not long-term QOL improvement with this treatment.<sup>1</sup> This latter  
 22 finding, however, was based on a single study.<sup>30</sup> AIT RCTs have longer follow-up periods (12 months to 3  
 23 years) and show similar results, with placebo patients either remaining at baseline or improving to a  
 24 lesser degree than the treatment arms.<sup>17,18,20</sup> As expected, patients with seasonal AR have worse QOL  
 25 during seasons in which they are exposed to allergens and improved QOL outside of these seasons.<sup>31</sup>

26  
 27 **Aggregate grade of evidence:** B (Level 1: 6 studies, level 2: 35 studies, level 3: 15 studies; **TABLE IX.A.1.**)  
 28 **Benefit:** Successful treatment of AR leads to improved overall and disease specific QOL.  
 29 **Harm:** Depending on the specific treatments for AR, there are variable levels of harm. [**TABLE II.C.**]  
 30 **Cost:** Treatments for AR have variable costs.  
 31 **Benefits-harm assessment:** The benefits of treating patients with AR to improve QOL likely outweigh risks of treatment.  
 32 **Value judgment:** Validated measures of QOL should be utilized in future studies of treatments for AR.  
 33 **Policy level:** Recommendation.  
 34 **Intervention:** Validated measures of QOL should be utilized in future studies of treatments for AR.  
 35

1

2 **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 <sup>1</sup>	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 <sup>3</sup>	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 <sup>2</sup>	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 <sup>4</sup>	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 <sup>5</sup>	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 <sup>6</sup>	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 <sup>32</sup>	2021	2	Cross-sectional	AR, n=40	RQLQ		AR negatively impacts QOL
Passali et al <sup>11</sup>	2021	2	Cross-sectional	AR, n=1063	Sniffin' Sticks olfactory test		Olfactory dysfunction in 44% of AR patients
Bosnic-Anticevich et al <sup>24</sup>	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 <sup>17</sup>	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 <sup>27</sup>	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 <sup>25</sup>	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 <sup>30</sup>	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 <sup>33</sup>	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 <sup>34</sup>	2018	2	Cross-sectional	Users of <i>Allergy Diary</i> 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 <sup>35</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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 <sup>38</sup>	2015	2	Cross-sectional	Adolescents (n=6,407):	VAS		-AR in 15.8-19.4%

				-Likely AR from stratified sample, n=515 -Cluster sample, n=814		-AR impacts QOL, sleep, emotions, and memory
Bousquet et al <sup>13</sup>	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 <sup>39</sup>	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
Katellaris et al <sup>40</sup>	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 <sup>22</sup>	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 <sup>41</sup>	2012	2	Cross-sectional	Primary care patients, n=616	SF-36, generic HRQL, WPAI	AR impacts productivity to a greater magnitude than hypertension and DM type II, but less than the impact of depression
Meltzer et al <sup>42</sup>	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 <sup>12</sup>	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 <sup>18</sup>	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 <sup>14</sup>	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 <sup>43</sup>	2009	2	Cross-sectional	AR, n=404	Symptom scale, nocturnal RQLQ, WPAI, MOS-12 Sleep, PANAS-X	-Nasal congestion more strongly correlated to outcomes -Ocular symptoms can have significant impact on QOL
Witt et al <sup>44</sup>	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 <sup>45</sup>	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 <sup>46</sup>	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 <sup>47</sup>	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 <sup>15</sup>	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 <sup>20</sup>	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 <sup>19</sup>	2006	2	DBRCT	AR (n=34): -SLIT, n=19 -Placebo, n=15	RQLQ	-QOL significantly affected by AR -SLIT improved QOL compared to placebo
Bachert et al <sup>16</sup>	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 <sup>48</sup>	2003	2	DBRCT	Seasonal AR (n=183):	RQLQ, problem-free days	Enzyme potentiated desensitization does not

				-Enzyme potentiated desensitization, n=90 -Placebo, n=93		improve QOL or symptom scores compared to placebo
Gerth van Wijk et al <sup>49</sup>	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 <sup>50</sup>	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 <sup>7</sup>	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 <sup>23</sup>	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 <sup>10</sup>	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 <sup>51</sup>	2019	3	Cohort	AR undergoing SCIT, n=120	RQLQ, ARIA	-SCIT treatment increases QOL -Reduction in asthma symptoms with SCIT
Gillman et al <sup>52</sup>	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 <sup>53</sup>	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 <sup>54</sup>	2017	3	Cohort	AR treated with SLIT, n=191	RQLQ	SLIT significantly improved QOL

Schwanke et al <sup>55</sup>	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 <sup>26</sup>	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 <sup>56</sup>	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 <sup>57</sup>	2013	3	Non-randomized cohort	Perennial AR treated with desloratadine-montelukast, n=40	Acoustic rhinometry, RQLQ	Desloratadine-montelukast improves nasal obstruction and QOL
Demoly et al <sup>58</sup>	2013	3	Cohort	AR, n=990	VAS, RQLQ, TSS	VAS can detect QOL variations with high sensitivity
Ciprandi et al <sup>59</sup>	2010	3	Cohort	AR undergoing SLIT, n=167	RQLQ	-QOL significantly affected by AR -SLIT improves QOL and symptoms
Cadario et al <sup>60</sup>	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 <sup>61</sup>	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 <sup>31</sup>	2001	3	Cohort	Seasonal AR, n=33	SF-36, SAT-P	QOL significantly affected by AR during peak season

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

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

9

10

## 11 IX.A.2. Sleep disturbance

12

13 AR affects 20-30% of adults and children with OSA and sleep disordered breathing (SDB).<sup>62,63</sup> Multiple  
14 studies have investigated the relationship between AR and sleep in adults and children. The general  
15 conclusion from the aggregate data is that similar to overall and rhinitis specific QOL, AR negatively  
16 impacts sleep quality, and the successful treatment of AR reduces sleep disturbance. Overall, the data is  
17 of low to moderate strength, with the overall quality of the data being higher for adults than for the  
18 pediatric population. For the adult population, there is strong evidence supporting the conclusion that  
19 AR negatively impacts sleep.<sup>64-68</sup> This data deals with subjective reporting of daytime sleepiness, sleep  
20 quality, and symptoms usually through validated tools, in the setting of testing the effect of INCS and  
21 montelukast. [TABLES IX.A.2.-1 and IX.A.2.-2]

22

23 In children, lower quality data suggest that AR is associated with sleep disturbance in the form of  
24 increased risk of snoring, SDB, and OSA. However, the findings here are not uniform, with some studies  
25 suggesting that while the prevalence of AR is high in the OSA population, AR might not impact disease  
26 severity.<sup>63,69</sup> Furthermore, AR has been suggested to be a risk factor for deterioration of OSA QOL after  
27 adenotonsillectomy.<sup>70</sup> Additionally, AR may increase the risk of nocturnal enuresis in children.<sup>71</sup>

28

29 Two studies looked at variations in sleep symptoms with changes in nasal inflammation over time. Nasal  
30 cytokine level alterations are associated with changes in the polysomnogram (PSG)<sup>72</sup> and AR patients  
31 have worse PSG parameters and sleep disturbance when their symptoms are present or during their  
32 peak allergen season.<sup>73</sup> The data on PSG parameters in adults is mixed. Most studies that perform PSG  
33 found that AR worsens PSG parameters;<sup>62,72-81</sup> however two studies found either no difference or a  
34 modest change.<sup>82,83</sup>

35

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

7 **Aggregate grade of evidence:** B (Level 2: 5 studies, level 3: 8 studies, level 4: 50 studies **TABLES IX.A.2.-1**  
 8 and **IX.A.2.-2**).

9 **Benefit:** AR negatively impacts sleep quality. Successful management of AR leads to decreased sleep  
 10 disturbance in adults and children.

11 **Harm:** Medical management of AR is generally low risk and medications have low side-effect profiles.  
 12 AIT is associated with rare serious adverse events. **[TABLE II.C.]**

13 **Cost:** Associated costs consist of the direct costs of allergy testing and medical management, and  
 14 indirect cost of increased time and effort for AIT.

15 **Benefits-harm assessment:** The benefits of treating patients with AR may outweigh any associated risks.

16 **Value judgment:** In patients with AR, the successful control of symptoms with medical management or  
 17 AIT can lead to important improvements in sleep disturbance. The level of available evidence is stronger  
 18 for the adult population compared with the pediatric population.

19 **Policy level:** Treatment of AR to improve sleep disturbance -- Recommended in adults. Option in  
 20 children.

21 **Intervention:** INCS, oral antihistamines, montelukast, and AIT are appropriate options, when medically  
 22 indicated, to improve sleep disturbance in patients with AR.

23

24 **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 <sup>88</sup>	2021	2	SRMA	28 AR articles, n=8515 AR patients	RQLQ, ESS, PSQI	Treatment of AR improves subjective sleep quality
Liu et al <sup>79</sup>	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 <sup>64</sup>	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 <sup>68</sup>	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 <sup>89</sup>	2018	3	Prospective cohort	AR, n=670	Sleep quality, MOSSS	AR symptoms negatively impact sleep quality
Parikh et al <sup>87</sup>	2014	3	Prospective cohort	OSA and rhinitis, n=43	ESS, symptoms scores, CPAP compliance	-Control of rhinitis (with varying regimens of INCS, antihistamines, leukotrienes inhibitors, anticholinergics, etc.) important for OSA control -Rhinitis control assessed via symptoms scores, OSA control assessed via ESS -No difference between AR and non-allergic rhinitis
Acar et al <sup>74</sup>	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 <sup>90</sup>	2012	3	Prospective cohort	AR, n=2275	TSS, RQLQ, PSQI	AR disease severity has strong relationship with sleep disturbance
Gurevich et al <sup>65</sup>	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 <sup>66</sup>	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 <sup>67</sup>	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 <sup>80</sup>	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 <sup>81</sup>	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 <sup>91</sup>	2019	4	Survey study	AR, n=511	Sleep questionnaire	AR negatively impacts sleep metrics and daily functioning
Berson et al <sup>78</sup>	2018	4	Case-control	-AR, n=67 -Non-allergic rhinitis, n=33	ESS, PSG	AR worsens sleep quality
Roxbury et al <sup>92</sup>	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 <sup>93</sup>	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 <sup>62</sup>	2017	4	Cross-sectional	OSA, n=240, 27% with AR	PSG	AR does not influence severity of OSA
Bozkurt et al <sup>83</sup>	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 <sup>94</sup>	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 <sup>76</sup>	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 <sup>95</sup>	2012	4	Case-control	-OSA and AR, n=37 -OSA without rhinitis, n=75	ESS, stress, score, fatigue score, coping score, RQLQ	AR in OSA increases stress and fatigue, worsens sleepiness and QOL
Meng et al <sup>82</sup>	2011	4	Case-control	-Persistent AR, n=98 -Control, n=30	PSG	PSG parameters showed modest changes in persistent AR patients
Rimmer et al <sup>85</sup>	2009	4	Case-control	-Persistent AR, n=10 -Control, n=10	Actigraphy	AR has increased sleep fragmentation and reduced sleep quality
Udaka et al <sup>96</sup>	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 <sup>97</sup>	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 <sup>98</sup>	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 <sup>99</sup>	2004	4	Uncontrolled open-label study	AR, n=651	NRQLQ, PSQI	Treatment with triamcinolone improves nocturnal rhinitis QOL and sleep quality
Stuck et al <sup>100</sup>	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 <sup>72</sup>	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 <sup>86</sup>	2000	4	Survey study	Subjects from TESOAD with sleep problems/snoring, n=437	Questionnaire	AR risk factor for snoring
Young et al <sup>75</sup>	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 <sup>101</sup>	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 <sup>73</sup>	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 <sup>77</sup>	1981	4	Case-control	-AR, n=14 -Control, n=7	PSG	AR patients had 10-fold increase in micro-arousals vs controls

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



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

3

4

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**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 <sup>102</sup>	2013	2	SRMA	18 articles	Association between AR and SDB	Most studies show association between AR and SDB in children, but all studies were low level of evidence
Lai et al <sup>71</sup>	2018	3	Controlled cohort study	-AR, n=327,928 -Non-allergic rhinitis, n=327,061	Questionnaire on nocturnal enuresis	AR increases risk of nocturnal enuresis
Lee et al <sup>103</sup>	2021	4	Survey study	Adolescents, n=1936, 23.7% with AR	Sleep questionnaire	AR associated with inappropriate sleep duration
Liu et al <sup>63</sup>	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 <sup>104</sup>	2019	4	Cross-sectional	AR children at high altitude, n=99	PSG	AR in children at high altitude associated with more severe OSA
Bilgilişoy Filiz et al <sup>69</sup>	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 <sup>105</sup>	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 <sup>93</sup>	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 <sup>106</sup>	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 <sup>107</sup>	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 <sup>70</sup>	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 <sup>108</sup>	2015	4	Cross-sectional	Non-white Latino and African	Clinical evaluation and follow-up	Poor AR and asthma control related to high frequency of sleep

				American urban children, n=195		problems and poor sleep hygiene
Poachanukoon et al <sup>109</sup>	2015	4	Case-control	-AR, n=65 -Control, n=104	Questionnaire	Higher incidence of sleep disturbance in AR
Kwon et al <sup>110</sup>	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 <sup>111</sup>	2010	4	Cross-sectional	Children undergoing T&A for OSA, n=578	PSG	39% of OSA children have AR pre-operatively
Li et al <sup>112</sup>	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 <sup>113</sup>	2010	4	Case series	Children with rhinitis, n=302	History	Upper airway obstruction associated with non-allergic rhinitis
Barone et al <sup>114</sup>	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 <sup>115</sup>	2009	4	Cross-sectional	Turkish children, n=1030	Questionnaire	AR associated with habitual snoring (OR 3.7; 95% CI 1-13)
Liukkonen et al <sup>116</sup>	2008	4	Cross-sectional	Children in Helsinki, n=2100	Questionnaire	AR more common in snorers
Kalra et al <sup>117</sup>	2006	4	Cross-sectional	Children in CCAAPS, n=681	Questionnaire	29% of patients with HS have positive SPT, significant association
Goldbart et al <sup>118</sup>	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 <sup>119</sup>	2005	4	Cross-sectional	School children, n=3047	Questionnaire	AR associated with witnessed apnea
Sogut et al <sup>120</sup>	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 <sup>121</sup>	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 <sup>122</sup>	2004	4	Cross-sectional	Children with AR undergoing SPT, n=202	History	17% of AR patients reported HS
Mansfield et al <sup>123</sup>	2004	4	Case series	Children with AR, n=14	PSG, RQLQ	Treating AR decreases AHI
Anuntaseree et al <sup>124</sup>	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 <sup>125</sup>	1997	4	Case series	Children with HS, n=39	PSG	Positive skin test associated with OSA
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1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; SDB=sleep disordered  
2 breathing; OSA=obstructive sleep apnea; PSG=polysomnogram; PSQI=Pittsburgh Sleep Quality Index; IRLSSG:  
3 international restless leg syndrome study group criteria; ACT=Asthma Control Test; ESS=Epworth Sleepiness Scale;  
4 HDM=house dust mite; T&A=tonsillectomy and adenoidectomy; REM=rapid eye movement sleep; AHI=apnea-  
5 hypopnea index; OSA-18=18-item quality of life survey for obstructive sleep apnea; SPT=skin prick test;  
6 QOL=quality of life; OR=odds ratio; CI=confidence interval; CCAAPS=Cincinnati Allergy and Air Pollution Study;  
7 HS=habitual snoring; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

## 10 IX.B. Societal burden

12 AR has a high prevalence globally and imposes negative effects on QOL and therefore a burden to  
13 individuals and society. Due to its chronicity and prevalence, AR poses a significant socioeconomic  
14 burden.<sup>126,127</sup> The true burden of AR involves direct, indirect, and societal costs. Direct costs relate to  
15 financial expenditures on healthcare related to AR, including the diagnosis, prevention, and  
16 management of disease. Indirect costs are due to loss of productivity related to disease including job  
17 loss, absenteeism, and presenteeism. Additional costs include costs due to reduced QOL and societal  
18 costs related to an individual's symptoms and subsequent reduced QOL.<sup>128-131</sup>

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

29 AR leads to increased direct costs in countries around the world.<sup>128</sup> A 2021 US study demonstrated that  
30 AR patients had annual mean costs of \$218 (US) for clinic visits and procedures, and additional \$111 (US)  
31 for medications.<sup>134</sup> In a 2020 Danish study comparing 350 AR patients to controls, those with AR spent  
32 an additional €208 per year in direct costs.<sup>138</sup> In a 2016 study of 8,001 Swedish residents, direct costs  
33 attributable to AR were €210 per individual per year.<sup>144</sup> A 2017 French study demonstrated median  
34 direct costs of €159 for AR without asthma and €375 for AR with asthma.<sup>145</sup> Studies from Turkey showed

1 increased costs of \$79 to \$139 (US) for AR patients.<sup>146</sup> Studies from South Korea and India also  
2 demonstrate significant direct costs.<sup>147-149</sup>

3  
4 Despite its perception as a nuisance disorder, AR has significant effect on QOL and accounts for  
5 substantial indirect costs related to missed work or school and poorer productivity. AR results in 3.5  
6 million missed workdays and 2 million missed school days.<sup>150</sup> However, indirect costs account for a  
7 larger proportion of the burden of AR than the direct costs.<sup>137</sup> In the US, AR has been shown to  
8 contribute to greater than \$5 billion (US) in lost productivity yearly.<sup>151</sup> These costs include absenteeism,  
9 but health impairments of AR are often not severe enough to cause absenteeism. AR symptoms can  
10 interfere with cognitive functioning, resulting in fatigue and impaired learning, concentration, and  
11 critical thinking leading to presenteeism or reduced productivity while at work.<sup>152</sup> As such, presenteeism  
12 accounts for the majority of reduced productivity related to AR.<sup>153-155</sup>

13  
14 In the US, AR is the most prevalent condition among the workforce, and accounted for 52 symptomatic  
15 days per year with a mean productivity loss of \$518 (US) per employee per year.<sup>156</sup> In the UK, impaired  
16 productivity and/or missed work occurred as a result of AR in 52% of patients.<sup>143</sup> In India, 37% percent of  
17 surveyed patients with AR endorsed presenteeism and AR was responsible for \$460 (US) loss per patient  
18 annually.<sup>149</sup> In Sweden, indirect costs were calculated to be €751 per patient annually.<sup>144</sup> In the  
19 Netherlands, indirect costs were estimated to be €3681 per patient annually, and presenteeism  
20 accounted for the majority of lost productivity.<sup>138</sup> In a Spanish study, presenteeism made up 95% of the  
21 loss in productivity and was estimated €1772 per year.<sup>153</sup>

22  
23 Additionally, there are indirect economic losses that come from caregivers missing work while a child is  
24 absent from school. In a Swedish study, the cost of caregiver absenteeism comprised 19% of the mean  
25 total costs per year. The cost related to caregiver absenteeism was highest for women aged 30-44  
26 years.<sup>157</sup>

27  
28 AR is also the most prevalent chronic disorder among children, as such it has a significant impact on  
29 education.<sup>158,159</sup> On any given day in the US, approximately 10,000 children are absent from school  
30 because of AR.<sup>160</sup> AR can alter sleep quality resulting in daytime sleepiness, impaired cognition, and  
31 poorer memory in children that significantly affects the learning process and impacts school  
32 performance.<sup>79,159,161</sup> Even when present during school hours, children with AR exhibit decreased

1 productivity. Conditions associated with AR such as rhinosinusitis, ETD and associated conductive  
2 hearing loss may enhance the learning dysfunction.<sup>159</sup>

3  
4 Additionally, AR has been associated with negative impact on mental health with functional decline as  
5 well as major depression, further reducing overall QOL.<sup>35,162,163</sup> This relationship has been shown in  
6 studies from Europe, the US, and Asia.<sup>163</sup>

7  
8 AR represents a significant personal and socioeconomic burden that will likely worsen as the prevalence  
9 continues to increase.<sup>164,165</sup> It can reduce productivity and QOL in affected patients and contribute to  
10 comorbid conditions. This results in a significant impact to the overall health system.<sup>160</sup>

11  
12

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- 41



## 1 X. Evaluation and diagnosis

### 3 X.A. History and physical examination

#### 4 X.A.1. History

5  
6 A crucial component in the diagnosis of suspected AR rests on clinical history.<sup>1-5</sup> This includes symptoms  
7 experienced, timing of symptoms, duration, frequency, patient occupation/school/home environmental  
8 exposures that elicit symptoms, and any measures or medications that improve or worsen symptoms.<sup>1-6</sup>  
9 Other comorbid conditions in the past medical history, such as asthma, OSA, family history of atopic  
10 disorders, and medications currently taken should be gathered.<sup>1-6</sup> Patient response to self-treatment  
11 with over-the-counter medications is helpful information, and with advancing technology mobile  
12 applications may allow for the potential collection of patient symptomatology to identify symptom  
13 patterns that may be very useful for treating providers.<sup>7</sup>

14  
15 Classic symptoms of AR include nasal congestion or obstruction, nasal pruritis, rhinorrhea, and sneezing.  
16 In addition, patients may complain of other symptoms associated with comorbidities including ocular  
17 pruritis, erythema, and/or tearing (allergic conjunctivitis), oral cavity or pharyngeal pruritis (allergic  
18 pharyngitis), throat clearing, and wheezing or cough (reactive airway disease and/or asthma).<sup>1-6</sup> Snoring  
19 or sleep-disordered breathing, aural congestion or pruritis, and wheezing are other frequent  
20 symptoms.<sup>3-6</sup> In the coronavirus disease 2019 (COVID-19) era, symptoms of hyposmia or anosmia,  
21 cough, and/or sore throat, which potentially may also be associated with AR, may cause confusion, and  
22 should prompt consideration for other diagnoses, such as active COVID-19 infection.<sup>6,8,9</sup>

23  
24 Patients with suspected AR will commonly present with multiple complaints, frequently with two or  
25 more symptoms.<sup>6,7,9</sup> Perennial AR patients have a tendency to report more congestive symptoms (sinus  
26 pressure, nasal blockage/congestion, and snoring) than seasonal AR patients.<sup>8</sup> Also, perennial AR  
27 patients more frequently complain of sore throat, cough, sneezing, rhinorrhea, and postnasal drip.<sup>6</sup> Prior  
28 to the COVID-19 pandemic, symptoms of rhinorrhea, sneezing, sniffing, hyposmia/anosmia, nasal  
29 obstruction, and itchy nose ranked highest in diagnostic utility among symptoms of AR; however, the  
30 diagnostic utility of hyposmia/anosmia, nasal obstruction and congestion may be less given the overlap  
31 in COVID-19 symptomatology.<sup>8 6,10</sup>

32  
33 Despite the dearth of high-level evidence, many guidelines suggest that history of two or more  
34 symptoms consistent with AR is sufficient for making the diagnose of AR.<sup>1-4,9,10</sup> **[TABLE X.A.1.]** Since AR

1 lacks pathognomonic physical examination findings, physical examination alone to diagnose AR has been  
 2 shown to have poor predictive value.<sup>11</sup> The reliability and predictive value of the patient history for AR  
 3 exceeds that of the physical exam alone.<sup>11</sup> In clinical practice, the presumptive diagnosis of AR is often  
 4 made by only history, even more so during the pandemic with increased utilization of telemedicine  
 5 where a physical examination is limited.<sup>9,10,12</sup>

6  
 7 **Aggregate grade of evidence:** D (Level 4: 5 studies, level 5: 7 guidelines or expert recommendations;

8 **TABLE X.A.1.)**

9 **Benefit:** Improves accuracy of diagnosis, avoids unnecessary referrals, testing, or treatment.

10 **Harm:** Potential misdiagnosis or inappropriate treatment.

11 **Cost:** Minimal.

12 **Benefits-harm assessment:** Preponderance of benefit over harm.

13 **Value judgments:** Using history to make a presumptive diagnosis of AR is reasonable and would not  
 14 delay treatment initiation. History should be combined with physical examination, which may not be  
 15 possible in some scenarios such as telemedicine. Confirmation with diagnostic testing is required for  
 16 progression to AIT or targeted avoidance therapy, or desirable with inadequate response to treatment.

17 **Policy level:** Recommendation.

18 **Intervention:** Despite low level evidence specifically addressing this area, history is essential in the  
 19 diagnosis of AR.

20

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

1 LOE=level of evidence; AR=allergic rhinitis; VAS=visual analog scale; SPT=skin prick test; sIgE=allergen-specific  
 2 immunoglobulin E; COVID-19=coronavirus disease 2019; AIT=allergen immunotherapy  
 3 \*Seidman et al Clinical Practice Guideline LOE upgraded to 4 in other ICAR sections; although recommended, direct  
 4 evidence for history and physical exam in AR remains poor and substantiates LOE 5 designation in this section  
 5  
 6

7 **X.A.2. Physical examination**

8  
 9 Whenever possible, it is important to include physical examination as part of the evaluation of  
 10 suspected AR patients.<sup>1-4,9,12</sup> Telemedicine may complicate this part of the evaluation, but a limited  
 11 visual examination may be obtained.<sup>12</sup> An assessment of head and neck organ systems should be  
 12 completed with the use of any necessary personal protective equipment.<sup>1-3,12</sup> If there are patient  
 13 complaints of wheezing or coughing with allergic triggers or comorbid conditions of asthma, the physical  
 14 examination may include auscultation of the lungs.<sup>4</sup>  
 15

1 An unremarkable physical examination is common for AR patients, particularly those with intermittent  
 2 exposure.<sup>8</sup> Observation alone may reveal possible signs suggestive of AR, which can be useful during  
 3 telemedicine visits. These signs include mouth-breathing, nasal itching or a transverse supratip nasal  
 4 crease, throat clearing, periorbital edema, or “allergic shiners” (dark discoloration of the lower lids and  
 5 periorbital area).<sup>1,3</sup> Ear examination may reveal retraction of the tympanic membrane or transudative  
 6 fluid, although evidence for association of effusion with AR is low level. Anterior rhinoscopy may reveal  
 7 IT hypertrophy, congested/edematous nasal mucosa, purplish or bluish nasal mucosa, and clear  
 8 rhinorrhea.<sup>1-3</sup> Eye examination may reveal conjunctival erythema and/or chemosis.<sup>1,3</sup>

9  
 10 Physical examination by itself is more variable and poorly predictive of the diagnosis of AR when  
 11 compared to history-taking, with the average sensitivity, specificity, positive predictive value, and  
 12 negative predictive values of the patient history higher than those of the physical examination.<sup>11</sup> Most  
 13 guidelines recommend a physical examination as part of the diagnosis of AR, despite a lack of high level  
 14 evidence; however, pandemic conditions and the utilization of telemedicine may limit the completeness  
 15 or possibility of physical examination.<sup>12</sup> [TABLE X.A.2.] Without a physical examination, other potential  
 16 causes of symptoms such as CRS may not be fully evaluated or eliminated, so if there are limits placed  
 17 by telemedicine, additional diagnostic measures may need to be considered, such as a CT scan of the  
 18 sinuses. A patient history combined with a physical examination improves diagnostic accuracy.<sup>11</sup>

19  
 20 **Aggregate grade of evidence:** D (Level 4: 2 studies, level 5: 6 guidelines; TABLE X.A.2.)

21 **Benefit:** Possible improved diagnosis of AR with physical examination findings, along with evaluation  
 22 and/or exclusion of alternative diagnoses.

23 **Harm:** Possible patient discomfort from routine examination, not inclusive of endoscopy.

24 **Cost:** Minimal.

25 **Benefits-harm assessment:** Preponderance of benefit over harm, potential misdiagnosis and  
 26 inappropriate treatment if used in isolation.

27 **Value judgments:** Telemedicine is a safe and useful tool in pandemic conditions but does limit what can  
 28 be gleaned from physical examination. Without the use of nasal endoscopy, it is possible some physical  
 29 examination findings may be missed.

30 **Policy level:** Recommendation.

31 **Intervention:** When possible, physical examination should be performed with appropriate personal  
 32 protective equipment to aid in the diagnosis of AR and exclusion of other conditions. When combined  
 33 with patient history, it increases diagnostic accuracy and may exclude alternative causes of symptoms.

34

35 **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 <sup>11</sup>	2011	4	Cross-sectional	Adults with AR	-History	Physical examination alone yields unreliable and

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

1 LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; sIgE=allergen-specific immunoglobulin E; COVID-  
2 19=coronavirus disease 2019

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

5  
6

### 7 X.A.3. Nasal endoscopy

8

9 Diagnostic nasal endoscopy may complement the evaluation of patients with suspected AR. Several case

10 series and cross-sectional studies have evaluated the association of endoscopic findings with the

11 diagnosis and severity of AR. **[TABLE X.A.3.]**

12 Ziade et al<sup>13</sup> studied a prospective cohort of adult patients with AR symptoms and skin testing

13 confirmation, showing that mucosal edema and bluish discoloration of the ITs were highly predictive of

14 the severity of AR disease ( $p < 0.05$ ) when comparing patients with mild versus moderate/severe AR.

1 Conversely, early studies by Jareoncharsri et al<sup>14</sup> and Eren et al<sup>15</sup> evaluated a population of adults and  
2 children with AR confirmed by allergy testing, concluding that findings of nasal endoscopy do not  
3 provide a reliable diagnosis or correlate with specific nasal symptoms of AR.

4  
5 Additionally, Ameli et al<sup>16</sup> evaluated a large cohort of children with suspected AR and confirmed with  
6 skin testing, reporting that endoscopic findings of IT or MT septal contact as well as pale mucosa and  
7 large adenoid volume were highly predictive for AR. Notably, there were conflicting results in a previous  
8 study by the same group that reported no predictive role of pale mucosa as an endoscopic sign for AR.<sup>17</sup>  
9 The possible explanation could be related to the smaller sample analyzed in the previous study.

10  
11 Polypoid change of the MT has also been also correlated with the diagnosis of AR as shown by White et  
12 al,<sup>18</sup> who described 16 patients with polypoid changes/polyps of the MT, all of which had positive allergy  
13 testing. Hamizan et al<sup>19</sup> reported that multifocal, diffuse, and polypoid edema – the highest grades of  
14 MT edema – had the strongest association with allergy, with positive predictive values of 85.15%, 91.7%,  
15 and 88.9%, respectively. Brunner et al<sup>20</sup> compared the clinical characteristics of patients with isolated  
16 polypoid change of the MT versus paranasal sinonasal polyposis, finding a higher prevalence of AR in  
17 patients with polypoid MT changes compared to patients with conventional sinonasal polyposis (83% vs  
18 34%, p<0.001).

19  
20 Central compartment atopic disease (CCAD), first described in the multi-institutional case series by  
21 DelGaudio et al<sup>21</sup> in 2017, is a phenotype of nasal inflammatory disease which presents with isolated  
22 polypoid changes involving the superior nasal septum with or without the MT and/or superior turbinate,  
23 and is strongly associated with inhalant allergy. All patients in the series had positive allergy testing. In a  
24 subsequent case series, the same authors found that 81.9% of patients with AERD had central  
25 involvement of disease, with 100% of patients with endoscopic central compartment disease having  
26 clinical AR.<sup>22</sup> (See Section XIII.B.3. Central Compartment Atopic Disease for additional information on this  
27 topic.)

28  
29 Despite early inconsistent reports, the current body of evidence has shown that certain nasal endoscopy  
30 findings, particularly central compartment polypoid changes, are predictive factors for the presence and  
31 severity of AR and nasal endoscopy may aid in the identification or exclusion of other possible causes of  
32 symptoms, such as nasal polyposis or CRS.

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

1 LOE=level of evidence; AR=allergic rhinitis; AERD=aspirin exacerbated respiratory disease; CCAD=central  
 2 compartment atopic disease; PCMT=polypoid changes of the middle turbinate; CT=computed tomography  
 3  
 4

5 **X.A.4. Radiologic studies**  
 6

7 Radiographic workup is not recommended for the routine diagnosis of AR. Although some radiographic  
 8 findings have been associated with AR, there are no high-quality studies demonstrating a role for  
 9 imaging in the diagnosis of AR.  
 10

11 For patients that undergo imaging, certain radiologic patterns described in the literature may indicate an  
 12 allergic role in their disease process. Several studies have demonstrated association between  
 13 inflammatory changes to the central compartment mucosa and aeroallergen reactivity, resulting in the  
 14 CRS phenotype of CCAD.<sup>23-27</sup> Other studies have described evidence of radiographic changes among  
 15 patients with known AR, including the association for smaller maxillary sinuses and enlargement of the  
 16 septal swell region.<sup>28,29</sup>  
 17

18 Radiology studies incur additional cost and demonstrate little diagnostic value for AR. There is also  
 19 concern for ionizing radiation with CT scanning, along with risk for future malignancy.<sup>30-32</sup> These factors  
 20 preclude the routine utilization of radiographic studies for the diagnosis of AR.  
 21

22 **Aggregate grade of evidence:** D (Level 3: 1 study, level 4: 7 studies; **TABLE X.A.4.**)

23 **Benefit:** Some radiologic findings, particularly those associated with central compartment  
 24 edema/polyposis, may alert the clinician to the possibility of an associated allergic etiology.

25 **Harm:** Unnecessary radiation exposure, unnecessary cost.

26 **Cost:** High equipment and processing costs. Additional costs for interpretation of studies by radiologist.

27 **Benefits-harm assessment:** Preponderance of harm over benefit.

28 **Value judgments:** Long-term risks of ionizing radiation outweigh potential benefit.

29 **Policy level:** Recommendation against.

30 **Intervention:** Routine use of imaging is not recommended for the diagnosis of AR.  
 31

32 **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
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Lee et al <sup>26</sup>	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 <sup>27</sup>	2020	4	Cross-sectional	Patients with CRSwNP	-Nasal endoscopy -CT scan -Allergy testing	Allergic phenotype of CRSwNP has worse symptomatic and radiologic disease burden
Hizli et al <sup>29</sup>	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 <sup>25</sup>	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 <sup>23</sup>	2018	4	Cross-sectional	CRS patients without sinus surgery	-CT scan -Allergy testing	Central radiologic disease patterns associated with inhalant allergy
Sharhan et al <sup>33</sup>	2018	4	Cross-sectional	Patients with septal deviation	-CT scan -Allergy testing	IT size is not associated with AR
DelGaudio et al <sup>21</sup>	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 <sup>28</sup>	2015	4	Cross-sectional	Patients with nasal symptoms and suspected AR	-Allergy testing -CT scan	Patients with AR showed smaller overall maxillary sinus volumes

1 LOE=level of evidence; CRS=chronic rhinosinusitis; CCAD=central compartment atopic disease; CRSwNP=chronic  
2 rhinosinusitis with nasal polyposis; CT=computed tomography; IT=inferior turbinate; AR=allergic rhinitis  
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## 5 X.B. Skin testing

### 6 X.B.1 Skin prick testing

7  
8 SPT, in conjunction with clinical history and physical examination, can confirm the diagnosis of AR and  
9 help to differentiate AR from non-allergic types of rhinitis. The confirmation of an IgE mediated process  
10 can guide avoidance measures and direct appropriate pharmacologic therapy. Allergy testing is crucial  
11 for initiation of AIT, and therefore, skin testing should be utilized in eligible patients when AIT is being  
12 considered.  
13

14 SPT is performed with lancets, which come in a variety of forms. Generally, lancets are designed to limit  
15 skin penetration depth to 1 mm. However, varying amounts of pressure applied to the delivery device  
16 can alter the depth of skin penetration, which ultimately influences the skin reaction to an antigen.<sup>34</sup>

17 Prick testing devices can come as single or multiple lancet devices. Multiple lancet devices have the  
18 advantage of being able to rapidly apply multiple antigens to the skin at one time with a more consistent

1 amount of pressure.<sup>35,36</sup> Wheal size, sensitivity, and reproducibility all differ from one device to another;  
2 therefore, any clinician performing SPT must thoroughly familiarize themselves with the testing device  
3 they choose to utilize in their practice.<sup>35-37</sup> The lancet can be dipped into a well containing an antigen  
4 and then applied to the skin, or droplets of antigen can be placed on the skin and then using the lancet,  
5 a prick made through the droplet. When an antigen is applied to the skin of a sensitized patient, the  
6 antigen cross-links IgE antibodies on the surface of cutaneous mast cells resulting in degranulation and  
7 release of mediators (including histamine) which leads to the formation of a wheal and flare reaction  
8 within 15-20 minutes.<sup>38,39</sup>

9  
10 The volar surfaces of the forearms and the back are the most common testing sites for SPT. Choice of  
11 site is directed by the age and size of the patient, the presence of active skin conditions in a testing  
12 location, or significant tattooing in the testing area, which could impact interpretation. Reactivity of  
13 different body sites can vary, as the back is overall more reactive than the forearm. Within each site,  
14 there may be variability as well, as middle and upper parts of the back are more reactive than the lower  
15 back. Tests should be applied 2 cm or greater apart as placing them closer to one another can allow  
16 spreading of allergen solution between test sites.<sup>40</sup> After approximately 20 minutes, the results are read  
17 by measuring the size of the wheal by its greatest diameter. Wheals that are greater than or equal to 3  
18 mm in diameter, when compared to the negative control, are considered positive.

19  
20 The number and choice of antigens used in testing vary considerably between clinical practices. A panel  
21 of antigens representing an appropriate geographical profile of allergens that a patient would routinely  
22 be exposed to is recommended. Positive (histamine) and negative (saline, 50% glycerin or 50%  
23 glycerinated human serum albumin with saline) controls should always be included. Regarding allergen  
24 extracts, variability in quality and potency between commercially available extracts has been  
25 demonstrated.<sup>41,42</sup> Therefore, whenever possible, standardized allergens should be used.<sup>43</sup> With  
26 advancements in molecular biology, new techniques for extraction, characterization, and production of  
27 allergens have been developed allowing for production of recombinant or purified allergens which may  
28 increase the sensitivity, specificity and diagnostic accuracy of tests.<sup>44</sup>

29  
30 Given the limited depth of penetration, SPT is safe with very rare reports of anaphylaxis and no reported  
31 fatalities.<sup>45</sup> SPT can be performed in any age group and is of value in pediatric populations given the  
32 speed at which multiple antigens can be applied and the limited discomfort experienced during testing.

1 Aside from an excellent safety profile, SPT has reported sensitivity and specificity of around 80%.<sup>43,45,46</sup> It  
2 is felt to be more sensitive than serum sIgE testing with the added benefits of lower cost and immediate  
3 results.<sup>45,47,48</sup> Despite numerous studies aimed at comparing SPT, single intradermal tests, and serum  
4 sIgE testing, evidence marking one form of testing as superior to the others is lacking.<sup>2</sup>

5  
6 Skin testing is not appropriate in all patients. Absolute contraindications to SPT in the evaluation of AR  
7 include uncontrolled or severe asthma, severe or unstable cardiovascular disease, and pregnancy. Skin  
8 conditions including dermatographia and AD are relative contraindications to SPT given the possibility of  
9 false positives. Concurrent  $\beta$ -blocker therapy is also a relative contraindication.<sup>49</sup> Certain medications  
10 and skin conditions can interfere with skin testing and are covered in detail in other sections. (*See*  
11 *Section X.B.4. Issues that may Affect the Performance or Interpretation of Skin Tests for additional*  
12 *information on this topic.*)

13  
14 Several errors may occur during SPT and impact the results and reliability. Since heterogeneity can be  
15 introduced when using multiple different test devices, it is recommended that the same device type be  
16 used routinely in one's clinical practice to improve the reliability, comparability, and interpretation of  
17 testing.<sup>50</sup> Personnel who apply tests should be appropriately trained and periodically monitored for  
18 quality control. Common errors with SPT include placing the test sites too close together (less than 2  
19 cm), pressing too hard or creating deep punctures that cause bleeding, insufficient penetration of the  
20 skin by the puncture instrument, and spreading of allergen solutions across the field during the test by  
21 wiping away the solution.<sup>50</sup>

22  
23 There is a large body of evidence detailing the use of SPT in clinical practice. Based upon several  
24 prospective studies and systematic reviews, SPT has been demonstrated to be a safe method of allergy  
25 testing with sensitivity and specificity of greater than 80%. **[TABLE X.B.1.]** It has not been shown to be  
26 inferior to serum sIgE testing or single intradermal testing and is less expensive than serum sIgE testing.  
27 SPT does carry a risk of anaphylaxis, but no deaths from SPT have been reported. It is also associated  
28 with some discomfort during testing; however, the discomfort is generally less than that experienced  
29 during an intradermal test. Reviewing the available literature, a preponderance of benefit over harm  
30 exists for SPT. Therefore, the use of SPT is recommended in situations where the diagnosis of AR needs  
31 to be confirmed or a patient with presumed AR has failed appropriate empiric medical therapy and AIT  
32 is being considered.

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**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 <sup>51</sup>	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 <sup>52</sup>	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 <sup>48</sup>	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 <sup>2</sup>	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 <sup>45</sup>	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 <sup>53</sup>	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 <sup>54</sup>	2004	4	Prospective case-control	- <i>Alternaria</i> SPT positive - <i>Alternaria</i> single intradermal #2 positive - <i>Alternaria</i> 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 <i>Alternaria</i> antigen
Krouse et al <sup>55</sup>	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 <sup>56</sup>	2004	4	Prospective case-control	-NPT positive -NPT negative	Wheal size that best identifies clinical allergy to cat based on NPT	On SPT with cat antigen, a wheal size of $\geq 3$ mm had a sensitivity of 100% and specificity of 74.1%; improved with increasing size of wheal
Pumhirun et al <sup>57</sup>	2000	4	Prospective case-control	Perennial rhinitis patients	Compared sensitivity and specificity of intradermal test to SPT and sIgE assay for <i>D. pteronyssinus</i> and <i>D. farinae</i>	-SPT for <i>D. pteronyssinus</i> and <i>D. farinae</i> 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 <sup>50</sup>	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 <sup>58</sup>	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
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1 LOE=level of evidence; SRMA=systematic review and meta-analysis; SPT=skin prick test; AR=allergic rhinitis;  
2 N/A=not applicable; s=antigen-specific; IgE=immunoglobulin E; NPT=nasal provocation test; SET=skin endpoint  
3 titration; RAST=radio allegro-sorbent test; PPV=positive predictive value; NPT=negative predictive value  
4 \*LOE upgraded from typical assignment of 5 due to systematic review of the literature, extensive history of  
5 guideline development, and peer review process  
6  
7

### 8 X.B.2. Intradermal skin testing 9

10 Intradermal skin testing is one of the oldest forms of allergy testing, originally described in 1911. In this  
11 technique, 0.02-0.05mL of diluted allergen extract is introduced into the dermis with a needle. The  
12 dilutions used are 100 to 1000-fold less concentrated than those used for SPT. The response is measured  
13 at 10-15 minutes after injection. A significant wheal and flare reaction suggests the presence of  
14 preformed IgE bound to the surface of cutaneous mast cells, and thus a type 1 hypersensitivity to the  
15 tested allergen. Intradermal testing is considered to be more sensitive than SPT, but not necessarily  
16 more capable of identifying clinically relevant allergy.<sup>45</sup> Intradermal testing may be used as a primary  
17 diagnostic modality and its performance for some allergens, such as *Alternaria*, may be similar to SPT or  
18 in vitro testing.<sup>59</sup> A more common approach is to perform intradermal testing after a negative SPT to  
19 identify lower level allergic sensitivity. Some allergists also use intradermal testing in a titrated fashion  
20 (using multiple allergen dilutions) with the goal of more accurately quantifying allergic sensitization or as  
21 a means to select a starting dose for AIT.<sup>60</sup> Intradermal dilutional testing (IDT) is roughly equivalent to  
22 SPT in the diagnosis of inhalant allergy,<sup>53</sup> and IDT endpoint correlates with SPT wheal size.<sup>61</sup> However,  
23 the role of intradermal testing for aeroallergen sensitivity is controversial due to concerns about the  
24 performance characteristics (sensitivity and specificity) of single intradermal tests relative to SPT.<sup>62</sup>  
25

26 As with any skin test, intradermal skin testing should be performed in conjunction with appropriate  
27 positive and negative controls. A negative control should include appropriately diluted test solutions  
28 (e.g., glycerin for aqueous glycerinated extracts). A positive control should contain diluted histamine  
29 base (e.g., 0.10mg/mL).<sup>45</sup> Measurement of the wheal and flare response is used to determine a positive  
30 result; however, thresholds for a positive test may vary because studies have not been performed to

1 standardize test grading. A wheal size 2-4 mm larger than the negative control is often used as the  
2 threshold for a positive test.<sup>45,62</sup>

3  
4 Assessment of the sensitivity and specificity of intradermal testing is hampered by multiple variables in  
5 the published studies. These include the concentration and volume of allergen injected, the definitions  
6 of a positive test, variation in allergens tested, and the 'gold standard' comparator used for analysis.<sup>63</sup> As  
7 a stand-alone diagnostic test for AR, using studies with nasal provocation as the reference standard,  
8 estimates for sensitivity for intradermal testing range between 60-79%, while specificity is in the range  
9 of 68-69%.<sup>52,53</sup> In comparison, a meta-analysis of SPT trials had pooled estimates of 88.4% sensitivity and  
10 77.1% specificity for SPT,<sup>64</sup> suggesting superiority of SPT as a stand-alone allergy diagnostic test.

11 Nevertheless, intradermal tests are still used when a highly sensitive skin test is desired. This may be  
12 particularly important when testing with non-standardized allergen extracts (e.g., molds, trees). **[TABLE**  
13 **X.B.2.]**

14  
15 Intradermal tests are also employed when SPT is negative but history strongly suggests an allergic  
16 sensitivity, and may be particularly useful in patients with lower skin sensitivity.<sup>45</sup> Negative intradermal  
17 testing may be helpful in ruling out IgE mediated disease.<sup>62</sup> On the other hand, the addition of  
18 intradermal testing in the setting of SPT negativity may result in 20% more positive allergy skin testing  
19 results, and the clinical significance of these results is an important question that needs to be resolved.<sup>65</sup>  
20 Positive intradermal tests may merely be due to non-specific irritant phenomena.

21  
22 Because intradermal testing has traditionally been considered more sensitive than SPT, it is often used  
23 as an add-on test in the setting of a negative SPT result when allergy is suspected. Theoretically, an  
24 intradermal test will be able to identify a clinically significant sensitivity that is otherwise not detected  
25 on SPT. However, many studies have failed to show an added benefit of intradermal testing in this  
26 setting. For example, Krouse et al<sup>55</sup> showed that adding intradermal testing to SPT only increased the  
27 sensitivity from 87% to 93% for Timothy grass allergy when nasal provocation was used as the  
28 comparator. In a similar study with *Alternaria*, Krouse, et al<sup>54</sup> determined that adding intradermal  
29 testing to SPT increased the sensitivity from 42% to 58%. These studies suggest marginal increase in  
30 sensitivity that may vary based upon the allergen being tested.

31

1 Nelson et al<sup>66</sup> studied individuals with a history of seasonal AR and clinical history of grass allergy. One  
2 group had negative SPT but positive intradermal tests, while another group had negative SPT and  
3 negative intradermal tests. In both groups, 11% of individuals had a positive nasal challenge with  
4 timothy grass, demonstrating that the addition of an intradermal test did not improve the diagnostic  
5 accuracy of skin testing as judged by the 'gold standard' of nasal provocation plus clinical history.  
6 Additionally, in a study of patients with clinical cat allergy and negative SPT, a positive intradermal test  
7 did not increase the likelihood of a positive cat allergen challenge.<sup>52</sup> There was no difference between  
8 those who had positive or negative intradermal testing (24% vs 31%). Thus, while about 30% of patients  
9 with a clear clinical history of cat allergy had a positive cat allergen challenge despite a negative SPT, the  
10 addition of an intradermal test did not improve the diagnostic accuracy of skin testing.

11  
12 Schwindt, et al<sup>67</sup> studied 97 subjects with allergic rhinoconjunctivitis symptoms. SPT was followed by  
13 intradermal testing if SPT was negative. If patients were SPT negative and intradermal test positive, a  
14 nasal challenge was performed against 5 different allergens. If SPT with the multi-test II device was  
15 negative, only 17% of subjects had a positive intradermal test that corresponded with clinical history.  
16 None of these positive intradermal results corresponded with a positive nasal challenge. Taken together,  
17 these studies suggest that intradermal testing may not improve the diagnosis of allergy in subjects with  
18 a negative SPT.

19  
20 Intradermal testing for inhalant allergens is considered safe. However, systemic reactions, such as  
21 anaphylaxis, and even death, have been reported after intradermal testing. The risks of intradermal  
22 testing may be reduced by testing with more dilute solutions in individuals with suspected high-level  
23 sensitivity or by performing SPT as an initial screening test. The risk of intradermal testing is significantly  
24 higher in medication allergy and IgE-mediated food allergy and therefore not recommended.<sup>68</sup>

25  
26 In summary, intradermal testing is an option for the diagnosis of AR due to aeroallergens, especially  
27 when using non-standardized allergen extracts. This form of testing demonstrates no clear superiority  
28 over SPT when comparing sensitivity and specificity, though results may vary by allergen tested. Single  
29 dilution intradermal testing has not been adequately studied in comparison to IDT, though IDT results  
30 may approximate SPT results, especially in patients with high level sensitivity. For some allergens such as  
31 *Alternaria*, there appears to be a gain in sensitivity when intradermal testing is used as a confirmatory  
32 test following negative SPT.



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**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 <sup>65</sup>	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 <sup>69</sup>	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 <sup>67</sup>	2005	3	Cohort	97 subjects: -SPT followed by IDST if SPT(-) -If SPT(-) and IDST(+) positive, nasal challenge performed for 5 allergens	Using history as gold standard, SPT, IDST and nasal challenge results compared	-If SPT(-), only 17% had (+) IDST that corresponded with history -None corresponded with (+) nasal challenge -If SPT(-), then (+) IDST unlikely to identify clinically relevant sensitivity
Simons et al <sup>70</sup>	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 <sup>52</sup>	1999	3	Prospective cohort	120 patients with symptoms from cat exposure	Cat exposure challenge, symptom scores, FEV <sub>1</sub>	IDST added little value beyond SPT and RAST
Niemeijer et al <sup>63</sup>	1993	3	Cohort	-497 patients with suspected allergy	IDST, RAST, clinical history	-Ideal cutoff for positive IDST is wheal diameter 0.7 times the size of histamine control

				-Standardized grass pollen, tree pollen, cat, HDM tested		-IDST has 83% predictive value vs RAST and 77% predictive value vs history
Niemeijer et al <sup>71</sup>	1993	3	Cohort	41 patients tested with varying concentrations of Phleum and <i>D. pteronyssinus</i>	-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 <sup>72</sup>	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 <sup>73</sup>	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 <sup>61</sup>	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 <sup>74</sup>	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 <sup>75</sup>	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 <sup>76</sup>	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 <sup>53</sup>	2004	4	Case series	62 patients with ragweed allergy	Nasal provocation, rhinomanometry	Sensitivity and specificity of IDT comparable to SPT
Krouse et al <sup>55</sup>	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 <sup>54</sup>	2004	4	Prospective case-control	44 patients with AR: - -Group I: SPT(+) -Group II: SPT(-), IDST(+)	Nasal allergen provocation for <i>Alternaria</i> compared to skin tests	IDST after SPT increased the sensitivity from 42% to 58%

				-Group III: SPT(-), IDST(-)		
Nelson et al <sup>66</sup>	1996	4	Prospective case-control	70 subjects: -Group I: SAR, SPT(-), IDST(+) -Group II: SAR, SPT(+) -Group III: SAR, SPT(-), IDST(+) -Group IV: no rhinitis	Nasal challenge with Timothy grass compared to skin tests	(+) IDST after (-) SPT did not indicate the presence of clinically significant sensitivity
Escudero et al <sup>59</sup>	1993	4	Prospective case-control	-66 patients, 31 with <i>Alternaria</i> 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 <sup>77</sup>	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 <sup>78</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; IDST=intradermal skin test; (-)=negative; (+)=positive; sIgE-allergen-  
2 specific immunoglobulin E; IDT=intradermal dilutional testing; FEV<sub>1</sub>=forced expiratory volume in one second;  
3 RAST=radioallergosorbent test; HDM=house dust mite; AIT=allergen immunotherapy; SAR=seasonal allergic rhinitis

### 6 X.B.3. Blended skin testing techniques

7  
8 The combined use of SPT and intradermal testing for a specific antigen is referred to as “blended”  
9 allergy testing.<sup>61,74,79</sup> One example, originally described by Krouse and Krouse<sup>80</sup> as a method to establish  
10 an “end-point” for a specific antigen, was described as “modified quantitative testing” (MQT) and serves  
11 as an example of a blended technique. MQT involves an algorithm where a SPT is used initially to apply  
12 an antigen. Depending upon the SPT result, an intradermal test may or may not be applied.<sup>61,74,79,80</sup> With  
13 these results, the algorithm is used to determine an endpoint for each antigen tested.<sup>61,74,79,80</sup> The  
14 endpoint is considered to be a safe starting point for AIT.<sup>80</sup> Other protocols may combine the use of SPT  
15 and intradermal testing but not for the purposes of establishing an endpoint.<sup>73,81</sup> Instead, an intradermal  
16 test may be used following a negative SPT to determine allergen sensitization.<sup>73,81</sup>

1 AIT based on the results of MQT has shown to be successful and to induce immune system changes in  
 2 line with other skin testing techniques.<sup>80</sup> However, literature is lacking on protocols involving blended  
 3 skin testing. [TABLE X.B.3.]

4  
 5 Specifically for MQT, advantages attributed to it include the provision of both qualitative data  
 6 (sensitization to a specific allergen) and quantitative data (testing endpoint upon which AIT starting dose  
 7 can be based) in less time than IDT.<sup>61,74,79</sup> Disadvantages include the additional risk and time involved in  
 8 placing intradermal tests. MQT has been shown to be more cost-effective when the prevalence of AR in  
 9 a population is 20% or higher when compared to IDT and in-vitro testing methods.<sup>82</sup> 5

10

11 **Aggregate grade of evidence:** D (Level 4: 7 studies; TABLE X.B.3.)

12 **Benefit:** Ability to establish an endpoint in less time than intradermal dilutional testing, potential to  
 13 determine allergen sensitization after negative SPT.

14 **Harm:** Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma  
 15 symptoms, anaphylaxis, inaccurate test results, and misinterpreted test results. Additional time and  
 16 discomfort versus SPT alone. See Table II.C.

17 **Cost:** Moderate cost of testing procedure.

18 **Benefits-harm assessment:** Preponderance of benefit over harm.

19 **Value judgments:** While AIT can be based off SPT results alone, endpoint-based AIT may have possible  
 20 benefits of decreased time to therapeutic dosage.

21 **Policy level:** Option.

22 **Intervention:** Blended skin testing techniques, such as MQT, are methods that can be used to determine  
 23 a starting point for AIT or confirm allergic sensitization.

24

25 **TABLE X.B.3. Evidence table – Use of blended skin testing techniques in the diagnosis of allergic**  
 26 **rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Erel et al <sup>73</sup>	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 <sup>81</sup>	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 <sup>79</sup>	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 <sup>82</sup>	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 <sup>61</sup>	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. <sup>4</sup>	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. <sup>3</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; ID=intradermal; SPT=skin prick test; HDM=house dust mite;  
2 sIgE=allergen specific immunoglobulin E; MQT=modified quantitative testing; IDT=intradermal dilutional testing;  
3 AIT=allergen immunotherapy; sIgG4=allergen specific IgG4; SNOT-20=Sinonasal Outcome Test (20 item);  
4 AOS=Allergy Outcome Scale; RSDI=Rhinosinusitis Disability Index; QOL=quality of life  
5  
6

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

##### 8 X.B.4.a. Medications

9  
10 Medications that inhibit mast cell degranulation or block histamine H<sub>1</sub> receptors antagonists may  
11 suppress appropriate skin test responses. For this reason, it is important to assess the medications  
12 patients are taking prior to allergy skin testing.  
13

14 There is substantial variation in the suppressive effects that H<sub>1</sub> antihistamines have on the allergen and  
15 histamine induced wheal and flare responses,<sup>83,84</sup> with the duration of suppression dependent on the  
16 tissue concentration and half-life of the medication.<sup>85</sup> Orally ingested antihistamines typically suppress  
17 skin test responses for 2-7 days after stopping the medication.<sup>86,87</sup> Topical antihistamines may also  
18 suppress skin wheal and flare responses.<sup>88</sup> Furthermore, H<sub>2</sub> receptor antagonists like ranitidine can  
19 reduce skin whealing responses,<sup>89,90</sup> and a combined suppressive effect of H<sub>1</sub> and H<sub>2</sub> antihistamines on  
20 skin whealing has been demonstrated.<sup>91</sup> Antidepressants with antihistaminic properties (such as  
21 doxepin) impair the wheal and flare,<sup>92</sup> but newer antidepressant classes such as selective serotonin  
22 reuptake inhibitors do not alter allergy skin test reactivity.<sup>93</sup> **[TABLES X.B.4.a.-1 and X.B.4.a.-1]**  
23

24 Omalizumab, a monoclonal anti-IgE antibody, suppresses the allergy the skin test response by  
25 interfering with IgE mediated mast cell degranulation. A placebo-controlled RCT noted significant  
26 reduction in the allergen-induced skin wheal response after 4 months of omalizumab;<sup>94</sup> whereas skin  
27 test response returned to normal within 8 weeks of discontinuation of omalizumab in another study.<sup>49</sup>  
28

1 Hill and Krouse<sup>95</sup> and Simons et al<sup>96</sup> found no effect of montelukast on intradermal skin tests, and  
 2 Cuhadaroglu et al<sup>97</sup> noted that allergic patients treated with zafirlukast had no change in SPT results.  
 3 Therefore, leukotriene modifying agents do not appear to affect skin test results.

4  
 5 Most studies indicate that systemic steroid treatment does not alter skin test results,<sup>98,99</sup> but some less  
 6 rigorous retrospective studies contradict these findings.<sup>100,101</sup> Topical steroid treatment does suppress  
 7 the wheal and flare reaction in treated skin areas, according to several studies.<sup>102-105</sup> Allergy skin tests  
 8 should not be performed in areas that are being treated with topical steroid medications in order to  
 9 avoid false negative results.

10

11 Several classes of medications have not been adequately studied with respect to their effect on allergy  
 12 skin test responses. Benzodiazepines have been implicated as possibly suppressing skin test  
 13 responses.<sup>106,107</sup> Calcineurin inhibitors demonstrate conflicting findings. Tacrolimus has been shown to  
 14 inhibit SPT whealing,<sup>105</sup> whereas pimecrolimus does not appear to affect skin whealing responses.<sup>108</sup>  
 15 Herbal preparations are understudied in this area, so it is unclear which of these agents could interfere  
 16 with allergy skin test responses. More et al<sup>109</sup> performed a double-blind placebo-controlled, single dose  
 17 crossover study in 15 healthy volunteers, examining the histamine induced skin test response. None of  
 18 the 23 herbal supplements evaluated suppressed the histamine induced wheal response.

19

20 All allergy skin testing should be performed after application of appropriate positive controls (e.g.,  
 21 histamine) to verify that the histamine induced skin test reaction is intact at the time of testing. This  
 22 practice helps to mitigate against unknown factors – potentially medications – causing inappropriate  
 23 interpretation of skin test results.

24

25

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

<b>H<sub>1</sub> antihistamines</b>	Should be discontinued 3-7 days prior to testing. <b>Aggregate Grade of Evidence:</b> A (Level 2: 3 studies, level 3: 3 studies, level 4: 1 study)
<b>H<sub>2</sub> antihistamines</b>	Ranitidine may suppress skin whealing response, leading to false negative results. Should be discontinued 2 days prior to testing. <b>Aggregate Grade of Evidence:</b> A (Level 2: 2 studies, level 3: 1 study, level 4: 1 study)
<b>Topical antihistamines (nasal, ocular)</b>	Should be discontinued 2 days prior to testing. <b>Aggregate Grade of Evidence:</b> Unable to determine from one Level 2 study.
<b>Anti-IgE (omalizumab)</b>	Results in negative allergy skin test results. May suppress skin whealing response for 4-6 months. <b>Aggregate Grade of Evidence:</b> A (Level 2: 1 study, level 3: 1 study)

<b>Leukotriene modifying agents</b>	May be continued during testing. <b>Aggregate Grade of Evidence:</b> A (Level 2: 2 studies, level 3: 1 study)
<b>Tricyclic antidepressants</b>	Antidepressants with antihistaminic properties suppress allergy skin test responses. Should be discontinued 7-14 days prior to testing. <b>Aggregate Grade of Evidence:</b> B (Level 2: 1 study, level 4: 1 study)
<b>Topical (cutaneous) corticosteroids</b>	Skin tests should not be placed at sites of chronic topical steroid treatment. <b>Aggregate Grade of Evidence:</b> A (Level 2: 3 studies, level 3: 1 study)
<b>Systemic corticosteroids</b>	Systemic corticosteroid treatment does not significantly impair skin test responses. <b>Aggregate Grade of Evidence:</b> C (Level 2: 1 study, level 3: 1 study, level 4: 2 studies; conflicting results)
<b>Selective serotonin reuptake inhibitors (SSRIs)</b>	Do not suppress allergy skin test responses. <b>Aggregate Grade of Evidence:</b> C (Level 3: 1 study, level 4: 1 study)
<b>Benzodiazepines</b>	May suppress skin test responses. Should be discontinued 7 days prior to testing. <b>Aggregate Grade of Evidence:</b> C (Level 4: 2 studies)
<b>Topical calcineurin Inhibitors (tacrolimus, picrolimus)</b>	Conflicting results regarding skin test suppression. <b>Aggregate Grade of Evidence:</b> C (Level 2: 2 studies; conflicting results)

1

2

**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 <sup>105</sup>	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 <sup>90</sup>	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 <sup>108</sup>	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 <sup>95</sup>	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 <sup>109</sup>	2003	2	RCT	15 subjects received single-blind dose of placebo, fexofenadine, 23 other herbals	Histamine 1mg/mL wheal at baseline and 4 hours after	-Fexofenadine significantly reduced SPT wheal size vs placebo

					dose of herbal preparation	-None of the 23 herbal preparations showed significant effect on wheal size vs placebo
Noga et al <sup>94</sup>	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 <sup>88</sup>	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 <sup>96</sup>	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 <sup>110</sup>	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 <sup>89</sup>	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 <sup>104</sup>	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 <sup>92</sup>	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 <sup>103</sup>	1987	2	DBRCT	17 patients with AR treated with topical clobetasol x1 week	-Histamine SPT -Allergen SPT	Topical clobetasol significantly suppresses allergen induced wheal and flare response
Slott and Zweiman <sup>99</sup>	1974	2	DBRCT, crossover	15 atopic patients treated with methylprednisolone	Intradermal wheal size for histamine, allergen, and compound 48/80	No effect of 7 days methylprednisolone on intradermal wheal size



Cook et al <sup>186</sup>	1973	2	DBRCT	18 adults with skin test positive AR treated with chlorpheniramine, tripelemamine, 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 <sup>93</sup>	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 <sup>49</sup>	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 <sup>102</sup>	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 <sup>97</sup>	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 <sup>98</sup>	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 <sup>87</sup>	1988	3	Cohort	23 healthy individuals treated with dexchlorpheniramine, astemizole, cyproheptadine, loratidine, or terfenadine x2 days	-Effect on histamine SPT wheal -Duration of SPT wheal suppression	-All antihistamines suppressed SPT wheal response to histamine -Duration of suppression exceeded 72 hours for all agents tested
Long et al <sup>83</sup>	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 <sup>84</sup>	1983	3	Cohort	10 atopic subjects received injection of ketotifen, clemastine,	Inhibition of allergen and histamine induced wheals	Ketotifen, clemastine, and chlorpheniramine but not sodium cromoglycate

				chlorpheniramine or sodium cromoglycate		significantly inhibit skin whealing responses
Harvey & Schocket <sup>91</sup>	1980	3	Cohort	10 healthy subjects treated with hydroxyzine, cimetidine, 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 <sup>101</sup>	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 <sub>2</sub> blockers and older age associated with negative histamine control test
Shah et al <sup>106</sup>	2010	4	Retrospective cohort	Histamine SPT responses in patients with exposure to a variety of medications	SPT wheal area and SPT positivity	-H <sub>1</sub> 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 <sub>2</sub> antagonists not independently associated with wheal suppression
Duenas-Laita et al <sup>107</sup>	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 <sup>100</sup>	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

1 LOE=level of evidence; SPT=skin prick test; DBRCT=double-blind randomized controlled trial; AD=atopic dermatitis;  
2 AR=allergic rhinitis; RCT=randomized controlled trial; LTD4=leukotriene D4; BID=twice daily; ICU=intensive care  
3 unit; SSRI=selective serotonin reuptake inhibitor; SNRI=selective norepinephrine reuptake inhibitor; TID=three  
4 times daily  
5  
6

#### 7 X.B.4.b. Skin conditions

8  
9 Allergy skin tests rely upon the wheal and flare reaction induced by allergen-specific mast cell  
10 degranulation. However, mast cell degranulation can occur via a variety of non-immunologic  
11 mechanisms including minor skin trauma. Individuals with an exaggerated 'triple response of Lewis' are  
12 considered to have 'dermatographia' or 'urticaria factitia,' and may comprise 2-5% of the population.<sup>45</sup>  
13 Dermatographism may interfere with interpretation of allergy skin tests. Therefore, a negative control  
14 test should also be performed at the time of skin testing. In general, the negative control test consists of  
15 a prick with an applicator device (including the diluent), or placement of an intradermal wheal with inert

1 diluent, in the case of intradermal testing. While an allergen induced skin wheal and flare may be  
 2 compared to that induced by a test with mere diluent, results must always be interpreted with caution  
 3 in the setting of dermatographia.

4  
 5 The skin of patients with other urticarias, AD, allergic contact dermatitis, etc. also may not respond  
 6 appropriately to the trauma, histamine, glycerin, or allergen that are inherent in skin testing. Skin  
 7 reactions could be exaggerated, or the effect of allergen-induced mast cell degranulation could be  
 8 obscured. Common sense dictates that allergy skin tests should not be performed at sites of active  
 9 dermatitis, but clinical studies to investigate this phenomenon are lacking.<sup>111</sup> In some cases it may be  
 10 preferable to perform in vitro sIgE testing in patient with skin disease or dermatographism, but this is  
 11 not based on data or outcomes from controlled studies.

12  
 13 **Aggregate grade of evidence:** N/A (no identified studies)

14 **Benefit:** Correct identification of aeroallergen sensitivity.

15 **Harm:** Discomfort of skin test.

16 **Cost:** Low-moderate.

17 **Benefits-harm assessment:** Accurate skin test results justify discomfort and negligible cost of control  
 18 tests.

19 **Value judgments:** In vitro allergy tests may be more appropriate than skin tests, in patients with  
 20 dermatographia, urticaria, or other generalized dermatitis.

21 **Policy level:** Recommendation.

22 **Intervention:** Allergy skin tests should be performed in areas without active dermatitis or other lesions.  
 23 Positive and negative control tests should be used in conjunction with allergy skin testing for AR.

## 26 X.C. In vitro testing

### 27 X.C.1. Serum total IgE

28  
 29 IgE is the hallmark immunoglobulin in atopic disease. Atopy, or reactivity to otherwise innocent  
 30 allergens can be determined by dermal reactivity (e.g., SPT), or by determining sIgE to a certain allergen  
 31 in serum. The total IgE (tIgE) level in serum can also be determined. As atopy is not disease-specific, the  
 32 question arises whether serum tIgE has any place in the evaluation and diagnosis of AR.

33  
 34 From the literature, roughly two study approaches to determine the role of tIgE are identified:  
 35 population-based studies (e.g., birth cohorts, school health surveys, or general population approaches)  
 36 and hospital-based studies including patients visiting otorhinolaryngology or allergy clinics. Data from  
 37 the first approach show conflicting evidence. In some studies, tIgE is related to AR diagnosis;<sup>112-115</sup> in  
 38 others it is less clear.<sup>116,117</sup> Moreover, it seems from these studies that other comorbidities, especially

1 asthma, give rise to elevated tIgE.<sup>114,115</sup> However, the presence of asthma is not accounted for in most  
 2 studies, possibly confounding the outcomes. Another weakness of population-based studies is that the  
 3 diagnosis of AR depends on questionnaires, symptom-scores, or self-reported diagnosis. This might lead  
 4 to overdiagnosis of AR in these studies as the distinction with non-allergic rhinitis, common colds, or  
 5 other nasal diseases can be challenging. **[TABLE X.C.1.]**

6  
 7 Hospital-based studies have the advantage of improved diagnostics but have the risk of selection bias.  
 8 At any rate, these studies also show a mixed picture about the role of tIgE in the diagnosis of AR. Overall,  
 9 the levels of tIgE are higher in AR versus non-allergic rhinitis<sup>118-120</sup> or versus controls.<sup>121,122</sup> Some studies  
 10 investigated the correlation between serum sIgE and tIgE<sup>123,124</sup> showing a good overall fit. In hospital-  
 11 based studies, the influence of asthma is seen as well<sup>125</sup> but again not accounted for in most reports.

12  
 13 Taken together, an elevated tIgE is indicative of an atopic condition,<sup>126</sup> though not necessarily AR  
 14 specifically. As such, tIgE is not required in the diagnostic pathway for AR. Many authors conclude that  
 15 obtaining a serum tIgE can be helpful but is only a preliminary or supportive criterion for AR. Especially if  
 16 a SPT is performed, there seems to be little added value of obtaining a serum tIgE, as it requires  
 17 venipuncture which can be bothersome for children. In population-based studies, tIgE can be supportive  
 18 of AR, given that the study methodology allows for differentiation between atopic conditions such as  
 19 asthma or AD in the study population.

20  
 21 Although in general obtaining a serum tIgE is not advised as a routine diagnostic approach, it can be  
 22 needed or helpful in specific situations. For example, it has been suggested that monitoring of the  
 23 efficiency of AIT may be done by evaluating the ratio between sIgE and tIgE; this is discussed in detail in  
 24 a position paper from EAACI.<sup>127</sup> Allergic broncho-pulmonary aspergillosis is the only clinical condition  
 25 described to date, where the presence of high levels of tIgE is strictly related to disease severity.<sup>50</sup>  
 26 However, these specific cases are exceptions to the rule that serum tIgE is not needed for the diagnosis  
 27 and evaluation of AR.

28  
 29 **Aggregate grade of evidence:** C (Level 2: 4 studies, level 3: 11 studies; **TABLE X.C.1.**)

30 **Benefit:** Possibility to suspect allergy or atopy in a wide screening.

31 **Harm:** Cost of test, undergoing of venipuncture, low level does not exclude AR.

32 **Cost:** Low, dependent on country and local healthcare environment.

33 **Benefits-harm assessment:** Slight preponderance of benefit over harm. In addition, the ratio tIgE/sIgE  
 34 may be useful to interpret the real value of sIgE production and predict treatment outcomes with AIT.

- 1 **Value judgments:** The evidence does not support routine use.  
 2 **Policy level:** Option.  
 3 **Intervention:** Assessment of tIgE may be useful to assess overall atopic status; furthermore, in selected  
 4 cases it might help guide therapy (i.e., monitor efficacy of AIT).  
 5  
 6

**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 <sup>115</sup>	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 <sup>116</sup>	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 <sup>114</sup>	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 <sup>113</sup>	2007	2	Whole-population birth cohort	478 children (5 years) from MAAS	tIgE levels and correlation with current rhinitis or rhinoconjunctivitis	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 <sup>122</sup>	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 <sup>121</sup>	2019	3	Retrospective case-control	155 patients, mean age 33.2 years: -113 AR cases (per ARIA) -42 controls	tlgE levels in AR versus controls	-Mean log tlgE in cases: 5.65 (IgE 814.36 IU/ml), and in controls: 4.43 (tlgE 96.62 IU/ml), p<0.001 -No difference between age groups
Li et al <sup>120</sup>	2016	3	Retrospective cohort	610 adults, 349 with AR, median age 27.0 (23.0-42.0) years, from otolaryngology department	tlgE levels in AR versus NAR	tlgE: AR 166.0 (58.4-422.5) IU/mL, NAR 68.8 (24.5-141.0) IU/mL, p<0.001
Park et al <sup>117</sup>	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 tlgE at baseline and development of allergic symptoms at follow-up	-In 191 children without allergic sensitization initially, tlgE >17.7 IU/mL associated with risk for allergic sensitization (46.3% sensitivity; 85.3% specificity; OR 4.8) -tlgE may be helpful to predict sensitization but not complaints
Chung et al <sup>124</sup>	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 tlgE	-tlgE >150 IU/mL: AUC 0.88, 89.6% PPV, ~52% NPV (estimated from figure) -tlgE <10 IU/ml: 89.6% NPV
Karli et al <sup>123</sup>	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 tlgE, categorized as <20 U/ml, 20-100 U/ml and >100 U/ml	-23.7% had tlgE <20 U/ml -38.3% had tlgE between 20-100 U/ml -33.8% had tlgE >100 U/ml -108 had positive sIgE for inhalant allergens, 85.2% of these had tlgE above 20 U/ml
Demirjian et al <sup>126</sup>	2012	3	Prospective cohort	125 consecutive patients, mean age 57 years, referred to allergy/immunology clinic, 89 with AR by SPT	tlgE as predictor of atopy	tlgE levels >140 IU/mL is suggestive of an atopic etiology for patients with rhinitis signs/symptoms
Jung et al <sup>119</sup>	2011	3	Prospective cohort	442 consecutive patients with AR symptoms, median age 33 (8-76) years, from otolaryngology department	Discrimination of AR (defined as symptoms with positive sIgE)	-tlgE of 98.7 IU/ml strong predictor of AR: AUC 0.79 (0.74-0.83), 75.2% sensitivity, 69.7% specificity, OR 6.93 (95% CI 4.29-9.62), 71.3% PPV, 73.7% NPV -tlgE (IU/mL): AR 468.6 ± 733.4, NAR 118.4 ± 180.8, p<0.001
Kalpakioglu & Kavut <sup>118</sup>	2009	3	Retrospective case-control	323 consecutive and unselected patients	tlgE levels between AR and NAR	-tlgE: AR 261 (359), NAR 126 (172), p<0.01

				from tertiary clinic, mean age 31.8 years, 205 with AR, asthma equally present in both groups		-Differences in complaints and seasonality between AR and NAR
Satwani et al <sup>125</sup>	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 <sup>112</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; ARIA=Allergic Rhinitis and its Impact on Asthma; SPT=skin prick test;  
2 tIgE=total immunoglobulin E; OR=odds ratio; CI=confidence interval; PPV=positive predictive value; NPV=negative  
3 predictive value; PATCH=Prediction of Allergies in Taiwanese Children; AUC=area under the curve;  
4 NHANES=National Health and Nutrition Examination Survey; sIgE=allergen-specific immunoglobulin E;  
5 MAAS=Manchester Asthma and Allergy Study; NAR=non-allergic rhinitis  
6  
7

### 8 X.C.2. Serum allergen specific IgE

9  
10 Determining the presence of sIgE that verifies allergen sensitization is the cornerstone of diagnostic  
11 testing in suspected allergic conditions. The assessment of sIgE can be done by skin tests, serological  
12 immunoassays and/or cellular immunoassays.<sup>50</sup>  
13

14 Serological immunoassays detect and measure the level of serum sIgE. Innovations in molecular biology  
15 have revolutionized the procurement, characterization, and production of allergens through  
16 recombinant and phage methods.<sup>128</sup> The ability to perform serum sIgE immunoassays with recombinant  
17 or highly purified allergens has increased the sensitivity, specificity, and diagnostic accuracy of these  
18 tests.<sup>44</sup> Additionally, development of miniature computer-driven autoanalyzers and nanotechnology-  
19 based devices, enhanced signal detection instrumentation, and new solid phase chip and particle  
20 materials have improved the diagnostic accuracy and consistency of in vitro tests.<sup>129,130</sup> Furthermore,  
21 increased knowledge of molecular allergen components allow clinicians to predict the risk of severe  
22 allergic reactions and to identify the most appropriate AIT extract selections for each patient.<sup>130</sup>  
23

24 Derived from the original radio allegro-sorbent test (RAST), new methods of sIgE immunoassay, like  
25 enzyme-linked immunosorbent assay (ELISA), fluorescent enzyme immunoassays, and/or

1 chemiluminescent assays are available. These measurements of serum sIgE can be done using single  
2 allergen (singleplex: one assay per sample) or through a predefined panel that includes several allergens  
3 (multiplex: multiple assays per sample). Singleplex tests allow the clinician to choose select allergens as  
4 dictated by the clinical history.<sup>50</sup> Multiplex tests provide results of a broad array of preselected allergens.

5  
6 The multiplex test is important in diagnosis of polysensitized patients. Multiplex platforms are slowly  
7 being implemented in many allergy care centers outside of research and tertiary care centers, although  
8 currently the most widely used systems are singleplex. Some, like Thermo Fisher ImmunoCAP, have an  
9 extensive amount of scientific literature demonstrating their efficacy.<sup>131</sup> Each test has certain  
10 characteristics based on the detection method used, the dynamic range of reading of the instrument,  
11 time and conditions for the incubation, amount of allergen in the tube, and characteristics of the anti-  
12 IgE.<sup>50,130</sup> There are three different kinds of serum sIgE assays available: qualitative, semi-quantitative,  
13 and quantitative. Qualitative assays are useful to determine if the patient is sensitized to common  
14 allergens, providing positive, negative, or borderline sIgE results to a mix of allergens without measuring  
15 the IgE concentration. Semi-quantitative assays grade response by reporting a series of classes (e.g.,  
16 class I to VI). Quantitative assays report sIgE antibody concentration. Most singleplex platforms are  
17 quantitative assays; multiplex is semi-quantitative.

18  
19 Multiplex platforms or panels of 10-12 selected allergens (i.e., pollens, cat, mite) will detect up to 95% of  
20 patients who would have been identified on a larger battery.<sup>132,133</sup> If the test is negative, absence of  
21 allergy is probable.<sup>129</sup>

22  
23 Serum sIgE testing may also be beneficial for selecting allergens for AIT. In polysensitized patients, it can  
24 be difficult to determine the most relevant allergen(s) on SPT. In these situations, molecular allergy  
25 using components will help to discriminate the most relevant allergens and thus better guide AIT.<sup>134</sup> In  
26 addition, serum sIgE seems to correlate with the severity of AR symptoms.<sup>135-139</sup> Since patients with  
27 more severe symptoms appear to respond better to AIT than those with milder symptoms, serum sIgE  
28 may help in the selection of candidates for AIT and possibly predicting the response.<sup>135,140</sup>

29  
30 SPT has advantages and disadvantages when compared to sIgE tests. As a general concept, SPT is more  
31 sensitive, whereas serum sIgE detection is more quantitative than SPT.<sup>50</sup>

32



1 There are several advantages of serum sIgE over skin testing. The safety profile is excellent as the risk for  
2 anaphylaxis is non-existent. It is the preferred testing method in individuals at high risk for  
3 anaphylaxis.<sup>141</sup> Undergoing SPT is also limited by the presence of certain medical conditions.<sup>141</sup> When  
4 SPT is contraindicated, serum sIgE testing offers a safe and effective option for determining the  
5 presence of IgE mediated hypersensitivities. Additionally, where certain medications can alter SPT  
6 results, serum sIgE testing is not similarly impacted. Finally, in very young patients in which SPT may  
7 prove too stressful, serum sIgE can be considered.

8

9 There are some important limitations to serum sIgE testing. While patients are accepting of both in vitro  
10 and in vivo allergy testing, many prefer SPT because it allows for immediate feedback and visible  
11 results.<sup>140</sup> Unless molecular allergy diagnostic approach with allergenic components is used (precision  
12 allergy medicine diagnosis or PAMD@),<sup>130</sup> serum sIgE to regular allergens cannot accurately predict the  
13 risk of severe allergic reaction. If PAMD@ is not used, cross-reacting allergens and poly-sensitizations  
14 can confound in vitro testing, leading to false positive results.<sup>142</sup>

15

16 While SPT results may vary based on the quality of the extracts, as well as clinicians administering and  
17 interpreting the test, serum sIgE testing results can vary from one laboratory to another. One study sent  
18 blinded samples of the same sera, diluted and undiluted, to 6 major commercial laboratories and  
19 compared the results to the expected curve from an ideal assay. Out of the 6 laboratories, only 2  
20 demonstrated precision and accuracy in their results.<sup>143</sup> Further studies have demonstrated poor  
21 agreement on results from testing the same sera by different commercially available assay systems.<sup>143-</sup>  
22 <sup>145</sup> These factors introduce notable heterogeneity in serum sIgE testing. Clinicians should be familiar with  
23 the platform used for serum sIgE testing at their institution and to understand any limitations inherent  
24 to that platform.

25

26 Studies have shown that serum sIgE testing has a sensitivity ranging between 67-96% and specificity of  
27 between 80-100%.<sup>48,52,57,145,146</sup> Further, serum sIgE correlates well with NPT and SPT for AR  
28 diagnosis.<sup>48,57,78,145,147</sup> While there is good evidence to show that serum sIgE is often equivalent to SPT, it  
29 is generally accepted that SPT is more sensitive.<sup>2,52,148</sup> A recent position paper from the World Allergy  
30 Organization (WAO) stated that skin tests are still considered first line and that serum sIgE testing  
31 should be considered as a complimentary or alternative diagnostic tool.<sup>50</sup> Based on the literature, serum

1 sIgE testing is a reasonable alternative to SPT and is safe to use in patients who are not candidates for  
 2 SPT. All sIgE tests should be evaluated within the framework of a patient's clinical history. [TABLE X.C.2.]

3  
 4 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 2 studies, level 3: 6 studies, level 4: 6 studies,  
 5 level 5: 1 study; TABLE X.C.2.)

6 **Benefit:** Confirms diagnosis and directs appropriate pharmacological therapy while possibly avoiding  
 7 unnecessary/ineffective treatment, guides avoidance, directs AIT.

8 **Harm:** Adverse events from testing including discomfort from blood draw, inaccurate test results, false  
 9 positive test results, misinterpreted test results.

10 **Cost:** Moderate cost of testing.

11 **Benefits-harm assessment:** Preponderance of benefit over harm.

12 **Value judgments:** Patients can benefit from identification of their specific sensitivities. Further, in some  
 13 patients who cannot undergo SPT, serum sIgE testing is a safe and effective alternative.

14 **Policy level:** Recommendation.

15 **Intervention:** Serum sIgE testing may be used in patients who cannot undergo allergy skin testing. Use  
 16 of highly purified allergen or recombinants can increase the sensitivity, specificity, and diagnostic  
 17 accuracy of sIgE tests. Rigorous proficiency testing on the part of laboratories may also improve  
 18 accuracy.

19

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tian et al <sup>149</sup>	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 <i>D. pteryonyssinus</i> 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 <sup>150</sup>	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 $\geq$ 90%
van Hage et al <sup>151</sup>	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 <sup>152</sup>	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 <sup>52</sup>	1999	3	Prospective cohort	-Patients with cat allergy determined by history	Compared the predictive values of SPT, ID and RAST in diagnosis of cat allergy	-SPT and RAST values had excellent efficiency in cat allergy diagnosis -ID added little to the diagnostic evaluation

				-Cat exposure model		-Sensitivity and specificity of RAST were 69% and 100%, respectively
Tschopp et al <sup>148</sup>	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 <sup>147</sup>	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 <sup>146</sup>	1986	3	Prospective cohort	Children aged 4-19 years	Diagnostic levels by MAST and RAST were compared to skin test reactions for ragweed, grass, house dust mite	-MAST: sensitivity 59%, specificity 97%, efficiency 72% -RAST: sensitivity 67%, specificity 97%, efficiency 78% -Neither MAST nor RAST was as sensitive as skin test
Wide et al <sup>148</sup>	1967	3	Prospective cohort	31 allergic patients	Acoustic rhinometry of minimal nasal cavity cross-sectional area	Good correlation between provocation tests and in-vitro tests for allergy
Bignardi et al <sup>153</sup>	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 <sup>154</sup>	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 <i>T. putrescentiae</i>
Seidman et al <sup>2</sup>	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 <sup>45</sup>	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 <sup>57</sup>	2000	4	Prospective case-control	Perennial rhinitis patients	Compared sensitivity and specificity of ID to SPT and sIgE assay for <i>D. pteronyssinus</i> and <i>D. farinae</i>	-Serum sIgE for <i>D. pteronyssinus</i> and <i>D. farinae</i> 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 <sup>78</sup>	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 <sup>50</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; sIgE=allergen-specific immunoglobulin E;  
2 OR=odds ratio; AUSROC= areas under the summary receiver operating curve; SPT=skin prick test; PPV=positive  
3 predictive value; NPV=negative predictive value; AR=allergic rhinitis; RAST=radio allergo-sorbent test;  
4 ID=intradermal; MAST=multiple allegro-sorbent test; NPT=nasal provocation test; IgE=immunoglobulin E  
5 \*LOE upgraded due to established methodology, several rounds of review, long history of EBM guideline  
6 development  
7  
8

### 9 X.C.3. Nasal allergen specific IgE

10  
11 AR is frequently diagnosed by history alone in clinical practice.<sup>155</sup> When objective testing for  
12 confirmation of the diagnosis is needed, SPT or in vitro testing for serum sIgE is performed. However,  
13 the nasal mucosa of patients with AR has been shown to produce sIgE locally, providing a potential  
14 alternative method for objective testing for AR.<sup>156-161</sup>

15

1 Collection of nasal secretions is typically done by nasal lavage, through absorption of the secretions with  
2 absorbent materials, or directly with solid sIgE testing substrates.<sup>162-165</sup> Collection of mucosal tissue can  
3 be achieved with either tissue biopsy or with a cytology brush.<sup>159,166</sup> There is no consensus on which  
4 technique is superior, and most appear to yield similar results in identifying nasal sIgE.<sup>167,168</sup> Cut-off  
5 values for nasal sIgE levels that indicate a diagnosis of AR are debated and consensus has yet to be  
6 established. It is generally accepted that levels of nasal sIgE will be lower than levels of serum sIgE in  
7 patients with AR.<sup>164,169,170</sup> **[TABLE X.C.3.]**

8

9 Outside of a few circumstances, the clinical utility of nasal sIgE testing in patients with AR is limited.  
10 However, in patients with negative SPT and negative serum sIgE with a history suggestive of AR, nasal  
11 sIgE testing may detect sIgE in their nasal secretions and/or mucosa.<sup>163,165,171-178</sup> This phenomenon is  
12 referred to as LAR. LAR is a type of rhinitis characterized by typical allergic symptoms with local sIgE  
13 production and positive response to NPT, without positive SPT or serum sIgE testing.<sup>179</sup> (*See Section*  
14 *VI.A.3. Local IgE Production and Section X.D.2. Local Allergen Challenge Testing for additional*  
15 *information on these topics.*) The strictest diagnostic criteria for LAR require a positive NPT and evidence  
16 of sIgE in nasal secretions or nasal mucosa, as some studies have shown sIgE in control patients with  
17 negative results on NPT.<sup>180-183</sup>

18

19 Currently, patients with negative SPT and/or negative serum sIgE testing are given the diagnosis of non-  
20 allergic rhinitis. Several studies have investigated the results of nasal sIgE testing in patients with non-  
21 allergic rhinitis to achieve a greater understanding of what portion of patients diagnosed with non-  
22 allergic rhinitis have evidence of LAR. A recent systematic review of studies that measured nasal sIgE in  
23 mucus collected from the nasal cavity in patients diagnosed with non-allergic rhinitis showed sIgE to be  
24 present in 7.4-13.4% of subjects.<sup>184</sup> The results of this study contrast with a 2017 systematic review that  
25 analyzed the results of NPT in patients with AR and non-allergic rhinitis. The 2017 study found 24.7% of  
26 patients with non-allergic rhinitis had positive NPT.<sup>185</sup> This analysis did not include measurements of  
27 nasal sIgE limiting direct comparison to the more recent study. The origin of this disagreement between  
28 these two reviews is unclear but may be related to low quantities of nasal sIgE in nasal secretions or  
29 flaws in the methodology for testing for nasal sIgE.

30

31 Differentiating LAR from non-allergic rhinitis is important in patients with symptoms of rhinitis that are  
32 not adequately managed with pharmacologic therapy. While both would typically respond to treatment,

1 identification of offending allergens in LAR may permit allergen avoidance and/or allow for treatment  
 2 with AIT. Patients who are classified as non-allergic rhinitis would not typically be candidates for AIT;  
 3 however, for patients with LAR, treatment with AIT is an option.<sup>179</sup> In this population, early studies  
 4 suggest that AIT can decrease symptoms and medication usage and improve QOL.<sup>186</sup> Therefore, in  
 5 patients with symptoms of AR but negative SPT and/or negative in vitro testing for serum sIgE whose  
 6 symptoms are not fully controlled on appropriate pharmacologic therapy, assessment of nasal sIgE to  
 7 investigate for possible LAR could be considered.

8

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

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

13 **Harm:** Measurement of nasal sIgE is minimally invasive. No significant adverse effects have been  
 14 reported. Possible discomfort from sample collection.

15 **Cost:** Associated costs include the direct costs of testing and indirect cost of increased time and effort  
 16 for performing nasal sIgE diagnostic test.

17 **Benefits-harm assessment:** The benefits of identifying patients with an allergic component to their  
 18 rhinitis may outweigh associated risks.

19 **Value judgments:** In patients with non-allergic rhinitis who also have risk factors for atopic disease and  
 20 have inadequate response to pharmacotherapy, testing for nasal sIgE may be helpful in confirming a  
 21 diagnosis of LAR and allowing for treatment with AIT. There is no consensus for levels of nasal sIgE that  
 22 indicate sensitivity.

23 **Policy level:** Option.

24 **Intervention:** Measurement of nasal sIgE is an option in patients with non-allergic rhinitis suspected of  
 25 having LAR to support this diagnosis and guide AIT if pharmacologic therapies are inadequate.

26 Consensus for levels of nasal sIgE indicating AR need to be established.

27

28

**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 <sup>184</sup>	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 <sup>182</sup>	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 <sup>181</sup>	2020	2	Cross-sectional	Collection via nasal lavage: -AR, n=25 -NAR, n=25 -Control, n=18	NPT, nasal sIgE, serum sIgE, SPT	Nasal sIgE does not predict response to NPT in patients with NAR

Schiavi et al <sup>187</sup>	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 <sup>169</sup>	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 <sup>164</sup>	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 $\geq 0.1450$ kUA/L is an optimum cut point for differentiating subjects with LAR and AR from controls
Gelardi et al <sup>180</sup>	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 <sup>183</sup>	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 <sup>172</sup>	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 <sup>188</sup>	2016	2	Cross-sectional	Collection via nasal lavage: -NAR children, n=12 -AR children, n=15 -NAR adults, n=9 -AR adults, n=15	Nasal sIgE	-AR with higher nasal sIgE to HDM than NAR, no difference between adults and children -Correlation between nasal and serum IgE only in children
Bozek et al <sup>189</sup>	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 <sup>190</sup>	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 <sup>171</sup>	2012	2	Cross-sectional	Collection via cellulose membrane: -Perennial AR, children, n=20 -Perennial NAR, children, n=36	NPT, nasal sIgE	Nasal sIgE to <i>Alternaria</i> detected in 69% of positive NPT
Lopez et al <sup>173</sup>	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 <sup>191</sup>	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 <sup>192</sup>	2009	2	Cross-sectional	Collection via mucosal biopsy: -AFRS, n=11 -CRSsNP, n=8 -Control, n=9	Nasal sIgE, tIgE, histologic immunolocalization	Nasal sIgE to fungi and other antigens found in mucosa of subjects with AFRS
Rondon et al <sup>176</sup>	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 <sup>175</sup>	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 <sup>177</sup>	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 <sup>174</sup>	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 <sup>161</sup>	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 <sup>158</sup>	1997	2	Cross-sectional	Collection via mucosal biopsy: -Seasonal AR, n=11 -Perennial AR, n=10 -Control, n=10	Nasal sIgE to grass and HDM	sIgE to grass and HDM found in seasonal and perennial AR subjects, respectively



Takhar et al <sup>160</sup>	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 <sup>157</sup>	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 in the nasal mucosa of AR patients
Huggins & Brostoff <sup>165</sup>	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 <sup>193</sup>	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 <sup>167</sup>	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 <sup>170</sup>	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 <sup>163</sup>	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 <sup>194</sup>	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 <sup>166</sup>	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 <sup>178</sup>	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 <sup>168</sup>	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 <sup>159</sup>	2003	4	Case-control	Collection via mucosal biopsy: -AR, n=6	Nasal IgE heavy chain	Somatic hypermutation, clonal expansion, and class switching occurs within the

				-Control, n=1		nasal mucosa of AR patients
Sensi et al <sup>195</sup>	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 <sup>156</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; NAR=non-allergic rhinitis; sIgE=allergen-  
2 specific immunoglobulin E; AR=allergic rhinitis; NPT=nasal provocation test; tIgE=total immunoglobulin E;  
3 LAR=local allergic rhinitis; SPT=skin prick test; RCT=randomized controlled trial; SLIT=sublingual immunotherapy;  
4 VAS=visual analog scale; IgE=immunoglobulin E; ECP=eosinophil cationic protein; NARES=non-allergic rhinitis with  
5 eosinophilia syndrome; AFRS=allergic fungal rhinosinusitis; CRSsNP=chronic rhinosinusitis without nasal polyps;  
6 HDM=house dust mite; Ig=immunoglobulin  
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#### 9 X.C.4. Correlation between skin testing and in vitro sIgE testing

10  
11 Factors that influence sensitivity and specificity of SPT include patient demographics, technician  
12 expertise, specific methodologies employed, quality of reagents, and what allergen is being tested.<sup>196-202</sup>  
13 SPT wheal size and sensitivity depend on the choice of control reagents used for testing, specific device  
14 selection, angle of penetration, amount of allergen, and skill of the technician.<sup>50,196,198</sup> A 2016 SRMA  
15 indicates that SPT is an accurate test that when utilized along with a detailed clinical history, helps  
16 confirm the diagnosis AR.<sup>51</sup>  
17

18 The performance and reliability of serum sIgE testing depends on choice of reagents, age of equipment,  
19 and patient demographics.<sup>69</sup> Sensitivity and specificity are affected by the cutoff value of a positive  
20 test.<sup>203</sup> In a Korean population, SPT was found to be superior to ImmunoCAP for measuring HDM  
21 sensitivity if the patient was less than 30 years of age; for the group older than age 50, ImmunoCAP was  
22 more sensitive.<sup>204</sup>  
23

24 Several studies have compared serum sIgE to SPT.<sup>52,150,153,154,203,205,206</sup> Both techniques yield good  
25 sensitivity and are generally well correlated; however, interpretation of the results depends to some  
26 extent upon the gold standard reference used to define allergic status, namely environmental chambers,  
27 nasal challenge, and validated questionnaires.  
28

29 Microarray allergy testing systems have been introduced more recently to offer a comprehensive in  
30 vitro allergen test panel. There are several commercially available multiplex platforms: Thermo Fisher

1 ImmunoCAP ISAC (Immuno-solid phase Allergen Chip) which contains 112 allergen molecules; MADx  
 2 Allergen Explorer 2 (ALEX2) containing 117 purified allergens plus 178 allergenic components and  
 3 Euroline microstrips.<sup>130</sup> The implementation of molecular allergy diagnostic approach (PAMD@) is  
 4 increasingly entering into routine care.

5

6 Selection and interpretation of allergen testing is not based on sensitivity and specificity alone. The  
 7 intended physiological mechanism to be evaluated also needs to be considered. SPT measures end-  
 8 organ pathological mechanisms associated with sIgE bound to the surface of mast cells. Serum sIgE and  
 9 microarray approaches measure circulating IgE that may or may not represent downstream allergic  
 10 inflammatory responses.

11

12 The average pooled sensitivity of SPT is 85% which tends to be slightly higher than that of serum sIgE.<sup>51</sup>  
 13 This can vary depending on the allergen being tested and the characteristics of the patient. SPT is often  
 14 chosen as the first line diagnostic instrument to detect sensitivity to aeroallergens based on accuracy,  
 15 convenience, cost, and speed. In cases where dermatographism is present and/or patients are unable to  
 16 wean off medications that affect skin testing, serum sIgE testing may be a better choice.

17

18 The role of small volume blood testing through emerging microarray multiplex (multiple assays per  
 19 sample) technology is evolving. Multiplex assays are especially suited for use in patients with complex  
 20 sensitization patterns or symptoms. In polysensitized patients, PAMD@ makes it possible to distinguish  
 21 between primary and cross-sensitization. This is very important for appropriate prescription of AIT.  
 22 Specific molecular sensitization patterns obtained in multiplex platforms may predict the risk for AR and  
 23 asthma. PAMD@ is beginning to be used worldwide.

24

25 **Aggregate Grade of Evidence:** B (Level 1: 3 studies, level 2: 5 studies, level 3: 4 studies, level 4: 5 studies,  
 26 level 5: 2 studies, **TABLE X.C.4.**)

27

28 **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 <sup>51</sup>	2016	1	Systematic review	AR	SPT accuracy	Various factors determine SPT accuracy
Westwood et al <sup>131</sup>	2016	1	Systematic review	AR	Microarray results	Utility and cost of microarray testing needs further validation

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

1 LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; sIgE=allergen-specific immunoglobulin E; RCT-  
2 randomized controlled trial; HDM=house dust mite; RAST=radio allegro-sorbent test; AIT=allergen  
3 immunotherapy; ID=intradermal; PAMD@=precision allergy molecular diagnostic applications  
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### 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.<sup>209</sup>

In HDM sensitive children, BAT has excellent sensitivity (82-100%) and specificity (96-100%).<sup>210</sup> Similar findings were reached in 31 grass pollen sensitive adults: sensitivity 87-100% and specificity 100%.<sup>211</sup> 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.<sup>212</sup> BAT is also able to distinguish between AR based on HDM allergy and irrelevant HDM-sensitization.<sup>213</sup> For birch allergy, BAT sensitivity was shown to increase after the pollen season compared to placebo.<sup>214</sup> Results of BAT are valid in both in-season and pre-season measurements.<sup>215</sup> 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.<sup>216</sup>

#### **[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.<sup>217</sup> 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.<sup>218</sup> In another study, long-term differences were found between HDM and grass pollen sensitive

1 patients treated with dual SLIT or placebo; basophil activation in the treatment group was significantly  
2 decreased after 24 months compared with baseline.<sup>219</sup> SLIT for Parietaria showed reduced basophil  
3 activation in 16 patients after 12 months of treatment.<sup>220</sup>

4  
5 For grass pollen subcutaneous immunotherapy (SCIT), some changes were found in BAT outcomes in 16  
6 patients after 9 months of follow-up compared to placebo, but these changes were not correlated to  
7 clinical outcomes.<sup>221</sup> In another study with 50 grass pollen sensitized patients, SCIT gave a clear  
8 reduction in BAT outcomes 3-5 years after treatment.<sup>222</sup> These results were confirmed in a smaller study  
9 with 18 patients treated with grass pollen SCIT; here, early changes in BAT outcomes were related to  
10 late clinical improvement.<sup>223</sup>

11  
12 In HDM-sensitized patients, no apparent changes in BAT outcomes 24 months after SCIT were found,  
13 whereas in mugwort-sensitized patients, basophil reactivity was reduced at this timepoint.<sup>224</sup> Feng et  
14 al<sup>225</sup> were able to find changes in basophil activation after 2 years of SCIT for HDM in 35 patients. Two  
15 months of SCIT in HDM sensitive patients with (n=24) or without (n=19) other sensitizations showed  
16 improved clinical scores but increased BAT outcomes, especially in polysensitized patients.<sup>226</sup> When  
17 comparing SCIT and SLIT in grass pollen-sensitive patients, both lowered basophil sensitivity compared  
18 to controls at 15 months. However, the effect was larger in SCIT.<sup>227</sup>

19  
20 The evidence summarized above suggests that BAT is possibly of value in long-term outcomes of AIT and  
21 possibly more sensitive in SCIT treated patients. However, the lack of correlation of BAT outcomes to  
22 clinical parameters in many studies shows that the application in BAT to evaluate AIT in clinical practice  
23 is not obvious.

24  
25 The studies mentioned above used either CD63 or CD203c positivity as marker for basophil activation. In  
26 a small study with 16 SLIT-treated patients, both markers were compared, showing that both were  
27 sensitive to treatment, but only CD203c data were correlated to clinical improvement.<sup>220</sup> Ma and Qiao<sup>228</sup>  
28 used a mixed cohort of 18 children treated for AR showing that both CD63 and CD203c-based BAT  
29 correlated to clinical remission of symptoms. This suggests that technical choices in the execution of BAT  
30 influence outcomes and usability in practice.

31

1 In summary, the role of BAT in the diagnosis and evaluation of AR in clinical practice is limited. In most  
 2 cases a detailed history with sIgE measurements or skin testing will suffice. In specific cases (e.g., contra-  
 3 indication for skin testing or conflicting results), though, BAT could be considered. The use of BAT to  
 4 monitor reactivity to treatment is not advised in daily clinical practice.

5  
 6 **Aggregate grade of evidence:** C (Level 2: 5 studies, level 3: 13 studies, level 4: 1 study; **TABLE X.C.5.**)

7 **Benefit:** May help diagnose AR in specific cases where common approaches are not possible or show  
 8 conflicting results.

9 **Harm:** Discomfort of venipuncture.

10 **Cost:** Moderate cost of performing the test, plus venipuncture. Depending on the local situation and  
 11 availability.

12 **Benefits-harm assessment:** Balance of benefit and harm.

13 **Value judgments:** The evidence does not support routine use for the diagnosis of AR or for following AIT  
 14 response.

15 **Policy level:** Option.

16 **Intervention:** Application of BAT in specific situations where other diagnostic procedures for AR are not  
 17 possible or conflicting. Potentially useful for monitoring AIT if other methods fail or show conflicting  
 18 results.

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**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 <sup>214</sup>	2019	2	DBRCT	Blood donors with birch pollen allergy, pre-seasonal supplementation with <i>Agaricus blazei murill</i> 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 <sup>227</sup>	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 <sup>221</sup>	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 <sup>219</sup>	2012	2	RCT, phase 1	30 AR subjects with HDM and Timothy grass allergy treated	Clinical outcomes and laboratory markers, including BAT	-BAT based on CD203c positivity

				with dual SLIT (n=20) or placebo (n=10)		-HDM SLIT decreased basophil activation in treatment group at 24 months vs baseline -BAT can be useful to monitor changes from SLIT
Van Overtvelt et al <sup>218</sup>	2011	2	DBRCT	98 patients with grass pollen AR treated with SLIT or placebo for 4 months	Basophil activation after 2 and 4 months of therapy	-BAT based on CD203c positivity -No significant changes in basophil activation between groups at any of the time points
Ma & Qiao <sup>228</sup>	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 <sup>216</sup>	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 <sup>223</sup>	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 <sup>225</sup>	2020	3	Prospective cohort	55 subjects HDM asthma and/or AR; 21 patients under 15 years and 34 adults, SCIT (n=35) and regular treatment (n=20)	Changes in basophil reactivity up to 2 years of SCIT compared to regular treatment	-BAT based on CD63 positivity -0.15µg/ml allergen concentration: basophil activation decreased in the SCIT group from week 16 to 104



						<p>-15µg/ml allergen concentration: no changes in SCIT or control group</p> <p>-Basophil sensitivity can be used as marker for SCIT efficacy</p>
Zidarn et al <sup>213</sup>	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	<p>-BAT based on CD63 positivity</p> <p>-BAT threshold &gt;15%, 3.33ng/mL in symptomatic patients, 33.3ng/mL in asymptomatic group</p> <p>-BAT can help clinicians to distinguish between HDM-AR patients and asymptomatic subjects</p>
Caruso et al <sup>220</sup>	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	<p>-BAT based on CD63 or CD203c positivity</p> <p>-Both CD63 and CD203c BAT showed reduced activation after 12 months of SLIT vs control</p> <p>-Symptom reduction only related to reduced basophil activation based on CD203c</p>
Kim et al <sup>224</sup>	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	<p>-BAT based on CD63 positivity</p> <p>-For HDM no change observed</p> <p>-For mugwort, SCIT basophil reactivity was reduced after 24 months of SCIT</p> <p>-Basophil response not useful for reflecting clinical response of AIT for HDM and mugwort</p>
Ogurlur et al <sup>212</sup>	2017	3	Prospective cohort	47 children with AR (+/- asthma and AD) sensitized to HDM and/or grass pollen, 15 children without atopy (negative SPT)	Performance of BAT to diagnose AR	<p>-BAT based on CD63 positivity</p> <p>-Cut-off for HDM: 12.5% activated basophils, AUC 0.94, sensitivity 90%, specificity 73%, PPV 0.70, NPV 0.91</p> <p>-Cut-off for grass pollen: 11% activated basophils, AUC: 0.94, sensitivity 96%, specificity 93%, PPV 0.98, NPV 0.88</p>
Soyyigit et al <sup>226</sup>	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	<p>-BAT based on CD203c positivity</p> <p>-Polysensitized pts had significantly higher baseline BAT reactivity to 1.6 and 0.16 mg/mL allergen</p> <p>-After SCIT, BAT at 1.6 mg/mL of allergen significantly increased in the polysensitized</p>

Zidarn et al <sup>222</sup>	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	<ul style="list-style-type: none"> <li>-BAT based on CD63 positivity</li> <li>-At 0.1µg/ml grass pollen, baseline vs end of study nonsignificant</li> <li>-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</li> <li>-At 10µg/ml grass pollen: baseline 89.7% (14.2-100), end of study 67.3% (5.6-96.6), p=0.008</li> <li>-BAT is a possible biomarker for long-term clinical tolerance in AR</li> </ul>
Özdemir et al <sup>211</sup>	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	<ul style="list-style-type: none"> <li>-BAT based on CD203c positivity</li> <li>-At various concentrations of grass pollen extract, BAT distinguishes AR from control, with 100% specificity, sensitivity 87-100%</li> </ul>
González-Muñoz et al <sup>210</sup>	2008	3	Prospective cohort	24 children with HDM-based AR and/or asthma, atopic control group of 23 children with HDM negative SPT but positive to other allergens, non-allergic controls	Quality of BAT to diagnose HDM allergy	<ul style="list-style-type: none"> <li>-BAT based on CD63 positivity</li> <li>-Best testing parameters for HDM vs atopic controls: at 8% activated basophils as cut-off with 16µg/ml allergen concentration, AUC: 1.0, sensitivity 100%, specificity 100%</li> <li>-Analysis of allergen-induced CD63 upregulation by flow cytometry is reliable for diagnosis of HDM allergy in pediatric patients</li> </ul>
Saporta et al <sup>215</sup>	2001	3	Prospective cohort	13 adult patients with seasonal AR	Variance of BAT results pre- and in-season	<ul style="list-style-type: none"> <li>-BAT based on CD63 positivity</li> <li>-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)</li> <li>-BAT can be used both pre-season and in-season to diagnose seasonal AR</li> </ul>
Nagao et al <sup>217</sup>	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	<ul style="list-style-type: none"> <li>-BAT based on CD203c positivity</li> <li>-Reduction of CD203c expression was found after SCIT in 4 patients</li> <li>-Does not confirm BAT is useful for monitoring all patients</li> </ul>

1 LOE=level of evidence; DBRCT=double-blind randomized controlled trial; BAT=basophil activation test; CD=cluster  
2 of differentiation; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy;  
3 SLIT=sublingual immunotherapy; HDM=house dust mite; SPT=skin prick test; AIT=allergen immunotherapy;  
4 AD=atopic dermatitis; AUC=area under the curve; PPV=positive predictive value; NPV=negative predictive value  
5 \*LOE downgraded due to very small number of patients  
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#### 8 X.C.6. Component resolved diagnostic testing 9

10 The implementation of molecular allergy diagnostic approach, or PAMD@, is increasingly entering into  
11 routine clinical care.<sup>130</sup> Although PAMD@ may initially appear complex to interpret, with increasing  
12 experience, the information gained is relevant and allows improved management of allergic diseases. By  
13 measuring sIgE to purified natural or recombinant allergens, PAMD@ allows clinicians to evaluate  
14 allergen sensitization at the individual protein level, thus allowing potential identification of disease-  
15 eliciting molecules.

16  
17 In addition to potentially improving diagnostic accuracy, molecular diagnostics (MD) can also aid in  
18 distinguishing cross-reactivity phenomena from true co-sensitization and resolving low-risk markers  
19 from high-risk markers of disease activity. When compared to diagnosis based on sIgE determination  
20 and/or SPT with raw commercial extracts, MD may improve the identification of disease-causing  
21 allergen sources and the prescription of AIT.<sup>130,229-232</sup> Changes in AIT prescriptions as a result of MD have  
22 demonstrated cost-effectiveness.<sup>233</sup> A real-life study showed that although SPT was less expensive, MD  
23 allowed a more precise prescription of AIT, which substantially reduced treatment costs and the  
24 combined costs for diagnosis and treatment.<sup>234</sup> MD may also aid with risk stratification by identifying  
25 certain patterns of sensitization to pollen allergens that are at higher risk of adverse reaction during  
26 AIT.<sup>235,236</sup> Clinicians should keep in mind that all in vitro test results should be evaluated in context of the  
27 clinical history since allergen sensitization does not necessarily imply clinical symptoms.

28  
29 Patients with a broader polymolecular IgE sensitization pattern to mites, epithelia and pollen allergens  
30 have a trend toward more severe disease and more comorbidities.<sup>237,238</sup> The presence of IgE antibodies  
31 against allergenic molecules may be determined using a singleplex or multiplex measurement platform  
32 (ISAC, Thermofisher-Scientific, Uppsala, Sweden; Alex<sup>2</sup> MacroArray Diagnostics, Vienna, Austria). It  
33 should be noted that the results of singleplex and multiplex platforms are not interchangeable, and, in  
34 general, sensitivity is higher for singleplex platforms.<sup>130,229</sup> Singleplex platforms are quantitative assays  
35 and multiplex are semi-quantitative.

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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.<sup>239</sup> Recently, Der p 23 has been described also as a frequent allergen and associated with increased asthma risk.<sup>130,240</sup> Other good markers of sensitization are Lep d 2 for *Lepidoglyphus destructor* (storage mite, with limited cross-reactivity with other HDMs)<sup>241</sup> and Blo t 5 for *Blomia tropicalis* (non-Pyroglyphidae mite).<sup>242</sup> 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.<sup>243,244</sup> 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.<sup>245</sup>

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

Alt a 1 is a major allergen that is recognized in approximately 80–100% of *Alternaria*-allergic patients.<sup>255</sup> 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.<sup>229,256</sup>

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.<sup>236,257</sup> 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.<sup>258</sup>

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 2 In summary, PAMD@ in AR can help to better define the sensitization, better predict disease severity,  
 3 better select patients and allergens for AIT and may predict the efficacy of AIT. However, it is not  
 4 recommended for routine use in daily clinical practice at this time.

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 6 **COMPONENT RESOLVED DIAGNOSTIC TESTING – Aggregate grade of evidence:** C (Level 2: 4 studies,  
 7 level 3: 2 studies, level 4: 11 studies, level 5: 1 study; **TABLE X.C.6.-3**)

8 **Benefit:** Reliable. May help in identification and selection of suitable allergens for AIT, as well as possibly  
 9 improving safety of AIT.

10 **Harm:** Discomfort of venipuncture.

11 **Cost:** Moderate cost of testing, minimal cost of venipuncture; depends in local availability.

12 **Benefits-harm assessment:** Balance of benefit and harm.

13 **Value judgments:** Molecular diagnosis may be a useful tool for diagnosis of AR in some scenarios,  
 14 especially in polysensitized patients.

15 **Policy level:** Option.

16 **Intervention:** Molecular diagnosis is an option for diagnosis of AR by specialists.  
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	<b>Specific component</b>	<b>Percent sensitization</b>	<b>Cross-reactivity</b>
<b>DOG</b>	Can f 1-lipocalin* Can f 2-lipocalin* Can f 3-serum albumin*  Can f 4-lipocalin Can f 5-arginine esterase, prostatic kallikrein Can f 6- lipocalin* Can f 7-epididymal secretory protein E1	50-90% 20-33% 25-59%  35-46% 30-70%; monosensitization 25%  23-61% 17%	Fel d 7  70-80% with other serum albumins  Fel d 4 and Equ c 1
<b>CAT</b>	Fel d 1-secretoglobin* Fel d 2-serum albumin*  Fel d 3-cystatin Fel d 4-lipocalin* Fel d 5W-IgA Fel d 6W-IgM Fel d 7-lipocalin* Fel d 8-latherin-like protein	90%; monosensitization 30% 14-54%  10%38% 63%; monosensitization 6% 38% ? 38% 19%	70-80% with other serum albumins  Can f 6 and Equ c 1  Can f 1
<b>DOMESTIC HORSE</b>	Equ c 1-lipocalin*  Equ c 2-lipocalin Equ c 3-serum albumin*  Equ c 4-latherin Equ c 6-lysozime	76-100%  50% 36%  77% ?	Can f 6 and Fel d 4  70-80% with other serum albumins

\*allergens currently available for molecular diagnosis

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<b>TABLE X.C.6.-2. POLLEN ALLERGENS</b>			
<b>POLLEN</b>	<b>Specific components</b>	<b>Percent sensitization<sup>130</sup></b>	<b>Cross-reactivity components</b>
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)* 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)	95% 55% 60% 70% 50-95% 44-75% 10% 32-43% 15% 50%	Phl p 4 (berberines) Phl p 7 (polcalcins) Phl p 11 (trypsin inhibitors) Phl p 12 (profilin) Phl p 5 & Phl p 2 & Phl p 6
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 (?)	90% 50% ? 80%	Ole e 2 (profilins) Ole e3 (polcalcins)

	Ole e 5 (superoxide dismutase)	35%	
	Ole e 6 (?)	15%	
	Ole e 7 (LTP)*	47%	
	Ole e 8 (polcalcin)	?	
	Ole e 9 (glucanase)*	68%	
	Ole e 10 (X8 domain protein)	90%	
	Ole e 11 (pectin methylesterase)	?	
	Ole e 12 (isoflavone reductase)	4-33%	
Japanese cedar	Cry j 1 (pectate lysases)	98%	Japanese cedar, Mountain cedar and cypress pollen
	Cry j 2 (polygalacturonase)	82%	
Cypress	Cup a 1 (pectate lysases)*	100%	Cup a 4 and polcalcins
	Cup a 3 (thaumatin-like)	50%	
	Cup a 4 (polcalcin)	10%	
Ash	Fra e 1 (Ole 1-like)	87%	Fra e 1 and Ole e 1
Plane tree	Pla a 1 (invertase inhibitor)*	87%	Pla a 3 (LTP)
	Pla a 2 (polygalacturonases)*	83%	
	Pla a 3 (LTP)*	45%	

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

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**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 <sup>259</sup>	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 <sup>260</sup>	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 <sup>261</sup>	2014	2	Observational study	651 children with moderate-to-severe pollen-related AR, positive SPT to grass, cypress, olive, mugwort, pellitory, and/or Betulaceae pollen	-IgE sensitization to Phl p 1, Phl p 5, Bet v 1, Cup a 1, Art v 1, Ole e 1, Par j 2, and Phl p 12 (profilin) -AIT prescription was modeled on SPT responses first and then remodeled considering CRD	After CRD, AIT prescription or composition was changed in 42%
Letran et al <sup>262</sup>	2013	2	Observational study	175 patients with a diagnosis of spring pollinosis	-SPT -In vitro study of the application of a specific recombinant	Choice of immunotherapy was changed in more than 50% of patients

					IgE protocol (nOle e 1, rPhl p 1-5b, rPhl p 12, rPhl p 7, and rPru p 3)	
Nolte et al <sup>263</sup>	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 <sup>236</sup>	2015	3	Cohort	192 patients with rhinitis and/or asthma sensitized to grass pollen receiving 4-week uposing 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 <sup>264</sup>	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 <sup>245</sup>	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 <sup>265</sup>	2019	4	Retrospective case series	Patients with HDM-induced respiratory allergy who received AIT extract for at least 3 years	-Serum levels of <i>D. pteronyssinus</i> components (Der p 1, Der p 2, Der p 10, and Der p 23 and Lep d 2) -VAS and/or the Global Score of Combined Rhinitis and Asthma Symptoms and Rescue Medication	No association between the clinical efficacy of AIT based on HDM and sensitization to mite allergens
Chen et	2019	4	Retrospective	Patients with	-Post hoc analysis of	-Der p 1, Der p 2, and Der p



al <sup>266</sup>			case series	HDM allergy treated with AIT in a double-blind placebo-controlled clinical study	serum IgE and IgG reactivity against a comprehensive panel of HDM allergens -Respiratory symptoms during controlled HDM exposure in the Vienna Challenge Chamber	23 were the most frequently recognized <i>D. pteronyssinus</i> 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 <sup>267</sup>	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 <sup>234</sup>	2017	4	Case series	95 patients with pollen-induced allergy	-SPT with a local panel of tree pollen, grass pollen, and weed pollen allergen extracts -sIgE for marker allergen molecules (nArt v 1, nArt v 3, rAmb a 1, rPhl p 1, rPhl p 5, rBet v 1) -Direct and indirect costs	-Costs for SPT-based diagnosis lower than the costs for allergen molecule-based sIgE -Allergen molecule-based serology was more precise in detecting disease-causing allergen sources
Uriarte & Sastre <sup>248</sup>	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 <sup>268</sup>	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 <sup>269</sup>	2012	4	Case series	141 patients with allergic rhinoconjunctivitis and/or asthma sensitized to pollen with or without concomitant food allergy	-SPT -Micro-array-based panel of allergens (ISAC) -Indication of AIT and use of allergens following EAACI recommendations, based on clinical history and SPT results before and after obtaining the ISAC results	-Agreement in AIT indication before and after ISAC results found in only 46% of patients -Very low agreement regarding indication and use of allergens for AIT before and after performing molecular diagnosis
Tripodi et al <sup>270</sup>	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 <sup>271</sup>	2006	4	Case series	Olive pollen extract batches from several suppliers were analyzed	Not applicable	-Batches analyzed for Ole e 1 and Ole e 9 content as well as biological activity -10-fold variation between the extreme values was found for the biological activity of the batches analyzed

						-Ole e 1 concentration showed a 25-fold variation -Variability of Ole e 9 concentration extremely high, up to 161 times
Schoos et al <sup>249</sup>	2021	5	Review	Studies on CRD for pet components published between 1997 and mid-2020	Not applicable	CRD has a role in developing patient-tailored treatment that could reduce health care costs, save time for patients, reduce adverse effects, and improve patient quality of life

1 LOE=level of evidence; AR=allergic rhinitis; SPT=skin prick test; AIT=allergen-specific immunotherapy;  
2 sIgE=allergen-specific immunoglobulin E; Ig=immunoglobulin; CRD=component resolved diagnostics;  
3 SLIT=sublingual immunotherapy; EAACI=European Academy of Allergy and Clinical Immunology; HDM=house dust  
4 mite; VAS=visual analog scale  
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## 7 X.D. Allergen challenge testing

### 8 X.D.1. Environmental exposure chambers (allergen challenge chambers)

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10 Environmental exposure chambers (EEC) have been used for decades to study the impact of exposures  
11 to well-defined atmospheres of a variety of substances such as allergens, particulate and gaseous air  
12 pollutants, chemicals, or climate conditions. Valid exposure conditions with high temporal and spatial  
13 stability are technically demanding, limiting the number of EECs worldwide. In addition to the  
14 opportunity to use EEC for mechanistic studies on the effect of environmental pollutants on human  
15 health, it is also an interesting way to do efficacy testing of new drugs by allergen challenge in the  
16 chamber setting with induction of symptoms in patients with allergic disease. Presently, there are 15  
17 allergen challenge chamber (ACC) facilities around the globe focusing on allergen exposure.<sup>272</sup>  
18

19 Our understanding of the pathophysiology of allergic diseases has been enhanced by ACC studies. A  
20 prime example of this is knowledge gained that controlled allergen exposure exacerbates atopic  
21 dermatitis.<sup>273</sup> Also, the impact of exposure with pollen allergen fragments<sup>274</sup> and the aggravating effect  
22 of diesel exhaust particles on AR symptoms has been shown.<sup>275</sup> Furthermore, the importance of the  
23 integrity of the epithelial barrier for induction of local and systemic inflammatory responses has been  
24 investigated in patients with allergic rhinoconjunctivitis using the ACC setting,<sup>276</sup> as well as severity  
25 phenotypes of allergic asthma and rhinoconjunctivitis.<sup>277,278</sup>  
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1 The use of ACC in clinical trials for efficacy testing of investigational new drugs and their acceptance by  
2 regulatory authorities is peremptorily dependent on the technical and clinical validation of ACCs. ACC  
3 have been intensively validated regarding specificity and dose-dependency of symptom induction, as  
4 well as technical aspects such as temporal stability and spatial homogeneity of the allergen exposure.<sup>279-</sup>  
5 <sup>287</sup> Also, repeatability of outcome measures in the ACC has been systematically investigated and verified  
6 for TNSS,<sup>288</sup> peak nasal inspiratory flow (PNIF),<sup>289</sup> conjunctivitis symptoms,<sup>290,291</sup> and inflammatory nasal  
7 biomarkers.<sup>292</sup> Remarkably, epigenetic changes in peripheral blood mononuclear cells and nasal  
8 epithelia after allergen challenge have recently been demonstrated, with baseline epigenetic status  
9 predicting symptom severity.<sup>293</sup> With the given level of technical and clinical validation, ACC have been  
10 used in clinical drug development to study pharmacological properties of new drugs during phase 2  
11 trials, such as optimal dose,<sup>294-296</sup> onset of action,<sup>297-303</sup> and duration of action.<sup>304-306</sup> In this respect,  
12 numerous clinical trials have been conducted using parallel-group or cross-over designs in order to test  
13 the efficacy of drugs with prophylactic therapeutic potential, such as INCS,<sup>307-311</sup> or with immediate  
14 therapeutic activity, such as antihistamines.<sup>312-318</sup> Novel anti-inflammatory compounds,<sup>319-323</sup> drug-free  
15 nasal fluids,<sup>324,325</sup> and probiotics<sup>326,327</sup> have also been tested by this method. Additionally, the efficacy of  
16 AIT<sup>328-339</sup> and air cleaners<sup>340,341</sup> has been tested, as well as the influence of allergic nasal symptoms on  
17 the absorption of nasally applied drugs.<sup>342</sup> Major advantages in the ACC setting compared to field  
18 studies are better signal-to-noise ratios, a safeguarded minimum level of symptomatology in the ACC,  
19 and reproducibility of symptoms through allergen dose consistency allowing intra-individual  
20 comparisons.

21

22 A variety of validation studies of allergen atmospheres in ACCs have been published, including  
23 grass,<sup>279,284</sup> birch,<sup>280</sup> HDM,<sup>285,343,344</sup> Japanese cypress,<sup>345</sup> and ragweed.<sup>346</sup> While regulatory authorities  
24 accept the use of ACC in phase 2 of drug development, they have been reluctant to approve them in  
25 pivotal phase 3 studies because their clinical validation is still imperfect.<sup>347-349</sup> Differences between  
26 natural exposure and ACC studies exist, for example with regards to exposure time (continuous versus  
27 intermittent), exposure atmosphere complexity (natural mix versus artificial purity), selection of study  
28 population (all-comers versus allergen challenge responders), and sample size (higher in field studies  
29 than in ACC to achieve comparable statistical power). To promote the implementation of ACC in phase 3  
30 clinical trials, an EAACI initiated task force gathers and evaluates data on their clinical validation.  
31 Minimal technical requirements have already been identified.<sup>350</sup> Hybrid approaches combining ACC and  
32 field study might provide proper robustness to determine drug efficacy.<sup>272,351</sup>

1

2 In summary, numerous well-designed RCTs using technically validated ACCs for efficacy testing of  
3 investigational new drugs with detailed analysis of dose-response, onset of action, and duration of  
4 action underline the value of ACCs in clinical drug development of AR medicines.

5

6

### 7 X.D.2. Local allergen challenge testing

8

9 Challenging target organs with allergens could demonstrate reactivity when SPT and/or serum IgE tests  
10 are unconvincing or inconsistent with patient symptoms and exam. NPT and conjunctival provocation  
11 test (CPT) may be used for AR and rhinoconjunctivitis diagnosis, respectively, in these circumstances.<sup>352-</sup>

12 <sup>354</sup>

13

14 NPT aims to reproduce the upper airway response to nasal allergen exposure.<sup>355,356</sup> The only test  
15 fulfilling such requirements directly is the EEC; allergens administered during NPT usually exceed the  
16 levels of natural exposure. (*See Section X.D.1. Environmental Exposure Chambers for additional*  
17 *information on this topic.*) NPT can be administered by several devices: syringes, droppers, sprays, or  
18 disks, each with limitations.<sup>355</sup> Positive NPT can be assessed by symptom scales, rhinometry, PNIF, nasal  
19 lavage inflammatory markers, and nasal nitric oxide (nNO).<sup>356</sup> NPT contraindications include acute  
20 rhinosinusitis, recent AR exacerbation, history of anaphylactic reactions, severe general diseases  
21 (cardiopulmonary diseases with reduced lung capacity), and pregnancy.<sup>357</sup> Reported sensitivities and  
22 specificities of NPT range between 83.7-93.3% and 72.7-100%, respectively. [TABLE X.D.2.] A  
23 standardized NPT, suggested by Gosepath et al,<sup>357</sup> has been defined by the EAACI position paper,  
24 although NPT utilization for AR diagnosis may decrease due to emerging tools like molecular allergy  
25 diagnostics and BAT.<sup>209,358-360</sup>

26

27 The characteristics and safety of NPT were investigated in 518 children and 5830 adults by Eguiluz-  
28 Gracia et al,<sup>361</sup> with 11,499 challenges and only four local adverse reactions noted. Reproducibility,  
29 positive and negative predictive values of three consecutive NPT in 710 subjects were 97.32%, 100%,  
30 and 92.91%, respectively, with no false-positive results. Comparison between NPT and EEC in patients  
31 with cat allergy resulted in similar clinical and immunological responses. The authors suggested that  
32 selecting a specific allergen challenge method should depend on the study objectives and costs when  
33 investigating cat allergy.<sup>362</sup> Regarding HDM, Wanjun et al<sup>363</sup> studied the relationship between the

1 severity of AR and various diagnostic tests noting that NPT, SPT wheal size, and serum sIgE correlated  
2 with each other; only NPT was associated with the nasal symptom severity. Joo et al<sup>364</sup> evaluated the  
3 EAACI NPT protocol, concluding that standardized NPT could help diagnose AR caused by HDM. Finally,  
4 Xiao et al<sup>365</sup> found that, in assessing HDM allergic patients' candidacy for AIT, NPT is valuable and safe  
5 for confirming the diagnosis before treatment, especially in Der p 1-positive or low sIgE patients.

6  
7 NPT is crucial in diagnosing occupational rhinitis and LAR. Occupational rhinitis diagnosis requires  
8 "objective demonstration of the causal relationship between rhinitis and the work environment through  
9 NPT with the suspected agent(s)".<sup>366</sup> Occupational rhinitis diagnosis is challenging and should be  
10 suspected in patients with adult-onset rhinitis; NPT is the gold standard for diagnosis when  
11 immunological tests are unavailable or unreliable.<sup>367</sup>

12  
13 For LAR, the SPT and serum sIgE are negative and diagnosis requires the measurement of local IgE in  
14 nasal secretions or a positive NPT.<sup>368</sup> Measuring local sIgE in the clinic is not readily available or practical,  
15 making NPT critical. Of note, NPT with HDM, pollens, and *Alternaria* was positive in 100% of 22 adults  
16 with previously diagnosed LAR,<sup>369</sup> however, in 28 children with non-allergic rhinitis, NPT was positive in  
17 only 25% of subjects.<sup>370</sup> In another study involving 62 symptomatic patients with negative SPT, the  
18 prevalence of LAR to HDM was 24.2%, with sneezing noted as a more dominant symptom in LAR versus  
19 non-allergic rhinitis.<sup>371</sup>

20  
21 CPT is generally performed by instilling 20-30µL of an allergen solution into the inferolateral quadrant of  
22 the conjunctiva, using a control diluent in the contralateral eye.<sup>352</sup> A positive CPT response results in a  
23 reaction 5-20 minutes after testing with ocular itching/pruritis, tearing, redness/conjunctival erythema,  
24 and possibly edema. A study of 20 children with seasonal rhinoconjunctivitis tested three times with CPT  
25 reported good reproducibility.<sup>372</sup> CPT sensitivity and specificity in HDM-allergic patients were reported  
26 as 90% and 100%, respectively.<sup>373</sup> A systematic review contributed to the EAACI guidelines for the  
27 practice of CPT with grade B evidence for identifying the allergen trigger.<sup>374</sup> It was concluded that  
28 allergists should be more familiar with CPT due to its simplicity. However, symptom scales need to be  
29 validated, allergen extract standardization should be improved, and CPT indications in patients with  
30 non-allergic conjunctivitis remain uncertain. Only one recent trial has been published which assessed a  
31 group of children monosensitized to Can f 5 from dogs. Interestingly, reference SPT and CPT

1 demonstrated different reactions to male and female dog extracts, suggesting tolerance to female  
2 dogs.<sup>375</sup>

3

4 **Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 7 studies; **TABLE X.D.2.**)

5 **Benefit:** May assist in confirming diagnosis of AR in specific cases when immunological tests are  
6 unavailable or unreliable. NPT is crucial in diagnosing occupational rhinitis and LAR.

7 **Harm:** Not necessary if first- and second- line tests are indicative for AR diagnosis.

8 **Cost:** Depending on the local situation and availability of equipment and staff, costs may be high.

9 **Benefits-harm assessment:** Balance of benefit and harm.

10 **Value judgments:** The evidence does not support routine use for diagnosis of AR, but provocation  
11 testing is useful for diagnosis of occupational rhinitis and LAR.

12 **Policy level:** Option for diagnosis of AR when skin or in vitro tests are equivocal or unreliable.  
13 Recommendation for diagnosis of LAR and occupational rhinitis.

14 **Intervention:** Application of NPT is useful in LAR and to confirm occupational rhinitis.

15

16

**TABLE X.D.2. Evidence table – Provocation testing for the diagnosis of allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Larson et al <sup>362</sup>	2020	2	RCT	Patients with cat allergy: -24 patients: NPT then EEC -12 patients: EEC then NPT -28-day delay between test modalities	-TNSS -PNIF -Expression of cytokine and chemokine genes	-EEC showed higher magnitude in TNSS and PNIF than NPT -RT-PCR showed type 2 immune response after both types of allergen challenge
Gelis et al <sup>376</sup>	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 <sup>364</sup>	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 <sup>361</sup>	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-Falta et al <sup>377</sup>	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 <sup>378</sup>	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 <sup>379</sup>	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 $\geq 6.5$ : 90.6% sensitivity, 77.4% specificity -Acoustic rhinometry: 73.4% sensitivity, 58.1% specificity
Agarwal et al <sup>380</sup>	2013	3	Cohort	11 patients with mold allergy -11 controls	Results of NPT by optical rhinometry	No significant difference between allergic and control subjects

1 LOE=level of evidence; RCT=randomized controlled trial; NPT=nasal provocation test; EEC=environmental exposure  
2 chamber; TNSS=Total Nasal Symptom Score; PNIF=peak nasal inspiratory flow; RT-PCR=reverse transcriptase  
3 polymerase chain reaction; VAS=visual analog scale; EAACI=European Academy of Allergology and Clinical  
4 Immunology; HDM=house dust mite; MCA=minimal cross-sectional area; TNV=total nasal volume; AR=allergic  
5 rhinitis; SPT=skin prick test; NPT-R=rapid nasal provocation test  
6  
7

## 8 X.E. Nasal cytology and histology

9  
10 Nasal cytology (NC) is a diagnostic procedure that evaluates cell types present in the nasal mucosa.<sup>381</sup> NC  
11 starts with sampling the surface cells of the nasal mucosa; typically with a Rhino-probe (Arlington  
12 Scientific, Springville, UT, USA).<sup>382</sup> After sampling, staining using the May-Grunwald-Giemsa method  
13 allows identification of inflammatory (i.e., eosinophils, neutrophils, mast cells, and lymphocytes) and  
14 normal cells (ciliated and mucinous). At least 50 microscopic fields of the slides are then examined  
15 through a 1000x optical microscope.<sup>381</sup> NC may directly detect bacteria, viruses, and fungi, as well as  
16 biofilms, demonstrating that biofilm is present not only in infectious rhinitis, but also in inflammatory  
17 and/or immune-mediated diseases.<sup>383</sup> Specific cytological patterns can aid in classifying various forms of  
18 rhinitis, including AR, non-allergic rhinitis, and overlapping forms. The predominant cell type assessed  
19 by NC in AR is the eosinophil, followed by mast cells and basophils.<sup>384-387</sup> Elevated nasal eosinophil  
20 counts had an OR of 1.14 (95% CI 1.10-1.18) of identifying AR.<sup>385</sup> NC in poly-allergic patients showed a



1 more intense inflammatory infiltrate than in mono-allergic patients,<sup>386</sup> and demonstrated seasonal  
 2 changes of inflammatory cells, probably due to changes in allergen exposure.<sup>388</sup>

3  
 4 Studies on NC performance in diagnosing AR or non-allergic rhinitis are limited. **[TABLE X.E.-1]** In 2021, a  
 5 study on 387 patients assessed the diagnostic performance of NC showing 100% sensitivity (95% CI 97-  
 6 100), 49.6% specificity (95% CI 43-56%); positive predictive value (PPV) of 56% (95% CI 50-62%), and  
 7 negative predictive value (NPV) of 100% (95% CI 96-100%) with a non-allergic rhinitis prevalence of  
 8 39%.<sup>389</sup> The accuracy of the test was 69.5% (95% CI 64.6-74.0%). Such performance does not help to  
 9 identify when it might be valuable to use, particularly with poor PPV. The ability of the NC to identify  
 10 subjects affected by non-allergic rhinitis helps the clinician to inform the patient about the possibility or  
 11 the reason for the low efficacy of the AR therapy in mixed rhinitis. NC has been evolving in the last years,  
 12 and novel approaches have recently been proposed using nasal scraping to collect samples for  
 13 measurement of inflammatory mediators and cytokines.<sup>390,391</sup>

14  
 15 Nasal histology (NH) was the only technique to study nasal tissues and cells for many decades. Biopsy-  
 16 based investigations in the 1990's allowed researchers to define the role of the different inflammatory  
 17 cells in AR.<sup>392</sup> After a tissue sample is taken from the MT, it is placed in buffered formalin and then  
 18 stained with reagents (Giemsa, hematoxylin/eosin, periodic acid-Schiff, Masson trichrome, azure A, and  
 19 chloroacetate esterase).<sup>393,394</sup> The slides are then examined by an optical double-headed light  
 20 microscope.

21  
 22 NC made it possible to obtain similar information as NH but without the potential risk for bleeding and  
 23 allowing sequential sampling. Furthermore, following allergen challenge, NC revealed an increase in  
 24 inflammatory cells not detected by histology; thus suggesting that the nasal secretions, which the NC  
 25 collects together with the cells, and the nasal mucosa may represent two distinct cellular compartments  
 26 with different expression of inflammatory cells.<sup>395</sup> While NH is useful in pathophysiology research, it is  
 27 hardly feasible for routine clinical use due to the expertise in tissue sampling and biopsy processing  
 28 required.<sup>396</sup> **TABLE X.E.-2** shows studies on AR as evaluated by NH.

29  
 30 **Aggregate grade of evidence – nasal cytology:** C (Level 1: 1 study, level 3: 3 studies, level 4: 3 studies;  
 31 **TABLE X.E.-1)**

32 **Benefit:** Low costs and low invasiveness. Could help to detect eosinophils in non-allergic rhinitis and to  
 33 diagnose a mixed rhinitis.

34 **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 <sup>397</sup>	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 <sup>389</sup>	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 <sup>398</sup>	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 <sup>385</sup>	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 <sup>386</sup>	2015	4	Case-control	AR patients, n=83: -Monosensitized, n=35 -Polysensitized, n=48	Comparison of NC cell counts	Higher number of eosinophils (p=0.005) and mast cells (p=0.001) in polysensitized patients

Gelardi et al <sup>399</sup>	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 <sup>387</sup>	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)

1 LOE=level of evidence; NARES=non-allergic rhinitis with eosinophilia syndrome; NC=nasal cytology; NAR=non-  
2 allergic rhinitis; PPV=positive predictive value; NPV=negative predictive value; SPT=skin prick test; NPT=nasal  
3 provocation test; LAR=local allergic rhinitis; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval;  
4 NARMA=non-allergic rhinitis with mast cells; NARESMA=non-allergic rhinitis with eosinophils and mast cells;  
5 ARIA=Allergic Rhinitis and its Impact on Asthma  
6  
7

**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 <sup>400</sup>	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 <sup>401</sup>	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 <sup>402</sup>	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 <sup>403</sup>	2008	2	RCT	19 patients, ragweed pollen AR: -AIT, n=12 -Placebo, n=7	Allergen-induced CD4+, CD4+ CD25+, IL-10-, TGF-β-positive cells in nasal biopsies pre- and post-pollen season	-No histologic differences at baseline -After pollen season: AIT group had increase in CD4+CD25+ cells vs placebo group and vs baseline
Rak et al <sup>404</sup>	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 pre-season and compared to in-season AIT group
Plewako et al <sup>405</sup>	2002	2	RCT, single-blind	30 patients with grass pollen AR:	Anti-CD4, CD8, anti-eosinophil peroxidase, anti-	Eosinophil peroxidase-positive staining cells significantly increased in the placebo-treated

				-Omalizumab, n=19 -Placebo, n=11	human neutrophil lipocalin, IgE and FcεRI in nasal biopsies	group but not in the actively treated group
Pullerits et al <sup>406</sup>	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 <sup>407</sup>	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 <sup>408</sup>	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 <sup>409</sup>	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

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

#### 6 X.F. Rhinometry, acoustic rhinometry, and peak nasal inspiratory flow

7  
8 Subjective measures of nasal obstruction have proven difficult to quantify as patient perceptions vary  
9 widely and often do not correlate with examination findings. Therefore, objective measures of nasal  
10 obstruction have been developed which measure physiologic parameters (e.g., peak nasal  
11 inspiratory/expiratory flow [PNIF/PNEF], airflow resistance or rhinomanometry) and non-physiologic  
12 parameters (e.g., nasal cavity cross-sectional area and volume, or acoustic rhinometry). These measures  
13 may be utilized pre- and post-decongestion to distinguish between nasal obstruction secondary to  
14 dynamic or fixed structural deformities. Objective tests can also be used to assess the effectiveness of  
15 interventions or treatments, to provide objective data when clinical examination findings are not  
16 consistent with patient symptoms, to evaluate a response in NPT and as a medicolegal tool.

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

Rhinomanometry has certain disadvantages. It is expensive, time consuming and requires trained personnel.<sup>421</sup> 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.<sup>410,422</sup> 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.<sup>410,411</sup> Logarithmic measures taken during 4PR correlate significantly with subjective scores of nasal obstruction.<sup>423</sup> 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.<sup>424</sup> Further, acoustic rhinometry may overestimate the cross-sectional area of the posterior nasal cavity due to leakage into patent sinuses.<sup>425</sup>

**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

1 cause of obstruction.<sup>426-428</sup> A SRMA reported mean PNIF values in normal adults of 128.4L/min and  
 2 97.5L/min for obstructed adults.<sup>429</sup> However, standardized values have yielded inconsistent results due  
 3 to multiple confounding factors including patient effort, pulmonary status, nasal valve collapse,  
 4 smoking, height and recent physical exercise.<sup>430,431</sup> It would appear that PNEF correlates best with  
 5 symptoms of nasal obstruction.<sup>432</sup> PNIF/PNEF measures should be supported by subjective measures to  
 6 improve diagnostic accuracy.<sup>433</sup>

7  
 8 In summary, many papers have reported a lack of correlation between objective measures of nasal  
 9 patency and subjective perceptions of nasal obstruction.<sup>434</sup> Possible reasons for this discrepancy include  
 10 the failure to accommodate septal deviations and to evaluate individual nasal cavities separately and  
 11 measuring values at one single pressure rather than the entire breathing cycle. In fact, correlations  
 12 between objective and subjective measures have been found when nasal cavities were assessed  
 13 individually.<sup>423,434-437</sup> It has also been shown that patient symptoms do not necessarily correlate with the  
 14 degree of measured obstruction.<sup>423,435,438</sup> This discordance has been illustrated in studies that applied  
 15 substances such as menthol or local anaesthetic to the nasal mucosa, resulting in a subjective change in  
 16 nasal airflow with no corresponding change in resistance.<sup>439-445</sup> Therefore, nasal cavity volume, airflow  
 17 and resistance may only be a few of many factors contributing to the sensation of nasal obstruction.<sup>424</sup>  
 18 <sup>424</sup> Finally, whilst symptoms are paramount, objective measures of the nasal airway are useful beyond  
 19 correlating with patient symptoms. They are useful in identifying or excluding other causes of nasal  
 20 obstruction (such as psychiatric or sensory pathology), in nasal allergen challenges, in patient selection  
 21 for surgery, and in the research setting.<sup>446</sup>

22  
 23 **Aggregate grade of evidence – rhinomanometry:** B (Level 1: 2 studies, level 2: 2 studies, level 3: 5  
 24 studies, level 4: 4 studies, level 5: 6 studies; **TABLE X.F.-1**).

25 **Benefit:** Rhinomanometry is useful to improve patient selection for surgery, distinguish between  
 26 structural and functional causes of nasal obstruction, diagnose nasal valve collapse, clarify conflicting  
 27 symptoms and exam findings, use as a medicolegal tool and in nasal allergen challenges. Four-phase  
 28 rhinomanometry correlates with subjective scores.

29 **Harm:** Low. Rhinomanometry has limited effectiveness in patients with complete nasal obstruction or  
 30 septal perforation. The equipment is not portable and therefore requires a clinic visit and trained staff.  
 31 The procedure may be considered time consuming.

32 **Cost:** High.

33 **Benefits-harm assessment:** Benefits outweigh harm.

34 **Value judgments:** For some patients, it may be important to avoid unnecessary costs in the diagnosis of  
 35 AR; therefore, this procedure is less preferred.

36 **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 <sup>424</sup>	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 <sup>447</sup>	2008 <sup>#</sup>	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 <sup>448</sup>	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 <sup>449</sup>	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 <sup>450</sup>	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 <sup>451</sup>	2019	3	Prospective validating cohort	AR and asthma, AR without asthma, n=24	NAC, cytokines, ARM at 3cm, RM, FEV <sub>1</sub> , TNSS, NSS	-No significant association between RM and symptom scores -RM had poor-fair reproducibility, not a practical test
Garcia et al <sup>436</sup>	2016 <sup>#</sup>	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 <sup>452</sup>	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 <sup>434</sup>	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 <sup>453</sup>	2021	4	Case-control	AR or AR+asthma, 6-12 years old, gender matched controls, n=160	nNO, FEV <sub>1</sub> , 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 <sup>454</sup>	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 <sup>455</sup>	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 <sup>435</sup>	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 <sup>456</sup>	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 <sup>412</sup>	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 <sup>457</sup>	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 <sup>292</sup>	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 <sup>458</sup>	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 <sup>459</sup>	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

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

1 Evaluation; AAR=anterior active rhinomanometry; Reff=effective resistance; VR=vertex resistance; L=logarithmic  
 2 value; NAC=nasal allergen challenge; FEV<sub>1</sub>=forced expiratory volume in 1 second; TNSS=Total Nasal Symptom  
 3 Score; NSS=nasal symptom score; CFD=computational fluid dynamics; CT=computed tomography; mCSA=mean  
 4 cross-sectional area; 4PR=four phase rhinomanometry; NSD=nasal septal deviation; nNO=nasal nitric oxide;  
 5 ECP=eosinophil cationic protein; NPT=nasal provocation test; MCCT=mucociliary clearance time; POCT=point of  
 6 care test; FeNO=fractional exhaled nitric oxide  
 7 \*LOE downgraded due to failure to include relevant studies and for misclassifying one included study  
 8 \*\*LOE downgraded as not blinded and study was in-vitro using a nasal model which excludes the elasticity of the  
 9 human nose which impacts nasal obstruction throughout all phases of nasal breathing  
 10 \*\*\*LOE downgraded as not all patients in the AR group were diagnosed with SPT or RAST  
 11 \*\*\*\*LOE downgraded as only included 3 studies  
 12 \*\*\*\*\*LOE downgraded due to the limited number of patients  
 13 \*\*\*\*\*LOE downgraded as retrospective and not blinded  
 14 #paper not included in systematic review.<sup>448</sup>  
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**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 <sup>448</sup>	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 <sup>460</sup>	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 <sup>451</sup>	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 <sub>1</sub> , TNSS, NSS	-ARM closely associated with symptom scores -ARM had excellent reproducibility
Aksoy et al <sup>437</sup>	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 <sup>436</sup>	2016 <sup>#</sup>	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 <sup>2</sup>
Isaac et al <sup>461</sup>	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 <sup>455</sup>	2016	4	Case-controlled validation	Children with AR and controls undergoing NPT, 7-18 years old, n=40	ARM, RM	Comparing ARM to AAR, cut-off to end NPT represented by reduction of 19-21% in nasal volume in the first 5cm had the highest sensitivity and specificity
Wandalsen et al <sup>462</sup>	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 <sup>435</sup>	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 <sup>457</sup>	2018	5	Position paper	Patients with nasal obstruction (including AR)	Evaluation of nasal obstruction	ARM better than RM for NPT
Ozturk et al <sup>463</sup>	2004	5****	Prospective case-control intervention	-Children aged 7-18 years with grass pollen AR and age-matched healthy controls, n=52 -Impact of triamcinolone 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 <sup>448</sup>

- 1 LOE=level of evidence; AR=allergic rhinitis; ARM=acoustic rhinometry; PROM=patient reported outcome measure;
- 2 NAC=nasal allergen challenge; NOSS=Lebel nasal ocular symptom score; PPV=positive predictive value;
- 3 NPV=negative predictive value; RM=rhinomanometry; FEV<sub>1</sub>=forced expiratory volume in 1 second; TNSS=Total
- 4 Nasal Symptom Score; NSS=nasal symptom score; CCCRC=Connecticut Chemosensory Clinical Research Center;
- 5 CFD=computational fluid dynamics; CT=computed tomography; NOSE=Nasal Obstruction Symptom Evaluation;
- 6 VAS=visual analog scale; mCSA=mean cross-sectional area; NPT=nasal provocation test; AAR=anterior active
- 7 rhinomanometry; MCCT=mucociliary clearance time
- 8 \*LOE downgraded due to failure to include relevant studies and for misclassifying one included study.
- 9 \*\*Study used unvalidated subjective scoring systems, was not blinded and only 22% of population had AR
- 10 \*\*\*LOE downgraded as no data provided for correlation analysis
- 11 \*\*\*\*LOE downgraded due to uneven groups

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3**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 <sup>429</sup>	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 <sup>448</sup>	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 <sup>433</sup>	2021	3***	Cross-sectional, blinded	Rhinitis and control, n=256	PNIF, SNOT-22, VAS	-PNIF cut-off of $\leq 95$ L/min diagnostic for AR (72% sensitivity, 80% specificity, 64% PPV, 76% NPV) -Diagnostic accuracy of PNIF increased to 97.6% when combined with SNOT-22 or VAS -Weak correlation between PNIF and SNOT-22 and VAS
Sikorska-Szaflik and Sozanska <sup>464</sup>	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 <sup>465</sup>	2018	3	Non controlled, non-randomized clinical trial	AR undergoing AIT, n=19	TNSS, PNIF	Modest correlation between TNSS and PNIF
Boelke et al <sup>289</sup>	2017 <sup>##</sup>	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 <sup>428</sup>	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 <sup>457</sup>	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
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1 LOE=level of evidence; AR=allergic rhinitis; PROM=patient reported outcome measure; VAS=visual analog scale;  
 2 NOSE=Nasal Obstruction Symptom Evaluation; PNIF=peak nasal inspiratory flow; SRMA=systematic review and  
 3 meta-analysis; SNOT-22=Sinonasal Outcome Test (22 item); PPV=positive predictive value; NPV=negative  
 4 predictive value; QOL=quality of life; KINDL-R=generic assessment of health related quality of life for children and  
 5 adolescents; AIT=allergen immunotherapy; TNSS=Total Nasal Symptom Score; PNEF=peak nasal expiratory flow;  
 6 NMCCT=nasal mucociliary clearance time; MCID=minimal clinically important difference  
 7 \*LOE downgraded due to heterogeneity of included studies  
 8 \*\*LOE downgraded due to failure to include relevant studies and for misclassifying one included study  
 9 \*\*\*LOE downgrade due to vague inclusion criteria  
 10 \*\*\*\*LOE downgraded as study involved grass pollen exposure, yet participants were atopic to grass and/or birch  
 11 pollen and/or HDM  
 12 \*\*\*\*\*LOE downgraded due to lack of blinding and significant gender asymmetry  
 13 ## Paper excluded from both systematic reviews<sup>429,448</sup>  
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16 **X.G. Exhaled nitric oxide**

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 18 NO is a volatile gas which functions as a vasodilator, bronchodilator, neurotransmitter, and  
 19 inflammatory mediator in the airway.<sup>466</sup> NO is formed in the upper and lower respiratory tract with high  
 20 concentrations found in the nasal cavity and paranasal sinuses,<sup>467-469</sup> and NO synthase is upregulated in  
 21 ciliated respiratory epithelium and inflammatory cells in atopic patients. In adults, sex, menstrual cycle,  
 22 pregnancy, recent consumption of high nitrate foods, recent exercise, and tobacco exposure may modify  
 23 NO levels.<sup>470</sup> Height and body surface area may also modify NO in pediatric population.<sup>470-473</sup>  
 24

25 **Fractional exhaled nitric oxide (FeNO).** FeNO is a measurement of NO in orally exhaled breath. The  
 26 American Thoracic Society published recommendations for FeNO measurement.<sup>474</sup> Briefly, the  
 27 participant inhales through a NO filter to remove ambient NO. Then exhalation through a flow restrictor  
 28 results in airflow limitation and creates a positive pressure exhalation, closing the velum and preventing  
 29 contamination of the measurement with nasal NO. The orally exhaled breath is analyzed.  
 30

31 Although FeNO is highly variable in the healthy population, elevated levels are indicative of various  
 32 types of inflammation in the respiratory tract. Elevated levels are found in AR, asthma, COPD,  
 33 bronchiectasis, pulmonary sarcoidosis, and acute lung allograft rejection.<sup>475</sup> FeNO is primarily utilized in  
 34 the diagnosis and monitoring of therapeutic response and compliance in asthma,<sup>476-479</sup> but recent  
 35 research has attempted to expand this testing for diagnosis of AR. Small studies have shown increased  
 36 FeNO in AR patients, especially those with concomitant asthma.<sup>480-483</sup> This finding was also seen in a

1 large population study from the Netherlands which showed independent association of elevated FeNO  
2 in patients with positive skin testing, eczema, or AR.<sup>475</sup> [TABLE X.G.-1]

3  
4 FeNO is positively correlated with symptoms of AR and allergic sensitization in pediatric patients, with  
5 one study showing a sensitivity and specificity of 81.1% and 78.6%, respectively, at a FeNO cut-off level  
6 of 18.4 ppb.<sup>473</sup> Pediatric patients also show decreased FeNO after appropriate medical therapy.<sup>484-486</sup>

7  
8 There are potential cofounders when using FeNO as a biomarker. First, a wide variety of normal results  
9 for FeNO are possible in a given population and are influenced by age, sex, smoking status, and lab  
10 sampling.<sup>487</sup> Additionally, there is no agreed upon cut off to indicate an abnormal result for the diagnosis  
11 of AR versus asthma.<sup>474</sup>

12  
13 **Nasal nitric oxide (nNO).** Due to the non-invasive nature of NO measurement, there is interest in using  
14 this tool to differentiate allergic and non-allergic rhinitis. nNO is measured by chemiluminescence. A  
15 small catheter is placed into one nostril and ambient nasal gas is measured while the patient orally  
16 exhales through a flow resistor tube to ensure the velum is closed and only nasal cavity gas is  
17 measured.<sup>488</sup> nNO is reduced in several rhinologic diseases, including primary ciliary dyskinesia and  
18 cystic fibrosis, but is elevated in AR.<sup>484,488-490</sup>

19  
20 Three small case-control studies have shown significant increase in nNO when comparing non-atopic  
21 healthy adults with atopic adults without asthma.<sup>489,491,492</sup> Additionally, two systematic reviews (total  
22 n=953 and n=4093, respectively) showed significant increase in nNO in healthy controls versus patients  
23 with AR.<sup>493,494</sup> However, these results conflict with other small case control studies showing no  
24 difference.<sup>495-497</sup> There is a reported nNO increase during pollen season in AR patients,<sup>492</sup> and reduction  
25 after appropriate medical treatment of atopy.<sup>470</sup> [TABLE X.G.-2]

26  
27 Various factors influence nNO values including medication use, recent allergen exposure, recent viral  
28 respiratory infection, and concomitant asthma. Additionally, there is no standardized application of nNO  
29 measurement, with groups performing testing on a variety of analyzers with variations in sampling flow  
30 rate and carbon dioxide monitoring.<sup>498</sup> Even small differences in testing application dramatically changes  
31 captured NO, making comparisons across research groups and establishment of normative values  
32 challenging.<sup>488</sup> There is currently no agreed upon cut off point for the diagnosis of AR.

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**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 <sup>482</sup>	2020	4	Case-control	Pediatric patients with: -Allergic asthma, n=29 -Asthma+AR, n=38 -AR, n=43 -Healthy controls, n=28	-Laboratory evaluation (eosinophil, IgE) -SPT -Spirometry -FeNO	-Elevated FeNO in allergic asthma and asthma+AR vs AR and healthy controls -No difference in FeNO between AR and healthy controls
Choi et al <sup>483</sup>	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 <sup>480</sup>	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 <sup>499</sup>	2008	4	Case-control	-Healthy children -Asymptomatic atopy -AR without recent exacerbation	-Allergy sensitization -FeNO -Spirometry	-All groups had statistically higher FeNO vs controls -FeNO higher in patients with active AR, allergic asthma



				-AR with one exacerbation in last month -Allergic asthma without rhinitis -Allergic asthma with rhinitis -All groups, n=15		without rhinitis, and allergic asthma and rhinitis vs asymptomatic atopy and AR without recent exacerbation
Van Asch et al <sup>475</sup>	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 <sup>473</sup>	2003	4	Cohort	-Australian birth cohort -Participants examined at age 11, n=155	-Spirometry -FeNO -Eosinophils -SPT	-Elevated FeNO in children with asthma, atopy, recent wheeze vs controls -FeNO >18.4 ppb had 81.1% sensitivity and 78.6% specificity for diagnosis of AR
Martin et al <sup>491</sup>	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

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

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**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 <sup>494</sup>	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 <sup>493</sup>	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
Kalpakioglu et al <sup>492</sup>	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 <sup>489</sup>	2012	4	Case-control	-AR, n=35 -Healthy controls, n=34	-nNO -FeNO	-nNO significantly higher in AR -FeNO significantly higher in

					-Laboratory evaluation (eosinophils, IgE)	AR
Moody et al <sup>496</sup>	2006	4	Case-control	-Perennial AR -Non-atopic subjects	-Validated symptom questionnaire -FeNO -nNO	-nNO levels were not elevated in subjects with perennial AR vs non-atopics -nNO was higher in HDM and cat allergic subjects
Maniscalco et al <sup>495</sup>	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 <sup>497</sup>	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 <sup>486</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; nNO=nasal nitric oxide; AR=allergic rhinitis;  
2 NAR=non-allergic rhinitis; TNSS=Total Nasal Symptom Score; FeNO=fractional exhaled nitric oxide;  
3 IgE=immunoglobulin E; HDM=house dust mite; NO=nitric oxide  
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## 6 X.H. Use of validated subjective instruments and patient reported outcome measures

7  
8 Validated clinical outcome surveys (VCOS) are simple, effective tools that may be used to evaluate and  
9 screen patients with suspected or known AR. They can be helpful in establishing a diagnosis of AR,  
10 assessing severity, or evaluating treatment response. Typical survey questions inquire about symptoms  
11 such as congestion, rhinorrhea, and sneezing; the questions may be referring to that instant, or to a time  
12 period of days or weeks. Although objective testing such as allergy skin testing and sIgE serology can  
13 help confirm or rule out the diagnosis, clinical history is indispensable in the evaluation of AR.<sup>500</sup> In  
14 resource-poor settings, SPT, serologic testing, or other advanced technologies, may not be available to  
15 confirm the diagnosis.<sup>52,131,204,501</sup> Furthermore, VCOS offer a more structured and standardized means of  
16 obtaining the clinical history and assessing treatment response.  
17

1 These patient reported outcome measures focus on varying aspects of AR.<sup>502</sup> They may primarily be  
2 symptom severity surveys such as the TNSS, or health-related QOL questionnaires such as the RQLQ.  
3 Surveys of medication usage (Daily Medication Score), disease prediction (Respiratory Allergy  
4 Prediction), and disease control (Rhinitis Control Test) are also available. VCOS can be cross-validated  
5 with more objective tools such as NPT and SPT. These instruments are routinely utilized in clinical trials  
6 as objective, standardized measures to assess the efficacy of AR medications and are widely accepted in  
7 the academic allergy and rhinology community.<sup>503-508</sup> Recently, VCOS have been adapted for use in  
8 smartphone applications that track AR symptomatology and medication use.<sup>509-514</sup>

9  
10 **TABLE X.H.-1** lists several frequently used VCOS, outlining the targeted disease, number of questions,  
11 score range, symptoms and/or medication questions included, and the context in which each is typically  
12 employed.<sup>515-533</sup> The TNSS is typically administered as a daily survey comprised of only 4 questions  
13 focusing on runny nose, nasal itching, sneezing, and congestion. Some studies have used the TNSS as a  
14 reflective score calculated as the average of both the 12-hour nighttime and 12-hour daytime average  
15 (rTNSS). The TNSS score can be combined with questions about rescue medication use to yield the Daily  
16 Combined Score and the Total Combined Rhinitis Score. Both have been used in many therapeutic  
17 intervention studies. The RQLQ is a more comprehensive survey that asks the patient to reflect upon the  
18 past week and includes global QOL questions.<sup>534</sup> It can be administered either in the office or at home so  
19 that it may be easier to obtain daily scores. A limitation of this test may be potential recall bias  
20 attributable to the 7-day recall period. **[TABLE X.H.-2]**

21  
22 The Control of Allergic Rhinitis and Asthma Test (CARAT-10) evaluates rhinoconjunctivitis and asthma  
23 symptoms with a recall period of the preceding 4 weeks giving a broader evaluation of seasonal  
24 symptom control.<sup>523</sup> The Respiratory Allergy Prediction (RAP) test is a 9-question survey incorporating  
25 upper and lower respiratory queries as well as a question about medication use. It was validated in a  
26 study in which primary care physicians used it as a screening tool to determine whether patients needed  
27 referral for allergy testing.<sup>530</sup>

28  
29 If conjunctivitis is to be assessed simultaneously with rhinitis symptoms, then the Rhinitis Total  
30 Symptom Score (RTSS) can be combined with Rescue Medication Score (RMS) to yield the combined  
31 score (CS).<sup>531</sup> The Rhinosinusitis Disability Index (RSDI) was initially developed for CRS, but was validated

1 for AR, non-allergic rhinitis and nasal obstruction. It has the unique property of evaluating sexual  
 2 function in AR patients.<sup>532,533</sup> The SNOT-22 has also been validated for use in AR patients.<sup>535</sup>

3  
 4 In summary, VCOS are simple, effective tools that may be used to assist in making the diagnosis of AR,  
 5 and in evaluating the efficacy of various therapies.

6  
 7 **Aggregate grade of evidence:** B (Level 1: 2 studies, level 2: 2 studies, level 3: 5 studies, level 4: 13  
 8 studies; **TABLE X.H.-2**)

9 **Benefit:** Validated surveys offer a simple point-of-care option for screening and tracking symptoms,  
 10 QOL, and control of allergic disease.

11 **Harm:** Minimal. Time to complete survey. Potential risk of misdiagnosis when based on survey data  
 12 alone.

13 **Cost:** No financial burden to patients. Some fees associated with validated tests used for clinical  
 14 research.

15 **Benefits-harm assessment:** Preponderance of benefit over harm. Risk of misdiagnoses leading to  
 16 unnecessary additional testing. Likewise, there is a risk that false negative responses may lead to delay  
 17 in testing and further management.

18 **Value judgments:** Validated surveys may be used as a screening tool and primary or secondary outcome  
 19 measure.

20 **Policy level:** Recommendation.

21 **Intervention:** Validated surveys may be used to screen for AR, follow treatment outcomes and as a  
 22 primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathological  
 23 scenarios.

24  
 25

**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
<b>TNSS:</b> Total Nasal Symptom Score	AR	4	Yes	No	0-12	Simple daily symptom score to evaluate AR severity and control; used in clinical trials
<b>DMS:</b> Daily Medication Score	AR, AC, asthma	Varies	No	Yes	0-36 <sup>a</sup>	Varies depending on medication scoring
<b>DCS:</b> Daily Combined Score	AR, AC, asthma	Varies	Yes	Yes	0-48 <sup>a</sup>	Combined symptom and medication score for clinical trials
<b>TCRS:</b> Total Combined Rhinitis Score	AR	Varies	Yes	Yes	0-24 <sup>a</sup>	The sum of the combined symptoms medication scores
<b>Mini-RQLQ:</b> Mini-Rhinoconjunctivitis Quality of Life Questionnaire	Rhinoconjunctivitis	14	Yes	No	0-84	Shortened version of RQLQ often used in clinical trials
<b>RQLQ:</b> Rhinoconjunctivitis	Rhinoconjunctivitis	28	Yes	No	0-168	Reflective assessment of previous week's

Quality of Life Questionnaire						symptoms; often used in clinical trials
<b>RhinAsthma</b> (RhinAsthma children also available)	Rhinitis, asthma	30	Yes	No	120	Able to differentiate patients with rhinitis from those with both rhinitis and asthma
<b>VAS:</b> Visual Analog Scale	Rhinitis	1 or more	Yes	No	0-10 cm	Tool may be used to evaluate multiple symptomatology
<b>RCAT:</b> Rhinitis Control Assessment Test	AR, NAR	6	Yes	No	6-30 <sup>b</sup>	Self-assessment of rhinitis symptom control
<b>ARCT:</b> Allergic Rhinitis Control Test	AR	5	Yes	Yes	5-25 <sup>b</sup>	Self-assessment of ongoing AR symptoms control
<b>CARAT-10:</b> Control of Allergic Rhinitis and Asthma Test; CARATKids available for children	AR, NAR, asthma	10	Yes	Yes	0-30 <sup>b</sup>	Used to compare groups in clinical trials
<b>ACS:</b> Allergy Control Score	Rhinitis, AC, asthma	10+ meds	Yes	Yes	0-60	Combined tool used for clinical trials and daily clinical practice
<b>RC-ACS:</b> Rhinoconjunctivitis Allergy Control Score	Rhinitis, AC	7+ meds	Yes	Yes	0-42	Similar to ACS but without asthma related questions
<b>RAP:</b> Respiratory Allergy Prediction	AR, asthma	9+ meds	Yes	Yes	0-9	Used to determine the need for referral and additional testing
<b>SFAR:</b> Symptom Score for Allergic Rhinitis	AR	8	Yes	No	0-16	Weighted score used to detect prevalence of AR
<b>RMS:</b> Rescue Medication Score	Rhinoconjunctivitis	Meds	No	Yes	0-3	Evaluates medication use only
<b>RTSS:</b> Rhinoconjunctivitis Total Symptom Score	Rhinoconjunctivitis	6	Yes	No	0-18	Evaluates symptoms only
<b>CS:</b> Combined Score	Rhinoconjunctivitis	6+ meds	Yes	Yes	0-3	Combined scores of RTSS/6 + RMS/2
<b>RSDI:</b> Rhinosinusitis Disability Index	AR, CRS, NAR	30	Yes	No	0-120	Physical, function, emotional subscales and total scores
<b>SNOT-22:</b> Sinonasal Outcome Test, 22-item	CRS, AR	22	Yes	No	0-110	Includes rhinologic and non-rhinologic domains
<b>Global Assessment:</b> Global Assessment of Severity of Allergy	Total nasal and non-nasal symptoms	1	Yes	No	1-7	Single question about rhinitis severity

1

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

1 <sup>a</sup>Maximum score may vary depending on specific number of symptom related questions and specific medication  
 2 score included.

3 <sup>b</sup>Higher score equates to better control of disease. A score of 0 denotes zero control of symptoms.

4

5 **TABLE X.H.-2 Evidence table – Use of validated clinical outcome surveys for the diagnosis of allergic**  
 6 **rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Calderon et al <sup>536</sup>	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 <sup>507</sup>	2014	1	Systematic review	Seasonal AR	Comparison of scoring systems used in clinical trials investigating SLIT efficacy for seasonal AR	Multiple differences in trial scoring methods/design, making comparison difficult
Fonseca et al <sup>523</sup>	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 <sup>520</sup>	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 <sup>512</sup>	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 <sup>509</sup>	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 <sup>530</sup>	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 <sup>522</sup>	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 <sup>524</sup>	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 <sup>526</sup>	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 <sup>510</sup>	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 <sup>535</sup>	2020	4	Case series	Patients with AR	SNOT-22, EQ-5D, RCAT	SNOT-22 reliable and responsive in patients with AR
Kupczyk et al <sup>537</sup>	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 <sup>527</sup>	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 <sup>538</sup>	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 <sup>511</sup>	2017	4	Case series	1136 app users	VAS-global, VAS-nasal, VAS-ocular, VAS-asthma, VAS-work	-Significant correlation between VAS-global and VAS-work -Significant correlation between VAS-work and WPAI-AS
Emons et al <sup>539</sup>	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 <sup>508</sup>	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 <sup>518</sup>	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 <sup>515</sup>	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 <sup>521</sup>	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 <sup>525</sup>	2003	4	Case series	148 consecutive patients: -46 asthma -53 ARC -49 asthma+ARC	RHINASTHMA	-RHINASTHMA differentiates patients with rhinitis from those with rhinitis+asthma -In stable condition, RHINASTHMA showed good reliability

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

13  
14



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## 1 XI. Management

### 3 XI.A. Allergen avoidance and environmental controls

#### 4 XI.A.1. House dust mites

5  
6 HDMs are a common trigger of AR.<sup>1</sup> Therefore, reducing exposure to HDM through physical barriers and  
7 chemical treatments are potentially important options in the management of AR.<sup>1-5</sup> [TABLE XI.A.1.]

8  
9 Physical techniques for HDM reduction, including heating, ventilation, barrier methods, air filtration,  
10 vacuuming and ionizers, have shown inconsistent results for the treatment of AR.<sup>6-12</sup> While several  
11 interventions have reduced the concentration of environmental HDM antigens,<sup>6-10</sup> an associated  
12 improvement in clinical symptoms has not been reliably demonstrated. Ghazala et al<sup>6</sup> and Terreehorst  
13 et al<sup>10</sup> demonstrated a reduction in HDM antigen concentration with impermeable bedding as an  
14 isolated intervention but found no clinical benefits. Similar findings were reported by Antonicelli et al<sup>13</sup>  
15 following a trial of high-efficiency particulate air (HEPA) filtration.

16  
17 Acaricides in household cleaners have been utilized as a chemical technique to reduce HDM  
18 concentration. Geller-Bernstein et al<sup>14</sup> evaluated an acaricide spray in the bedrooms of patients with  
19 HDM sensitization, demonstrating improved mean symptom scores versus control patients without  
20 acaricide. Similar findings were reported by Kneist et al.<sup>7</sup> Using a cross-over study design, Chen et al<sup>15</sup>  
21 investigated an acaricide containing bag placed beneath bed mattresses in children with AR and asthma,  
22 reporting improved AR symptom scores and disease specific QOL (measured using the RQLQ) for those  
23 in the intervention group compared to control.

24  
25 Overall, no serious adverse effects were reported from the evaluated interventions. None of the studies  
26 evaluated cost-effectiveness.

27  
28 Recent findings, as well as a 2010 Cochrane review<sup>16</sup> suggest acaricides, either as a single measure or in  
29 combination with other measures, are the most effective intervention for reducing HDM levels and  
30 improving AR symptoms.

31  
32 **Aggregate grade of evidence:** B (Level 1: 2 studies, level 2: 12 studies; TABLE XI.A.1)

33 **Benefit:** Potential improvement in AR symptoms and QOL with reduced concentration of environmental  
34 HDM antigens.

35 **Harm:** None.

- 1 **Cost:** Mild to moderate. However, cost-effectiveness was not evaluated.
- 2 **Benefits-harm assessment:** Benefit outweighs harm.
- 3 **Value judgments:** There is supporting evidence for the use of acaricides in reducing HDM concentration
- 4 in children who have AR coexistent with asthma. In adults and children without concomitant asthma,
- 5 the use of acaricides with/without bedroom-based control programs for reducing HDM concentration
- 6 are promising, but further, high-quality studies are needed to evaluate clinical outcomes.
- 7 **Policy level:** Option.
- 8 **Intervention:** Acaricides used independently or alongside environmental control measures such as air
- 9 filtration devices, could be considered as options in the management AR.

10

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Nurmatov et al <sup>1</sup>	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 <sup>16</sup>	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 <sup>15</sup>	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 <sup>12</sup>	2019	2	Single-blind parallel RCT	-Children with AR, daily vacuuming of room and bed mattress, n=20 -Children with AR, daily vacuuming of room only, n=20	-Symptom scores -Vacuum dust weight -HDM (Der p 1 and f 1) concentration	-Symptoms were lower in the intervention group after the 2-week trial -Weight of dust collected was less for the intervention group -Concentrations of Der p 1 and f 1 did not change in either group
Berings et al <sup>11</sup>	2017	2	Pilot, double blind, crossover RCT	-Adults with AR and probiotic	-HDM (Der p 1) concentration -Symptom scores	-No difference in HDM levels between

				impregnated bedding, n=20 -Adults with AR and placebo bedding, n=20	-QOL scores -Use of reliever medication	intervention and placebo bedding -Differences in secondary outcome measures between intervention and placebo not significant
Stillerman et al <sup>17</sup>	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 <sup>18</sup>	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 <sup>6</sup>	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 <sup>10</sup>	2003	2	Double-blind RCT	-Children with atopy and HDM impermeable bedding -Children with atopy without HDM impermeable bedding	-Rhinitis-specific VAS -Daily symptom score -Nasal allergen provocation -Der p 1 and Der f 1 concentration	Impermeable encasings significantly reduce allergen concentration, without difference in symptoms or nasal provocation testing
Moon and Choi <sup>8</sup>	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 <sup>14</sup>	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 <sup>7</sup>	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 <sup>13</sup>	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 <sup>9</sup>	1990	2	Double-blind crossover RCT	-Adults with atopy and Enviracare HEPA filtration -Adults with atopy and placebo filtration	-Particulate counts in bedroom air -Symptom and medication scores -Patients' subjective response to treatment	Enviracare HEPA filtration associated with improved particulate counts and symptom/medication scores

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

5

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## 7 XI.A.2. Cockroach

8

9 Measures to control cockroach allergen concentrations within the home environment have been  
10 targeted at eliminating infestations and abating cockroach allergen. The three main intervention  
11 strategies used are: (1) education-based methods consisting of house cleaning measures and sealing  
12 cracks and crevices in highly infested areas; (2) physical methods using insecticides or bait traps; and (3)  
13 treatments combining educational-based interventions with physical methods.<sup>19</sup> The greatest challenges  
14 in controlling cockroach infestation and reducing allergen concentrations are in densely populated  
15 inner-city areas that contain multi-occupant housing.<sup>20,21</sup>

16

17 Most studies contain one or more interventions focused on German cockroach (*Blattella germanica*  
18 antigen 1 and 2 [Bla g 1, Bla g 2]) allergen levels,<sup>22-30</sup> however some studies included treatments  
19 targeted at reducing multiple allergens (e.g., HDM, cockroach, rodent, cat, dog).<sup>31,32</sup> The majority of  
20 studies were RCTs designed to evaluate the efficacy of specific environmental control measures in  
21 reducing environmental allergens. These studies used a variety of interventions that included home-

1 based education as well as physical methods such as pest control and insecticides.<sup>22-27,31,32</sup> Although Bla  
2 g 1 and Bla g 2 allergen levels were reduced below 8U/g in some homes, clinical benefits in sensitized  
3 individuals were not achieved.<sup>23,26-29</sup> One study found Bla g 1 concentrations could be decreased below  
4 targeted thresholds for most apartments using a building-wide cockroach control program.<sup>30</sup> **[TABLE**  
5 **XI.A.2.]**

6  
7 The most effective treatment for eliminating infestation and reducing allergen load was professional  
8 pest control.<sup>24</sup> In one study that monitored cockroach populations and allergen concentrations over a  
9 12-month period, findings revealed that insecticide bait traps placed by professional entomologists were  
10 more effective in reducing cockroach populations and cockroach allergen compared to dwellings that  
11 received numerous commercial applications of insecticide formulations to baseboards, cracks, and  
12 crevices.<sup>22</sup> Bait traps, including labor and monitoring costs, were estimated to be less expensive than  
13 commercially applied insecticide sprays.<sup>22</sup> The expense of integrated home management that consists of  
14 professional cleaning, education, and pest control was not found to be cost-effective. Thus, most  
15 investigators focused on assessing the efficacy of single interventions, such as extermination alone, in  
16 assessing potential cost benefits.<sup>24,33</sup> Arbes et al<sup>24</sup> and Sever et al<sup>33</sup> have noted that these measures were  
17 not found to be cost effective. Detailed information may be found in their publications, as this  
18 discussion was beyond the scope of this section. Families often had difficulty adhering to home-based  
19 intervention regimens over the course of the study, which reduced the efficacy of these treatments and  
20 subsequently resulted in increased cockroach allergen levels.<sup>27</sup>

21  
22 Although cockroach count could be significantly reduced in single-family homes using bait traps,  
23 reinfestation and high allergen levels remained an ongoing problem in multi-family buildings.<sup>29</sup>  
24 Effectively controlling cockroach infestation and allergen levels within multi-family buildings and  
25 apartments requires implementation of a building-wide management program.<sup>30</sup> Thus, it is difficult to  
26 dramatically reduce cockroach allergen levels in the home unless a significant reduction in cockroach  
27 counts is maintained over time.<sup>22</sup> Most studies did not include clinical endpoints. However, those that  
28 did evaluate clinical outcomes focused on asthma symptoms, hospitalizations or emergency room visits,  
29 and medication usage.<sup>31,32</sup> No studies included any assessment of symptoms or clinical endpoints  
30 associated with AR.

31

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Le Cann et al <sup>19</sup>	2017	1	SR of RCTs	Home group interventions: -Education-based methods -Physical methods -Combination of both Interventions, also included control measures for multiple allergens (HDM, CR, cat, dog)	-Allergic and respiratory symptoms (cough, daytime symptoms, wheeze, nighttime symptoms) -Lung function -Medication use -Urgent care use for respiratory symptoms	Supported effectiveness of home interventions in decreasing respiratory symptoms and urgent care use
Sever et al <sup>22</sup>	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 <sup>31</sup>	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 <sup>23</sup>	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 <sup>24</sup>	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 <sup>32</sup>	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 <sup>25</sup>	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 <sup>26</sup>	2001	2	RCT	-Professional cleaning; insecticide bait traps, sodium hypochlorite	No direct clinical endpoints	-Professional extermination treatments reduced CR numbers and

				-Control homes: no cleaning, extermination, or bleach solution		reduced median allergen levels by 80-90% -Cleaning solution did not add any improvements -Unclear if this level of reduction is sufficient to have clinical benefits in CR-sensitized individuals
Gergen et al <sup>27</sup>	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 <sup>30</sup>	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 <sup>29</sup>	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 <sup>28</sup>	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
--	--	--	--	--	--	--

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

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XI.A.3. Pets

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

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

- 1 **Benefit:** Decreased environmental antigen exposure with possible reduction in symptoms and  
 2 secondary prevention of asthma.  
 3 **Harm:** Emotional distress caused by removal of household pets. Financial and time costs of potentially  
 4 ineffective intervention.  
 5 **Cost:** Low to moderate.  
 6 **Benefits-harm assessment:** Equivocal.  
 7 **Value judgments:** While several studies have demonstrated an association between environmental  
 8 controls and reductions in environmental antigens, only a single, multi-modality RCT has demonstrated  
 9 clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity. The secondary  
 10 prevention and treatment of asthma in sensitized individuals must also be considered.  
 11 **Policy level:** Option.  
 12 **Intervention:** Pet avoidance and environmental control strategies, particularly multi-modality  
 13 environmental controls among patients with diagnosed Fel d 1 sensitivity, may be presented as an  
 14 option for the treatment of AR.  
 15  
 16

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bjornsdottir et al <sup>39</sup>	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 <sup>40</sup>	1998	2	RCT	-Cat sensitive adults with HEPA filter -Cat sensitive adults with placebo	-Cat allergen levels (airborne and settled dust) -Symptom scores -Medication scores -Spirometry	HEPA filters associated with reduced airborne, but not settled dust, cat allergen levels without effect on disease activity
Hodson et al <sup>42</sup>	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 <sup>41</sup>	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 <sup>34</sup>	2015	4	Cohort	Patients with diagnosed allergy	-Sensitization to household animals -Compliance with avoidance	Avoidance recommendations may be impractical with high rates of sensitization, indirect

					recommendations and EC	exposure, and low rates of compliance
--	--	--	--	--	------------------------	---------------------------------------

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

#### 3 4 5 [XI.A.4. Rodents](#)

6  
7 Only a few high-quality studies have been published on rodent (i.e., mouse, rat, guinea pig, and  
8 hamster) avoidance and interventions to reduce exposure specifically related to AR. Most studies focus  
9 on changes in mouse allergen levels and asthma-related outcomes in inner-city children, which may not  
10 directly correlate with AR symptoms in other populations.<sup>31,43-47</sup> While some RCTs have been conducted  
11 for mouse allergen, none have been performed for non-mouse rodent allergens. Demonstrating efficacy  
12 of rodent avoidance or interventions targeted to reduce exposure is difficult as most environmental  
13 interventions lead to non-specific removal of multiple allergens.<sup>48</sup> **[TABLE XI.A.4.]**

14  
15 Observation studies of early exposure to rodents in childhood have yielded mixed results when  
16 evaluating future risk of rodent sensitization and the development of AR or allergic asthma.<sup>49-52</sup> Larger  
17 controlled studies are needed.

18  
19 **Avoidance of workplace rodent exposure.** Removal of rodent exposure is a management option for AR  
20 and asthma in those that are sensitized; however, as exposure can occur in various environments,  
21 comprehensively accomplishing this is challenging. When exposure primarily occurs at the workplace  
22 (e.g., laboratory worker handling rodents), reduction of allergen exposure can be accomplished by  
23 changing jobs or roles, use of personal protective devices, maintaining ventilation systems, and proper  
24 staff training.<sup>48,53</sup>

25  
26 **Rodents as pets or pests.** As various rodents can be kept as pets, many sensitized individuals or their  
27 caregivers are reluctant to remove the rodent from the living space, similar to other furry animals.<sup>34,54</sup>  
28 Conversely, individuals are generally willing to comply with recommendations to remove things they  
29 consider pests. Rodent predators such as cats can reduce rodent populations but are unlikely to  
30 eliminate an infestation. One observational inner-city study showed that the number of cats and cat  
31 allergen levels are inversely correlated with mouse allergen levels.<sup>55</sup> No clinical outcomes were reported  
32 in this study. No recommendations can be made at this time, but the risks likely outweigh potential



1 benefit due to the high reported co-sensitization rate for cat and mouse allergens, which could lead to  
2 worsening of allergic symptoms with cat introduction.<sup>55</sup>

3

4 ***Integrated pest management for rodent infestation.*** Integrated pest management (IPM) encompasses  
5 the initial removal of allergen reservoirs and habit modifications to reduce the risk of infestation  
6 recurrence.<sup>48</sup> These interventions include home-based education, rodent extermination via traps and  
7 rodenticide, HEPA filtration, sealing of holes and cracks with copper mesh, and thorough cleaning.  
8 Singular interventions, such as placing rodent traps alone, are unlikely to provide meaningful benefit,  
9 which is consistent with cockroach allergen mitigation literature.<sup>48</sup> (*See Section XI.A.2. Allergen*  
10 *Avoidance – Cockroach for additional information on this topic.*)

11

12 Several RCTs have been performed to evaluate the efficacy of integrated pest management in reducing  
13 indoor allergen levels; however, only six specifically address mouse allergen.<sup>31,43-47</sup> Integrated pest  
14 management methods were highly variable between these studies, making direct comparisons difficult.  
15 In addition, the outcome measures evaluated were primarily mouse antigen levels and asthma-related  
16 outcomes (no rhinitis outcomes were reported) in low-income, inner-city populations, which limits the  
17 generalizability of the results. Three out of the six showed a reduction of mouse antigen levels with  
18 integrated pest management, one did not report this outcome, and two showed no significant  
19 difference. Asthma-related clinical endpoint results were mixed, but one study that utilized extensive  
20 integrated pest management interventions showed an increase in FEV<sub>1</sub> (forced expiratory volume in 1  
21 second) in inner-city children when  $\geq 75\%$  reduction of mouse allergen levels was achieved.<sup>44</sup>

22

23 In summary, avoidance measures for work-related exposures and pet rodent exposures may have  
24 significant benefit. For rodent infestations, integrated pest management reduces mouse allergen levels  
25 in the household, but meaningful clinical improvement remains unclear in mouse-sensitized  
26 patients.<sup>31,43-47</sup> The generalizability of rodent-specific integrated pest management RCTs is very limited  
27 as they all mainly included low-income, inner-city populations in the Northeastern US. No well-  
28 conducted studies have evaluated allergen reduction interventions for other rodents. Future research  
29 should concentrate on the effects of integrated pest management on rodent allergen levels in non-  
30 inner-city populations, rhinitis outcomes, and determining which interventions are highest yield to  
31 maximize cost-efficiency.

32

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

2 **TABLE XI.A.4.)**

3 **Benefit:** Reduces rodent allergen levels (specifically mouse allergen) but no information on AR  
4 outcomes.

5 **Harm:** Reduction in QOL of patient due to removal of pet rodent to whom patient is emotionally  
6 attached. Change in job position or role if primary rodent exposure is work-related.

7 **Cost:** Direct costs include the cost of interventions such as extermination and mitigating causal factors  
8 or loss of income if a job change occurs. Indirect costs include time off work for pest control  
9 appointments.

10 **Benefits-harm assessment:** Balance of benefit and harm.

11 **Value judgments:** Careful patient selection based on exposure history. Heterogeneity of integrated pest  
12 management protocols makes quantification of benefit difficult.

13 **Policy level:** Option.

14 **Intervention:** Avoidance likely improves rodent-specific allergen exposure, especially when the  
15 interaction can be eliminated such as when it is work-related or with a pet rodent. Integrated pest  
16 management should be considered in select patients, such as pediatric inner-city patients that suffer  
17 from asthma and are mouse sensitized.

18

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Matsui et al <sup>43</sup>	2017	2	RCT	-Professional integrated pest management + pest management education -Pest management education alone	-Primary outcome: maximal asthma symptom days -Secondary outcomes: mouse antigen levels, spirometry measurements	No significant difference in any outcome measure between the interventions
DiMango et al <sup>47</sup>	2016	2	RCT	-Multifaceted indoor allergen avoidance measures -Sham intervention	-Allergen levels (cat, dog, HDM, CR, mouse) -Asthma-related outcomes (medication score, FEV <sub>1</sub> 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 <sup>45</sup>	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 <sup>31</sup>	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 <sup>46</sup>	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 <sup>44</sup>	2020	3	RCT*	-Professional integrated pest management + education -Education alone	Lung function	Mouse allergen reduction was related to an increase in prebronchodilator FEV <sub>1</sub>
Jacobs et al <sup>51</sup>	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 <sup>50</sup>	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 <sup>49</sup>	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 <sup>54</sup>	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 <sup>34</sup>	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 <sup>48</sup>	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 <sup>55</sup>	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 <sup>52</sup>	2002	4	Observational cross-sectional	2729 primary school-aged children using parent-completed questionnaire on pet ownership	Allergen sensitization, symptoms, and atopic diagnoses	Furry pet (cat, dog, rodent) ownership associated with a lower risk of sensitization to pollen
Sakaguchi et al <sup>53</sup>	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

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

4 \*LOE downgraded due to selective outcome reporting

5 \*\*LOE downgraded due to selective sampling

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

#### 10 XI.A.5. Pollen

12 For pollen sensitized patients, avoidance or environmental control measures are often the first  
13 recommended intervention to decrease exposure and symptoms.<sup>56</sup> This approach is derived from the  
14 experience in which nasal or inhalational allergen challenges induce inflammatory changes and clinical  
15 symptoms after exposure.<sup>57</sup> Education and avoidance measures often involve personal behavior  
16 changes, particularly when pollen counts are elevated. While complete avoidance of pollen triggers is  
17 rarely achievable, it also has undesirable consequences such as avoiding the outdoors.<sup>58</sup> A more realistic  
18 goal is a reduction in exposure to pollens rather than complete elimination<sup>59</sup> Further, evidence  
19 supporting such recommendations is often limited to expert opinion and clinical experience.

1 Dominant aeroallergens may vary significantly by geographical location, climate, and season.  
2 Understanding an individual's specific sensitization pattern is best characterized by the combination of  
3 history and physical examination along with skin testing or serum sIgE testing. This combined with local  
4 pollen data can guide when a patient may be most likely exposed to a particular allergen and, therefore,  
5 when avoidance measures may be most effective. Local pollen counts can be ascertained by various  
6 sources including local media, phone applications, and trusted internet websites.

7  
8 Practical interventions for pollen avoidance include keeping windows in homes and cars closed, drying  
9 clothes indoors, and staying inside when possible.<sup>60</sup> Cabin air filters in cars, pollen screens, eyeglasses,  
10 and mouth-nose covering masks may reduce exposures.<sup>61</sup> Pollen counts tend to be higher on sunny,  
11 windy days with lower humidity.<sup>56</sup> HEPA filters in air purifiers can decrease exposure and, when studied  
12 in *Artemisia* pollen sensitized patients, led to decreased allergy symptom scores compared to placebo  
13 filters.<sup>62</sup> For individuals able to change immediate landscaping, choosing entomophilous or insect  
14 pollinated plants may be helpful in addition to selecting plants less likely to induce allergic symptoms.<sup>63</sup>  
15 While allergen avoidance is endorsed by national and international guidelines,<sup>64,65</sup> the clinical efficacy of  
16 these interventions has not been rigorously evaluated.

17  
18 The previously mentioned pollen avoidance approaches apply more generally to one's surroundings.  
19 There have also been attempts with physical barriers in direct or close contact with mucosal membrane  
20 surfaces where pollens may adhere and cascade immune responses. One study enrolled 70 individuals  
21 with seasonal AR (primarily to grass) or polysensitized individuals without perennial sensitizations,  
22 where patients were randomized to receive wraparound eyeglasses in addition to medical treatment  
23 versus medical treatment alone for three successive pollen seasons.<sup>66</sup> Patients provided wraparound  
24 glasses had improved ocular and nasal symptoms, in addition to improved RQLQ compared to medical  
25 therapy alone. Nasal filters have also been used as an avoidance tool to prevent symptoms of AR. In a  
26 randomized, double-blind placebo-controlled crossover trial, 65 grass sensitized adults were monitored  
27 in a natural exposure setting at a park while either wearing a nasal filter or placebo.<sup>67</sup> Patients wearing  
28 nasal filters had significantly reduced TNSS scores compared to placebo. Other barrier protection  
29 measures have been assessed, including cellulose powder applied to the nose, pollen blocker cream,  
30 and microemulsion. In a systematic review, 15 RCTs involving data of these measures from 1154  
31 patients were assessed with subgroup analysis according to the type of barrier protection studied.<sup>68</sup>  
32 Compared to placebo, the barrier protection methods assessed each had improved symptom control by

1 meta-analysis without increased adverse events (of note, nasal filter was not analyzed by meta-analysis  
 2 due to insufficient data). Most of the included studies were small with heterogeneous study designs, but  
 3 overall barrier methods may offer non-pharmacologic, symptomatic improvement to motivated  
 4 patients. [TABLE XI.A.5.]

5  
 6 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 3 studies; TABLE XI.A.5.)

7 **Benefit:** Decreased symptoms and medication use with potential for improved QOL.

8 **Harm:** Interventions may vary in cost and efficacy of each may be inadequately defined.

9 **Cost:** Generally low monetary cost depending on strategy.

10 **Benefits-harm assessment:** Equivocal, most interventions with lower harm but not well-defined  
 11 benefits.

12 **Value judgments:** Most pollen avoidance measures are based on clinical and expert opinion although  
 13 trial-based evidence is available for some interventions.

14 **Policy level:** Option.

15 **Intervention:** Pollen avoidance strategies are generally well tolerated and lower cost, non-medication-  
 16 based interventions that may have benefit with minimal harm to the patient, but further RCTs with  
 17 larger populations would be needed to better characterize efficacy.

18

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Chen et al <sup>68</sup>	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 <sup>69</sup>	2020	2	RCT, double-blind	90 patients with <i>Artemisia</i> (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 <sup>66</sup>	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 <sup>67</sup>	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

20 LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial; QOL=quality  
 21 of life; HEPA=high-efficiency particulate air; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; AR=allergic  
 22 rhinitis; TNSS=Total Nasal Symptom Score  
 23  
 24

## 1 XI.A.6. Occupational

2  
3 Occupational rhinitis may be secondary to allergic or irritant responses and has been associated with a  
4 variety of agents, including animals, particulate matter from woods, grains, chemicals, and other  
5 substances.<sup>57</sup> Early diagnosis is crucial not only for managing rhinitis symptoms but also potentially  
6 preventing the development of coexisting occupational asthma.<sup>70,71</sup> Regarding management, the most  
7 common strategy is avoidance or implementation of environmental controls. However, it is critical to  
8 prevent sensitization through appropriate occupational hygiene and safety practices with surveillance of  
9 symptoms and exposures in high risk environments.<sup>72</sup>

10  
11 Accurate diagnosis of occupational rhinitis may be suggested by periods of improvement during work  
12 avoidance such as planned time away from the workplace, when not exposed regularly to occupational  
13 allergens. Nasal provocation tests may be pursued but the validity of this testing is often poorly  
14 defined.<sup>56</sup> For patients with high clinical suspicion of occupational rhinitis, complete avoidance is  
15 recommended as the safest and most effective therapeutic option. If this is not possible due to  
16 socioeconomic consequences or otherwise, environmental control measures to reduce exposure may be  
17 an acceptable alternative.<sup>73</sup> This may be accomplished with escalating interventions, starting with  
18 avoidance by the use of less problematic materials, improving ventilation of the areas involved, reducing  
19 time spent working with implicated materials, or utilizing protective gear for the patient.<sup>70</sup>

20  
21 Symptom improvement has been reported in clinical settings following effective avoidance. In a  
22 prospective study, 20 patients with specific inhalation challenge-confirmed occupational rhinitis  
23 (exposures including flour, animal proteins, tea, isocyanates, resins, acrylates) were assessed at  
24 diagnosis and follow up, with a mean time interval of  $4.7 \pm 1.3$  years.<sup>74</sup> At follow up assessment, all  
25 patients had been removed from exposure and reported significant decreases in nasal symptoms and  
26 improvement in QOL. Similarly, a separate Finnish cohort of 119 patients was diagnosed with  
27 occupational rhinitis (exposures including flour, animal proteins, storage mites, latex, flowers or indoor  
28 plants, dried egg powder, organic acid anhydrides with human serum proteins, abache wood dust,  
29 human dandruff, and enzymes) with an average of 10 years since diagnosis. Health-related QOL for  
30 those no longer exposed to occupational allergens was similar to healthy controls, while it was impaired  
31 among those with continued exposures.<sup>75</sup> Thus, complete avoidance appears to improve rhinitis  
32 symptoms and QOL, and when feasible, may be the best approach. [TABLE XI.A.6.]

33

1 However, if complete avoidance is not able to be achieved, there can be benefit to treatment  
 2 approaches including decreased levels of exposure. In a group of 36 patients with latex-induced  
 3 occupational asthma and a median follow up time of 56 months, 20 subjects with reduced exposure had  
 4 improved asthma severity along with reduced rhinitis symptom severity scores.<sup>76</sup> The other 16 patients  
 5 without ongoing exposure (defined as latex gloves never used in the working environment) also had  
 6 improvement in asthma and rhinitis symptom severity but had more loss of income and work disability.  
 7 In a separate cross-sectional survey of patients with occupational asthma to platinum salts, transfer to  
 8 low-exposure areas at work resulted in improved rhinitis symptoms compared to high exposure areas.<sup>77</sup>  
 9 Where avoidance or decreased exposure by job location is not achievable, personal protective  
 10 equipment may be sufficient to decrease symptoms of occupational rhinitis. In a group of agricultural  
 11 workers, predominately with occupational asthma to cow dander or grains, use of a powered dust  
 12 respirator helmet worn over a period of 10 months resulted in significantly reduced rhinitis symptoms  
 13 and improved morning peak flow rate.<sup>78</sup>

14

15 Overall, while most of the evidence is limited to small observational studies, complete avoidance of an  
 16 inciting agent in occupational rhinitis likely provides the best improvement in symptoms and QOL and  
 17 should be pursued when possible. Alternatively, occupation-specific interventions to decrease exposure  
 18 may offer benefit to patients when complete avoidance cannot be accomplished. Further  
 19 characterization of levels of exposure and most effective means of decreasing exposure is needed. (*See*  
 20 *Section V.B.3 Occupational Rhinitis for additional information on this topic.*)

21

22 **Aggregate grade of evidence:** C (Level 3: 5 studies; **TABLE XI.A.6.**)

23 **Benefit:** Decreased allergen exposure may lead to reduction in symptoms, improvement in QOL, and  
 24 possible reduced likelihood of developing occupational asthma.

25 **Harm:** Potential for socioeconomic harm with loss of wages or requiring changes in occupation.

26 **Cost:** Individually may vary if avoidance results in loss of income; for employers, potentially high cost  
 27 depending on interventions or environmental controls required.

28 **Benefits-harm assessment:** Where possible from a patient-centered perspective, in occupational rhinitis  
 29 complete avoidance is likely beneficial in improving health quality compared to ongoing exposures.

30 **Value judgments:** Based primarily on observational studies, allergen avoidance or decreasing exposure  
 31 is recommended for all patients but can be nuanced depending on the resulting socioeconomic impact.

32 **Policy level:** Recommendation.

33 **Intervention:** Patients should be counseled to avoid or decrease exposure to inciting agents in  
 34 occupational respiratory disease.

35

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
-------	------	-----	--------------	--------------	--------------------	-------------



Castano et al <sup>74</sup>	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 <sup>75</sup>	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 <sup>76</sup>	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 <sup>78</sup>	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

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

2

3

#### 4 [XI.B. Pharmacotherapy](#)

##### 5 [XI.B.1. Antihistamines](#)

##### 6 [XI.B.1.a. Oral H<sub>1</sub> antihistamines](#)

7

8 In AR, IgE binds to mast cells and basophils which triggers the release of histamine. The effects of

9 histamine include vasodilation, smooth muscle bronchoconstriction, increased endothelial permeability

10 and sensory nerve stimulation, contributing to the classic symptoms of AR.<sup>79</sup> Antihistamines are inverse

11 agonists of histamine and cause histamine receptors to convert to an inactive state.<sup>80</sup> Antihistamines are

12 classified as first, second, and third generation. However, herein we classify the second and third

13 generation as newer-generation antihistamines. **[TABLE XI.B.1.a.-1]** First-generation antihistamines

14 (e.g., diphenhydramine and chlorpheniramine) have anticholinergic side effects and can cross the blood-

15 brain barrier, resulting in central nervous system effects such as sedation and drowsiness.<sup>81,82</sup> These side

1 effects can be more pronounced in the elderly, so first generation antihistamines should be used with  
2 caution.<sup>83</sup> Newer-generation antihistamines (e.g., bilastine, cetirizine, desloratadine, fexofenadine,  
3 levocetirizine, loratadine) block peripheral H<sub>1</sub> receptors without crossing the blood-brain barrier which  
4 prevents central nervous system side effects. Several newer-generation antihistamines are metabolized  
5 in the liver by cytochrome p450 enzymes. As a result, prescribers should be conscious of concomitant  
6 administration of other drugs that are either processed by cytochrome p450 or drugs that are  
7 cytochrome p450 inducers because concurrent administration can either increase or decrease the  
8 plasma concentration of the antihistamine.<sup>82</sup>

9

10 Given their use since the 1940s, there are numerous RCTs regarding the use of oral antihistamines for  
11 the management of AR. With this in mind, a summary of the highest grade of evidence published is  
12 provided. **[TABLE XI.B.1.a.-2]**

13

14 There are several published guidelines regarding the use of oral antihistamines for the management of  
15 AR. In 2004 the ARIA group and EAACI released recommendations regarding the pharmacological criteria  
16 that commonly used AR medications should meet. Taking into consideration the efficacy, safety, and  
17 pharmacology, newer-generation antihistamines were shown to have a favorable risk-benefit profile and  
18 were recommended over first-generation oral antihistamines for the treatment of AR.<sup>84</sup> The 2015  
19 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Clinical Practice  
20 Guidelines and the 2019 Canadian Society of Allergy and Clinical Immunology position statement also  
21 recommended newer-generation antihistamines over first-generation antihistamines for the  
22 management of AR.<sup>81,85</sup>

23

24 The ARIA guidelines 2010 revision made a strong recommendation for newer-generation antihistamines  
25 that are non-sedating and do not interact with cytochrome p450.<sup>86</sup> The ARIA guidelines 2016 revision  
26 made several recommendations regarding when to consider the use of oral antihistamines, taking into  
27 context other drugs available for the management of seasonal and perennial AR.<sup>87</sup> In 2020, the ARIA  
28 group published the first GRADE-based guidelines that integrated real-world patient-reported  
29 experience and clinical studies to inform the management of AR.<sup>88</sup> It provided a treatment algorithm  
30 that, in a nuanced manner, considered a patient's symptom severity with past and current medication  
31 use to clarify the role of newer-generation antihistamines for the management of AR.<sup>88</sup> The standard  
32 dosing for newer-generation antihistamines is listed in **TABLE XI.B.1.a.-1.**

1

2 The decision on which newer-generation antihistamine to prescribe should be individualized to the  
3 patient and the dosing, drug interactions, side effects, the onset of action, and cost should be  
4 considered. A large study that examined all e-prescriptions of oral antihistamines (n=2280) in Poland in  
5 2018 found that approximately 1 in 5 prescriptions was not redeemed.<sup>89</sup> This finding suggests the need  
6 for further studies regarding patient adherence to oral antihistamines, noting that various factors could  
7 influence patient adherence including lack of trust in the prescriber, cost and availability of the  
8 medication over the counter.

9

10 Excluding oral antihistamines only available by prescription, the cost of most newer-generation oral  
11 antihistamines is similar at ~\$2 per day.<sup>90</sup> As newer-generation oral antihistamines have fewer central  
12 nervous system side effects than first-generation oral antihistamines, their indirect costs to society are  
13 lower than first-generation oral antihistamines.<sup>79,82,90</sup> The indirect costs amongst newer-generation oral  
14 antihistamines are similar given the similar side effect profiles.

15

16 **Aggregate grade of evidence:** A (Level 1: 19 studies, level 4: 5 studies; TABLE XI.B.1.a.-2)

17 **Benefit:** Reduction in symptoms of AR.

18 **Harm:** Compared to first-generation oral antihistamines, newer-generation antihistamines have fewer  
19 central nervous system and anticholinergic side effects. The side effects of first-generation  
20 antihistamines can be more pronounced in the elderly. See TABLE II.C.

21 **Cost:** Inexpensive. Given their improved side effect profile, newer-generation oral antihistamines also  
22 have lower indirect costs than first generation oral H<sub>1</sub> antihistamines.

23 **Benefits-harm assessment:** The benefits outweigh harm for use of newer-generation H<sub>1</sub> oral  
24 antihistamines for AR.

25 **Value judgments:** First-generation oral antihistamines are not recommended for the treatment of AR  
26 because of their central nervous system and anticholinergic side effects.

27 **Policy level:** Strong recommendation for the use of newer-generation oral antihistamines for AR.

28 **Intervention:** Newer-generation oral antihistamines can be considered in the treatment of AR.

29

30 **TABLE XI.B.1.a.-1 List of commonly used newer-generation antihistamines<sup>85</sup>**

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 (Clarinet)	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

<b>Fexofenadine (Allegra)</b>	1-3 h	>24 h	Unlikely	11-15 h	60 mg BID or 180 mg QD	2-11 y: 30 mg BID
<b>Levocetirizine (Xyzal)</b>	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
<b>Loratadine (Claritin)</b>	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

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

2  
3

**TABLE XI.B.1.a.-2 Evidence table – Oral H<sub>1</sub> antihistamines for allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Miligkos et al <sup>91</sup>	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 <sup>92</sup>	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 <sup>93</sup>	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 <sup>94</sup>	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 <sup>95</sup>	2015	1	SR of 4 RCTs	Adult patients treated with -Bilastine -Cetirizine -Desloratadine	-Subjective and objective measures -TNSS -RQLQ	-Bilastine has similar efficacy to other second-generation oral antihistamines -Improved TNSS & RQLQ, good safety profile
Compalati et al <sup>96</sup>	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 <sup>97</sup>	2013	1	SR of 10 clinical trials	Patients (n=140,853;	-TSS -TNSS	Second-generation levocetirizine

				≥12 years old ) treated with: -Desloratadine -Ebastine -Fexofenadine -Levocetirizine		significantly improved symptom scores, especially in severe AR
Compalati et al <sup>98</sup>	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 <sup>99</sup>	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 <sup>100</sup>	2011	1	SR of 7 RCTs	AR patients (n=2238; ≥6 years old treated with: -Levocetirizine -Loratadine	-TSS -DNS -DES	Improvement in TSS, total 5 symptoms score, daytime nasal symptoms, and QOL
Bachert <sup>101</sup>	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 <sup>102</sup>	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 <sup>103</sup>	2007	1	SR of 8 RCT	Patients (≥12 years old) treated with desloratadine	Reviewed multiple outcomes in relation to the ARIA definitions of AR: -TSS -TNSS	Desloratadine is well tolerated and efficacious for intermittent and persistent AR with

					-TNNSS -PNIF -Intermittent, persistent, seasonal, perennial AR	reductions in congestion, TSS, TNSS, TNNSS, and improved QOL
Canonica et al <sup>104</sup>	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 <sup>105</sup>	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 <sup>106</sup>	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 <sup>107</sup>	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 <sup>108</sup>	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 <sup>109</sup>	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 <sup>110</sup>	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 <sup>111</sup>	2015	4	Review of CS: ARIA, EAACI, Royal College of Paediatrics and Child Health	Oral antihistamines	---	Second-generation, non-sedating, antihistamines are recommended for mild-moderate AR and in combination for

						severe AR; sedating antihistamines should not be used
Seidman et al <sup>85</sup>	2015	4	SR with guideline (9 CPGs, 81 SR & 177 RCTs)	Patients ( $\geq 2$ years old) treated with OAH	-Relieving allergy symptoms -Adverse events	Strong recommendation to use non-sedating OAH, benefits outweigh harm
Brozek et al <sup>86</sup>	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 <sup>84</sup>	2004	4	ARIA/EAACI criteria for antihistamines	Desloratadine	ARIA/EAACI criteria efficacy, safety, pharmacology	Desloratadine recommended for treating patients with AR

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

10

11

### 12 [XI.B.1.b. Oral H<sub>2</sub> antihistamines](#)

13

14 Our understanding of the role of the H<sub>2</sub> receptor in mediating histamine-related nasal symptoms in AR is  
15 limited. There is no data comparing H<sub>2</sub>-receptor antagonism efficacy to common first line therapy such  
16 as INCS, and only a few relatively small studies have investigated the impact of H<sub>2</sub>-receptor antagonism.  
17 Most importantly, the clinical significance of the changes associated with H<sub>2</sub> antihistamines has not been  
18 clearly defined. Nonetheless, H<sub>2</sub> antihistamines possess relatively low risk (drug-drug interactions  
19 through decreased gastric acidity and inhibition of cytochrome p450)<sup>112</sup> and low cost and have been  
20 supported by some studies for use in patients with recalcitrant nasal airway obstruction in combination  
21 with oral H<sub>1</sub> antihistamines.

22

23 There have been several RCTs that investigated the efficacy of H<sub>2</sub> antihistamines in improving objective  
24 measures such as nasal airway resistance and nasal secretion. Wood-Baker et al<sup>113</sup> compared oral cetirizine  
25 to oral ranitidine. Objective measures of nasal airway resistance showed greater improvement with

1 ranitidine; however, objective measures of nasal secretion decreased more with cetirizine. Despite very  
2 few studies showing efficacy of H<sub>2</sub> blockers alone, several studies have emphasized their potential utility  
3 in combination with H<sub>1</sub> antagonists. Taylor-Clark et al<sup>114</sup> found similar improvement in nasal airway  
4 resistance between cetirizine and ranitidine, but a significant improvement with the use of combination  
5 therapy. Wang et al<sup>115</sup> also showed improvement in nasal airflow with combination therapy of  
6 cimetidine and cetirizine. Havas et al<sup>116</sup> measured the nasal airflow resistive response to topical  
7 histamine and also found that combined histamine antagonism with diphenhydramine hydrochloride  
8 and cimetidine was significantly more effective in reducing the nasal resistive response than H<sub>1</sub>  
9 antagonist alone. However, not all data regarding combination therapy has been conclusive with other  
10 studies finding no improvement in nasal airflow with the addition of an H<sub>2</sub> antihistamine.<sup>117,118</sup>  
11 Moreover, the clinical significance of these objective measures remain unclear. **[TABLE XI.B.1.b.]**  
12

13 Alternatively, several studies have investigated the impact of H<sub>2</sub> antagonism on symptoms by employing  
14 PROMs. Subjects were asked to report some combination of congestion, blockage, itch, drainage,  
15 sneeze, eye symptoms and asthma with a categorical severity measure. Three of the four studies  
16 examined symptoms after nasal allergen challenge, and none of these demonstrated efficacy of H<sub>2</sub>  
17 antihistamines in diminishing allergic symptoms, either alone, or conjunction with an H<sub>1</sub>  
18 antihistamine.<sup>115,117-119</sup> The majority of RCTs investigating the efficacy of H<sub>2</sub> antihistamines are within the  
19 context of pre-treatment of a patient prior to a nasal histamine or allergen challenge. Only one study  
20 investigated the impact of an H<sub>2</sub> antagonist, cimetidine, in conjunction with chlorpheniramine in a real-  
21 world setting. Carpenter et al<sup>119</sup> randomized 23 subjects with known late-summer AR to receive  
22 alternating two-week courses of either chlorpheniramine plus placebo during the season, or  
23 chlorpheniramine plus cimetidine. Symptom scores were recorded twice daily along with adjuvant  
24 medical therapies taken (specifically, oral corticosteroids). A significant reduction in medication use was  
25 reported by patients receiving both H<sub>1</sub> and H<sub>2</sub> antagonists (28 corticosteroid days vs 44 corticosteroid  
26 days, p<0.02) and decreased symptoms scores during one of the eight weeks when weed pollen counts  
27 were high. A limitation of this study is its utilization of a first-generation antihistamine which is no longer  
28 utilized as first-line treatment of rhinitis symptoms. No current studies exist comparing INCS with second  
29 generation antihistamines in combination with H<sub>2</sub> blockers.  
30

31 The data existing on the use of H<sub>2</sub> antihistamines in AR is limited in scope and quality, with very little  
32 addition to the literature in the past decade. The objective findings of improved nasal airway resistance



1 suggest that the H<sub>2</sub> histamine receptor does modulate nasal tissue response to histamine.<sup>113-116</sup>  
 2 However, the clinical significance of this mechanism is not clear, particularly in the context of modern  
 3 treatment algorithms.<sup>115-119</sup> Given the relatively manageable side effect profile and costs of H<sub>2</sub>  
 4 antihistamines, they may offer patients with otherwise recalcitrant AR symptoms an additional  
 5 treatment option. However, additional investigation on the efficacy of H<sub>2</sub> antihistamines in combination  
 6 with other topical medications may be beneficial in the future.

7  
 8 **Aggregate grade of evidence:** B (Level 2: 7 studies; **TABLE XI.B.1.b.**)

9 **Benefit:** Decreased objective nasal resistance, and improved symptom control in 4 studies when used in  
 10 combination with H<sub>1</sub> antagonists.

11 **Harm:** Drug-drug interaction (p450 inhibition, inhibited gastric secretion and absorption). See **TABLE**  
 12 **II.C.**

13 **Cost:** Increased cost associated with H<sub>2</sub> antagonist over H<sub>1</sub> antagonist alone.

14 **Benefits-harm assessment:** Unclear benefit and possible harm.

15 **Value judgments:** No studies evaluating efficacy of H<sub>2</sub> antihistamines in context of INCS. There were 2  
 16 studies that showed no benefit for H<sub>2</sub> antagonist when used alone or as an additive to H<sub>1</sub> antagonist  
 17 therapy.

18 **Policy level:** No recommendation. Available does not adequately address the benefit of H<sub>2</sub>  
 19 antihistamines in AR.

20 **Intervention:** Addition of an oral H<sub>2</sub> antagonist to an oral H<sub>1</sub> antagonist may improve symptom control in  
 21 AR, but data is limited.

22  
 23 **TABLE XI.B.1.b. Evidence table – Oral H<sub>2</sub> antihistamines for allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Taylor-Clark et al <sup>114</sup>	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 <sup>117</sup>	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 <sup>115</sup>	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 <sup>113</sup>	1996	2	RCT	Allergy challenge with premedication:	-Nasal lavage fluid protein	-Ranitidine improved nasal resistance more than

				-PO cetirizine -PO ranitidine	concentration -Nasal airway resistance	cetirizine -Cetirizine decreased total protein and albumin more than ranitidine
Havas et al <sup>116</sup>	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 <sup>119</sup>	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 <sup>118</sup>	1982	2	RCT	Allergy challenge with premedication: -PO cimetidine -Placebo	-Symptoms (congestion, itch, drainage, sneeze) -Nasal airway resistance -Nasal secretion weight	-No difference in subjective scores -Increased secretion and sneeze count, no difference in nasal resistance

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

#### 2 3 4 XI.B.1.c. Intranasal antihistamines

5  
6 Two formulations of intranasal antihistamine are currently available in North America for use as a  
7 topical spray, azelastine hydrochloride and olopatadine hydrochloride. The English-language literature  
8 was systematically reviewed for clinical trials of either of these formulations for the treatment of AR. A  
9 total of 44 papers were identified that reported results of RCTs of intranasal antihistamine  
10 monotherapy. This included 24 studies with an active treatment comparator arm<sup>120-143</sup> and 29 studies  
11 with an inactive placebo arm.<sup>123,124,128-130,132,134,136,138,140,141,144-161</sup> Monotherapy with azelastine was  
12 reported in 37 studies<sup>120,121,123,125-132,134-144,147-152,156-164</sup> while monotherapy with olopatadine was reported  
13 in 10 studies.<sup>122,124,145,146,149,151,153-155,163</sup> Some studies utilized multiple active treatment arms of  
14 antihistamine and/or corticosteroid. [TABLE XI.B.1.c.]

1  
2 Patient-reported symptom scores or QOL assessments were the most frequently utilized outcome  
3 measures in the included studies. The most common outcome measure was the TNSS (23 studies),  
4 which summarizes the severity of the cardinal symptoms of sneezing, itching, congestion, and runny  
5 nose. Other outcome measures included the RQLQ (7 studies), the Total Ocular Symptom Score (TOSS, 5  
6 studies), the Caregiver Treatment Satisfaction Questionnaire (2 studies), the Pediatric RQLQ (1 study),  
7 the SF-36 (1 study), the ESS (1 study), the Rhinitis Severity Score (1 study) and a Subjective Global  
8 Assessment (1 study). Multiple studies, particularly those published more than 20 years ago, relied upon  
9 arbitrary, non-validated symptom scores for reporting treatment outcomes (19 studies). A minority of  
10 studies included objective measures such as nasal lavage (3 studies), response to methacholine  
11 challenge (2 studies), nasal flow rate (2 studies), and rhinomanometry (1 study).

12  
13 The most frequent treatment duration was 14 days in the included studies, with a range from 2 days to  
14 8 weeks. Study enrollment ranged from 20 to 1188 subjects. In the 29 studies using placebo as a  
15 comparison group,<sup>123,124,128-130,132,134,136,138,140,141,144-161</sup> intranasal antihistamine showed superiority for the  
16 primary outcome of nasal symptom improvement. An active treatment comparator of a different  
17 medication was used in 24 studies.<sup>120-143</sup> The intranasal antihistamine spray treatment group  
18 consistently had a more rapid onset of action than the treatment comparator, occurring as early as 15  
19 minutes after administration, although this was not reported in all studies. Azelastine and olopatadine  
20 were directly compared in 3 studies, with no significant difference in symptom relief between  
21 agents.<sup>149,151,163</sup> Azelastine was compared with an experimental formulation of intranasal levocabastine  
22 in 2 additional studies, with either comparable or superior results for azelastine.<sup>162,164</sup> Levocabastine is  
23 not available as a commercial product.

24  
25 The active treatment comparators utilized in 24 studies consisted of an INCS or oral antihistamine.  
26 Twelve studies compared intranasal antihistamine with INCS, with the primary outcome of nasal  
27 symptom improvement favoring antihistamine in 2 studies,<sup>123,124</sup> INCS in 3 studies,<sup>130,132,159</sup> and showing  
28 equivalency in 7 studies.<sup>120-122,136,140,141,143</sup> Superiority of the antihistamine for treating ocular symptoms  
29 was found in 2 studies, one of which was nearly 30 years old.<sup>121,141</sup> The 3 studies showing superiority of  
30 INCS were over 20 years old and reported outcomes using heterogeneous non-validated symptom  
31 scores.

32

1 Intranasal antihistamine was compared to oral antihistamine monotherapy in 8 studies, with superiority  
2 of intranasal antihistamine in 3 studies,<sup>125,127,135</sup> and equivalency in 5 studies.<sup>129,137-139,142</sup> One study  
3 included a treatment arm with oral chlorpheniramine as a positive control without intent to compare  
4 efficacy with azelastine.<sup>134</sup> Azelastine monotherapy was at least as effective as combination therapy in a  
5 single study comparing azelastine spray versus oral loratadine plus intranasal beclomethasone.<sup>131</sup>  
6 Combination therapy with intranasal azelastine plus oral antihistamine was not found to confer  
7 additional benefit in 2 studies compared to intranasal azelastine monotherapy.<sup>128,129</sup> An overall dose-  
8 response relationship was found in 11 studies that included comparison of multiple dose concentrations  
9 of intranasal antihistamine.<sup>134,138,146-148,151-155,161</sup>

10

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

14

15 No study reported any serious adverse effects from use of an intranasal antihistamine. These  
16 formulations are noted to be generally well tolerated, with taste aversion being the most reported  
17 adverse effect. One study that compared a reformulated vehicle against the commercially available form  
18 of azelastine found no difference in taste aversion.<sup>147</sup> Olopatadine was reported to have better sensory  
19 attributes than azelastine in one study.<sup>163</sup> Other reported adverse effects were uncommon, with  
20 somnolence, headache, epistaxis and nasal discomfort each occurring in less than 10% of patients  
21 treated with azelastine or olopatadine. **[TABLE II.C.]**

22

23 In 2021, the US FDA approved azelastine hydrochloride as an over-the-counter formulation, making  
24 intranasal antihistamines available for the first time without a prescription. This change may remove  
25 some financial barriers to patient use and improve access to this medication as a treatment option for  
26 AR.

27

28 **Aggregate grade of evidence:** A (Level 2: 44 studies; **TABLE XI.B.1.c.**)

29 **Benefit:** Rapid onset; more effective for nasal congestion than oral antihistamines; more effective for  
30 ocular symptoms than INCS; consistent reduction in symptoms and improvement in QOL in RCTs  
31 compared to placebo.

32 **Harm:** Patient tolerance, typically related to taste aversion; less effective for congestion than INCS. See  
33 **TABLE II.C.**

34 **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 <sup>120</sup>	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 <sup>162</sup>	2011	2	DBRCT	-Azelastine 0.1% -Levocabastine hydrochloride 0.05% spray	rTNSS	Comparable symptom improvement
Howland et al <sup>144</sup>	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 <sup>145</sup>	2011	2	DBRCT	-Olopatadine 1.33mg BID -Placebo	-rTNSS -rTOSS -PRQLQ -CGTSQ-AR	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers
Kalpakioglu & Kavut <sup>121</sup>	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 <sup>146</sup>	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 <sup>147</sup>	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 <sup>122</sup>	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 <sup>148</sup>	2009	2	DBRCT	-Azelastine 0.82mg BID -Azelastine 0.56mg BID	TNSS	Both azelastine doses superior to placebo;

				-Placebo		greater improvement with higher dose
Shah et al <sup>149</sup>	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 <sup>150</sup>	2009	2	DBRCT	-Azelastine 0.82mg QD -Placebo	TNSS	Azelastine superior to placebo
Meltzer et al <sup>163</sup>	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 <sup>151</sup>	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 <sup>152</sup>	2007	2	DBRCT	-Azelastine 0.28mg QD -Azelastine 0.28mg BID -Placebo	TNSS	Azelastine both doses superior to placebo
Patel et al <sup>123</sup>	2007	2	DBRCT	-Azelastine 0.56mg QD -Mometasone furoate 0.2mg spray QD Placebo	TNSS	Azelastine superior to mometasone and placebo
Patel et al <sup>124</sup>	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 <sup>125</sup>	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 <sup>153</sup>	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 <sup>126</sup>	2006	2	DBRCT	-Azelastine 0.4mg QD -Desloratadine 5mg tablet QD -Placebo spray	TNSS	Azelastine superior to desloratadine and placebo
Corren et al <sup>127</sup>	2005	2	DBRCT	-Azelastine 0.56mg BID -Cetirizine 10mg tablet QD	-TNSS -RQLQ	Azelastine superior cetirizine for symptoms and QOL
Meltzer et al <sup>154</sup>	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 <sup>155</sup>	2005	2	DBRCT	-Olopatadine 2.66mg BID -Olopatadine 1.77mg BID -Placebo	TNSS	Olopatadine (both doses) superior to placebo

LaForce et al <sup>128</sup>	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 <sup>129</sup>	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 <sup>156</sup>	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 <sup>164</sup>	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 <sup>130</sup>	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 <sup>157</sup>	2000	2	DBRCT	-Azelastine 0.56mg BID -Placebo	-RSS -ESS	Azelastine superior to placebo for improving rhinorrhea and sleep quality
Berger et al <sup>131</sup>	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 <sup>132</sup>	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 <sup>158</sup>	1997	2	DBRCT	-Azelastine 0.28mg BID -Placebo	TNSS	Azelastine superior to placebo for children
Newson-Smith et al <sup>159</sup>	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 <sup>160</sup>	1997	2	DBRCT	-Azelastine 0.56mg spray BID + azelastine 0.5mg tablet BID	13-item symptom score	Azelastine spray showed limited benefit over placebo in patients already

				-Placebo spray + azelastine 0.5mg tablet BID		treated with systemic azelastine
LaForce et al <sup>134</sup>	1996	2	DBRCT	-Azelaatine 0.56mg QD -Azelaatine 0.56mg BID -Chlorpheniramine 12mg tablet BID -Placebo	8-item symptom score	Azelaatine superior to placebo at both doses; no comparison with chlorpheniramine
Charpin et al <sup>135</sup>	1995	2	DBRCT	-Azelaatine 0.28mg BID -Cetirizine 10mg tablet QD	8-item symptom score	Azelaatine superior for nasal stuffiness and rhinorrhea; no difference in other symptoms
Pelucchi et al <sup>136</sup>	1995	2	DBRCT	-Azelaatine 0.28mg BID -Beclomethasone dipropionate 0.1mg spray BID -Placebo	-8-item symptom score -Nasal lavage -Response to methacholine challenge	Azelaatine superior to placebo and comparable to beclomethasone for symptom improvement; neither treatment prevented bronchial responsiveness; no effect of azelaatine on eosinophils
Gastpar et al <sup>137</sup>	1994	2	DBRCT	-Azelaatine 0.28mg QD -Terfenadine 60mg tablet QD	13-item symptom score	Comparable symptom improvement
Meltzer et al <sup>138</sup>	1994	2	DBRCT	-Azelaatine 0.28mg QD -Azelaatine 0.28mg BID -Chlorpheniramine 12mg tablet BID -Placebo	11-item symptom score	Azelaatine comparable to chlorpheniramine and superior to placebo at both doses
Passali & Piragine <sup>139</sup>	1994	2	DBRCT	-Azelaatine 0.28mg BID -Cetirizine 10mg tablet QD	13-item symptom score	Azelaatine at least as effective as cetirizine
Ratner et al <sup>161</sup>	1994	2	DBRCT	-Azelaatine 0.28mg QD -Azelaatine 0.28mg BID -Placebo	8-item symptom score	Azelaatine twice-daily superior to placebo
Davies et al <sup>140</sup>	1993	2	DBRCT	-Azelaatine 0.28mg BID -Beclomethasone dipropionate 0.1mg spray BID -Placebo	-TNSS - Rhinomanometry	Azelaatine superior to beclomethasone and placebo for symptoms; no change in airway resistance with either treatment
Dorow et al <sup>141</sup>	1993	2	DBRCT	-Azelaatine 0.28mg BID -Budesonide 0.10mg spray BID -Placebo	13-item symptom score	Azelaatine comparable to budesonide for nasal symptoms and superior for ocular symptoms; both treatments superior to placebo
Gambardella <sup>142</sup>	1993	2	DBRCT	-Azelaatine 0.28mg BID -Loratadine 10mg tablet QD	-12-item symptom score -Global assessment	Azelaatine at least as effective as loratadine
Gastpar et al <sup>143</sup>	1993	2	DBRCT	-Azelaatine 0.28mg BID	-10-item symptom score	Azelaatine at least as effective as budesonide for



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

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

7

8

### 9 XI.B.2.a. Oral corticosteroids

10

11 Early work using the nasal challenge model has elucidated the anti-inflammatory effects of oral  
12 corticosteroids in AR. Pipkorn et al<sup>165</sup> premedicated patients with seasonal AR with either prednisone or  
13 placebo for 2 days prior to an allergen challenge. When compared to placebo, patients receiving  
14 prednisone demonstrated a significant reduction in sneezing as well as reduced levels of histamine and  
15 other mediators of vascular permeability in nasal lavages during the late phase response. Active  
16 treatment also reduced the priming response to consecutive allergen challenges. In similar placebo-  
17 controlled studies, Bascom et al<sup>166,167</sup> demonstrated a reduction in the influx of eosinophils and levels of  
18 eosinophil mediators (MBP and eosinophil derived neurotoxin) in nasal secretions during the late phase  
19 response in patients receiving 60mg oral prednisone for 2 days prior to nasal challenge. **[TABLE**  
20 **XI.B.2.a.]**

21

22 The efficacy of oral corticosteroids in seasonal clinical disease has also been demonstrated with less  
23 rigorous studies that did not include a placebo control. Schwartz et al<sup>168</sup> demonstrated that 15 days of  
24 cortisone (25mg QID [four times daily]) during the ragweed season resulted in significant relief of  
25 symptoms in 21 of 25 patients. Schiller and Lowell<sup>169</sup> showed that cortisone (100mg daily) for 4 day  
26 courses during the pollen season resulted in rhinitis symptom relief in 42 of 51 patients. Twenty of those  
27 patients had a relapse of symptoms within 7 days of cessation of therapy.<sup>169</sup> Oral hydrocortisone (40-  
28 80mg daily) has been shown to reduce symptoms of ragweed allergies.<sup>170</sup> In a placebo-controlled study  
29 performed during the ragweed season, Brooks et al<sup>171</sup> compared the efficacy of methylprednisolone (6,  
30 12, or 24mg PO [per os, by mouth] daily for 5 days) to placebo in controlling nasal symptoms. They  
31 reported a significant reduction in congestion, postnasal drainage, and ocular symptoms compared to  
32 placebo after 6mg and 12mg doses. The higher, 24 mg, dose was more effective and resulted in a  
33 significant reduction in all symptoms queried (congestion, runny nose, sneezing, itching, postnasal  
34 drainage, and ocular symptoms) compared to placebo. Snyman et al<sup>172</sup> performed a parallel, double

1 blind study comparing betamethasone 1mg alone to a combination of betamethasone and loratadine  
2 and loratadine alone in patients with severe AR. The group on oral steroids had a significant  
3 improvement from baseline in total nasal symptoms and was superior to loratadine alone.

4  
5 Although effective, oral corticosteroids have well recognized systemic adverse events,<sup>57</sup> and therefore,  
6 their use has been largely replaced by intranasal preparations. [TABLE II.C.] In a double-blind, placebo-  
7 controlled trial conducted during the ragweed season, the effect of intranasal flunisolide and its oral  
8 dose bioequivalent (an oral dose that would lead to similar systemic levels) were compared.<sup>173</sup> The  
9 intranasal preparation reduced rhinitis symptoms compared to placebo whereas the oral dosing did not,  
10 suggesting that INCS achieve their benefit primarily through local activity as opposed to systemic  
11 bioavailability.

12  
13 Karaki et al<sup>174</sup> compared the efficacy of INCS to systemic steroids by performing an open label, parallel,  
14 randomized trial during the cedar pollen season in Japan. Patients were randomized to receive  
15 loratadine 10mg daily alone, loratadine with intranasal mometasone furoate (200µg once daily), or  
16 loratadine with oral betamethasone 0.25mg twice daily for 1 week. Participants receiving any form of  
17 steroids demonstrated significantly reduced symptoms of sneezing, rhinorrhea, and nasal obstruction  
18 compared to loratadine alone, with no significant difference between the intranasal and oral  
19 preparations noted. The oral steroid was more effective than the INCS, however, in controlling allergic  
20 eye symptoms.

21  
22 In summary, oral corticosteroids are effective for the treatment of AR. However, given the significant  
23 systemic adverse effects related to using these agents for prolonged periods of time, and the availability  
24 of effective and less systemically available intranasal preparations, oral corticosteroids are not  
25 recommended for the routine treatment of AR.

26  
27 **Aggregate grade of evidence:** B (Level 2: 6 studies, level 3: 1 study, level 4: 3 studies; TABLE XI.B.2.a.)

28 **Benefit:** Oral corticosteroids can attenuate symptoms of AR and ongoing allergen induced inflammation.

29 **Harm:** Oral corticosteroids have multiple potential adverse effects, including hypothalamic-pituitary  
30 axis suppression. Prolonged use may lead to growth retardation in pediatric populations. See TABLE II.C.

31 **Cost:** Low.

32 **Benefits-harm assessment:** The risks of oral corticosteroids outweigh the benefits, given similar  
33 symptomatic improvement observed with the use of safer INCS.

34 **Value judgments:** In the presence of effective symptom control using INCS, the risk of adverse effects  
35 from using oral corticosteroids for AR outweighs potential benefits.

1 **Policy level:** Strong recommendation against routine use.

2 **Intervention:** Although not recommended for routine use in AR, certain clinical scenarios may warrant  
 3 the use of short courses of systemic corticosteroids, following a discussion of the risks and benefits with  
 4 the patient. For example, oral steroids could be considered in select patients with significant nasal  
 5 obstruction that precludes adequate penetration of intranasal agents (corticosteroids or  
 6 antihistamines). In these cases, a short course of systemic corticosteroids may improve congestion and  
 7 facilitate access of topical medications. No evidence supports this suggestion, and thus careful clinical  
 8 judgement and risk discussion are advocated.

9

10 **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 <sup>172</sup>	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 <sup>171</sup>	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 <sup>167</sup>	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 <sup>166</sup>	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 <sup>165</sup>	1987	2	Placebo-controlled, cross over, nasal challenge study	SAR out of season (n=13): prednisone 60mg PO daily for 2 days	Sneezes; levels of histamine, TAME-esterase, kinins, PGD <sub>2</sub> , LTC <sub>4</sub> /D <sub>4</sub> , albumin in nasal lavages	Prednisone inhibited the late phase response to nasal allergen challenge
Kwaselow et al <sup>173</sup>	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 <sup>174</sup>	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 <sup>170</sup>	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 <sup>169</sup>	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 <sup>168</sup>	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

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

#### 6 XI.B.2.b. Intranasal corticosteroids

##### 7 XI.B.2.b.i. Traditional spray application

8  
9 INCS have potent anti-inflammatory properties and lead to a significant reduction in mediator and  
10 cytokine release along with a significant inhibition in the recruitment of inflammatory cells to nasal  
11 secretions and the nasal mucosa.<sup>175-179</sup> INCS also reduce the antigen-induced hyperresponsiveness of the  
12 nasal mucosa to subsequent challenge.<sup>176,180,181</sup>

13  
14 Clinical trials in adults and children have demonstrated the effectiveness of INCS in the reduction of  
15 nasal symptoms in AR.<sup>182-184</sup> INCS also significantly improve patients' QOL<sup>183,185,186</sup> and sleep.<sup>187-191</sup> Onset  
16 of action starts at time points ranging from 3-5 hours to 60 hours after dosing.<sup>192-195</sup> Although the  
17 continuous daily use of INCS is overall superior,<sup>196,197</sup> studies have demonstrated the superiority of as  
18 needed use of intranasal fluticasone propionate over placebo<sup>198,199</sup> and one study showed equivalence  
19 of as needed to continuous dosing.<sup>200</sup> **[TABLE XI.B.2.b.i.-1]**

20  
21 INCS have beneficial effects on allergic eye symptoms,<sup>201-204</sup> secondary to a reduction in the naso-ocular  
22 reflex.<sup>205</sup> This effect is not equal among preparations.<sup>206</sup> Some, but not all, studies have suggested that  
23 INCS improve asthma control measures and asthma exacerbations.<sup>207-209</sup> **[TABLE XI.B.2.b.i.-2]**

24

1 In comparative studies there are no significant differences in efficacy between the available agents,<sup>185</sup>  
2 and one study shows an advantage of using double dosing.<sup>210</sup> INCS have shown superior efficacy to H<sub>1</sub>  
3 antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference  
4 in the relief of ocular symptoms.<sup>211-213</sup> However, for fast relief of nasal congestion (one hour after  
5 dosing) a combination of loratadine-pseudoephedrine was superior to intranasal fluticasone  
6 propionate.<sup>214</sup> INCS are more effective than LTRAs.<sup>213,215,216</sup> **[TABLE XI.B.2.b.i.-3]**

7  
8 Different preparations of INCS are comparable in efficacy, making sensory attributes an important factor  
9 in patient preference.<sup>217</sup> These include aftertaste, nose runout, throat rundown, and odor; there are  
10 minor differences between preparations.<sup>218</sup> Two intranasal nonaqueous preparations with  
11 hydrofluoroalkane aerosols, beclomethasone dipropionate and ciclesonide, address some of these  
12 concerns.<sup>219-224</sup>

13  
14 The most common side effects of INCS are a result of local irritation and include dryness, burning,  
15 stinging, blood-tinged secretions, and epistaxis. **[TABLE II.C.]** The incidence of epistaxis with different  
16 preparations ranges 4-8% over short treatment periods (2-12 weeks) with no differences between  
17 placebo and active therapy.<sup>225,226</sup> In studies carried over one year, epistaxis is as high as 20%.<sup>227,228</sup> Septal  
18 perforations are rare complications of INCS.<sup>229</sup> In a systematic review of biopsy studies in patients using  
19 INCS, none of the studies that evaluated atrophy of the nasal mucosa reported any atrophy with INCS.<sup>230</sup>  
20 Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis and adrenal  
21 insufficiency show no clinically relevant adverse effects.<sup>228,231-243</sup> Although there exists a report of  
22 association between INCS use and development of posterior subcapsular cataracts,<sup>244</sup> two systematic  
23 reviews of controlled trials did not demonstrate a clinically relevant impact of INCS on either ocular  
24 pressure, glaucoma, lens opacity, or cataract formation.<sup>245,246</sup> Therefore, it is reasonable to use these  
25 agents with caution in patients with increased intraocular pressure, glaucoma or cataracts. The effect of  
26 INCS on growth in children has been investigated in controlled short-term (2-4 weeks) and long-term (12  
27 months) studies. A meta-analysis of 8 RCTs showed that in the short-term, mean growth was  
28 significantly lower among children using INCS compared to placebo in trials using knemometry (n=4),  
29 but that in the long-term, there was no significant growth difference in studies using stadiometry  
30 (n=4).<sup>247</sup> The data suggest that INCS might have deleterious effects on short-term growth in children, but  
31 the heterogeneity of the results in the stadiometry studies (2 studies show growth increase and 2 show  
32 growth decrease) makes the effects on long-term growth suppression unclear. It is therefore wise to

1 check growth periodically in children on long-term INCS. [TABLE XI.B.2.b.i.-4]

2  
3 **Aggregate grade of evidence:** A (Level 1: 18 studies, level 2: 29 studies, level 3: 3 studies; TABLES  
4 XI.B.2.b.i.-1, XI.B.2.b.i.-2, XI.B.2.b.i.-3, XI.B.2.b.i.-4).

5 **Benefit:** INCS are effective in reducing nasal and ocular symptoms of AR. Studies have demonstrated  
6 superior efficacy compared to oral antihistamines and LTRAs.

7 **Harm:** INCS have known undesirable local adverse effects such as epistaxis with some increased  
8 frequency compared to placebo in prolonged administration studies. There are no apparent negative  
9 effects on the hypothalamic-pituitary axis. There might be some negative effects on short-term growth  
10 in children, but it is unclear whether these effects translate into long-term growth suppression. See

11 **TABLE II.C.**

12 **Cost:** Low.

13 **Benefits-harm assessment:** The benefits of using INCS outweigh the risks when used to treat seasonal or  
14 perennial AR.

15 **Value judgments:** INCS are first line therapy for the treatment of AR by virtue of their superior efficacy  
16 in controlling nasal symptoms. Subjects with seasonal AR should start prophylactic treatment with INCS  
17 several days before the pollen season with an evaluation of the patient's response a few weeks after  
18 initiation, including a nasal exam to evaluate for local irritation or mechanical trauma. Children receiving  
19 INCS should be on the lowest effective dose to avoid negative growth effects.

20 **Policy level:** Strong recommendation.

21 **Intervention:** The demonstrated efficacy of INCS, as well as their superiority over other agents, make  
22 them first line therapy in the treatment of AR.

23

24 **TABLE XI.B.2.b.i.-1 Evidence table – Intranasal corticosteroids (spray) for allergic rhinitis: clinical**  
25 **efficacy**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Rachelefsky et al <sup>186</sup>	2013	1	Systematic review	16 trials, children 2-18 years old with AR (n=2290 seasonal AR, n=800 perennial AR)	-Controlled studies $\geq 2$ weeks -Measures assessing impairment and/or risk of comorbidities	INCS improved risk outcomes associated with asthma & OSA
Rodrigo & Neffen <sup>183</sup>	2011	1	SRMA	-16 trials, n=5348 patients -FFNS vs placebo -Seasonal AR (7 studies), perennial AR (9 studies) -Adolescents & adults (13 studies, $\geq 12$ 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 <sup>182</sup>	2008	1	Meta-analysis of DBRCTs	-16 trials, n=2998 patients with AR -MFNS, n=1534 -Placebo, n=1464	-TNSS -Individual nasal symptoms -TNSS	MFNS significantly reduced TNSS, TNNSS, nasal stuffiness & congestion, rhinorrhea, sneezing, nasal itching

Thongngarm et al <sup>200</sup>	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 <sup>184</sup>	2019	2	Post-hoc analysis of 2 RCTs	-Patients with seasonal AR and moderate-severe nasal congestion, n=684 -MFNS vs placebo x15 days	Change from baseline in morning and evening reflective nasal congestion scores	-MFNS had significantly more patients who experienced >30% and >50% response in nasal congestion -In MFNS group, response greater during second week of treatment vs first
Yamada et al <sup>191</sup>	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 <sup>190</sup>	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 <sup>194</sup>	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 <sup>188</sup>	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 <sup>199</sup>	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 <sup>189</sup>	2003	2	DBRCT, crossover	-Patients with perennial AR, n=22 -Budesonide 128µg/day vs placebo x8 weeks	ESS; Functional Outcomes of Sleep Questionnaire; RQLQ; diary of nasal symptoms, sleep problems, daytime fatigue	Budesonide significantly improved daytime fatigue, somnolence, and quality of sleep vs placebo
Fokkens et al <sup>193</sup>	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 <sup>192</sup>	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 <sup>198</sup>	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 <sup>187</sup>	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 <sup>195</sup>	1998	2	DBRCT, parallel group	-Adults with perennial AR, n=273 -BANS -FPNS -Placebo -8-14 days (baseline), 6 weeks (treatment)	Mean combined nasal symptom scores (nasal blockage, runny nose, and sneezing)	-BANS decreased nasal symptoms more than FPNS -Both treatments decreased nasal symptoms vs placebo -Adverse events were mild and transient
Juniper et al <sup>196</sup>	1990	2	DBRCT, parallel group	-Ragweed-sensitive adults, n=60 -Aqueous BDNS 200µg BID -Aqueous BDNS 100µg as needed, up to 400µg daily	-Sneezing, stuffy nose, rhinorrhea, measured by a daily diary -QOL questionnaires -Rescue medication use (terfenadine)	Nasal symptoms, QOL, and rescue medication use significantly better in the regular-treated group vs to the as-needed group



Herman <sup>185</sup>	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 <sup>197</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; INCS=intranasal corticosteroid; OSA=obstructive sleep apnea;  
2 SRMA=systematic review and meta-analysis; FFNS=fluticasone furoate nasal spray; r=reflective; TNSS=Total Nasal  
3 Symptom Score; i=instantaneous; TOSS=Total Ocular Symptom Score; QOL=quality of life; DBRCT=double-blind  
4 randomized controlled trial; MFNS=mometasone furoate nasal spray; TNNSS=Total Non-Nasal Symptom Score;  
5 RCT=randomized controlled trial; PNIF=peak nasal inspiratory flow; RQLQ=Rhinoconjunctivitis Quality of Life  
6 Questionnaire; ESS=Epworth Sleepiness Scale; AHI=apnea-hypopnea index; WPAI-AS=Work Productivity and  
7 Activity Impairment-Allergy Specific; FPNS=fluticasone propionate nasal spray; BANS=budesonide aqueous nasal  
8 spray; BDNS=beclomethasone dipropionate nasal spray; BID=twice daily; TANS=triamcinolone aqueous nasal spray  
9

10 **TABLE XI.B.2.b.i.-2 Evidence table – Intranasal corticosteroids (spray) for allergic rhinitis: effect on**  
11 **comorbidities (ocular symptoms and asthma)**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Bielory et al <sup>204</sup>	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 <sup>208</sup>	2013	1	SRMA	Patients with AR and asthma, 18 trials, n=2162 patients	Pulmonary function, bronchial reactivity, asthma symptom scores, asthma specific	-INCS spray significantly improved FEV <sub>1</sub> , bronchial challenge, asthma symptom scores, morning/evening peak

					QOL, rescue medication use	expiratory flow, and rescue medication use -No significant changes in asthma outcomes with addition of INCS spray to orally inhaled corticosteroids
Bielory et al <sup>202</sup>	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 <sup>201</sup>	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
Taramarcas et al <sup>207</sup>	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 <sub>1</sub> , peak expiratory flow, methacholine test	Meta-analysis for asthma outcomes failed to show a statistically significant benefit of INCS
Ratner et al <sup>203</sup>	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 <sup>205</sup>	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 <sup>209</sup>	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

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; TANS=triamcinolone acetonide nasal  
 2 spray; FPNS=fluticasone propionate nasal spray; SRMA=systematic review and meta-analysis; QOL=quality of life;  
 3 INCS=intranasal corticosteroid; FEV<sub>1</sub>=forced expiratory volume in one second; DBRCT=double-blind randomized  
 4 controlled trial; TOSS=Total Ocular Symptom Score; r=reflective; FFNS=fluticasone furoate nasal spray

5

6 **TABLE XI.B.2.b.i.-3 Evidence table – Intranasal corticosteroids (spray) for allergic rhinitis: comparison**  
 7 **to other agents**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Khattiyawit-tayakun et al <sup>210</sup>	2019	1	SRMA	-12 studies, n=4166 -5 pediatric studies, n=1868 -5 adult studies, n=1414 -2 studies with mixed populations, n=884 -Double- vs standard-dose INCS	-TNSS -TOSS -Adverse events	-Adults: TNSS and TOSS scores favored double-dose INCS -Pediatric: TNSS, no difference; TOSS, insufficient data for analysis
Benninger et al <sup>213</sup>	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 <sup>215</sup>	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 <sup>212</sup>	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 <sup>211</sup>	1998	1	Meta-analysis of RCTs	-16 trials, subjects with AR, n=2267 -INCS vs oral antihistamines	Nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, nasal discomfort, total nasal symptoms,	-INCS had greater relief than oral antihistamines in nasal blockage, discharge, sneezing, nasal itch, postnasal drip, total nasal symptoms

					nasal resistance, eye symptoms, global ratings	-No significant differences between treatments for nasal discomfort, nasal resistance, eye symptoms
Ng et al <sup>214</sup>	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 <sup>216</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; INCS=intranasal corticosteroid; TNSS=Total  
 2 Nasal Symptom Score; TOSS=Total Ocular Symptom Score; SR=systematic review; RCT=randomized controlled trial;  
 3 AR=allergic rhinitis; US=United States; LTRA=leukotriene receptor antagonist; DBRCT=double-blind randomized  
 4 controlled trial; LP=loratadine-pseudoephedrine; FPNS=fluticasone propionate nasal spray; PNIF=peak nasal  
 5 inspiratory flow; MFNS=mometasone furoate nasal spray  
 6

7 **TABLE XI.B.2.b.i.-4 Evidence table – Intranasal corticosteroids (spray) for allergic rhinitis: side effects**  
 8 **and adverse events**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Sampieri et al <sup>243</sup>	2021	1	SRMA	-39 trials, n=1678, years of 1946-2020 -1 <sup>st</sup> and 2 <sup>nd</sup> 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 adrenocorticotrophic hormone stimulation)	-Pooled AI 0.70% -Short-term use: 0.48% -Medium term use: 1.13% -Long-term use: 1.67%
Valenzuela et al <sup>246</sup>	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%

						<ul style="list-style-type: none"> <li>-No cases of glaucoma in placebo or INCS at 12 months</li> <li>-Absolute increased incidence of developing posterior subcapsular cataract was 0.02%, nonsignificant increase</li> </ul>
Ahmadi et al <sup>245</sup>	2015	1	SR	<ul style="list-style-type: none"> <li>-19 studies (10 RCTs, 1 case-control, 8 case series), years of 1974-2013</li> </ul>	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 <sup>247</sup>	2015	1	SR of RCTs	<ul style="list-style-type: none"> <li>-8 studies, n=755, years of 1988-2013</li> <li>-Knemometry, n=342</li> <li>-Stadiometry, n=413</li> <li>-INCS for AR in children 3-12 years old</li> </ul>	Interval change in growth	<ul style="list-style-type: none"> <li>-Knemometry: mean growth significantly lower among children using INCS vs placebo</li> <li>-Stadiometry: no significant growth difference in INCS vs placebo</li> </ul>
Verkerk et al <sup>230</sup>	2015	1	SR	<ul style="list-style-type: none"> <li>-34 studies (11 RCTs, 5 cohort, 20 case series), years of 1946-2013</li> <li>-21 studies of rhinitis patients</li> <li>-13 studies of CRS patients</li> <li>-INCS with or without control group</li> </ul>	Histopathology assessment	<ul style="list-style-type: none"> <li>-No histological evidence for deleterious effects of INCS on human nasal mucosa</li> <li>-Significant reduction in odds of developing squamous metaplasia with INCS</li> </ul>
Hampel et al <sup>242</sup>	2015	2	DBRCT	<ul style="list-style-type: none"> <li>Patients with perennial AR (6-11 years old) treated for 6 weeks:</li> <li>-BDP nasal aerosol 80µg/day, n = 67</li> <li>-Placebo, n=32</li> </ul>	Change from baseline in 24-hour serum cortisol	<ul style="list-style-type: none"> <li>-No decrease in serum cortisol from baseline in either group</li> <li>-Serum cortisol concentration-time profiles similar for placebo and BDP groups at baseline and week 6</li> </ul>
Meltzer et al <sup>226</sup>	2009	2	Sub-analysis of 3 DBRCTs	<ul style="list-style-type: none"> <li>-Children (6-11 years old) with AR, n=948</li> <li>-Once-daily treatment with either FFNS 55µg, FFNS 110µg, or placebo</li> </ul>	Adverse event monitoring, nasal examinations, ophthalmic examinations, 24-hour urine cortisol, serum cortisol	<ul style="list-style-type: none"> <li>-Epistaxis 4% in active and placebo groups</li> <li>-No difference between groups for IOP</li> <li>-No posterior subcapsular cataracts</li> <li>-No difference in HPA measures between groups</li> </ul>
Ratner et al <sup>228</sup>	2009	2	RCT	<ul style="list-style-type: none"> <li>-Children (6-11 years old) with perennial AR treated for 12 months, n=255</li> <li>-MFNS 100µg daily</li> </ul>	Symptom control and safety	-Appropriate symptom control in both groups

				-BDPNS 168µg daily		-Incidence of epistaxis was 12.7% with MFNS and 9.4% for BDPNS
Tripathy et al <sup>241</sup>	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 <sup>240</sup>	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 <sup>225</sup>	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 <sup>239</sup>	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 <sup>238</sup>	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 <sup>237</sup>	2007	2	Two phase 3 RCTs,	-Children (2-5 years old) with perennial AR treated for 6 or 12 weeks	-Cortisol levels -Systemic exposure of ciclesonide	-Changes in plasma

			parallel group	-Ciclesonide 200µg daily	and its active metabolite, des-CIC, examined at end of 6-week study	or urine cortisol levels with ciclesonide were not significantly different from placebo -Serum concentrations of ciclesonide and des-CIC were below the lower limit of quantification in many samples
Rosenblut et al <sup>227</sup>	2007	2	DBRCT, parallel group	-Patients with perennial AR treated for 12 months, n=806 -FFNS 110µg -Placebo	Adverse events, 24-hour urine cortisol, nasal and ophthalmic examinations, electrocardiograms, clinical laboratory tests	-Incidence of adverse events similar to placebo, except epistaxis (active treatment 20%) -No clinically meaningful differences in ophthalmic parameters and 24-h urine cortisol excretion
Galant et al <sup>236</sup>	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

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

### 9 XI.B.2.b.ii. Non-traditional application

10  
11 INCS are typically administered with metered devices for AR. Alternate routes of delivery (irrigation and  
12 nebulization) have been studied. Periasamy et al<sup>248</sup> conducted a prospective, single center double-blind  
13 RCT in 52 patients with AR. Patients received buffered hypertonic saline nasal irrigation (60ml each  
14 nostril twice daily) with either a placebo or a budesonide respule (0.5mg/2ml) for 4 weeks. Patients  
15 were assessed using the SNOT-22 questionnaire, visual analog scale (VAS) for sneezing, nasal  
16 obstruction, itching, and nasal discharge, and nasal endoscopy findings. SNOT-22, VAS, and endoscopy  
17 score improved from baseline in both groups. The group on budesonide had significantly more  
18 improvement than the saline only group in SNOT-22 and VAS but not endoscopy scores. Study results  
19 suggest a beneficial effect of saline irrigations on AR symptoms that is enhanced when steroids are  
20 added. [TABLE XI.B.2.b.ii.]

1

2 Brown et al<sup>249</sup> investigated the effect of budesonide administered by nebulization in patients with  
3 perennial AR. Patients received either budesonide (0.25mg) or placebo (saline) delivered by nebulization  
4 once daily for 4 weeks. The patients on budesonide had significant increases in PNIF, decreases in  
5 symptoms and improvement in QOL compared to baseline but the changes were not significantly  
6 different from placebo.

7

8 Some studies evaluated the effect of corticosteroids in patients with both asthma and AR. Profita et al<sup>250</sup>  
9 randomized children with rhinitis and asthma to either nebulized beclomethasone (administered via  
10 face mask breathing through mouth and nose) or placebo twice daily for 4 weeks. Compared to baseline,  
11 concentrations of nasal IL-5 were significantly decreased, and nasal pH levels were significantly  
12 increased after beclomethasone treatment. Nasal symptom scores showed a significant reduction in  
13 obstruction, sneezing, and rhinorrhea after treatment with beclomethasone dipropionate, but no  
14 change after placebo. When the data were compared between beclomethasone and placebo groups,  
15 there were significant differences in favor of beclomethasone in nasal IL-5 and pH but not symptom  
16 scores. The significance of nasal pH increase is not clear but could lead to better mucociliary function.<sup>251</sup>

17 Active treatment did improve FEV<sub>1</sub> and asthma symptoms. In a similar study, Camargos et al<sup>252</sup>  
18 randomized patients with AR and asthma to either fluticasone propionate hydrofluoroalkane (FP-HFA)  
19 (100-150µg) inhaled through the nose (mouth closed) using a large volume spacer attached to a face  
20 mask or a nasal spray of isotonic saline plus oral inhalation of FP-HFA through a mouthpiece attached to  
21 the same spacer. After 8 weeks of treatment, there was a significant improvement in AR scores and  
22 nasal peak flow in the group who received FP-HFA through the nose compared to the group who  
23 received FP by mouth inhalation. There was a significant reduction in asthma scores and increase in FEV<sub>1</sub>  
24 values in both groups. Shaikh<sup>253</sup> performed an open, parallel crossover trial in patients with asthma and  
25 rhinitis and compared budesonide administered inhaled/intranasal to budesonide inhaler alone, exhaled  
26 through the nose. When exhaled through the nose, budesonide resulted in an improvement in nasal  
27 symptoms and nasal flow to a lesser extent than using intranasal budesonide but allowed for a  
28 significant reduction in the dose of intranasal budesonide required to improve nasal symptoms.

29

30 INCS are also used in drop form, usually for treatment of nasal polyps. In a few cases where they were  
31 used for AR, there was systemic absorption leading to unfavorable side effects such as growth inhibition  
32 and adrenal suppression<sup>254</sup> or iatrogenic Cushing syndrome.<sup>255</sup> In a study comparing fluticasone



1 propionate administered as nasal drops or aqueous spray, the drops had 8 times more systemic  
2 bioavailability than the spray.<sup>256</sup>

3  
4 **Aggregate grade of evidence:** B (Level 2: 4 studies, level 3: 1 study; **TABLE XI.B.2.b.ii.**) Some studies  
5 noted in the text above were not performed in patients with AR or were case reports so are not  
6 summarized in the table below.

7 **Benefit:** Nebulized steroids or those used via irrigation show some benefit in the treatment of AR in  
8 limited studies. Furthermore, steroids inhaled or exhaled through the nose in patients with asthma and  
9 rhinitis also show some benefit for rhinitis. Nasal steroid drops are not approved for treatment of  
10 rhinitis but are used in certain countries.

11 **Harm:** Nasal steroid drops have significant systemic side effects.

12 **Cost:** Low.

13 **Benefits-harm assessment:** The risks of using corticosteroid nasal drops for AR outweigh the benefits.  
14 Limited evidence suggests that nasal steroid irrigations for rhinitis lead to significant improvement of  
15 symptoms. Scarce evidence does not support routine recommendation for this route of therapy.

16 **Value judgments:** In the presence of effective symptom control using traditional spray administration  
17 for INCS, there is no solid data to support other routes of administration.

18 **Policy level:** Recommendation against routine use.

19 **Intervention:** There is some evidence that inhaled steroids, when exhaled through the nose might  
20 improve AR symptoms. Similar benefit is seen when steroids are inhaled by first passing through the  
21 nose. These routes might be useful in patients with both rhinitis and asthma.

22

23 **TABLE XI.B.2.b.ii. Evidence table – Intranasal corticosteroids (non-traditional application) for allergic**  
24 **rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Periasamy et al <sup>248</sup>	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 <sup>249</sup>	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 <sup>250</sup>	2013	2	DBRCT	Children with grass AR/asthma (n=40):	-Nasal and oral FeNO	-Nasal IL-5 significantly reduced & nasal pH

				-Nebulized BDP (400µg BID) -Placebo *Treatment for 4 weeks after a 2-week run-in *Inhalation via nose and mouth	-PFTs -Nasal and oral pH and IL-5 -Nasal and bronchial symptom scores	significantly increased with BDP -Reduction in nasal obstruction, sneezing, rhinorrhea with BDP, no change with placebo, no significant difference between groups
Camargos et al <sup>252</sup>	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 <sub>1</sub>	-Significant improvement in AR scores and PNIF in the nasal FP-HFA group - Significant reduction in asthma scores and increase in FEV <sub>1</sub> in both groups
Shaikh <sup>253</sup>	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)

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

7

8

### 9 XI.B.2.c. Injectible corticosteroids

10

11 Corticosteroids have been injected intramuscularly or into the turbinates for management of AR. Several

12 early studies demonstrated significant improvement in subjective allergy symptoms after intramuscular

1 corticosteroid injections. Four of these studies were single center RCTs with a placebo arm and modest  
2 numbers of participants.<sup>257-260</sup> [TABLE XI.B.2.c.]

3  
4 Studies comparing different intramuscular steroid preparations have showed improvement of  
5 symptoms with all variations but some differences in efficacy among them.<sup>261-264</sup> When compared to  
6 other agents, intramuscular corticosteroids demonstrated similar or superior efficacy in controlling  
7 symptoms of AR. Specifically, pre-seasonal betamethasone injection was as effective as daily oral  
8 prednisolone<sup>265</sup> and more effective than daily intranasal beclomethasone dipropionate in controlling  
9 nasal itching, congestion, rhinorrhea and eye symptoms.<sup>260</sup> In another seasonal study, a single injection  
10 of methylprednisolone was as effective as intranasal budesonide over a 3 week treatment period.<sup>266</sup>  
11 Although these studies show a favorable effect of intramuscular steroids on symptoms of AR, a recent  
12 systematic review was inconclusive based on a high risk of bias of the available studies that mostly dated  
13 back to more than 30 years ago.<sup>267</sup>

14  
15 Injectable corticosteroid preparations have significant potential side effects which can include adrenal  
16 suppression and growth retardation.<sup>268</sup> [TABLE II.C.] Injectable corticosteroids affected adrenal function  
17 in 2 out of 4 relevant studies.<sup>262,266</sup> [TABLE XI.B.2.c.] Evidence from a study of Danish National Registries  
18 shows that the relative risk and incidence of both osteoporosis and diabetes were higher in allergic  
19 individuals receiving at least one depot corticosteroid injection yearly for 3 consecutive years during the  
20 allergy season compared to those receiving AIT.<sup>269</sup> Laursen et al<sup>265</sup> reported that ACTH testing performed  
21 at 3 weeks showed significant suppression of adrenal function in the oral steroid treatment group but  
22 no evidence of suppression after a single corticosteroid injection. This discrepancy may relate to the  
23 short-lasting adrenal suppression after a single injection of corticosteroids compared to continuous  
24 administration of the oral formulation, although Kronholm<sup>261</sup> also did not show any effect of  
25 intramuscular preparations on adrenal function.

26  
27 Corticosteroid injection into the nasal turbinates has also been studied for the management of AR,  
28 however, this route is less widely utilized than previously observed. Several early reports detailed  
29 significant improvement in symptoms of AR in a large proportion of patients who received intra-  
30 turbinate injections of various steroid formulations.<sup>270-274</sup> A placebo-controlled, single-blind RCT showed  
31 that intra-turbinate injections of botulinum toxin A or triamcinolone in patients with perennial AR

1 resulted in improved control of nasal symptoms, including nasal congestion, compared to isotonic saline,  
2 although botulinum toxin had the longest duration of clinical effect.<sup>275</sup>

3  
4 Enthusiasm for intra-turbinate steroid injection has been tempered by reports of orbital complications  
5 associated with intra-turbinate, but not intramuscular, deposition. Complications have included  
6 transient visual loss and diplopia;<sup>276</sup> blurred vision and temporary blindness;<sup>277</sup> and temporary distorted  
7 vision, decreased visual acuity, and paresis of the medial rectus.<sup>277</sup> Martin reported on the rapid onset of  
8 ocular pain, blurred vision, and decreased visual acuity after an intra-turbinate injection of  
9 triamcinolone acetonide.<sup>278</sup> Symptoms were caused by choroidal and retinal arterial embolization and  
10 resolved completely within 24 hours. A more recent report detailed progression of glaucoma-related  
11 optic neuropathy after intra-turbinate injection associated with chorioretinal microvascular embolism.<sup>279</sup>  
12 The mechanism of embolization is likely related to retrograde flow from the anterior tip of the IT to the  
13 ophthalmic artery, followed by anterograde flow with the particles lodging in the end arteries of the  
14 choroid and retinal vessels. Larger particle size steroids (e.g., methylprednisolone) are thought to  
15 present higher risk than smaller sized particles (e.g., triamcinolone).<sup>278</sup> Moss et al<sup>280</sup> reported on  
16 personal experience with 152 turbinate and 85 intrapolyp injections of triamcinolone acetonide, noting  
17 one transient subjective decrease in vision after intrapolyp injection. They reviewed the literature for an  
18 estimated 117,000 individual intra-turbinate and polyp injections and reported an estimated visual  
19 complication rate of 0.003% (3 instances), with a 0.00% (0 instances) rate of permanent visual  
20 complications.

21  
22 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 11 studies, level 4: 2 studies; **TABLE XI.B.2.c.**)  
23 **Benefit:** Injectable corticosteroids improved symptoms of AR in clinical studies.  
24 **Harm:** Injectable corticosteroids have known undesirable adverse effects on the hypothalamic-pituitary  
25 axis, growth, osteoporosis, glycemic control and other systemic adverse effects, for varied periods of  
26 time after injection. Intraturbinate corticosteroids have a small but potentially serious risk of ocular side  
27 effects including decline or loss of vision. See **TABLE II.C.**  
28 **Cost:** Low.  
29 **Benefits-harm assessment:** In routine management of AR, the risk of serious adverse effects outweighs  
30 the demonstrated clinical benefit.  
31 **Value judgments:** Injectable corticosteroids are effective for the treatment of AR. However, given the  
32 risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of  
33 effective alternatives (e.g., INCS), injectable corticosteroids are not recommended for the routine  
34 treatment of AR.  
35 **Policy level:** Recommendation against.  
36 **Intervention:** None.

37  
38 **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 <sup>267</sup>	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 <sup>275</sup>	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 <sup>260</sup>	1988	2	Double blind, double dummy, placebo-controlled	Patients with SAR during season (n=30): -Intranasal beclomethasone dipropionate (400µg daily x4 weeks) -IM injection of 2ml betamethasone dipropionate/betamethasone disodium phosphate at beginning of season	Symptom scores (nasal blockage, rhinorrhea, sneezing, nasal itching, eye itching)	Depot injection was significantly more effective than placebo and intranasal preparation
Pichler et al <sup>266</sup>	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 <sup>258</sup>	1987	2	Double-blind, placebo-controlled, parallel	Patients with SAR during 2 consecutive allergy seasons (n=24), received injections each season:	-Sneezing and nose blowing during the day -Reflective symptom scores at end of day	-Marked beneficial effect of active treatment on nasal blockage lasting >4 weeks, moderate effect on eye symptoms

				-Methylprednisolone IM 80mg -Placebo		-Effect obtained irrespective of timing of therapy -Best to administer as soon as symptoms start during the season
Laursen et al <sup>265</sup>	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 <sup>262</sup>	1980	2	Prospective, randomized, parallel group	Patients with SAR during season (n=60) received one of 3 long-acting injections: -Betamethasone dipropionate (5mg) -Betamethasone disodium phosphate-acetate (3mg-3mg) -Methylprednisolone acetate (4 mg)	Symptom scores (rhinorrhea, congestion, ocular symptoms) at 1, 2, 4 weeks -Cortisol and glucose blood levels (n=38)	-All treatments led to significant reductions in nose and eye symptoms during season, no difference between groups -All preparations suppressed endogenous cortisol, in some cases >14 days post-injection, 2/3 injections increased blood glucose
Kronholm <sup>261</sup>	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 <sup>259</sup>	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 <sup>263</sup>	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 <sup>264</sup>	1968	2	Randomized, comparative	Patients with SAR (n=97) poorly responsive to	Patient satisfaction (none, poor, fair,	All treatments were beneficial with no difference between them

				hyposensitization or with no previous treatment received single injection: -Methylprednisone 80mg -Betamethasone phosphate-acetate (6mg-6mg) -Dexamethasone acetate-phosphate disodium (16mg-4mg) -Dexamethasone acetate 16mg	good, excellent) at 2 weeks	
Brown et al <sup>257</sup>	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 <sup>280</sup>	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 <sup>269</sup>	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

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

4

5

6 [XI.B.3. Decongestants](#)

7 [XI.B.3.a. Oral decongestants](#)

1  
2 Oral decongestants are medications that act on adrenergic receptors, which leads to vasoconstriction of  
3 small blood vessels (such as those in the nasal mucosa), resulting in relief of nasal congestion symptoms  
4 in AR patients. The most commonly used oral decongestants are pseudoephedrine and phenylephrine,  
5 which are sympathomimetic vasoconstrictors that differ in their selectivity to adrenoceptors.<sup>281</sup> Due to  
6 the oral administration of pseudoephedrine and phenylephrine, both drugs act systemically and can lead  
7 to side effects such as insomnia, headache, nervousness, anxiety, tremors, palpitations, urinary  
8 retention, increased blood pressure, and other adverse effects.<sup>85,282-284</sup> **[TABLE II.C.]**

9  
10 Our review of the literature found 12 studies that evaluate the use of oral decongestants in AR and are  
11 summarized in **TABLE XI.B.3.a**. Individual studies evaluating the effect of oral decongestants in AR  
12 patients as monotherapy during allergy season have shown that pseudoephedrine monotherapy led to  
13 improved symptom scores (total nasal symptom and individual symptom scores) compared to  
14 baseline.<sup>284-288</sup> One study also compared pseudoephedrine monotherapy against placebo and found that  
15 pseudoephedrine monotherapy is more effective in reducing total nasal symptom and nasal stuffiness  
16 scores than placebo.<sup>283</sup> With regard to the comparison of pseudoephedrine monotherapy against the  
17 combination therapy, including an oral antihistamine and pseudoephedrine, studies have shown that  
18 pseudoephedrine monotherapy is less effective than combination therapy in treating primary outcomes  
19 such as total nasal symptom and individual symptom scores.<sup>283-288</sup>

20  
21 Studies on the effectiveness of oral decongestants in AR patients as premedication monotherapy before  
22 allergy challenge have shown that pseudoephedrine is equally effective compared to montelukast<sup>289</sup> and  
23 more effective than placebo<sup>290,291</sup> in treating primary outcomes. One study showed that  
24 pseudoephedrine monotherapy was less effective than a combination therapy of an oral antihistamine  
25 and pseudoephedrine,<sup>290</sup> while another study showed no difference in outcome.<sup>291</sup> The results in head-  
26 to-head comparisons between antihistamine and pseudoephedrine monotherapy are contradictory.  
27 While some studies showed that antihistamine monotherapy was more efficient than  
28 pseudoephedrine,<sup>285,290</sup> other studies have had different findings.<sup>284-286,288,292</sup> Nonetheless, either  
29 monotherapy (i.e., pseudoephedrine or antihistamine) was more effective than placebo.<sup>283,285,290,291</sup>  
30 Interestingly, an analysis of the effectiveness of phenylephrine compared to placebo has shown that  
31 phenylephrine (up to doses of 40mg six times daily) is not superior to placebo in relieving nasal  
32 congestion symptoms in AR patients.<sup>293</sup>



- 1  
2 **Aggregate grade of evidence:** A (Level 2: 12 studies; **TABLE XI.B.3.a.**)  
3 **Benefit:** Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.  
4 **Harm:** Oral decongestants have known undesirable adverse effects. See **TABLE II.C.**  
5 **Cost:** Low.  
6 **Benefits-harm assessment:** Balance of benefit and harm for pseudoephedrine. Possible harm for  
7 phenylephrine.  
8 **Value judgments:** Little evidence for benefit in controlling symptoms other than nasal congestion.  
9 **Policy level:** Strong recommendation against for routine use in AR. In certain cases, combination therapy  
10 with an oral antihistamine may be beneficial to alleviate severe nasal congestion in short courses.  
11 **Intervention:** Although not recommended for routine use in AR, pseudoephedrine can be effective in  
12 reducing nasal congestion in patients with AR; however, it should only be used as short-term/rescue  
13 therapy after a discussion of the risks and benefits with the patient (comorbidities) and consideration of  
14 alternative intranasal therapy options.  
15  
16

**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 <sup>293</sup>	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 <sup>286</sup>	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 <sup>289</sup>	2005	2	DBRCT	SAR during season (n=58, 18-45 years old): -Montelukast 10mg daily -PSE HCL 240mg sustained release daily	-RQLQ -Nocturnal RQLQ -Total symptom score -PNIF	-PSE and montelukast were nearly equally effective and improved QOL scores, PNIF, symptom scores compared to baseline -PSE controlled nasal congestion better than montelukast
Pleskow et al <sup>294</sup>	2005	2	DBRCT	SAR during season (n=1047, 12-78 years old): -Desloratadine 5mg + PSE 240mg	-Total symptom score (excluding nasal congestion)	-Desloratadine-PSE provided additional

				sustained release daily -Desloratadine 5mg daily -PSE 240mg sustained release daily	-Nasal congestion score	benefit over individual components alone -Monotherapies were equally effective and led to improved symptom scores vs baseline
Sussman et al <sup>288</sup>	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 <sup>284</sup>	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 <sup>287</sup>	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 <sup>285</sup>	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 <sup>283</sup>	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 <sup>292</sup>	1993	2	DBRCT, cross-over	Allergen challenge with premedication: *First part -- AR (n=12, 12-40 years old) -PSE 60mg -Placebo, pretreatment Study protocol: 6 tablets on two days before challenge, 1 tablet on the morning of challenge day *Second part – perennial AR (n=17, 19-56 years old) -PSE 120mg -Terfenadine 60mg -PSE 120mg + terfenadine 60mg -Placebo Study protocol: 5 doses of medication BID on the 2 days before challenge, 1 dose on the morning of challenge day	-First part: nasal airway resistance after challenge -Second part: nasal itching, sneezing, rhinorrhea, blockage	There is benefit of combination therapy (PSE-terfenadine) over each individual component when administered alone for all nasal symptoms associated with AR
Henauer et al <sup>290</sup>	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 <sup>291</sup>	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

1 LOE=level of evidence; RCT=randomized controlled trial; SSAR=seasonal allergic rhinitis; PE=phenylephrine;

2 HCL=hydrochloride; DBRCT=double-blind randomized controlled trial; PSE=pseudoephedrine; BID=twice daily;

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

3

4

### 5 XI.B.3.b. Intranasal decongestants

6

7 INDC – oxymetazoline, xylometazoline, and phenylephrine – are alpha-adrenergic agonists acting as  
8 topical vasoconstrictors reducing edema/tissue thickness.<sup>65</sup> The highest level of evidence consists of 7  
9 RCTs<sup>295-301</sup> looking at short-term effects of INDC. There are also 3 RCTs<sup>302-304</sup> and 2 cohort studies<sup>305,306</sup>  
10 evaluating prolonged effects of INDC.

11

12 Clinically, short-term use results in reduction of nasal congestion/blockage, with little to no effect on  
13 allergic symptoms such as sneezing, rhinorrhea, or nasal itching.<sup>295,296,298,299</sup> Onset of action is within 10  
14 minutes,<sup>297</sup> and duration of the effect lasts up to 12 hours.<sup>301</sup> There are also improvements in objective  
15 measures of nasal congestion/blockage, including nasal airway resistance, measures of nasal cavity  
16 volume for airflow, and PNIF.<sup>296-300</sup> Measures of nasal cavity volume for airflow exhibit a clear dose-  
17 response relationship across doses ranging from 6.25 to 50µg, with nasal airway resistance requiring a  
18 higher threshold dose of 25µg before significant changes in nasal patency are seen.<sup>298</sup> Despite  
19 oxymetazoline's vasoconstrictive effects, it does not seem to affect histamine-induced plasma  
20 exudation.<sup>295</sup> The majority of studies compared INDC to placebo,<sup>295-298,300</sup> but Barnes et al<sup>299</sup> found that  
21 the decongestant response was stronger for intranasal xylometazoline after 15 minutes than daily  
22 administration of intranasal mometasone furoate after 28 days. It is worth noting that only 3 studies  
23 included patients with AR,<sup>299-301</sup> the remainder consisted of healthy participants.<sup>295-298</sup>

24

25 Rhinitis medicamentosa, which is a condition thought to result from prolonged usage of INDC, is  
26 characterized by an increase in symptomatic nasal congestion, thereby precluding a recommendation  
27 for long-term use of these medications. Studies to identify the duration of intranasal decongestant use  
28 that leads to rhinitis medicamentosa have shown variable results. Some studies show prolonged use (up  
29 to 6 weeks) does not produce any symptoms of rebound nasal congestion or objective markers of  
30 impaired decongestant response.<sup>303,305,306</sup> Another study, however, noted development of rhinitis  
31 medicamentosa after as little as 3 days of use.<sup>302</sup> This may be due to nasal hyperreactivity and mucosal  
32 swelling. Additionally, Graf et al<sup>304</sup> looked at the impact of the presence of the preservative  
33 benzalkonium chloride, which can be found in INDC sprays. Compared to oxymetazoline and placebo  
34 nasal sprays, a nasal spray with benzalkonium chloride alone induces mucosal swelling, suggesting the

1 presence of this preservative may aggravate rhinitis medicamentosa. (See Section V.B.2 Rhinitis  
 2 Medicamentosa for additional information on this topic.)  
 3  
 4 Known adverse effects of INDC include nasal discomfort/burning, dependency, dryness, increased  
 5 congestion, rhinitis medicamentosa, hypertension, anxiety, and tremors. [TABLE II.C.] One study noted  
 6 significantly decreased ciliary beat frequencies at 1000µg/mL, but no significant difference at  
 7 500µg/mL.<sup>307</sup> The 500µg/mL (0.5 mg/mL, 0.05%) concentration is typical for available formulations. In  
 8 sum, while intranasal decongestants are effective at reducing nasal congestion, short-term use of the  
 9 medication, approximately 3 days or less, is recommended to avoid the potential for rebound nasal  
 10 congestion and rhinitis medicamentosa.<sup>302</sup>

11  
 12 **Aggregate grade of evidence:** B (Level 2: 10 studies, level 3: 2 studies; TABLE XI.B.3.b.) Limitation -- only  
 13 3 studies included subjects with AR.

14 **Benefit:** Reduction in symptoms of nasal congestion/blockage and corresponding objective markers with  
 15 INDC compared to placebo.

16 **Harm:** Side effects include nasal discomfort/burning, dependency, dryness, hypertension, anxiety, and  
 17 tremors. See TABLE II.C. Potential for rebound congestion with long-term use.

18 **Cost:** Low.

19 **Benefits-harm assessment:** Harm likely outweighs benefit if used long-term, with adverse effects  
 20 appearing as early as 3 days.

21 **Value judgments:** INDC can be helpful for short-term relief of nasal congestion.

22 **Policy level:** Option for short-term use.

23 **Intervention:** INDC can provide effective short-term relief of nasal congestion in patients with AR during  
 24 an acute flare but recommend against chronic use due to risk of rhinitis medicamentosa.

25

26 **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 <sup>301</sup>	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 <sup>297</sup>	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 <sup>300</sup>	2014	2	RCT	Nasal congestion due to upper respiratory	-Inferior turbinate total volume	Up to and including 12 hours post-treatment,

				infection or hay fever (n=21): -Intranasal oxymetazoline -Placebo	-Middle turbinate total volume	there was a significant reduction in inferior and middle turbinate volumes with oxymetazoline vs placebo
Barnes et al <sup>299</sup>	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 <sup>303</sup>	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 <sup>296</sup>	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 <sup>298</sup>	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 <sup>302</sup>	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 <sup>304</sup>	1996	2	DBRCT	Healthy participants (n=30): -Intranasal oxymetazoline TID x28 days -Intranasal benzalkonium chloride TID x28 days -Placebo	-Nasal mucosal swelling -Subjective nasal stuffiness and secretions -Nasal reactivity	-Following 28 days of treatment (long-term), subjective nasal stuffiness, secretions, and reactivity were greatest with oxymetazoline -Increase in nasal mucosal swelling with benzalkonium chloride alone

Svensson et al <sup>295</sup>	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 <sup>305</sup>	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 <sup>306</sup>	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

1 LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; PNIF=peak nasal  
2 inspiratory flow; RCT=randomized controlled trial; TID=three times daily  
3 \*Limitation – only 3 of the listed studies specifically addressed the use of intranasal decongestants in patients with  
4 AR  
5  
6

#### 7 XI.B.4. Leukotriene receptor antagonists

8  
9 LTRAs have been studied and used in the treatment of AR. Montelukast is approved by the US FDA for  
10 the treatment of seasonal AR in adults and children over 2 years of age, and for perennial AR in adults  
11 and children over 6 months of age. Other LTRAs include pranlukast (approved for treatment of AR in  
12 Japan) and zafirlukast (FDA-approved for treatment of asthma).  
13

14 Since the 2018 ICAR-Allergic Rhinitis consensus statement,<sup>308</sup> the body of evidence surrounding LTRA  
15 monotherapy has grown. A systematic search revealed 15 SRMAs of RCTs published since 2014. This  
16 gave a total of 34 studies examining the use of LTRA in AR which are considered high-level evidence.  
17

#### 17 [TABLE XI.B.4.]

18  
19 Most recent studies<sup>309-313</sup> demonstrate concordance with previous findings that LTRA monotherapy is  
20 superior to placebo in controlling symptoms and improving QOL in both seasonal and perennial AR,  
21 except a single RCT<sup>314</sup> which showed no difference between the two. Yoshihara et al<sup>315</sup> found that LTRA  
22 showed promise as a prophylactic agent in children with seasonal AR when administered before the  
23 Japanese Cedar pollen season.  
24

25 However, there remains consistent evidence that LTRA is inferior to INCS in terms of symptom reduction  
26 and QOL improvement.<sup>216,316,317</sup> In a RCT by Chen et al,<sup>316</sup> LTRA was inferior to INCS in improving acoustic

1 rhinometry readings, concentrations of inflammatory mediators in nasal secretions, and the  
 2 inflammatory cell composition (Th1, Th2, Treg) from turbinate brush cytology. Dalgic et al<sup>318</sup> found LTRA  
 3 to be inferior to INCS in improving olfactory function in patients with seasonal AR. In comparison to oral  
 4 antihistamines, there remains mixed evidence for relative efficacy,<sup>319-321</sup> with recent studies favoring oral  
 5 antihistamines. Comparing diurnal symptoms of AR, Feng et al<sup>319</sup> found LTRA to be superior to oral  
 6 antihistamines for controlling nighttime symptoms, but inferior for daytime symptoms. LTRA  
 7 monotherapy was further compared against AIT and found to be inferior for symptom control.<sup>309,322</sup> Li et  
 8 al<sup>323</sup> compared LTRA monotherapy to acupoint-application of Chinese herbal medication and found no  
 9 difference in symptom control for children with perennial AR.

10

11 In March 2020, the US FDA announced a safety concern regarding montelukast and potential serious  
 12 neuropsychiatric events, including suicidal thoughts. A boxed warning, the FDA's most prominent  
 13 warning, was added to prescribing information. The FDA advised further that in AR, montelukast should  
 14 be reserved for patients who are not treated effectively with or cannot tolerate other allergy  
 15 medications.<sup>324</sup>

16

17 In their 2015 guidelines for AR, the American Academy of Otolaryngology-Head and Neck Surgery  
 18 recommended against LTRA monotherapy, as it was less effective than other first-line medications and  
 19 more costly.<sup>85</sup> In 2020, this guideline was endorsed by the American Academy of Family Physicians.<sup>325</sup> In  
 20 the same year, the Joint Task Force on Practice Parameters issued an update recommending against the  
 21 selection of LTRA as initial treatment of AR.<sup>65</sup>

22

23 While LTRA monotherapy has been consistently shown to be superior to placebo for the treatment of  
 24 AR, there is now significant evidence that alternative agents such as INCS are superior and less costly.<sup>308</sup>  
 25 Given the increased risk profile of LTRA highlighted by the FDA boxed warning, LTRA monotherapy is not  
 26 recommended as first-line therapy for patients with AR but may be considered in selected patients who  
 27 have contraindications to both oral antihistamines and INCS.

28

29 **Aggregate grade of evidence:** A (Level 1: 13 studies, level 2: 21 studies; **TABLE XI.B.4**)

30 **Benefit:** Consistent reduction in symptoms and improvement in QOL compared to placebo.

31 **Harm:** FDA boxed warning regarding neuropsychiatric side effects, including suicidal ideation.

32 Consistently inferior compared to INCS at symptom reduction and improvement in QOL. Equivalent or  
 33 inferior effect compared to oral antihistamines in symptom reduction and improvement of QOL. See

34 **TABLE II.C.**



- 1 **Cost:** Moderate.
- 2 **Benefits-harm assessment:** LTRAs are effective as monotherapy compared to placebo. However, there
- 3 is a consistently inferior or equivalent effect to other, less expensive agents used as monotherapy. Also,
- 4 there is an FDA boxed warning associated with LTRAs.
- 5 **Value judgments:** LTRAs are more effective than placebo at controlling both asthma and AR symptoms
- 6 in patients with both conditions. However, in the light of significant concerns over its safety profile and
- 7 the availability of effective alternatives such as INCS and oral antihistamines, evidence is lacking to
- 8 recommend LTRAs as monotherapy in the management of AR.
- 9 **Policy level:** Recommendation against LTRAs as first-line monotherapy for patients with AR. Option for
- 10 LTRA as monotherapy in patients with contraindications to other preferred treatments.
- 11 **Intervention:** LTRAs should not be used as monotherapy in the treatment of AR but can be considered in
- 12 select situations where patients have contraindications to alternative treatments.
- 13
- 14

**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 <sup>319</sup>	2021	1	SR of RCTs	-LTRA -OAH	-Symptoms -QOL -Adverse events	-LTRA superior for nighttime symptoms -OAH superior for daytime symptoms
Meltzer et al <sup>309</sup>	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 <sup>310</sup>	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 <sup>313</sup>	2016	1	Pooled analysis	-Montelukast -OAH -INCS -SLIT -Placebo	TNSS	-LTRA superior to placebo -LTRA inferior to OAH, INCS, SLIT
Wei <sup>312</sup>	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 <sup>320</sup>	2016	1	Network meta-analysis	-Montelukast -OAH	Symptoms	LTRA inferior to OAH
Devillier et al <sup>322</sup>	2014	1	SR of RCTs	-LTRA -SLIT -Placebo	Symptoms	-SLIT superior to LTRA -LTRA superior to placebo
Xu et al <sup>321</sup>	2014	1	SR of RCTs	-Montelukast -OAH	Symptoms	In SAR, OAH superior for daytime symptoms and LTRA superior for nighttime symptoms
Goodman et al <sup>326</sup>	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 <sup>327</sup>	2006	1	SR of RCTs	-Montelukast -OAH -INCS -Placebo	-Symptoms -QOL	-Montelukast improved symptoms and QOL compared to placebo -Montelukast was inferior to OAH and INCS
Rodrigo & Yanez <sup>328</sup>	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 <sup>215</sup>	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 <sup>329</sup>	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 <sup>216</sup>	2020	2	RCT	-Montelukast -INCS	TNSS	INCS superior to LTRA for symptom reduction
Li et al <sup>323</sup>	2020	2	RCT	-Montelukast -Chinese acupoint application -Combination therapy	-Symptoms -Serum IL-4, IFN- $\gamma$ , Th1/Th2	Combination LTRA and Chinese acupoint application superior to either therapy alone
Chen et al <sup>316</sup>	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 <sup>314</sup>	2018	2	RCT	-Montelukast -Placebo	Symptoms	No difference in LTRA vs placebo
Dalgic et al <sup>318</sup>	2017	2	RCT	-Montelukast -INCS -Montelukast + INCS	Olfactory testing	-No change with LTRA monotherapy -Combination therapy was superior to INCS

Okubo et al <sup>311</sup>	2017	2	RCT	-ONO-4053 (anti-PGD2) -Pranlukast -Placebo	Symptoms	-Pranlukast superior to placebo -ONO-4053 superior to pranlukast
Yoshihara et al <sup>315</sup>	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 <sup>317</sup>	2016	2	RCT	-Montelukast -INCS	Symptoms	INCS superior to LTRA
Endo et al <sup>330</sup>	2012	2	RCT	-Pranlukast -Placebo	Symptoms	Following artificial introduction of allergen, pranlukast prevented and reduced symptoms vs placebo
Wakabayashi et al <sup>331</sup>	2012	2	RCT	-Pranlukast -Placebo	Symptoms	Following artificial introduction of allergen in children, pranlukast prevented and reduced symptoms vs placebo
Day et al <sup>332</sup>	2008	2	RCT	-Montelukast -Levocetirizine -Placebo	Symptoms	-Both montelukast and levocetirizine improved symptoms following artificial allergen exposure -Levocetirizine was more effective than montelukast
Jiang <sup>333</sup>	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 <sup>289</sup>	2006	2	RCT	-Montelukast -Pseudoephedrine	-Symptoms -QOL -PNIF	Montelukast and pseudoephedrine had equivalent improvement of symptoms (except pseudoephedrine more effective for nasal congestion), QOL, PNIF
Patel et al <sup>334</sup>	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 <sup>335</sup>	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 <sup>336</sup>	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 <sup>337</sup>	2003	2	RCT	-Montelukast -Fluticasone	-Symptoms -QOL	Fluticasone was more effective than montelukast in reducing symptoms and improving QOL
van Adelsberg et al <sup>338</sup>	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 <sup>339</sup>	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 <sup>340</sup>	2002	2	RCT	-Montelukast -Loratadine -Placebo	-Symptoms -QOL -Peripheral eosinophil count	-Montelukast was more effective than placebo at reducing eosinophil count, and improving symptoms and QOL -Montelukast was not directly compared to loratadine
Pullerits et al <sup>341</sup>	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

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

6  
7

#### 8 XI.B.5. Intranasal cromolyn

9

10 Disodium cromoglycate (DSCG) [synonyms: cromolyn sodium, sodium cromoglycate, disodium 4,4'-

11 dioxo-5,5'-(2-hydroxytrimethylenedioxy)di(4H-chromene-2-carboxylate)] is a mast cell stabilizer that

1 inhibits the release of mast cell mediators that promote IgE-mediated inflammation.<sup>342,343</sup> DSCG is FDA-  
2 approved for adults and children (2 years and older) for the prevention and relief of nasal symptoms of  
3 AR and is available as an over-the-counter nasal spray. It has a rapid onset of action with efficacy lasting  
4 up to 8 hours, taken as 1 spray 3-6 times daily, and is primarily used to prevent the onset of symptoms  
5 prior to allergen exposure, but it also can be used to treat symptoms once they occur.<sup>344-347</sup>

6  
7 DSCG exhibits an excellent safety profile with only minor adverse effects including nasopharyngeal  
8 irritation, sneezing, rhinorrhea, and headache. There are very rare reports of immediate IgE-mediated  
9 reaction to the medication.<sup>348,349</sup> Due to its high safety profile, this medication can be considered for  
10 very young children and pregnant patients.<sup>350,351</sup>

11  
12 DSCG has been shown to be more effective than placebo patients with seasonal AR in controlling nasal  
13 symptoms of sneezing, rhinorrhea, and nasal congestion as treatment during their peak allergy  
14 season.<sup>352-356</sup> The largest double-blinded placebo-controlled trial included 1150 patients with seasonal  
15 AR treated for 2 weeks (580 patients on DSCG, 570 treated with placebo).<sup>352</sup> Patients received DSCG as a  
16 4% nasal solution, 1 spray every 4-6 hours, no more than 6 times per day. DSCG was significantly better  
17 than placebo in controlling overall symptom relief ( $p=0.02$ ), sneezing ( $p=0.01$ ), and nasal congestion  
18 ( $p=0.03$ ). Studies on the superiority of DSCG versus placebo in perennial AR have been controversial and  
19 with relatively small sample size.<sup>357-361</sup> In the most recent study that demonstrated a benefit of DSCG in  
20 perennial AR ( $n=14$ ), DCSG resulted in significant improvement in the symptoms scores of runny nose,  
21 nasal congestion, sneezing, and nose blowing, when compared to placebo ( $p<0.005$ ).<sup>357</sup> Additionally,  
22 factors that were found to be associated with a good clinical response to the medication included: (1)  
23 patients with higher IgE levels, (2) patients with markedly positive skin test reactions to foods and  
24 animal dander compared to pollen allergy, and (3) female gender.<sup>357</sup> **[TABLE XI.B.5]**

25  
26 In a small study, DSCG demonstrated similar efficacy for controlling nasal symptoms compared to oral  
27 antihistamines and significantly reduced the number of nasal eosinophils, whereas oral antihistamines  
28 did not.<sup>362</sup> When compared to intranasal antihistamines<sup>363,364</sup> and INCS,<sup>358,364-373</sup> DSCG has been shown to  
29 be less effective in controlling nasal symptoms. Ultimately, the role of DSCG as a primary treatment for  
30 AR is limited given its lower efficacy when compared to INCS and potential compliance challenges  
31 secondary to a frequent dosing regimen. The medication can also be administered as a preventive  
32 strategy, prior to allergen exposure to reduce the development of AR symptoms.

- 1  
2 **Aggregate grade of evidence:** A (Level 2 studies: 25 studies; **TABLE XI.B.5.**)  
3 **Benefit:** DSCG is effective in reducing sneezing, rhinorrhea, and nasal congestion.  
4 **Harm:** Rare local side effects.  
5 **Cost:** Low.  
6 **Benefits-harm assessment:** Preponderance of mild to moderate benefit over harm. Less effective than  
7 INCS and intranasal antihistamines.  
8 **Value judgments:** DSCG is useful for preventative short-term use in adult-patients, children (2 years and  
9 older), and pregnant patients with known exposure risks.  
10 **Policy level:** Recommendation as a second-line treatment in AR.  
11 **Intervention:** DSCG may be used as a second line treatment for AR in patients who fail INCS or intranasal  
12 antihistamines, or for short-term preventative benefit prior to allergen exposures.  
13  
14

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lejeune et al <sup>357</sup>	2015	2	DBRCT	Adults with mild-moderate persistent AR mono-sensitized to HDM: -DSCG QID, n=14 -Placebo, n=7	Nasal symptoms	DSCG was more efficacious than placebo
Pistios et al <sup>373</sup>	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 <sup>364</sup>	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 <sup>352</sup>	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 <sup>365</sup>	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 <sup>366</sup>	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 <sup>362</sup>	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 <sup>363</sup>	1991	2	DBRCT	Patients with SAR: -Levocabastine HCL 0.5mg/ml, 2 sprays each nostril QID, n=18 -DSCG 20mg/ml, 2 sprays QID, n=19 -Placebo, n=20	Nasal/ocular symptoms	Levocabastine was most efficacious
Schuller et al <sup>374</sup>	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 <sup>367</sup>	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 <sup>368</sup>	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 <sup>369</sup>	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 <sup>353</sup>	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 <sup>370</sup>	1981	2	RCT	Patients with SAR: -DSCG 2.6mg, 6 times daily, n=29 -Flunisolide spray 25µg BID, n=38	Nasal symptoms	Flunisolide was more efficacious than DSCG
Tandon & Strahan <sup>358</sup>	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 <sup>375</sup>	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 <sup>354</sup>	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 <sup>359</sup>	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 <sup>355</sup>	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 <sup>376</sup>	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 <sup>360</sup>	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 <sup>361</sup>	1976	2	DBRCT, cross-over	Perennial AR (n=34, 16-37 years old): -DSCG 4%, 6 times daily -Placebo	-Symptom score -Rescue medication use	DSCG was more efficacious than placebo
Knight et al <sup>356</sup>	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 <sup>371</sup>	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 <sup>372</sup>	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

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

5  
6

### 7 XI.B.6. Intranasal anticholinergics

8

9 IPB is a synthetic quaternary ammonium anticholinergic compound that is related to atropine. Effects of  
10 IPB have been explored prior to nasal methacholine challenge in patients with AR and was found to  
11 reduce rhinorrhea and sneezing with no effects on nasal airway resistance.<sup>377,378</sup> In addition,  
12 administration of IPB resulted in the reduction of rhinorrhea following cold air exposure and following  
13 the ingestion of hot soup, which suggested that this type of rhinorrhea is mediated through a reflex



1 leading to hypersecretion from nasal glands.<sup>379</sup> IPB is effective in controlling anterior rhinorrhea with no  
2 effect on nasal congestion or sneezing.<sup>380-385</sup> IPB is available at 0.03% and 0.06% concentration and is  
3 effective in adults and children with perennial rhinitis (0.03%) and common cold (0.06%).<sup>383,386</sup> It has a  
4 quick onset of action and short half-life and can be administered up to 6 times per day, with less than  
5 10% absorption over a range of 84µg/day to 336µg/day.<sup>387</sup>

6

7 Intranasal IPB is poorly absorbed, and systemic side effects have not been observed with therapeutic  
8 dosing, as plasma concentrations of greater than 1.8ng/ml are needed to produce systemic  
9 anticholinergic effects.<sup>387</sup> However, care should be taken to avoid overdosage that could lead to high  
10 serum concentrations of ipratropium. Side effects of topical IPB are mostly local. **[TABLE II.C.]**

11

12 IPB is FDA-approved for the treatment of seasonal AR in both adults and children (5 years and older). IPB  
13 also controls rhinorrhea in children and adults with perennial AR.

14

15 The largest study that compared IPB to placebo was conducted on perennial AR and perennial non-  
16 allergic rhinitis in pediatric patients aged 6-18 years.<sup>388</sup> A total of 204 patients were included in this  
17 double-blind RCT, divided equally between IPB and placebo subgroups. There was a significant  
18 reduction in the severity and duration of rhinorrhea and improvement in QOL in the IPB group. The  
19 effect was more pronounced in the perennial non-allergic rhinitis group compared to the perennial AR  
20 group. **[TABLE XI.B.6.]**

21

22 Evidence on the efficacy of IPB in seasonal AR is derived from two studies, a prospective study and a  
23 double-blind RCT. The prospective study included a total of 230 children aged 2-5 years old with  
24 seasonal or perennial AR and found that IPB was safe and effective in controlling rhinorrhea.<sup>386</sup> In the  
25 double-blind RCT cross-over trial (n=24), adults aged 18-49 with seasonal AR, perennial AR, and non-  
26 allergic perennial rhinitis the local pretreatment with IPB effect on methacholine challenge was  
27 studied.<sup>378</sup> IPB was found to be more effective than placebo in suppressing sneezing and nasal  
28 hypersecretion with no effect on nasal airway resistance.

29

30 When compared to other medications for treating AR, IPB has been shown to be equally effective  
31 compared to INCS with respect to nasal drainage. Despite its beneficial effects on rhinorrhea and  
32 sneezing, IPB was shown to be inferior to INCS in controlling sneezing.<sup>389</sup> No head-to-head studies have

1 compared IPB to other AR medications.

2

3 **Aggregate grade of evidence:** A (Level 2: 10 studies; level 3: 2 studies; **TABLE XI.B.6.**)

4 **Benefit:** Reduction of rhinorrhea with topical anticholinergics.

5 **Harm:** Care should be taken to avoid overdosage leading to systemic side effects. See **TABLE II.C.**

6 **Cost:** Low.

7 **Benefits-harm assessment:** Preponderance of benefit over harm in AR patients with rhinorrhea.

8 **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.

9 **Policy level:** Option.

10 **Intervention:** IPB nasal spray may be used as an adjunct medication to INCS in AR patients with persistent rhinorrhea.

11

12

13

14

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dockhorn et al <sup>390</sup>	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 <sup>389</sup>	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 <sup>391</sup>	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 <sup>383</sup>	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 <sup>388</sup>	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 <sup>392</sup>	1993	2	DBRCT	Perennial AR (n=18, 23-33 years old): -IPB 80µg QID -Placebo	Sneezing	IPB resulted in increase in nasal reactivity to histamine, increase in number of sneezes

Meltzer et al <sup>393</sup>	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 <sup>378</sup>	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 <sup>394</sup>	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 <sup>395</sup>	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 <sup>386</sup>	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 <sup>384</sup>	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

1 LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; IPB=ipratropium  
2 bromide; TIC=three times daily; BDP=beclomethasone dipropionate; RCT=randomized controlled trial; BID=twice  
3 daily; QOL=quality of life; PO=per os (by mouth); QID=four times daily; PND=postnasal drainage  
4  
5

## 6 XI.B.7. Biologics

7  
8 The biologics investigated for treating allergic conditions include omalizumab, mepolizumab, dupilumab,  
9 benralizumab and reslizumab.<sup>396</sup> These compounds work by targeting specific components of the  
10 pathways involved in type 2 inflammation. Omalizumab acts on IgE; dupilumab on the IL-4 receptor  
11 alpha subunit (recognized by IL-4 and IL-13); and mepolizumab, benralizumab and reslizumab on IL-5 or  
12 its receptor.<sup>396</sup> Only omalizumab and dupilumab have been studied specifically for AR. Biologics are  
13 currently FDA approved for the treatment of moderate to severe persistent asthma, AD, CRSwNP,  
14 chronic idiopathic urticaria, and eosinophilic esophagitis (EoE), but not for AR.<sup>397</sup>  
15

1 Omalizumab interferes with the allergic cascade by binding the serum free IgE molecules and preventing  
2 them from attaching to mast cells and basophils.<sup>398</sup> Trials using omalizumab as a monotherapy in  
3 treating AR have been favorable. **[TABLE XI.B.7.-1]** Two systematic reviews demonstrated decreased use  
4 of rescue medication, improvement of overall symptoms and QOL in patients treated with  
5 omalizumab.<sup>399,400</sup> The effectiveness of omalizumab monotherapy was assessed for both seasonal and  
6 perennial AR.<sup>401-405</sup> Omalizumab monotherapy achieved significant improvement of nasal symptom  
7 score, ocular symptom score, medication symptom score, and QOL with the corresponding reduction of  
8 emergency drug use and serum IgE levels. Together with the marked reduction of free serum IgE level,  
9 there was notable inhibition of specific inflammatory mediators tryptase and ECP in the nasal  
10 secretions.<sup>406,407</sup> When compared to suptast tosilate, a selective Th2 cytokine inhibitor (a drug  
11 sometimes used as a prophylaxis for atopic asthma), omalizumab was superior in treating patients with  
12 seasonal AR.<sup>408</sup>

13  
14 Studies showed favorable safety profiles with adverse events such as local injection site reactions and  
15 anaphylaxis, with no significant difference observed compared to placebo. The dosing is based on the  
16 total serum IgE level (IU/mL) and the body weight (kg) prior to the initiation of treatment where most  
17 studies used dosing from 75 to 375mg of omalizumab administered every 2-4 weeks and mean duration  
18 of treatment of 16 weeks. Given the weight-based dosing regimen, cost of treatment with omalizumab  
19 varies between \$10,000-32,000 per year.<sup>409</sup>

20  
21 Omalizumab has been evaluated as a combination therapy with AIT. This is addressed in *Section XI.D.10.*  
22 *Combination Biologic Therapy and Subcutaneous Immunotherapy.*

23  
24 Another biologic investigated for the treatment of allergic airway diseases is dupilumab, which works  
25 through binding of IL-4R $\alpha$  to inhibit IL-4 and IL-13.<sup>410</sup> Dupilumab was shown to be effective when  
26 administered as an adjunct treatment in patients with uncontrolled persistent asthma and comorbid  
27 AR.<sup>411</sup> Similar findings were observed in a post hoc analysis of patients having uncontrolled moderate-to-  
28 severe asthma and comorbid perennial AR receiving add on dupilumab therapy.<sup>412</sup> In another  
29 multicenter trial, combination therapy did not significantly improve total symptom score but it resulted  
30 in better tolerance to AIT with less withdrawal and fewer requirement of rescue medicine.<sup>413</sup> These  
31 results suggest dupilumab may have a role in treating AR, at the time of this writing it is not FDA  
32 approved for this indication. **[TABLE XI.B.7.-2]**

1  
2 In treating refractory AR that has failed optimal pharmacological treatment, biologics show promising  
3 results. Omalizumab has been the most studied and appears to be efficacious in symptom reduction,  
4 medicine use and improvement in QOL with favorable safety profile. Current limitations in the  
5 widespread use of biologics for the treatment of AR are related mostly to the high cost of treatment and  
6 lack of FDA approval. In addition, it is foreseeable that the use of biologics will be long-term and once  
7 discontinued the symptoms may recur. Although there is no subgroup analysis to determine the efficacy  
8 of biologics in AR with comorbid bronchial asthma, the cost to benefit analysis is expected to improve  
9 considerably in such cases.<sup>399</sup>

10  
11 **Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 8 studies, level 3: 2 studies; **TABLES XI.B.7.-1**  
12 **and XI.B.7.-2)**

13 **Benefit:** Omalizumab treatment resulted in improvement of symptoms, rescue medication and QOL as a  
14 monotherapy. Dupilumab data is less robust and needs further investigation.

15 **Harm:** Local reaction at injection site and risk of anaphylaxis.

16 **Cost:** High.

17 **Benefits-harm assessment:** Benefit outweighs harm.

18 **Value judgments:** Biologic therapies show promise for as a treatment option for AR; however, no  
19 biologic therapies have been approved by the US FDA for this indication.

20 **Policy level:** Option based upon published evidence, although not currently approved for this indication.

21 **Intervention:** Monoclonal antibody (biologic) therapies are not currently approved for the treatment of  
22 AR.

23

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

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

Casale et al <sup>403</sup>	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 <sup>402</sup>	2000	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	-Omalizumab superior to placebo in improving symptoms and QOL -Well tolerated
Casale et al <sup>401</sup>	1997	2	RCT	-Omalizumab -Placebo	-Symptoms -Rescue medication -QOL	-First dose-finding study -Safety confirmed

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; QOL=quality of life; RCT=randomized  
2 controlled trial; AR=allergic rhinitis  
3  
4  
5

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corren et al <sup>413</sup>	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 <sup>412</sup>	2020	3	Post hoc analysis of phase 3 study	-Add on therapy with dupilumab 200mg or 300mg -Placebo n=814	-RQLQ -Total and slgE	Both dupilumab doses superior to placebo
Weinstein et al <sup>411</sup>	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

6 LOE=level of evidence; RCT=randomized controlled trial; SCIT=subcutaneous immunotherapy; TNSS=Total Nasal  
7 Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; slgE=antigen-specific immunoglobulin E;  
8 SNOT=22=Sinonasal Outcome Test (22 item)  
9  
10

### 11 XI.B.8. Intranasal saline

12 Nasal saline is a frequently utilized therapy in the treatment of AR. The term “nasal saline”, however,  
13 encompasses a wide variety of therapeutic regimens. These can include differences in solution  
14 characteristics, such as salinity (hypertonic versus isotonic/normal saline) and buffering (buffered versus  
15 non-buffered), and differences in frequency, volume, and mode of administration.  
16  
17

1 This review included only Level 1 and 2 evidence published in the English language evaluating nasal  
2 saline in the treatment of AR. Search methodologies identified 9 RCTs in adults<sup>416-424</sup> [TABLE XI.B.8.-1]  
3 and 1 systematic review<sup>425</sup> and 8 RCTs<sup>426-433</sup> in children. [TABLE XI.B.8.-2] Three SRMAs<sup>434-436</sup> have been  
4 performed including both adults and children. [TABLE XI.B.8.-3] Compared to no irrigations, all found  
5 nasal symptoms/patient-reported disease severity were significantly better in the saline irrigation  
6 group.<sup>434-436</sup> Hermelingmeier et al<sup>434</sup> also identified a 24-100% reduction in medication usage, as well as  
7 an improvement of 30-37% in QOL, and suggested that children may benefit less than adults.

8  
9 **Adult population.** All studies found improvements in clinical outcomes with the utilization of nasal  
10 saline, with formulas varying in salinity, buffering, and frequency, volume, and mode of administration.  
11 Studies also varied in the types of AR evaluated.<sup>416-424</sup> Compared to no intranasal treatment, hypertonic  
12 saline was found to significantly improve outcomes, including nasal symptoms, QOL, and oral  
13 antihistamine use.<sup>417,419,421</sup> Ural et al<sup>418</sup> further compared hypertonic and isotonic saline irrigations,  
14 finding improved mucociliary clearance with the isotonic solution only. Looking at subjective outcomes  
15 with hypertonic versus isotonic solutions, however, Cordray et al<sup>416</sup> and Sansila et al<sup>422</sup> found QOL and  
16 symptom score were better with hypertonic solutions. Finally, Yata et al<sup>424</sup> evaluated both subjective  
17 and objective outcomes and found no difference between hypertonic and isotonic saline irrigations.  
18 Focusing on isotonic saline with various degrees of buffering, Chusakul et al<sup>420</sup> found that after 10 days  
19 buffered isotonic saline with mild alkalinity had the greatest impact on reducing nasal symptom scores  
20 and was preferred by most patients. Both Cordray et al<sup>416</sup> and Lin et al<sup>423</sup> found INCS had similar efficacy  
21 in improving nasal symptoms but showed statistically significant improvement in QOL outcomes  
22 compared to saline spray.

23  
24 **Pediatric population.** All studies found an improvement in clinical outcomes with the incorporation of  
25 nasal saline.<sup>425-433</sup> Compared to no irrigations, hypertonic and isotonic saline were found to improve  
26 outcomes, including nasal symptoms, oral antihistamine use, and QOL.<sup>427,428,433</sup> Supporting these  
27 findings, a 2019 SRMA found significantly better nasal symptom scores and a lower rate of rescue  
28 antihistamine use with hypertonic saline irrigations compared to the control group (isotonic saline and  
29 no irrigations).<sup>425</sup> Further, studies have shown that that hypertonic saline irrigations resulted in a greater  
30 improvement in nasal symptom scores in children than isotonic saline.<sup>429,430,432</sup> Finally, Li et al<sup>426</sup> and  
31 Chen et al<sup>431</sup> found an additive effect in the utilization of nasal saline spray as an adjunct to INCS when  
32 compared to either therapy independently.

1

2 Overall, there is substantial evidence to support the use of nasal saline in the treatment of AR. In adults,  
3 the data is conflicting regarding optimal salinity of the solution. In children, there is some data to  
4 support a hypertonic solution being more effective. Although nasal saline demonstrates improvement in  
5 symptoms and QOL outcomes when used alone, it is often implemented with other therapies, such as  
6 INCS, intranasal antihistamines, or oral antihistamines. In both adults and children, nasal saline appears  
7 to have an additive effect when used in combination with other standard AR treatments. Further, nasal  
8 saline is of relatively low cost and has an excellent safety profile. While adverse effects are rare, they  
9 can include nasal irritation, sneezing, cough, and ear fullness. [TABLE II.C.]

10

11 **Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 17 studies; TABLES XI.B.8-1, XI.B.8-2, and  
12 XI.B.8-3)

13 **Benefit:** Improved nasal symptoms and QOL, reduction in oral antihistamine use, and improved  
14 mucociliary clearance. Well-tolerated with excellent safety profile.

15 **Harm:** Nasal irritation, sneezing, cough, and ear fullness. See TABLE II.C.

16 **Cost:** Minimal.

17 **Benefits-harm assessment:** Preponderance of benefit over harm.

18 **Value judgments:** Nasal saline can and should be used as a first line treatment in patients with AR,  
19 either alone or combined with other pharmacologic treatments as evidence supports an additive effect.  
20 Hypertonic saline may be more effective in children. Data is otherwise inconclusive on optimal salinity,  
21 buffering, and frequency and volume of administration.

22 **Policy level:** Strong recommendation.

23 **Intervention:** Nasal saline is strongly recommended as part of the treatment strategy for AR.

24

25

**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 <sup>424</sup>	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 <sup>422</sup>	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 <sup>421</sup>	2017	2	RCT, no blinding	Patients with SAR: -Hypertonic saline spray TID	-Symptom score -Oral antihistamine use	Symptoms, oral antihistamine use, mucociliary clearance



				-No local or intranasal treatment	-Mucociliary clearance time	times significantly better in hypertonic saline group
Lin et al <sup>423</sup>	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 <sup>420</sup>	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 <sup>419</sup>	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 <sup>418</sup>	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 <sup>416</sup>	2005	2	SBRCT	Patients with SAR: -Dead Sea saline spray TID -Aqueous triamcinolone spray daily -Placebo nasal saline spray TID	RQLQ	After 7 days, Dead Sea saline group had clinically and statistically significant overall improvement from baseline but not as pronounced as the triamcinolone group, no improvement in the placebo group
Rogkakou et al <sup>417</sup>	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

- 1 LOE=level of evidence; DBRCT=double-blind randomized controlled trial; AR=allergic rhinitis; BID=twice daily;
- 2 VAS=visual analog scale; SBRCT=single-blind randomized controlled trial; QOL=quality of life; Rcq-
- 3 36=Rhinoconjunctivitis Quality of Life; TNSS=Total Nasal Symptom Score; RCT=randomized controlled trial;

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

3  
4

5 **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 <sup>425</sup>	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 <sup>433</sup>	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 <sup>432</sup>	2017	2	RCT, no blinding	Patients with AR: -Buffered hypertonic saline spray BID -Normal saline spray BID	-Total 5 symptom score -Nasal cytology -Pediatric RQLQ -Pittsburgh Sleep Quality Index	After 21 days, symptom scores significantly better in the buffered hypertonic group vs normal saline group
Chen et al <sup>431</sup>	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 <sup>429</sup>	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 <sup>430</sup>	2012	2	DBRCT	Patients with AR: -Buffered hypertonic saline BID -Normal saline irrigations BID *all groups allowed to continue to use previous	-Saccharin clearance time -TNSS -QOL score (Rcq-36) -Oral antihistamine use	-Over 4 weeks, greater improvement in saccharin clearance time and symptoms with buffered hypertonic saline -No significant difference in QOL or antihistamine use

				medications for control		
Li et al <sup>426</sup>	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 <sup>428</sup>	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 <sup>427</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized  
2 controlled trial; PC20=provocative concentrations of methacholine causing a 20% decrease in FEV<sub>1</sub>; QOL=quality of  
3 life; FeNO=fractional exhaled nitric oxide; BID=twice daily; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire;  
4 INCS=intranasal corticosteroid; SBRCT=single-blind randomized controlled trial; SAR=seasonal allergic rhinitis;  
5 DBRCT=double-blind randomized controlled trial; TNSS=Total Nasal Symptom Score; Rcq-36=Rhinoconjunctivitis  
6 Quality of Life; TID=three times daily  
7  
8

**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 <sup>436</sup>	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 <sup>435</sup>	2018	1	SRMA	Patients with AR: -Saline irrigations -No irrigations	-Patient-reported disease severity -Common adverse events	-Saline irrigations may reduce patient-reported disease severity vs no saline irrigation at up to 3 months in adults and children, with no reported adverse effects
Hermelingmeier et al <sup>434</sup>	2012	1	SRMA	Patients with AR: -Saline irrigations	-Nasal symptom score	-Up to 7 weeks, saline irrigations improve nasal

				-No irrigations	-Medicine use -Mucociliary clearance -QOL	symptoms, medicine use, and mucociliary clearance time, vs no therapy -Children benefit less than adults
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1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; INCS=intranasal  
2 corticosteroid; QOL=quality of life

### 3 4 5 [XI.B.9. Probiotics](#)

6  
7 The relationship between the microbiome and the development of atopy is complex and incompletely  
8 understood. The hygiene hypothesis theorizes that modern sanitized living conditions reduce microbial  
9 exposure resulting in inadequate immune priming. Low biodiversity in early life affects the immune  
10 system and can result in a pro-inflammatory response, including allergic over-sensitization. Conversely,  
11 appropriate microbial exposure in infancy influences gut biodiversity, thereby increasing regulatory T  
12 cell action and immune tolerance. *(See Section VI.J. Microbiome and Section VIII.G.3. Hygiene Hypothesis*  
13 *for additional information on this topic.)*

14  
15 Probiotics induce immunomodulatory effects on gut-associated lymphoid tissue. The gut microbiome  
16 and the immune system interact via dendritic cells, regulatory T cells, bacterial metabolites, and  
17 cytokines. Probiotic exposure induces a Th1 response via IL-12, IFN- $\gamma$ , with upregulation of T regulatory  
18 cells via IL-10 and TGF- $\beta$ . Furthermore, the allergy-associated Th2 pathway is suppressed through  
19 downregulation of IL-4, IgE, IgG1, and IgA.<sup>437</sup>

20  
21 Numerous RCTs have examined the therapeutic role of probiotic administration for the control of AR  
22 symptoms. Several high-quality meta-analyses have been performed on aggregate data from RCTs.  
23 Results in children and adults have been mixed.

24  
25 Guvenc et al<sup>438</sup> performed a meta-analysis of 22 RCTs comprising 2242 patient aged 2-65 years with  
26 seasonal or perennial AR who were treated with daily probiotic or placebo in addition to standard  
27 allergy therapies for 4 weeks to 12 months. The primary outcomes of the study were nasal/ocular  
28 symptom scores and QOL. Seventeen trials demonstrated clinical benefit of probiotics with  
29 improvement in nasal symptoms (standardized mean difference [SMD]) -1.23, p<0.001), ocular  
30 symptoms (SMD -1.84, p<0.001), total QOL (SMD -1.84, p<0.001), nasal QOL (SMD -2.30, p=0.006) and  
31 ocular QOL (SMD -3.11, p=0.005).

1

2 Zajac et al<sup>439</sup> performed a meta-analysis of 21 RCTs and two randomized crossover studies that included  
 3 1919 adult and pediatric patients with seasonal or perennial AR. Patients were treated with 3 weeks to  
 4 12 months of probiotic or placebo. The primary outcomes were validated QOL, symptom scores, and  
 5 immunologic variables. Seventeen studies demonstrated clinical benefit of probiotics for AR. Meta-  
 6 analysis demonstrated improvement in RQLQ global score (SMD -2.23, p=0.02) and RQLQ nasal  
 7 symptom score (SMD -1.21, p<0.00001). No effect of probiotic administration was found for Rhinitis  
 8 Total Symptom Score, total IgE, or sIgE.

9

10 Du et al<sup>440</sup> published a meta-analysis of 19 RCTs comprising a total of 5264 healthy children treated with  
 11 at least 6 months of probiotic or placebo. Ten RCTs reported no difference in the risk of developing AR  
 12 (RR 1.03; p=0.83) or a positive SPT (RR 0.74; p=0.13) after administration of oral probiotics.

13

14 Zuccotti et al<sup>441</sup> reported a meta-analysis of 17 RCTs comparing probiotics versus placebo in 4755  
 15 children. The primary endpoint was to determine if supplementation of probiotics in pregnancy or early  
 16 infancy reduced the relative risk of eczema, asthma, wheezing, and rhinoconjunctivitis. No significant  
 17 difference in terms of prevention of asthma, wheezing or rhinoconjunctivitis was noted (RR 0.91;  
 18 p=0.53), whereas the relative risk of eczema in the treatment group was significantly lower than controls  
 19 (RR=0.78; p=0.0003).

20

21 Probiotics are inexpensive and well tolerated in patients with minimal side effects (e.g., flatulence,  
 22 diarrhea, abdominal pain). The data from meta-analyses and RCTs suggests a potential benefit of  
 23 probiotics in reduction of symptoms of seasonal and perennial AR in both adults and children but  
 24 interpretation is limited by the heterogeneity of age, diagnosis, interventions, and outcomes included in  
 25 the studies. The current data indicate that administration of probiotics in infancy does not reduce the  
 26 diagnosis of most atopic diseases, with exception of eczema.

27

28 **Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 5 studies; **TABLE XI.B.9.**)

29 **Benefit:** Improved nasal/ocular symptoms or QOL in most studies.

30 **Harm:** Mild gastrointestinal side-effects.

31 **Cost:** Low.

32 **Benefits-harm assessment:** Balance of benefit and harm.

33 **Value judgments:** Minimal harm associated with probiotics. Heterogeneity across studies makes  
 34 magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific  
 35 recommendation for treatment.

- 1 **Policy level:** Option.  
 2 **Intervention:** Consider adjuvant use of probiotics for patients with symptomatic seasonal or perennial  
 3 AR.  
 4  
 5

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

Study*	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Du et al <sup>440</sup>	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 <sup>441</sup>	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 <sup>438</sup>	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 <sup>439</sup>	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 <sup>442</sup>	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 <sup>443</sup>	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 <sup>444</sup>	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 <sup>445</sup>	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 <sup>446</sup>	2017	2	RCT	-Probiotic vs placebo, n=40 children	-Total symptom score -mRQLQ	Improvement in AR symptoms and QOL with probiotic

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

8  
 9

## 10 XI.B.10. Combination therapy

### 11 XI.B.10.a. Oral antihistamine and oral decongestant

12

13 Oral antihistamines, commonly used for treatment of AR, target the H<sub>1</sub> histamine receptor, block  
 14 histamine receptor binding, and prevent histamine-mediated symptoms of AR such as pruritus,  
 15 sneezing, vasodilation, and flushing. The effect of oral antihistamines on nasal obstruction in AR may be  
 16 less pronounced. Oral decongestants such as phenylephrine or pseudoephedrine, which are typically  
 17 sympathomimetic drugs that target  $\alpha$ -1 receptors causing blood vessel constriction, cause more  
 18 pronounced nasal decongestion. Oral antihistamines can thus be combined with oral decongestants to  
 19 reduce histamine-mediated symptoms of AR while concomitantly improving nasal airflow.<sup>214,447-449</sup>

20

21 RCTs have demonstrated that combination antihistamine-decongestant medications including  
 22 fexofenadine-pseudoephedrine, desloratadine-pseudoephedrine, cetirizine-pseudoephedrine,  
 23 loratadine-pseudoephedrine and others reduce AR symptoms including rhinorrhea, nasal congestion,  
 24 nasal itching, and sneezing when compared to placebo.<sup>283,284,286-288,292,294,449-460</sup> Combination oral  
 25 antihistamine-oral decongestant medications have also been shown to reduce nasal congestion  
 26 symptoms vs. oral antihistamine alone or versus oral decongestant alone.<sup>283,284,286-288,292,294,449-460</sup> Studies  
 27 have also demonstrated that once daily dosing of combination oral antihistamine-oral decongestant  
 28 medications are statistically equivalent to twice daily dosing with regard to symptom relief<sup>461,462</sup> and that  
 29 different antihistamine-decongestant combinations are statistically equivalent in improving symptom  
 30 scores.<sup>462-466</sup> In some studies, oral antihistamine-oral decongestant combination medications are  
 31 reported to be superior to INCS with regard to improving AR symptoms, particularly nasal  
 32 congestion.<sup>214,467,468</sup> In contrast, cetirizine-pseudoephedrine was not superior to xylometazoline nasal  
 33 decongestant spray alone in improving nasal airflow and nasal obstruction symptoms.<sup>469</sup> [TABLE

### 34 XI.B.10.a.]

35

1 Oral antihistamines may cause sedation and dry mouth, especially in the case of first-generation  
 2 antihistamines such as doxylamine and diphenhydramine; oral antihistamines may also cause urinary  
 3 retention.<sup>447,448</sup> Oral decongestants, through their actions on  $\alpha$ -1 receptors may cause palpitations,  
 4 insomnia, jitteriness, and dry mouth. Oral decongestants or oral antihistamine-decongestant  
 5 combinations are typically not recommended by their manufacturers in patients under 12 years old,  
 6 while oral antihistamines other than cetirizine are typically not recommended in patients under age  
 7 2.<sup>447,448</sup> Over-the-counter sales of oral decongestants and oral antihistamine-oral decongestant  
 8 combinations are typically monitored or restricted given their potential use in the illicit manufacture of  
 9 methamphetamines. Oral decongestants should be used with caution in pregnant patients and patients  
 10 with cardiac arrhythmias, hypertension, or benign prostatic hypertrophy. Oral antihistamines should be  
 11 used with caution in patients with preexisting cardiac conditions, patients taking monoamine oxidase  
 12 inhibitors, narcotic pain medications or other sedating medications, and some antiseizure  
 13 medications,<sup>447,448</sup> [TABLE II.C.]

14

15 **Aggregate grade of evidence:** A (Level 2: 30 studies; TABLE XI.B.10.a.)

16 **Benefit:** Improved nasal congestion and total symptom scores (TSS) with combination oral  
 17 antihistamine-oral decongestants.

18 **Harm:** Oral decongestants can cause adverse events in patients with cardiac conditions, hypertension,  
 19 or benign prostatic hypertrophy and are not indicated in patients under age 12 or pregnant patients.  
 20 Oral antihistamines are not indicated in patients under two years of age, and caution should be  
 21 exercised in patients aged 2-5 years old. See TABLE II.C.

22 **Cost:** Low.

23 **Benefits-harm assessment:** Combination oral antihistamine-oral decongestant medications carry  
 24 relatively low risks of adverse events when used as needed for episodic AR symptoms in well-selected  
 25 patients. Risk may be higher if used daily or in patients with certain comorbidities. There is not a  
 26 preponderance of benefit or harm when used appropriately as a treatment option.

27 **Value judgments:** Oral antihistamine-oral decongestants may be an effective option for acute AR  
 28 symptoms such as nasal congestion and sneezing. Caution should be exercised with more long-term use.

29 **Policy level:** Option for episodic or acute AR symptoms.

30 **Intervention:** Combination oral antihistamine-oral decongestant medications may provide effective  
 31 relief of nasal symptoms of AR on an episodic basis. Caution should be exercised in chronic or long-term  
 32 use as the adverse effect profile of oral decongestants is greater for chronic use.

33

34 **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 <sup>214</sup>	2021	2	RCT	-Loratadine-PSE -Placebo tablet -Fluticasone propionate nasal spray -Placebo nasal spray	-TSS -PNIF	-Loratadine-PSE improved PNIF vs placebo tablet and vs fluticasone nasal spray



				(n=82)		-PNIF was not significantly different for fluticasone vs placebo nasal spray
North et al <sup>449</sup>	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 <sup>286</sup>	2009	2	RCT	-Desloratadine-PSE -Desloratadine + placebo tablet -PSE (n=598)	-TSS (without nasal congestion) -Nasal congestion	Desloratadine-PSE significantly reduced TSS and nasal congestion vs desloratadine-placebo and vs PSE
Chen et al <sup>461</sup>	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 <sup>462</sup>	2006	2	RCT	-Cetirizine-PSE -Loratadine-PSE (n=51)	TNSS	Both groups statistically equivalent in symptom scores
Nathan et al <sup>450</sup>	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 <sup>451</sup>	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 <sup>294</sup>	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 <sup>467</sup>	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 <sup>463</sup>	2004	2	RCT	-Fexofenadine-PSE -Loratadine-montelukast (n=72)	-RQLQ -Nasal symptoms -PNIF	-Fexofenadine-PSE and loratadine-montelukast equivalent in improving RQLQ, total symptom PNIF -Loratadine-montelukast superior in improving sleep
Meltzer et al <sup>452</sup>	2003	2	RCT	-Clemastine-PSE-acetaminophen -PSE-acetaminophen	Major symptom complex score	Clemastine-PSE-acetaminophen significantly reduced major symptom

				-Placebo (n=298)		complex score vs PSE- acetaminophen or placebo
Berkowitz et al <sup>453</sup>	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 <sup>469</sup>	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 <sup>454</sup>	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 <sup>288</sup>	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 <sup>455</sup>	1998	2	RCT	-Cetirizine-PSE -Placebo (n=24)	-Nasal obstruction -Nasal patency/airflow	Cetirizine-PSE significantly improved nasal airflow and nasal obstruction symptoms vs placebo
Kaiser et al <sup>470</sup>	1998	2	RCT	-Loratadine-PSE Qday -Loratadine-PSE BID -Placebo (n=469)	Total nasal and non-nasal symptom scores	Loratadine-PSE daily or BID was superior to placebo in reducing symptom scores
Serra et al <sup>456</sup>	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 <sup>457</sup>	1997	2	RCT	-Loratadine-PSE -Placebo (n=193)	-Nasal and pulmonary symptoms -Albuterol use -PEF, FEV <sub>1</sub>	Loratadine-PSE significantly reduced symptoms and improved PEF and FEV <sub>1</sub> vs placebo
Grosclaude et al <sup>284</sup>	1997	2	RCT	-Cetirizine-PSE -Cetirizine -PSE (n=687)	Daily congestion, sneezing, rhinorrhea, nasal	Cetirizine-PSE significantly improved symptoms vs cetirizine or PSE alone

					itching, ocular itching	
Bertrand et al <sup>287</sup>	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 <sup>464</sup>	1996	2	RCT	-Astemizole-PSE -Brompheniramine + phenylpropanolamine (n=64)	Nasal and eye symptoms	-Astemizole-PSE equivalent to brompheniramine for nasal obstruction symptoms -Brompheniramine-phenylpropanolamine superior to astemizole-PSE for rhinorrhea and itchy eyes
Williams et al <sup>458</sup>	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 <sup>283</sup>	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 <sup>468</sup>	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 <sup>465</sup>	1994	2	RCT	-Loratadine-PSE -Chlorpheniramine-PSE (n=131)	TSS	Loratadine-PSE was equally effective vs chlorpheniramine-PSE in improving TSS
Howarth et al <sup>292</sup>	1993	2	RCT	-Terfenadine-PSE -Terfenadine -PSE -Placebo (n=14)	TSS	Terfenadine-PSE significantly improved all symptoms vs placebo
Segal et al <sup>466</sup>	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 <sup>459</sup>	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 <sup>460</sup>	1989	2	RCT	-Loratadine-PSE -Loratadine -PSE -Placebo (n=435)	TSS	Loratadine-PSE more effective than loratadine, PSE, or placebo in reducing TSS

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

1 function test; QOL=quality of life; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; PEF=peak expiratory  
2 flow; FEV<sub>1</sub>=forced expiratory volume in 1 second; VAS=visual analog scale

### 5 XI.B.10.b. Oral antihistamine and intranasal corticosteroid

7 A combination of an oral antihistamine with INCS is a commonly used treatment option for patients with  
8 AR. First-generation antihistamines include diphenhydramine, chlorpheniramine, and hydroxyzine, while  
9 newer second-generation medications include cetirizine, levocetirizine, fexofenadine, loratadine, and  
10 desloratadine. Typically, second-generation antihistamines are preferred given their improved safety  
11 profile compared to first-generation antihistamines. INCS reduce inflammatory mediator and cytokine  
12 release; decrease the recruitment of nasal eosinophils, neutrophils, basophils, lymphocytes, monocytes,  
13 and macrophages; and can decrease hyperresponsive effects to antigen challenge. INCS have an  
14 excellent safety profile and low systemic absorption.

16 There have been several RCTs examining the use of oral antihistamine-INCS combinations in the  
17 treatments of AR. Pinar et al<sup>471</sup> used TNSS, rhinoconjunctivitis scores, and PNIF to compare 4 groups: (1)  
18 intranasal mometasone-oral desloratadine, (2) intranasal mometasone-oral montelukast, (3) intranasal  
19 mometasone alone, (4) placebo. This study found that intranasal mometasone with desloratadine or  
20 montelukast was superior to intranasal mometasone alone or placebo for improving TNSS and QOL.

#### 21 [TABLE XI.B.10.b.]

23 Anolik<sup>472</sup> examined TNSS and TSS in patients treated with intranasal mometasone-oral loratadine,  
24 intranasal mometasone alone, oral loratadine alone, or placebo. This study noted that intranasal  
25 mometasone plus loratadine and intranasal nasal mometasone alone were statistically equivalent for  
26 TNSS and TSS. All treatment groups were superior to placebo in improving TNSS and TSS. The study also  
27 reported that intranasal mometasone and mometasone-loratadine were superior to loratadine alone or  
28 placebo for TNSS and TSS, while loratadine alone was superior to placebo for TNSS.<sup>472</sup>

30 Barnes et al<sup>473</sup> compared RQLQ scores, PNIF, TNSS, and nasal nitric oxide in patients treated with  
31 intranasal fluticasone-oral cetirizine versus intranasal fluticasone-oral placebo. Their study found that  
32 nasal symptom score was statistically equivalent for cetirizine-fluticasone patients versus fluticasone-  
33 placebo patients.

1 Di Lorenzo et al<sup>474</sup> evaluated 5 groups: (1) oral cetirizine-intranasal fluticasone, (2) oral montelukast-  
 2 intranasal fluticasone, (3) intranasal fluticasone alone, (4) oral cetirizine-oral montelukast, or (5)  
 3 placebo. This study reported that all three treatment groups were superior to the placebo group in  
 4 improving TSS and rhinorrhea, sneezing, and nasal itching scores. They also noted that the fluticasone  
 5 alone and fluticasone-cetirizine groups were superior to placebo or cetirizine-montelukast in improving  
 6 TSS, nasal congestion on waking, and daily nasal congestion.

7  
 8 Ratner et al<sup>475</sup> examined intranasal fluticasone-oral loratadine versus fluticasone alone, loratadine alone,  
 9 or placebo. They found that fluticasone and fluticasone-loratadine were superior to loratadine only and  
 10 placebo groups for clinician and patient total and individual nasal symptom scores, and that loratadine  
 11 alone was equivalent to placebo for NSS. QOL improvement was greater for fluticasone and fluticasone-  
 12 loratadine compared to loratadine alone or placebo. QOL improvement was statistically equivalent for  
 13 fluticasone-loratadine versus fluticasone.

14  
 15 A SRMA in 2018 by Seresirikachorn et al<sup>476</sup> showed no added benefit for oral antihistamines plus INCS.  
 16 This is in contrast to intranasal antihistamines plus INCS, which did show additional benefit. Potential  
 17 side effects of oral antihistamine with INCS combinations are typically low and are included in the  
 18 combined table of AR treatment side effects. [TABLE II.C.]

19  
 20 **Aggregate grade of evidence:** A (Level 1: 1 study, level 2: 12 studies; TABLE XI.B.10.b.)

21 **Benefit:** The addition of oral antihistamine to INCS has not consistently demonstrated a benefit over  
 22 INCS alone for symptoms of AR.

23 **Harm:** Oral antihistamines generally not recommended in patients under 2 years old, and attention to  
 24 dosing is necessary in patients 2-12 years old. See TABLE II.C.

25 **Cost:** Low.

26 **Benefits-harm assessment:** Benefit likely outweighs potential harms in patients with significant nasal  
 27 congestion symptoms in addition to symptoms such as sneezing and ocular itching. Addition of an INCS  
 28 may be limited benefit versus potential harm in patients without significant nasal congestion symptoms.

29 **Value judgments:** Adding oral antihistamine to INCS spray has not been demonstrated to confer  
 30 additional benefit over INCS spray alone. INCS improves congestion with or without oral antihistamine.

31 **Policy level:** Option.

32 **Intervention:** Current evidence is mixed to support antihistamines as an additive therapy to INCS, as  
 33 several randomized trials have not demonstrated a benefit over INCS alone for symptoms of AR.

34  
 35 **TABLE XI.B.10.b. Evidence table – Combination therapy: oral antihistamine and intranasal**  
 36 **corticosteroid**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
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Seresirikachorn et al <sup>476</sup>	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 <sup>477</sup>	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 <sup>478</sup>	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 <sup>472</sup>	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 <sup>471</sup>	2008	2	RCT	-Montelukast-nasal mometasone -Desloratadine-nasal mometasone -Nasal mometasone -Placebo (n=95)	-TNSS -Rhinoconjunctivitis scores -PNIF	Desloratadine-mometasone and montelukast-mometasone superior to mometasone alone or placebo for symptom scores and QOL
Barnes et al <sup>473</sup>	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 <sup>479</sup>	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 <sub>1</sub>
Di Lorenzo et al <sup>474</sup>	2004	2	RCT	-Cetirizine-nasal fluticasone -Montelukast-nasal fluticasone -Cetirizine-montelukast	-Symptoms -Eosinophil count -ECP in nasal lavage	-All treatment groups superior to placebo in improving symptoms, rhinorrhea, sneezing, nasal itching scores -Groups treated with fluticasone alone or as combination therapy

				-Nasal fluticasone -Placebo (n=100)		superior to placebo or cetirizine-montelukast for TSS, nasal congestion on waking, daily nasal congestion -Combination of cetirizine-fluticasone showed no added benefit vs fluticasone alone for TSS
Lanier et al <sup>480</sup>	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 <sup>481</sup>	2000	2	RCT	-Cetirizine-nasal mometasone -Cetirizine-montelukast -Cetirizine (n=38)	-PNIF -Symptom diary	Cetirizine-mometasone statistically equivalent to cetirizine alone for PNIF and seasonal AR symptoms
Berger et al <sup>481</sup>	1999	2	RCT	-Loratadine-nasal beclomethasone -Nasal azelastine (n=3210)	-Physician assessment of need for rescue medication -Patient global evaluation	Need for rescue medication and the patient assessment of efficacy statistically equivalent for both groups
Ratner et al <sup>475</sup>	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 <sup>482</sup>	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
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1 LOE=level of evidence; SRMA=systematic review and meta-analysis; INCS=intranasal corticosteroid; OAH=oral  
 2 antihistamine; IAH=intranasal antihistamine; TNSS=Total Nasal Symptom Score; TOSS= Total Ocular Symptom  
 3 Score; QOL=quality of life; PNIF=peak nasal inspiratory flow; RCT=randomized controlled trial;  
 4 RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; TSS=total symptom score; PSE=pseudoephedrine;  
 5 PFT=pulmonary function test; FEV<sub>1</sub>=forced expiratory volume in 1 second; ECP=eosinophil cationic protein;  
 6 AR=allergic rhinitis; NSS=nasal symptom score

7  
8

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

10

11 The combination of oral antihistamine-LTRA and oral antihistamines in the treatment of AR was  
 12 reviewed as a therapeutic option in the previous ICAR-Allergic Rhinitis 2018 consensus statement.<sup>308</sup> An  
 13 updated systematic search revealed an additional 3 systematic reviews and 2 RCTs,<sup>310,312,483-485</sup> giving a  
 14 total of 17 studies meeting criteria for level 1 or 2 evidence. **[TABLE XI.B.10.c.]**

15

16 Combination oral antihistamine-LTRA has been shown to be superior to placebo in multiple RCTs. Recent  
 17 studies have sought to clarify the comparative efficacy of combination therapy against monotherapy  
 18 with LTRA or oral antihistamines, which was previously unclear. Compared to LTRA alone, Kim et al<sup>483</sup>  
 19 found that oral antihistamine-LTRA therapy was superior in reducing nasal symptoms. However, in  
 20 asthmatic patients, no difference was reported between the two treatment arms in improving  
 21 spirometry readings or Asthma Control Test scores.

22

23 Krishnamoorthy et al<sup>310</sup> found that oral antihistamine-LTRA therapy was superior to monotherapy with  
 24 either LTRA or oral antihistamines alone in improving daytime and nighttime symptoms of AR, as well as  
 25 ocular symptoms. Additional systematic reviews by Liu et al<sup>484</sup> and Wei<sup>312</sup> are concordant with these  
 26 findings.

27

28 There have been no new studies comparing combination oral antihistamine-LTRA therapy to  
 29 monotherapy with INCS. Previous evidence suggests that combination therapy is equivalent to, or less  
 30 effective than INCS alone for reduction of symptoms and nasal eosinophil counts.<sup>215,474,486,487</sup> Comparing  
 31 different antihistamines with LTRA, Mahatme et al<sup>485</sup> found that fexofenadine added to LTRA led to a  
 32 greater decrease in symptoms, although the combination with levocetirizine was more cost-effective.

33



1 Regarding objective measures, there is mixed evidence for the use of combination oral antihistamine-  
 2 LTRA. Cingi et al<sup>488</sup> found that combination oral antihistamine-LTRA was superior to oral antihistamines  
 3 alone in reducing nasal resistance on rhinomanometric testing, and Li et al<sup>489</sup> found that the former was  
 4 superior to the latter in increasing nasal volume as measured by acoustic rhinometry. However,  
 5 Moinuddin et al<sup>463</sup> found that there was no significant difference in PNIF values between the two.  
 6 Combination oral antihistamine-LTRA was superior to placebo in reducing peripheral and nasal  
 7 eosinophil counts, but inferior to INCS<sup>474</sup> and equivalent to oral antihistamines alone.<sup>483</sup>

8  
 9 It is important to note that in the Joint Task Force Practice Parameters,<sup>65</sup> INCS were recommended when  
 10 symptoms were not controlled with an oral antihistamine alone. Although the combination of LTRA and  
 11 oral antihistamines was previously found to be well tolerated with minimal concerns for drug  
 12 interactions,<sup>308</sup> recent concerns regarding the safety of LTRA have been raised, with the US FDA now  
 13 requiring a boxed warning for serious neuropsychiatric events on montelukast.<sup>324</sup>

14  
 15 Overall, the combination of oral antihistamine-LTRA is an effective therapy option when compared to  
 16 placebo. However, in view of the adverse effect profile of montelukast, we recommend the  
 17 consideration of other efficacious agents such as INCS which have been shown to result in superior  
 18 symptom control, and that combination LTRA-oral antihistamine therapy be reserved for rare patients  
 19 with contraindications to alternative treatments.

20  
 21 **Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 13 studies; **TABLE XI.B.10.c.**)

22 **Benefit:** Combination LTRA and oral antihistamine were superior in symptom reduction and QOL  
 23 improvement than placebo, and to either agent as monotherapy.

24 **Harm:** Boxed warning due to risks of mental health side effects limiting use for AR. See **TABLE II.C.**

25 **Cost:** Generic montelukast added to generic loratadine or cetirizine is more expensive per month than  
 26 generic fluticasone furoate nasal sprays, according to National Average Drug Acquisition Cost data  
 27 provided by the Centers for Medicare and Medicaid Services.

28 **Benefits-harm assessment:** Combination LTRA and oral antihistamine is superior to placebo, and  
 29 superior to either agent as monotherapy. However, there is an inferior effect versus INCS, which is also  
 30 less costly. In addition, there is a boxed warning associated with montelukast.

31 **Value judgments:** Combination therapy of LTRA and oral antihistamines is effective, but in light of  
 32 concerns over the safety profile of montelukast, and the availability of effective alternatives such as  
 33 INCS, evidence is lacking to recommend combination therapy in the management of AR.

34 **Policy level:** Recommendation against as first line therapy.

35 **Intervention:** Combination LTRA and oral antihistamines should not be used as first line therapy for AR  
 36 but can be considered in patients with contraindications to other alternatives. This combination should  
 37 be used judiciously after carefully weighing potential risks and benefits.

38

1 **TABLE XI.B.10.c. Evidence table – Combination therapy: oral antihistamine and leukotriene receptor**  
 2 **antagonist**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Krishnamoorthy et al <sup>310</sup>	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 <sup>484</sup>	2018	1	SR of RCTs	-Montelukast-OAH -OAH	Symptoms	LTRA-OAH superior to OAH alone
Wei <sup>312</sup>	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 <sup>215</sup>	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 <sup>483</sup>	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 <sup>485</sup>	2016	2	RCT	-Montelukast-levocetirizine -Montelukast-fexofenadine	Symptoms	-Both reduced symptoms -LTRA-levocetirizine greater decrease in symptoms -LTRA-fexofenadine more cost effective
Ciebiada et al <sup>490</sup>	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 <sup>491</sup>	2012	2	RCT	-Montelukast-loratadine -Montelukast-placebo	Symptoms	Active combination therapy with improved Total Symptom Score, and specifically sneezing and rhinorrhea
Cingi et al <sup>488</sup>	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 <sup>489</sup>	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 <sup>486</sup>	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 <sup>492</sup>	2008	2	RCT	-Montelukast-loratadine -Loratadine-placebo	-Symptoms -Turbinate hypertrophy	-No difference in symptoms in children treated with combination therapy or antihistamine alone -Turbinate swelling significantly reduced in combination therapy arm
Di Lorenzo et al <sup>474</sup>	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 <sup>463</sup>	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 <sup>487</sup>	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 <sup>493</sup>	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 <sup>494</sup>	2000	2	RCT	-Montelukast- loratadine -Montelukast -Loratadine -Placebo	-Symptoms -QOL	-Combination therapy improved symptoms and QOL vs placebo -Combination therapy not directly compared to monotherapy

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

#### 6 XI.B.10.d. Intranasal corticosteroid and intranasal antihistamine

8 Combination therapy of INCS plus intranasal antihistamine spray is available for the treatment of AR.

9 One combined formulation is currently available in North America for intranasal use as a combination of  
10 azelastine hydrochloride and fluticasone propionate (AzeFlu). This agent is alternatively designated in  
11 the literature as MP-AzeFlu or MP29-02 and is marketed in the US under the trade name Dymista  
12 (Viatris, Canonsburg, PA). A second combination of olopatadine and mometasone (OloMom) was FDA  
13 approved in January 2022 and is marketed in the US under the trade name Ryaltris (Glenmark  
14 Pharmaceuticals, Mahwah, NJ).

16 A systematic review of the English-language literature was performed for clinical trials of combination  
17 INCS and intranasal antihistamine for the treatment of AR. A total of 18 RCTs (16 double-blind, 2 non-  
18 blinded) evaluated the efficacy of combination therapy against either placebo or active control.<sup>495-512</sup> An  
19 additional 3 observational studies reported outcomes of AzeFlu as a single treatment arm.<sup>513-515</sup> This  
20 evidence has been summarized in 2 previous systematic reviews.<sup>476,516,517</sup> **[TABLE XI.B.10.d.]**

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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<sup>512,515</sup> and 1 study with a 52-week duration.<sup>512</sup> 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.<sup>501-503,505-508</sup> Superiority of combination therapy with AzeFlu was also demonstrated over active treatment with fluticasone propionate monotherapy in 6 studies.<sup>504-506,508,510,512</sup> Similarly, superiority of combination therapy with AzeFlu was demonstrated over active treatment with azelastine hydrochloride monotherapy in 4 studies.<sup>505,506,508,512</sup> 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.<sup>510</sup>

OloMom was compared to olopatadine or mometasone monotherapy in 4 studies, all of which showed superiority of the combination therapy.<sup>495,497-499</sup> One study comparing AzeFlu with OloMom found comparable symptom reduction.<sup>499</sup> 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.<sup>509</sup> 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.<sup>507</sup> 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.<sup>517</sup>

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

1 placebo in improving symptoms and QOL.<sup>502,512</sup> Several studies reporting time to onset of AzeFlu was  
 2 more rapid than INCS alone.  
 3  
 4 No study reported serious adverse effects from the use of combination INCS plus intranasal  
 5 antihistamine. This combination therapy was generally well tolerated, with the most common adverse  
 6 effect being taste aversion. Other reported adverse effects occurred in less than 5% of cases in any  
 7 study, and included somnolence, headache, epistaxis, and nasal discomfort. **[TABLE II.C.]** One study that  
 8 compared combination therapy of fluticasone propionate with either azelastine or olopatadine reported  
 9 more treatment-related events for the azelastine group than the olopatadine group.<sup>509</sup> Ocular changes  
 10 such as increased intraocular pressure and cataract formation are unlikely; nonetheless, caution may be  
 11 warranted in patients with a history of glaucoma.<sup>246</sup> Additional specific patient factors may be  
 12 considered when selecting options for combination therapy.

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 14  
 15 **Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 18 studies, level 4: 3 studies; **TABLE**  
 16 **XI.B.10.d.**)

17 **Benefit:** Rapid onset; more effective for relief of multiple symptoms than either INCS or intranasal  
 18 antihistamine alone.

19 **Harm:** Patient tolerance, especially due to taste. See **TABLE II.C.**

20 **Cost:** Moderate financial burden for combined formulation. Concurrent use of individual intranasal  
 21 antihistamine and corticosteroid sprays is likely a more economical option.

22 **Benefits-harm assessment:** Preponderance of benefit over harm. Combination therapy with intranasal  
 23 antihistamine and INCS is consistently more effective than placebo or monotherapy. Low risk of non-  
 24 serious adverse effects.

25 **Value judgments:** High-level evidence demonstrates that combination spray therapy with INCS plus  
 26 intranasal antihistamine is more effective than monotherapy or placebo, as well as more effective than  
 27 combination of INCS plus oral antihistamine. The increased financial cost and need for prescription limit  
 28 the value of combination therapy as a routine first-line treatment for AR. When a combined formulation  
 29 is financially prohibitive, the concurrent use of 2 separate formulations (antihistamine and  
 30 corticosteroid) is an alternative option.

31 **Policy level:** Strong recommendation for the treatment of AR when monotherapy fails to control  
 32 symptoms.

33 **Intervention:** Combination therapy with INCS and intranasal antihistamine may be used as second-line  
 34 therapy in the treatment of AR when initial monotherapy with either INCS or antihistamine does not  
 35 provide adequate control.  
 36

37 **TABLE XI.B.10.d. Evidence table – Combination therapy: intranasal corticosteroid and intranasal**  
 38 **antihistamine**

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

1 LOE=level of evidence; SR=systematic review; AzeFlu=azelastine-fluticasone; FP=fluticasone propionate;  
2 TNSS=Total Nasal Symptom Score; INCS=intranasal corticosteroid; DBRCT=double-blind randomized controlled  
3 trial; TOSS=Total Ocular Symptom Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; QOL=quality of  
4 life; OloMom=olopatadine mometasone; r=reflective; i=instantaneous; PNSS=physician0assessed nasal symptom  
5 score; RCAT=Rhinitis Control Assessment Test; RCT=randomized controlled trial; EQ-5D=Euro-QOL-5D; VAS=visual  
6 analog scale; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire;  
7 TDI=threshold/discrimination/identification  
8  
9



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

2  
3 LTRAs have been studied and used in conjunction with INCS for the treatment of AR. Montelukast is the  
4 only LTRA approved by the FDA for the treatment of seasonal AR in adults and children over 2 years of  
5 age, and for perennial AR in adults and children over 6 months of age. However, a boxed warning from  
6 the FDA in 2020 advises restricting use of montelukast for AR due to serious neuropsychiatric events,  
7 ranging from behavioral changes to suicidal thoughts or behavior.<sup>324</sup> For patients with both asthma and  
8 AR, LTRAs may be considered with awareness of the mental health risks.

9  
10 Montelukast has been studied in combination with INCS to determine if add-on therapy to INCS provides  
11 improved outcomes. Nasal symptoms, olfaction, QOL, nasal airflow measures, and immunologic markers  
12 have been used to compare combination therapy with LTRA and INCS to INCS monotherapy for AR –  
13 with conflicting results reported in controlled trials. There is one meta-analysis<sup>518</sup> and eight controlled  
14 trials<sup>316,318,471,474,519-522</sup> where montelukast was studied as add-on therapy to INCS. The meta-analysis  
15 included four studies that used fluticasone propionate and one used budesonide as the INCS; all used  
16 oral montelukast as the LTRA. No difference was demonstrated in nasal symptoms, disease specific QOL,  
17 or adverse effects, when comparing combination therapy with LTRA and INCS to INCS as  
18 monotherapy.<sup>518</sup> However, significant improvement in ocular symptoms with combination therapy was  
19 reported in one RCT included in the meta-analysis. **[TABLE XI.B.10.e.]**

20  
21 Four trials demonstrated benefit with LTRA added to INCS.<sup>316,471,519,520</sup> Chen et al<sup>316</sup> studied budesonide  
22 alone or in combination with montelukast. Outcome measures of symptoms, nasal cavity volume, and  
23 expired NO all demonstrated improvement in with combination therapy. A follow-up study by Chen et  
24 al<sup>519</sup> showed similar favorable outcomes in all three outcomes categories for combination therapy. Goh  
25 et al<sup>520</sup> reported a RCT with fluticasone propionate compared to montelukast-fluticasone propionate;  
26 combination therapy demonstrated improvement in symptom scores and QOL. Pinar et al<sup>471</sup> reported a  
27 trial with mometasone alone or in combination with desloratadine or montelukast. Add-on montelukast  
28 had superior improvement in symptoms and QOL compared to all other active treatment groups after 1  
29 month of treatment but not at 3 months (when all active treatment groups showed comparable  
30 efficacy).

31  
32 Four other studies did not show additional benefit with add-on montelukast.<sup>318,474,521,522</sup> Di Lorenzo et  
33 al<sup>474</sup> studied symptoms and eosinophil-specific inflammatory markers in 4 cohorts: fluticasone

1 propionate alone, cetirizine-fluticasone propionate, montelukast-fluticasone propionate, and cetirizine-  
 2 montelukast. There was no additional benefit to add-on montelukast besides a decrease in nasal itching  
 3 with the combination therapy of montelukast-fluticasone propionate compared to fluticasone  
 4 propionate alone. Inflammatory markers were not different when LTRA was added to INCS.

5  
 6 Esteitie et al<sup>521</sup> studied symptoms and QOL in patients on fluticasone propionate compared to  
 7 montelukast-fluticasone propionate. There was no additional benefit to add-on montelukast for nasal  
 8 symptom scores and QOL measures.

9  
 10 Dalgic et al<sup>318</sup> studied objective measures of olfactory function in patients on mometasone furoate,  
 11 montelukast, or montelukast-mometasone. They found no difference in olfactory function with  
 12 combination therapy. Florincescu-Gheorghe et al<sup>522</sup> studied eosinophils in nasal secretions and  
 13 symptoms in patients on mometasone furoate, desloratadine-mometasone furoate, and montelukast-  
 14 mometasone furoate. There was no additional benefit to adding montelukast to mometasone furoate  
 15 for all outcomes measured.

16  
 17 Overall, there are varying outcomes from trials reporting combination therapy with LTRA and INCS.  
 18 Differences in the corticosteroid preparation may affect study findings -- two studies with budesonide  
 19 had favorable outcomes, whereas those with fluticasone propionate and mometasone furoate had  
 20 variable outcomes. There was heterogeneity between the studies with variations in allergy sensitizations  
 21 and seasonal symptoms, and the studies had modest sample sizes. Given the FDA boxed warning<sup>324</sup> and  
 22 variable study outcomes, use of LTRA with INCS should primarily be considered for patients with co-  
 23 morbid asthma, rather than AR alone. Proper counselling regarding mental health risks to patients and  
 24 families, highlighting the importance of monitoring for any neuropsychiatric symptoms regardless of  
 25 prior history of psychiatric disorders.

26  
 27 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 8 studies; **TABLE XI.B.10.e.**)

28 **Benefit:** Some studies demonstrate improvement of symptoms and QOL with combination therapy. One  
 29 meta-analysis did not show benefit with the exception of ocular itching.

30 **Harm:** Boxed warning due to risks of serious neuropsychiatric events limiting use for AR. See **TABLE II.C.**

31 **Cost:** Low.

32 **Benefits-harm assessment:** Boxed warning for AR limits use. If comorbid asthma and AR, treatment is an  
 33 option with consideration of mental health risks.

34 **Value judgments:** Possibly useful for symptom control, especially in patients with comorbid asthma,  
 35 however, boxed warning limits use in AR without asthma.

- 1 **Policy level:** Option as combination therapy if co-morbid asthma present and mental health risks are  
 2 considered. Not recommended for AR alone.  
 3 **Intervention:** Consider use in patients with AR and asthma, after weighing therapeutic benefits against  
 4 risks of mental health adverse effects.

5  
 6 **TABLE XI.B.10.e. Evidence table – Combination therapy: intranasal corticosteroid and leukotriene**  
 7 **receptor antagonist**

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

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

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#### 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  $\alpha$ -receptor agonists, and decrease nasal congestion by reducing nasal mucosal volume through sympathomimetic vasoconstriction of mucosal blood vessels.<sup>523</sup> Prolonged use of INDCs alone has been shown to cause rhinitis medicamentosa,<sup>524</sup> 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.<sup>525-529</sup> Three of these studies also reported no rhinitis medicamentosa in patients receiving combination therapy.<sup>526,527,529</sup> In contrast, Baroody et al,<sup>530</sup> 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<sup>527</sup> 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<sup>531</sup> 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.<sup>65</sup> The 2015

1 AAO-HNSF Clinical Practice Guideline for AR cautions that such combination therapy with INDC should  
2 be limited to a few days to prevent rebound congestion.<sup>85</sup>

3  
4 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 5 studies, level 3: 1 study; **TABLE XI.B.10.f.**)  
5 **Benefit:** Some evidence in randomized studies of benefit from addition of INDC to INCS therapy in  
6 refractory AR patients. The evidence regarding the magnitude of effect is unclear, and a meta-analysis  
7 that tried to estimate this effect was significantly limited by study heterogeneity and low sample size (2  
8 trials).

9 **Harm:** See **TABLE II.C.**

10 **Cost:** Low.

11 **Benefits-harm assessment:** Balance of benefit and harm with current evidence base.

12 **Value judgments:** While combination therapy of INDC and INCS is superior to INCS therapy alone with  
13 low risk of tachyphylaxis in patients with refractory AR, the magnitude of effect is still unclear. There  
14 may be a role in patients with AR refractory to INCS and intranasal antihistamine combination therapy  
15 prior to consideration of surgery or in patients uninterested in surgery.

16 **Policy level:** Option.

17 **Intervention:** Short-term combination therapy with INCS and INDC may be considered in patients with  
18 AR refractory to combination therapy with INCS and intranasal antihistamine prior to consideration of IT  
19 reduction or in patients declining surgery.

20

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

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Khattiyawittayakun et al <sup>531</sup>	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 <sup>525</sup>	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 <sup>529</sup>	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 <sup>527</sup>	2013	2	RCT	705 participants: -Mometasone-oxymetazoline (3 sprays pn Qday nasal spray	TNSS	-Combination therapy significantly more effective in improving nasal congestion than mometasone alone,

				-Mometasone-oxymetazoline (1 spray pn Qday) nasal spray; -Mometasone nasal spray -Oxymetazoline (2 sprays pn BID) nasal spray -Placebo		oxymetazoline alone, and placebo -No dose-dependent relationship seen with oxymetazoline in combination therapy
Matreja et al <sup>526</sup>	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 <sup>530</sup>	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 <sup>528</sup>	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

1 LOE=level of evidence, SRMA=systematic review and meta-analysis; RCT=randomized controlled trial;  
2 INCS=intranasal corticosteroid; INDC=intranasal decongestant; TNSS=Total Nasal Symptom Score; PNIF=peak nasal  
3 inspiratory flow; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; AR=allergic rhinitis; pn=per nostril;  
4 Qday=daily; BID=twice daily  
5 \*Downgraded LOE due to very small size of RCT and lack of AR/non-allergic rhinitis subgroup analysis  
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#### 8 XI.B.10.g. Intranasal corticosteroid and intranasal ipratropium

10 Current treatment algorithms for children<sup>532,533</sup> and adult patients<sup>65,85</sup> with moderate to severe AR with  
11 insufficient symptom control or treatment failure based on INCS monotherapy uniformly recommend  
12 adding nasal IPB to the established INCS therapy if one of the main symptoms is predominant or  
13 refractory rhinorrhea. Although most guidelines recommend the combined use of both INCS and IPB in  
14 those patients, only one study assessed the effectiveness of this combination therapy in AR patients.  
15 Dockhorn et al<sup>390</sup> conducted a double-blind RCT in patients with AR and non-allergic rhinitis and

1 demonstrated that the combination therapy of 14 days of IPB 0.03%, 42µg per nostril TID and  
 2 beclomethasone dipropionate, 84µg per nostril BID was superior to either agent alone and placebo in  
 3 reducing the severity and duration of rhinorrhea. The combination therapy resulted in a clinically  
 4 relevant reduction in severity and duration of rhinorrhea in 74% and 66% of patients respectively,  
 5 compared to 57% and 50% for IPB monotherapy, 64% and 54% for beclomethasone dipropionate  
 6 monotherapy, and 47% and 38% for placebo. Of note, in evaluation of nasal congestion alone,  
 7 combination therapy was more effective than IBP monotherapy or placebo, but not statistically better  
 8 than beclomethasone dipropionate alone. Similarly, better improvements in QOL PROMs, including the  
 9 SF-36 Health Survey and the RQLQ, were seen in the combination therapy group relative to  
 10 monotherapy or placebo. The QOL effects of the combination therapy were most pronounced on the  
 11 three RQLQ questions that focus on rhinorrhea. A clinically relevant improvement from: “somewhat  
 12 troubled-extremely troubled” at baseline to “not troubled-hardly troubled” after two weeks of  
 13 treatment was found in 48.8% of patients with the combined treatment compared to 38.9%, 25.2%, and  
 14 16% in the IPB, beclomethasone dipropionate, and placebo groups. The combination therapy was  
 15 generally well tolerated. The most reported adverse effects included nasal dryness, epistaxis, blood-  
 16 streaked sputum, nasal irritation, and congestion. [TABLE II.C.] Interestingly, the percentage of patients  
 17 reporting these adverse events was comparable to the treatment groups receiving monotherapy. Of  
 18 note, this study population included patients with both AR and non-allergic rhinitis and therefore these  
 19 conclusions may only apply to this combination population. Nonetheless, as there is only evidence that  
 20 the combination therapy effectively controls rhinorrhea, add-on IPB should only be prescribed if one of  
 21 the predominant refractory symptoms is rhinorrhea. [TABLE XI.B.10.g.]

22  
 23 **Aggregate grade of evidence:** Unable to determine based on one study. (Level 2: 1 study; TABLE  
 24 XI.B.10.g.)

25 **Benefit:** Reduction of rhinorrhea in INCS-treatment refractory AR.

26 **Harm:** Usually, no systemic anticholinergic activity if administered intranasally in the recommended  
 27 doses. See TABLE II.C.

28 **Cost:** Low.

29 **Benefits-harm assessment:** Benefit for combined INCS and IPB therapy in patients with treatment  
 30 refractory AR and the main symptom of rhinorrhea.

31 **Value judgments:** No evidence for benefits in controlling symptoms other than rhinorrhea. Evidence is  
 32 limited, but results are encouraging for patients with persistent rhinorrhea.

33 **Policy level:** Option.

34 **Intervention:** Combining IPB with beclomethasone dipropionate can be more effective than either agent  
 35 alone for the treatment of rhinorrhea in refractory AR in children and adults. Although multiple  
 36 consensus guidelines have recommended, and there is evidence to support this recommendation, it is  
 37 important to note that there has only been one RCT to study the efficacy of combined INCS and IPB

1 therapy compared to either agent alone, and this study was performed in a combined population of  
 2 patients with AR and non-allergic rhinitis.

3  
 4 **TABLE XI.B.10.g. Evidence table – Combination therapy: intranasal corticosteroid and intranasal**  
 5 **ipratropium**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dockhorn et al <sup>390</sup>	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

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

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 9  
 10 **XI.B.11. Non-traditional and alternative therapies**

11 **XI.B.11.a. Acupuncture**

12  
 13 Since the 5<sup>th</sup> century BC, acupuncture has been used as a therapeutic modality for otolaryngologic  
 14 disorders.<sup>534</sup> A central tenet of Traditional Chinese Medicine (TCM) is the concept of *qi*, which represents  
 15 the body's vital energy and flows through a network of meridians beneath the skin.<sup>535</sup> Acupuncture  
 16 involves insertion of thin needles at specific acupoints located along these meridians with the goal of  
 17 achieving a therapeutic "*de qi*" effect.<sup>536</sup> Studies have shown that acupuncture may potentially reset the  
 18 Th2-Th1 imbalance by modulating IgE and IL-10 levels in patients with AR significantly more than  
 19 controls.<sup>537,538</sup> Acupuncture has an excellent safety profile with only mild reported adverse effects.<sup>538,539</sup>

20 **[TABLE SE/AE]**

21  
 22 Several SRMAs have been performed on acupuncture for the treatment of AR. In 2008, Roberts et al<sup>539</sup>  
 23 reviewed 7 RCTs and found a high degree of heterogeneity between studies with most studies being of  
 24 low quality. No overall effects of acupuncture on AR symptom scores or use of relief medications were  
 25 identified. In 2009, Lee et al<sup>540</sup> performed a systematic review with pooled analysis of 152 patients  
 26 demonstrating that the results of acupuncture for AR are mixed – with acupuncture superior to sham  
 27 acupuncture in symptom scores for perennial AR, but not for seasonal AR. In 2015, a meta-analysis by  
 28 Feng et al<sup>538</sup>, which included 13 studies, showed a significant improvement of nasal symptoms, RQLQ  
 29 scores, and use of rescue medications in the group receiving acupuncture. This meta-analysis included  
 30 data from a large multicenter RCT (n=422) demonstrating improvement of seasonal AR with true



1 acupuncture.<sup>541</sup> In 2020, a systematic review by Wu et al<sup>542</sup> analyzed 15 RCTs and found acupuncture as  
 2 a useful adjunct to allopathic standard of care or as monotherapy for AR. Yin et al<sup>543</sup> reviewed 39  
 3 studies, which included several studies from China and a meta-analysis showing that acupuncture was  
 4 superior to sham acupuncture with improvement in nasal symptom and RQLQ scores. [TABLE XI.B.11.a.]

5  
 6 Most important to note is the paucity of trials with head-to-head comparisons between acupuncture  
 7 and standard conventional AR medication, with most RCTs using medication primarily as rescue  
 8 treatment. The uncontrolled use of AR medications can significantly impact outcomes and underscores  
 9 the critical need for comparative effectiveness research, as prioritized by the National Academy of  
 10 Medicine.<sup>544</sup>

11  
 12 **Aggregate grade of evidence:** A (Level 1: 4 studies, level 2: 1 study; TABLE XI.B.11.a.)  
 13 **Benefit:** Improvement of QOL and symptoms. Fairly well tolerated with no systemic adverse effects.  
 14 **Harm:** Needle sticks associated with minor adverse events including skin irritation, erythema,  
 15 subcutaneous hemorrhage, pruritus, numbness, fainting, and headache. Electroacupuncture can  
 16 interfere with pacemakers and other implantable devices. Caution is recommended in pregnant patients  
 17 as some acupoints can theoretically induce labor. Need for multiple treatments and possible on-going  
 18 treatment to maintain any benefit gained. Relatively long treatment period.  
 19 **Cost:** Moderate-high. Cost and time associated with acupuncture treatment; multiple treatments  
 20 required.  
 21 **Benefits-harm assessment:** Balance of benefit and harm.  
 22 **Value judgments:** The evidence is generally supportive of acupuncture. Acupuncture may be  
 23 appropriate for some patients to consider as an adjunct/alternative therapy.  
 24 **Policy level:** Option.  
 25 **Intervention:** In patients who are interested in avoiding medications, acupuncture can be suggested as a  
 26 possible therapeutic adjunct.  
 27

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

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

				-Conventional medication (2 RCTs)	-RQLQ -Rescue medication use	scores for perennial AR, but not for seasonal AR
Roberts et al <sup>539</sup>	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 <sup>543</sup>	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

1 LOE=level of evidence; SR=systematic review; RCT=randomized controlled trial; RQLQ=Rhinoconjunctivitis Quality  
2 of Life Questionnaire; SRMA=systematic review and meta-analysis; AR=allergic rhinitis

3 \*Relevant prior studies are included in the SRMAs

4 \*\*LOE downgraded due to unclear risk of bias for allocation concealment; insufficient blinding of participants,  
5 personnel, and outcome assessments; short treatment duration (most studies 2-4 weeks) and lack of follow up

6  
7

8 **XI.B.11.b. Other complementary modalities**

9

10 Several SRMAs and RCTs have been performed on complementary interventions other than traditional  
11 acupuncture. These include: (1) ear acupressure;<sup>545</sup> (2) acupoint catgut implantation;<sup>546</sup> (3) acupoint  
12 herbal patching;<sup>547</sup> (4) sphenopalatine ganglion acupuncture – a modern version of acupuncture  
13 developed by a Chinese otolaryngologist in the 1960s and first reported in 1990 for the treatment of  
14 AR,<sup>548-551</sup> and (5) moxibustion/thunder fire moxibustion – a therapy based upon TCM theory that entails  
15 the burning of mugwort leaves as a warming treatment to promote circulation of qi.<sup>543,552,553</sup> SRMA  
16 results are mixed, with several of the SRMAs including studies of low methodological quality or high risk  
17 of bias. [TABLE XI.B.11.b.]

18

19 **Aggregate grade of evidence:** Uncertain. Various complementary modalities assessed. Studies included  
20 in several SRMAs had poor methodological quality or high risk of bias.

21 **Benefit:** Unclear but some of these complementary therapies may be able to provide symptomatic  
22 relief.

23 **Harm:** Minimal side effects reported.

24 **Cost:** Moderate-high cost of therapies with multiple treatments required.

25 **Benefits-harm assessment:** Unknown.

26 **Value judgments:** There is lack of sufficient evidence to recommend the use of these interventions in  
27 AR.

28 **Policy level:** No recommendation.

29 **Intervention:** None.

30

31 **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 <sup>543</sup>	2020	2 <sup>a</sup>	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 <sup>548</sup>	2019	2 <sup>b</sup>	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 <sup>553</sup>	2020	3 <sup>c</sup>	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 <sup>547</sup>	2015	3 <sup>d</sup>	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 <sup>551</sup>	2020	4 <sup>c</sup>	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 <sup>546</sup>	2014	4 <sup>e</sup>	SR	-Catgut Implantation at acupoints -Conventional medicine -Moxibustion in mid-summer	-Improvement in AR symptom -Clinical efficacy rate	No conclusion could be made due to several methodological shortcomings and risk of bias for 1 included trial
Zhang et al <sup>545</sup>	2010	4 <sup>f</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; RQLQ=Rhinoconjunctivitis Quality of Life  
 2 Questionnaire; AR=allergic rhinitis; SGA=sphenopalatine ganglion acupuncture; TNSS=Total Nasal Symptom Score;  
 3 VAS=visual analog scale; TFM=thunder fire moxibustion; TNNSS= Total Non-Nasal Symptom Score; SF-36=Short  
 4 Form-36; SR=systematic review  
 5 \*Relevant prior studies are included in the SRMAs  
 6 <sup>a</sup>LOE downgraded due to unclear risk of bias for allocation concealment; insufficient blinding of participants,  
 7 personnel, and outcome assessments; short treatment duration (most studies were 2-4 weeks) and lack of follow  
 8 up  
 9 <sup>b</sup>LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation  
 10 concealment; attrition bias with incomplete outcome data  
 11 <sup>c</sup>LOE downgraded due to lack of blinding of participants, personnel, outcome assessments; allocation concealment;  
 12 selective reporting bias  
 13 <sup>d</sup>LOE downgraded due to high risk of bias, including lack of details about randomization, allocation concealment,  
 14 no intention-to-treat analysis, proper blinding in the majority of included studies, and heterogeneity of study  
 15 subjects with AR  
 16 <sup>e</sup>LOE downgraded since only 1 RCT met inclusion criteria for SR, with high risk of bias due to lack of validated  
 17 outcome measure, details about randomization, allocation concealment, blinding of participants and personnel,  
 18 selective reporting bias, and no intention-to-treat analysis  
 19 <sup>f</sup>LOE downgraded due to lack of validated outcome measure, details about randomization, no blinding of  
 20 participants in all 5 studies included in SR, and no intention-to-treat analysis  
 21  
 22

### 23 XI.B.11.c. Honey

24  
 25 A long-held belief has been that honey is effective in treating symptoms of AR; however, evidence for  
 26 this is scarce. It is postulated that environmental antigens contained within locally produced honey  
 27 could, when ingested regularly, lead to the development of tolerance in a manner similar to SLIT.<sup>554</sup>  
 28 Primary sources of antigens can include pollen and microflora from the digestive tract of honeybees,  
 29 which typically contains microorganisms present in dust, air, and flowers.<sup>555</sup> It is important to note,  
 30 however, that heavy insect-borne pollens do not meet Thomen's postulates, as they are not airborne  
 31 and hence should not be able to induce allergic sensitivity. Studies in animals have demonstrated the  
 32 ability of honey to suppress IgE antibody responses against different allergens and to inhibit IgE-  
 33 mediated mast cell activation,<sup>556-558</sup> while studies in humans have demonstrated various anti-  
 34 inflammatory properties of honey.<sup>559,560</sup>  
 35

36 There have been three RCTs looking at honey in the treatment of AR. The studies all differed on  
 37 geographic location, length of treatment, dose of honey, and timing with respect to specific allergy  
 38 seasons. One double-blind RCT<sup>561</sup> and an additional RCT<sup>562</sup> showed a significant decrease in total  
 39 symptoms scores in the treatment group compared to control. In contrast, another double-blind RCT<sup>563</sup>  
 40 found no benefit of honey ingestion for the relief of AR symptoms compared to controls. [TABLE

41 **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,<sup>564</sup> and only the trial by Asha'ari et al<sup>561</sup> dosed patients at that level. In addition, the benefit of birch pollen honey in the trial by Saarinen et al<sup>562</sup> 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 <sup>561</sup>	2013	2	DBRCT	-Honey -Placebo	AR symptom scores	Improvement in overall and individual AR symptoms with honey
Saarinen et al <sup>562</sup>	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 <sup>563</sup>	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

1 There are a vast number of studies looking at the effectiveness of various herbs and supplements in the  
 2 treatment of AR; however, most are small and of poor quality. Herbal remedies that have been  
 3 subjected to more rigorous study are summarized in **TABLE XI.B.11.d.**

4  
 5 Herbs often contain active pharmacologic ingredients, which can be difficult to measure clinically.<sup>565</sup>  
 6 Given the lack of robust and repeated large double-blind placebo-controlled RCTs for any particular  
 7 herbal remedy, further research is needed before recommendations can be made regarding routine use  
 8 of any particular herb or supplement.

9  
 10 **Aggregate grade of evidence:** Uncertain.

11 **Benefit:** Unclear, but some herbs may be able to provide symptomatic relief.

12 **Harm:** Some herbs are associated with mild side effects. Also, the safety, quality and standardization of  
 13 herbal remedies and supplements are unclear.

14 **Cost:** Cost of herbal supplements.

15 **Benefits-harm assessment:** Unknown.

16 **Value judgments:** There is a lack of sufficient evidence to recommend the use of herbal supplements in  
 17 AR.

18 **Policy level:** No recommendation.

19 **Intervention:** None.

20

21 **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 <sup>566</sup>	Rash, soft stool, headache, changes in hematocrit, increased uric acid levels
<i>Astragalus membranaceus</i>	Unknown	DBRPCT comparing 80mg daily x 6 weeks; improvement in rhinorrhea, TSS, QOL <sup>567</sup>	Pharyngitis, rhinosinusitis
Aller-7	Possible antioxidant and anti-inflammatory pathways <sup>568-570</sup>	Two DBRPCTs showed some relief of symptoms with Aller-7, but some contradictory findings present <sup>571</sup>	Dry mouth, gastric discomfort
Benifuuki green tea	Catechins, EGCG and polyphenols inhibit type I and type IV hypersensitivity reactions <sup>572,573</sup>	DBRPCT showed 700mL Benifuuki green tea daily significantly reduced AR symptoms, improved QOL, suppressed peripheral eosinophils <sup>574</sup>	None reported
Biminne	Unknown	DBRPCT showed 12 weeks of Biminne significantly reduced sneezing <sup>575</sup>	None reported

Butterbur ( <i>Petasites hybridus</i> )	Inhibits leukotriene/histamine synthesis and mast cell degranulation <sup>576</sup>	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; <sup>565,571</sup> 1 DBRPCT demonstrated no benefit for PNIF, symptoms, QOL <sup>571</sup>  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. <sup>542</sup>	Hepatic toxicity, headache, gastric upset, headache, itchy eyes, diarrhea, fatigue, drowsiness
Capsaicin	Thought to desensitize and deplete sensory C-fibers and myelinated A- $\delta$ fibers, acting as a blocking agent of neuropeptides <sup>577-579</sup>	No evidence of a therapeutic effect of intranasal capsaicin in AR <sup>542,579,580</sup>	Mucosal irritation, burning, lacrimation, coughing.
Chlorophyll c2 ( <i>Sargassum horneri</i> )	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 <sup>581</sup>	None reported
Cinnamon bark, Spanish needle, acerola (ClearGuard)	Inhibits production of prostaglandin D2 <sup>582</sup>	DBRPCT showed 450mg CG TID comparable to loratadine 10mg in symptom reduction; CG prevented increase in prostaglandin D2 release following nasal allergen challenge <sup>582</sup>	None reported
Conjugated linoleic acid	Immune-modulating effects of humoral and cellular immune responses, decreased in vitro production of TNF- $\alpha$ , IFN- $\gamma$ , IL-5	DBRPCT showed that consuming 2g conjugated linoleic acid daily before and during birch pollen season improves sneezing and wellbeing <sup>583</sup>	None reported
Grapeseed extract	Unknown	DBRPCT showed no benefit of 100mg grapeseed extract BID on nasal symptoms, need for rescue medications, QOL <sup>584</sup>	None reported
Isoquercitrin	Flavonoid with anti-allergic and antioxidant effects	DBRPCT demonstrated 100 mg Isoquercitrin significantly improved ocular symptoms but not nasal symptoms <sup>585,586</sup>	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 <sup>587</sup>	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 <sup>588</sup>	None reported
<i>Nigella sativa</i> (Black seed)	-Inhibits histamine release from rat macrophages <sup>589</sup> -Thymoquinone may inhibit Th2 cytokines and eosinophil infiltration in airways <sup>590</sup>	<i>N. sativa</i> capsules (2 DBRPCTs) and <i>N. sativa</i> nasal drops (1 DBRPCT) improve AR symptoms; <sup>591-593</sup> 1 DBRPCT did not find significant differences between treatment and placebo <sup>591</sup>	Gastrointestinal complaints with oral intake, nasal dryness with topical drops
<i>Perilla frutescens</i>	Polyphenolic phytochemicals such as Rosmarinic acid inhibit inflammatory processes and the allergic reaction <sup>594-597</sup>	DBRPCT showed 50 mg or 200 mg <i>P. frutescens</i> enriched for rosmarinic acid did not significantly improve symptom scores <sup>598</sup>	None reported
Probiotics	Down-regulation of IL-5 and allergen-specific IgG4 <sup>599,600</sup>	<i>See Section XI.B.9. Probiotics for additional information on this topic.</i>	
L.RCM-101	Inhibits histamine release and prostaglandin E2 production <sup>601,602</sup>	DBRPCT showed 4 tablets of RCM-101 TID for 8 weeks significantly improved symptom scores and RQLQ <sup>603</sup>	Mild gastrointestinal side effects
Spirulina	-Reduces IL-4 levels, inhibits histamine release from mast cells <sup>604</sup> -Enhanced IgA levels and IFN- $\gamma$ , natural killer cell damage were increased <sup>605</sup>	DBRPCT showed 2000mg daily Spirulina significantly improved sneezing, rhinorrhea, congestion, and nasal itching <sup>606</sup>	None reported
Ten-Cha ( <i>Rubus suavissimus</i> )	Inhibits cyclooxygenase activity and histamine release by mast cells <sup>607</sup>	DBRPCT showed no significant improvement in symptom scores, RQLQ, or need for antihistamine with 400mg daily of Ten-Cha extract <sup>608</sup>	None reported
TJ-19**	Inhibits histamine signaling and IL-4 and IL-5 expression in a rat model <sup>609</sup>	DBRPCT showed 3g TJ-19 TID significantly improved sneezing, stuffy nose and rhinorrhea <sup>610</sup>	None reported
Tinofend ( <i>Tinospora cordifolia</i> )	Possibly through anti-inflammatory effects <sup>611</sup>	DBPRCT showed 300mg Tinofend x8 weeks significantly improved AR symptoms, also decreased eosinophils, neutrophils, goblet cells on nasal smear <sup>611</sup>	Leukocytosis



Tomato extract	Possibly inhibits histamine release	DBRPCT showed 360mg Tomato extract daily x8 weeks decreased sneezing score, rhinorrhea, nasal obstruction <sup>612</sup>	None reported
<i>Urtica dioica</i> (stinging nettle)	In vitro: antagonist/negative agonist activity against histamine-1 receptor, inhibits mast cell tryptase, prevents mast cell degranulation, inhibits prostaglandin formation <sup>613</sup>	-DBRPCT showed symptom improvement over placebo at 1 hour <sup>614</sup> -One systematic review showed no significant intergroup differences <sup>571</sup>	None reported
Vitamin C (ascorbic acid)	Acts as a water-soluble antioxidant with immune modulating effects <sup>615</sup>	DBRPCT showed that 2-week nasal application of ascorbic acid reduced nasal edema, mucus secretion, nasal obstruction <sup>615</sup>	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 <sup>616</sup> <i>-See Section VI.H. Vitamin D for additional information on this topic</i>	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 <sup>617</sup> -Another DBRPCT showed 400 IU per day of vitamin E had no effect on nasal symptoms or IgE levels <sup>618</sup>	None reported

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

5 \*All listed studies LOE 2

6 \*\*Not available in US; contains ephedra

7

8

9 [XI.B.11.e. Guideline summary recommendations for non-traditional and alternative therapies](#)

10

11 See **TABLE XI.B.11.e.** for a summary of current guideline recommendations for non-traditional and  
 12 alternative therapies for AR.

13

14 **TABLE XI.B.11.e. Summary of clinical practice guideline recommendations for non-traditional and**  
 15 **alternative therapies for allergic rhinitis**

Organization	Year	Statement	Guideline methodology
--------------	------	-----------	-----------------------

American Academy of Otolaryngology – Head and Neck Surgery Foundation <sup>85</sup>	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 <sup>619</sup>	2018	-Acupuncture is a safe treatment option, and most of the acupuncture methods employed can improve 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 <sup>620</sup>	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

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

### 5 XI.C. Intranasal procedural interventions

7 Although medical therapy has largely been considered the cornerstone of treatment for AR,  
8 surgical/procedural management may play a role when patients are refractory to medical treatment. In  
9 these instances, surgery aims to improve structural problems that may lead to nasal  
10 obstruction/congestion, or to directly address physiologic causes of symptoms (e.g., rhinorrhea, mucosal  
11 swelling).

13 The literature surrounding the role of septoplasty/septorhinoplasty as a structural treatment for AR has  
14 expanded recently. While early evidence suggested that AR patients may benefit less from  
15 septoplasty/septorhinoplasty than non-AR counterparts,<sup>621-623</sup> most of the recent literature suggests the  
16 contrary,<sup>624-633</sup> with overall low complication rates.<sup>634,635</sup> Kim et al<sup>636</sup> found that AR patients with septal  
17 deviation that underwent septoplasty with turbinoplasty had greater improvement in nasal obstruction  
18 than those that who underwent turbinoplasty alone. Nevertheless, the evidence is low-quality overall,  
19 with a preponderance of retrospective case series and no RCTs. Furthermore, many applicable studies  
20 did not directly evaluate the role of septoplasty/septorhinoplasty in AR, but instead include it

1 peripherally in the analysis. Therefore, in the properly selected patient, septoplasty/septorhinoplasty  
2 may represent an option at best. **[TABLE XI.C.-1]**

3  
4 IT surgery can improve symptoms by structurally reducing nasal obstruction/congestion caused by  
5 enlarged turbinates, reducing volume of mucosal tissue that reacts with allergens, and allow improved  
6 accommodation of AR-induced turbinate swelling.<sup>637</sup> Inferior turbinoplasty is done via various surgical  
7 techniques: (1) bony lateral outfracture; (2) energy-related submucous reduction techniques [e.g.,  
8 radiofrequency ablation, electrocautery, coblation, laser-assisted]; (3) microdebrider-assisted  
9 submucous reduction, and (4) bony and submucosal resection, including medial flap turbinoplasty.<sup>638</sup>  
10 Total turbinectomy or turbinate resection was not covered as part of this review as they are typically not  
11 performed for inflammatory disease.

12  
13 There are numerous studies investigating the efficacy of IT surgery for AR. Bony outfracture, the most  
14 atraumatic and conservative IT surgery,<sup>638</sup> can reduce the distance between IT and lateral nasal wall and  
15 enlarge the dimensions of the nasal airway when performed alone<sup>639,640</sup> or in conjunction with other  
16 techniques.<sup>641,642</sup> IT surgery via energy-related techniques<sup>641-700</sup> and via direct tissue  
17 removal<sup>629,633,636,640,644,647,668,669,672,673,675,681,701-713</sup> have both been extensively studied, with reported high  
18 efficacy in reducing symptoms and increasing nasal volume and airflow with minimal complications. Of  
19 note, botulinum toxin injection<sup>714-716</sup> and high-intensity focused ultrasound may also provide  
20 symptomatic relief,<sup>717,718</sup> though there remains limited evidence for their utility. As such, the current  
21 literature suggests that, in the properly selected AR patient with concomitant IT hypertrophy, IT surgery  
22 is an effective and safe treatment to reduce symptoms and improve QOL. More rigorous studies are  
23 warranted to directly compare various IT reduction techniques for optimal and durable outcomes.

24 **[TABLE XI.C.-2]**

25  
26 Another structural target is the nasoseptal swell body, with newer interventions directed towards  
27 volumetric reduction to improve airflow. Though ablation of the swell body (whether through  
28 radiofrequency, laser, or coblation) has shown promise in reducing symptoms,<sup>719-723</sup> its effectiveness has  
29 yet to be tested with an AR-specific cohort. However, the advent of devices intended for office use (e.g.,  
30 Vivaer<sup>®</sup>, Aerin Medical, Sunnyvale, CA) may provide opportunities for further study.

31

1 Rhinorrhea, as part of both AR and non-allergic rhinitis, may arise from overactivity of parasympathetic  
2 nerve fibers originating from the vidian nerve. A vidian neurectomy with permanent sectioning of the  
3 most proximally accessible nerve segment is a potential surgical approach to reduce rhinorrhea in these  
4 patients.<sup>723</sup> Evidence published from 2011 onwards provides support regarding its use in AR patients.  
5 Observational studies and a non-randomized controlled trial found that AR patients experienced  
6 improvements in sneezing, nasal discharge, obstruction, itching, and QOL.<sup>712,724-727</sup> A RCT and another  
7 non-randomized controlled trial of patients with both AR and chronic rhinosinusitis with nasal polyps  
8 found similar results, as well as improvement on pulmonary functions tests.<sup>728,729</sup> There remains some  
9 concern that symptom recurrence may be high based on earlier studies,<sup>730</sup> especially with longer-term  
10 follow up, though this remains in contention and recent series have reported durable outcomes.  
11 Additionally, vidian neurectomy also carries the risk of dry eye due to the rami lacrimales that diverge  
12 from the nerve.<sup>731</sup> Though recent evidence suggests that the properly selected patient does not  
13 experience symptomatic dry eye postoperatively,<sup>732</sup> newer, more directed techniques targeting distal  
14 nerve segments have been developed. Specifically, the posterior nasal nerve (PNN), a branch of the  
15 vidian, appears to be an appropriate target given its specific nasal innervation. Though there is no study  
16 that evaluates vidian and PNN neurectomy head-to-head in AR patients, PNN neurectomy has been  
17 similarly shown to be effective for reducing symptoms,<sup>711,733-739</sup> though one non-randomized controlled  
18 trial did not find a benefit to adding PNN neurectomy to microdebrider-assisted turbinoplasty.<sup>740</sup> Given  
19 the evidence, neurectomy is an option for treating refractory rhinorrhea following failed medical  
20 management. **[TABLES XI.C.-3 and XI.C.-4]**

21  
22 Alternatively, energy-based ablation of the PNN (RhinAer<sup>®</sup>, Aerin Medical, Sunnyvale, CA) utilizing  
23 radiofrequency or cryotherapy (ClariFix<sup>®</sup>, Stryker, Kalamazoo, MI) are office-based alternatives to direct  
24 nerve section. The earliest report of utilizing cryotherapy for this indication was by Terao et al<sup>741</sup> in 1983.  
25 Studies utilizing cryoablation, including a randomized, sham-controlled trial, have shown improvement  
26 in symptoms and QOL.<sup>742-748</sup> Though no study specifically evaluated an AR-specific cohort, many  
27 performed subgroup analysis (which showed similar improvement) or controlled for the presence of AR  
28 (which showed that AR did not modify outcomes). Similar results were seen with radiofrequency  
29 ablation, also in the form of a randomized, sham-controlled trial.<sup>749,750</sup> In-office endoscopic laser ablation  
30 of the PNN has also been reported with positive improvement.<sup>751</sup> These procedures seem to be well-  
31 tolerated, with minimal complication risk.<sup>752</sup> There is also evidence to suggest that appropriate response  
32 to ipratropium nasal spray seems to correlate with improved cryotherapy treatment response.<sup>748</sup>

1 Ultimately, as the current evidence is largely based on industry-sponsored studies with limited long-  
 2 term data, these interventions remain an option for properly selected patients. [TABLE XI.C.-5]

3

4 **Aggregate grade of evidence – septoplasty/septorhinoplasty:** C (Level 3: 1 study, level 4: 3 studies, level  
 5 5: 11 studies; TABLE XI.C.-1)

6 **Benefit:** Improved postoperative symptoms and nasal airway.

7 **Harm:** Risk of complications (e.g., septal hematoma or perforation, nasal dryness, cerebrospinal fluid  
 8 leak, epistaxis, unfavorable aesthetic change); persistent obstruction.

9 **Cost:** Surgical/procedural costs, time off from work.

10 **Benefits-harm assessment:** Potential benefit must be weighed against low risk of harm and cost of  
 11 procedure.

12 **Value judgments:** Properly selected patients with septal deviation impacting their nasal patency can  
 13 experience improved nasal obstruction symptoms.

14 **Policy level:** Option for those with obstructive septal deviation.

15 **Intervention:** Septoplasty/septorhinoplasty may be considered in AR patients that have failed medical  
 16 management and who have anatomic, obstructive features that may benefit from this intervention.

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19 **Aggregate grade of evidence – inferior turbinate surgery:** B (Level 1: 4 studies, level 2: 13 studies, level  
 20 3: 18 studies, level 4: 50 studies\*; TABLE XI.C.-2)

21 \*Level 1, 2, and 3 studies are listed in the table; level 4 studies are referenced.

22 **Benefit:** Improvement in rhinitis symptoms including nasal breathing, congestion, sneezing, and itching.  
 23 Improved nasal cavity area via objective measures, as well as increased QOL via subjective measures.

24 **Harm:** Risk of complications (e.g., swelling, crusting, empty nose syndrome, epistaxis).

25 **Cost:** Surgical/procedural costs, potential time off from work.

26 **Benefits-harm assessment:** Potential benefit outweighs low risk of harm.

27 **Value judgments:** Current evidence suggests that patients with AR who suffer from IT hypertrophy will  
 28 likely experience improvement in symptoms, nasal patency, and QOL.

29 **Policy level:** Recommendation in patients with medically refractory nasal obstruction.

30 **Intervention:** In AR patients with IT hypertrophy that have failed medical management, IT reduction is a  
 31 safe and effective treatment to reduce symptoms and improve nasal function. More studies are  
 32 warranted to directly compare IT surgery methods (e.g., radiofrequency ablation, laser-assisted,  
 33 microdebrider-assisted) for the most efficacious and long-lasting outcome.

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36 **Aggregate grade of evidence – neurectomy (vidian neurectomy, posterior nasal neurectomy):** B (Level  
 37 2: 3 studies, level 3: 5 studies, level 4: 7 studies, level 5: 2 studies; TABLES XI.C.-3 and XI.C.-4)

38 **Benefit:** Improvement in rhinorrhea.

39 **Harm:** Risk of complications (e.g., dry eye and decreased lacrimation, numbness in lip/palate, nasal  
 40 dryness, damage to other nerves).

41 **Cost:** Surgical/procedural costs, potential time off from work.

42 **Benefits-harm assessment:** Potential benefit must be balanced with low risk of harm but consider that  
 43 long-term results may be limited.

44 **Value judgments:** Patients may experience an improvement in symptoms.

45 **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 <sup>629</sup>	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 <sup>628</sup>	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 <sup>636</sup>	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 <sup>622</sup>	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 <sup>635</sup>	2021	5*	Retrospective case series	Heterogenous case series of patients undergoing septoplasty or septorhinoplasty +/-	Septal perforation rates	No AR patient had a septal perforation

				turbinoplasty, including those with AR		
Kim et al <sup>632</sup>	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 <sup>631</sup>	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 <sup>630</sup>	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 <sup>627</sup>	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 <sup>626</sup>	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 <sup>623</sup>	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 <sup>634</sup>	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 <sup>625</sup>	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 <sup>621</sup>	1988	5*	Retrospective case series	Heterogenous case series of patients undergoing septoplasty or submucous resection, including those with AR	-Patient satisfaction -Symptom questionnaire	AR patients were less satisfied post-op compared to non-AR patients, and had unchanged nasal secretion
Stoksted & Gutierrez <sup>624</sup>	1983	5*	Retrospective case series	Heterogenous case series of patients undergoing septorhinoplasty, including those with AR	Evaluation of normal nasal passages	Patients with AR reached post-operative normal nasal passages at lower rates

1 LOE=level of evidence; NOSE=Nasal Obstruction Symptom Evaluation; AR=allergic rhinitis;  
 2 RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; VAS=visual analog scale; OSA=obstructive sleep apnea;  
 3 IT=inferior turbinate; AHI=apnea hypopnea index; UPSIT=University of Pennsylvania Smell Identification Test;  
 4 SNOT-20=Sinonasal Outcome Test (20 items); RhinoQOL=Rhinosinusitis Quality of Life Survey  
 5 \*LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR  
 6 patients  
 7 \*\*LOE downgraded due to inclusion criteria of a unique population and low sample size  
 8 \*\*\* LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR  
 9 patients, as well as low number in the outcome of interest

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**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 <sup>672</sup>	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 <sup>668</sup>	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 <sup>753</sup>	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 <sup>648</sup>	2009	1	SR	RFA turbinoplasty	-Symptom questionnaires	Nasal RFA reduced IT mucous membrane volume and may decrease



					-Acoustic rhinometry -Rhinomanometry	subjective symptoms and nasal blockage, with only minor discomfort and side effects
Ghosh et al <sup>633</sup>	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 <sup>678</sup>	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 <sup>708</sup>	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 <sup>671</sup>	2015	2	Prospective randomized	-RFA turbinoplasty -Bipolar radiofrequency turbinoplasty	-Nasal obstruction severity/frequency -Nasal discharge -Sneezing -Hyposmia -Postnasal drip -Acoustic rhinometry	Similar subjective and objective outcomes between groups
Kaymakci et al <sup>641</sup>	2014	2	Prospective randomized	-RFA turbinoplasty with lateral displacement -RFA turbinoplasty alone	Severity/frequency of nasal obstruction	Post-operative nasal obstruction frequency/severity were significantly lower in RFA with lateral turbinate displacement vs RFA alone
Abtahi et al <sup>715</sup>	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 <sup>701</sup>	2013	2	Prospective randomized	Microdebrider-assisted inferior turbinoplasty: -Intratubinate -Extratubinate	-Nasal obstruction, rhinorrhea, sneezing, nasal itching, postnasal drip -Acoustic rhinometry	-Symptomatic improvement significantly higher with extratubinate treatment -Acoustic rhinometry showed significant but comparable improvement in both groups

Wei et al <sup>718</sup>	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 <sup>660</sup>	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 <sup>689</sup>	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 <sup>653</sup>	2010	2	Prospective randomized	-INCS -RFA turbinoplasty	-Anterior rhinomanometry -Nasal congestion -QOL	-RFA turbinoplasty provided more reduction in nasal congestion -QOL scores improved in both groups
Liu et al <sup>647</sup>	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 <sup>716</sup>	2003	2	RCT	Turbinates 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 <sup>681</sup>	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 <sup>629</sup>	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 <sup>709</sup>	2019	3	Case-control	-Submucosal turbinoplasty with resection of PNN branches in IT	Nasal obstruction, sneezing, nose blowing, mouth breathing, hyposmia	Rhinorrhea severity, detection threshold, and recognition threshold significantly lower after resection of the posterior

				-Submucosal turbinoplasty alone		nasal nerves with turbinoplasty
Zhong et al <sup>677</sup>	2019	3	Case-control	-High-intensity focused ultrasound -Plasma RFA	-Nasal obstruction, nasal discharge, sneezing, pain -QOL -Nasal endoscopy	Compared to plasma RFA, high-intensity focused ultrasound significantly reduces nasal symptoms and improves QOL
Parthasarathi et al <sup>702</sup>	2017	3	Case-control	Microdebrider IT surgery with or without septoplasty in: -AR -Non-allergic rhinitis	-SNOT-22 -Nasal obstruction -Global nasal function -Nasal airflow	-Nasal obstruction, SNOT-22, global nasal function, rhinitis/facial symptoms, sleep, psychological function improved in both groups -Global nasal function greater in AR group
Hamerschmidt et al <sup>713</sup>	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 <sup>670</sup>	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 <sup>654</sup>	2014	3	Prospective case-control	-RFA IT reduction with medical therapy -Medical therapy only	-Nasal obstruction, rhinorrhea, sneezing, itching -Rhinomanometry	Greater efficacy achieved in RFA group, especially in reducing turbinate volume
Tan et al <sup>712</sup>	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 <sup>754</sup>	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 <sup>755</sup>	2010	3	Prospective cohort	-RFA IT reduction with medical therapy -Medical therapy only	-Nasal obstruction, itching, rhinorrhea, sneezing -Rhinomanometry -Rhinomanometry	RFA group had more improvement in rhinoendoscopy clinical score
Chen et al <sup>706</sup>	2008	3	Retrospective cohort	-Microdebrider inferior turbinoplasty with lateralization -IT submucous resection	-VAS -Anterior rhinomanometry -Saccharin test	-Both groups experienced significant improvement in nasal obstruction, sneezing, rhinorrhea, snoring, rhinomanometric score, saccharin transit time

						-No differences between groups
Tani et al <sup>646</sup>	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 <sup>688</sup>	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 <sup>686</sup>	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 <sup>697</sup>	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 <sup>695</sup>	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 <sup>644</sup>	1999	3	Retrospective cohort	-Electrocautery vs cryotherapy vs laser vs submucosal resection -With vs without lateral displacement -Turbinectomy	-Rhinomanometry -Acoustic rhinometry -Mucociliary transport time -Secretory IgA -Symptoms	Submucosal resection with lateral displacement of the inferior turbinate had the greatest improvement in nasal respiratory function with the lowest long-term complications
LOE 4* studies <sup>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</sup>						

1 LOE=level of evidence; SR=systematic review; RFA=radiofrequency ablation; SRMA=systematic review and meta-  
 2 analysis; IT=inferior turbinate; NOSE=Nasal Obstruction Symptom Evaluation; RCT=randomized controlled trial;  
 3 AR=allergic rhinitis; QOL=quality of life; INCS=intranasal corticosteroid; PNN=posterior nasal nerve; SNOT-  
 4 22=Sinonasal Outcome Test (22 item); VAS=visual analog scale  
 5 \*LOE 4 studies referenced due to extensive number of studies in this group and multiple higher LOE studies  
 6 included in the table  
 7  
 8  
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**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 <sup>728</sup>	2020	2	RCT	Patients with AR + CRSwNP who underwent nasal	-VAS: nasal symptoms -TNSS	-Vidian neurectomy group had greater improvement in VAS nasal obstruction &

				<p>polypectomy, sinus surgery, and septoplasty (when indicated):</p> <ul style="list-style-type: none"> <li>-No further treatment</li> <li>-Vidian neurectomy</li> </ul>	<ul style="list-style-type: none"> <li>-PFT, methacholine challenge</li> </ul>	<p>rhinorrhea, but not sneezing or itching</p> <ul style="list-style-type: none"> <li>-TNSS was significantly improved in vidian neurectomy group vs controls</li> <li>-Number of patients with PFT impairment reduced more significantly in vidian neurectomy group</li> </ul>
Qi et al <sup>729</sup>	2021	3	Non-randomized controlled trial	<p>Patients with AR + CRSwNP underwent nasal polypectomies and inferior turbinate submucosal ablation and septoplasty (when indicated):</p> <ul style="list-style-type: none"> <li>-No further treatment</li> <li>-Selective vidian neurectomy (posterior nasal nerve and pharyngeal branch)</li> </ul>	<ul style="list-style-type: none"> <li>-VAS: nasal symptoms</li> <li>-Lund-Kennedy cores</li> <li>-Lund-Mackay scores</li> </ul>	<ul style="list-style-type: none"> <li>-All endpoints were significantly more improved in neurectomy cohort, with no increase in complications</li> <li>-Cure/recovery rate significantly higher in neurectomy group</li> </ul>
Tan et al <sup>712</sup>	2012	3	Non-randomized controlled trial	<p>AR patients chose to undergo one of the following:</p> <ul style="list-style-type: none"> <li>-Bilateral endoscopic vidian neurectomy</li> <li>-Partial inferior turbinectomy and/or septoplasty</li> <li>-Conservative treatment</li> </ul>	<ul style="list-style-type: none"> <li>-RQLQ</li> <li>-VAS for QOL</li> <li>-Patient-reported improvement in symptoms</li> </ul>	<ul style="list-style-type: none"> <li>-Both the neurectomy and septoplasty/turbinectomy group experienced improvement in RQLQ and VAS post-op</li> <li>-Neurectomy group showed significantly greater improvement than septoplasty/turbinectomy</li> <li>-Similar results were reported with symptom assessment</li> </ul>
Shen et al <sup>727</sup>	2021	4	Retrospective cohort	<p>AR patients who underwent:</p> <ul style="list-style-type: none"> <li>-Bilateral endoscopic vidian neurectomy</li> <li>-Subcutaneous immunotherapy</li> </ul>	<ul style="list-style-type: none"> <li>-VAS for nasal and ocular symptoms</li> <li>-RQLQ</li> </ul>	<ul style="list-style-type: none"> <li>-Both groups showed improvement in VAS; neurectomy showed higher clinical impact in improving nasal obstruction, rhinorrhea, eye itching, lacrimation</li> <li>-Both groups experienced significantly improved RQLQ score</li> <li>-No difference in improvement at 4 months, but there was a statistically significant difference at 12 months, neurectomy showed greater improvement</li> </ul>
Ai et al <sup>726</sup>	2018	4	Retrospective cohort	<p>Patient with AR and asthma who has received:</p> <ul style="list-style-type: none"> <li>-Conservative medical treatment</li> </ul>	<ul style="list-style-type: none"> <li>-RQLQ</li> <li>-VAS</li> <li>-TASS</li> <li>-AQLQ</li> <li>-Medication scores</li> </ul>	<ul style="list-style-type: none"> <li>-Neurectomy group experienced significant improvement in RQLQ, VAS, AQLQ, and medication scores vs medical management</li> </ul>

				-Bilateral endoscopic vidian neurectomy		-No difference in pre- and post-treatment TASS was noted in either group
Su et al <sup>725</sup>	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 <sup>724</sup>	2017	5	Retrospective cohort	Rhinitis patients (including those with AR) who underwent vidian neurectomy via: -Cold instrumentation -Laser-ablation	VAS: nasal obstruction, itching, sneezing, rhinorrhea	-Both groups experienced improvement -No comparison of results between groups -No AR-specific subgroup analysis

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; CRSwNP=chronic rhinosinusitis with  
 2 nasal polyposis; VAS=visual analog scale; TNSS=Total Nasal Symptom Score; PFT=pulmonary function test;  
 3 QOL=quality of life; TASS=Total Asthma Symptom Score; AQLQ=Asthma Quality of Life Questionnaire  
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**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 <sup>734</sup>	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 <sup>739</sup>	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 <sup>736</sup>	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 <sup>740</sup>	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 <sup>756</sup>	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 <sup>735</sup>	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 <sup>738</sup>	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 <sup>737</sup>	2017	4	Retrospective case series	AR patients that underwent PNN neurectomy after submucous inferior turbinectomy	TNSS	TNSS significantly improved
Ogawa et al <sup>711</sup>	2007	4	Retrospective case series	AR patients with inferior turbinate hypertrophy that underwent submucous turbinectomy combined with PNN neurectomy	-Symptoms (sneezing, rhinorrhea, nasal obstruction, severity), as classified by Okuda's criteria -Cytokine levels and histopathology	-Significant improvement in all symptoms -Many cytokines (e.g., IL-5) significantly decreased and inflammatory cells decreased
Makihara et al <sup>733</sup>	2021	5	Retrospective case series	AR patients that underwent: -PNN trunk resection in an underwater environment	-Subjective symptoms (rhinorrhea, sneezing, nasal obstruction) -Medication use	-All symptoms and medication scores improved in both groups -PNN trunk resection showed significantly greater improvement in

				-Resection of peripheral branches of PNN **All patients also underwent submucous inferior turbinectomy		medication scores, sneezing symptoms & rhinorrhea symptoms (but not nasal obstruction)
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1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; NN=posterior nasal nerve; VAS=visual  
 2 analog scale; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; SR=systematic review; SNOT-22=Sinonasal  
 3 Outcome Test (22 item); CRSwNP=chronic rhinosinusitis with nasal polyps; FESS=functional endoscopic sinus  
 4 surgery; TNSS=Total Nasal Symptom Score  
 5  
 6

7 **TABLE XI.C.-5. Evidence table – Cryotherapy/radiofrequency ablation of the posterior nasal nerves in**  
 8 **patients with allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Del Signore et al <sup>744</sup>	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 <sup>749,750</sup>	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 <sup>749</sup>	2021	4	Prospective case series	Heterogenous group undergoing radiofrequency neurolysis of PNN, including those with AR	rTNSS	-Significant improvement in TNSS, with 100% of patients improving at least 1 point at 52 weeks -AR subgroup analysis revealed improvement
Ow et al <sup>745</sup>	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 <sup>747</sup>	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 <sup>742</sup>	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 <sup>746</sup>	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 <sup>751</sup>	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 <sup>743</sup>	2020	5*	Prospective case series	Heterogenous group undergoing cryotherapy of PNN at middle and inferior meatus, including those with AR	-rTNSS -NOSE -SNOT-22 -VAS for rhinorrhea, congestion -mini-RQLQ -Physician-derived CGI-I -Endoscopic images	-Significant improvements in all surveys -Physicians deemed improvement in 89.7% of patients -36% of inferior turbinates had reduced congestion on endoscopy -No subgroup analysis of AR patients
Yoo et al <sup>748</sup>	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 <sup>741</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; PNN=posterior nasal nerve; r=reflective; TNSS=Total Nasal Symptom  
2 Score; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; NOSE=Nasal Obstruction Symptom Evaluation; CGI-  
3 I=Clinical Global Impressions-Improvement Scale; SNOT-22=Sinonasal Outcome Test (22 item); VAS=visual analog  
4 scale  
5 \*LOE downgraded due to indirectness of evidence owing to a heterogenous sample that was not focused on AR  
6 patients

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## 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 has a disease-modifying effect through induction of immunologic tolerance.<sup>757</sup> 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.<sup>757,758</sup> 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.<sup>759</sup> 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.<sup>760,761</sup>

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.<sup>762-764</sup> 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.<sup>762</sup>

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.<sup>765</sup> 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.<sup>766,767</sup> In a double-blind

1 RCT of 812 children (5-12 years old) with clinically relevant AR and no history of asthma, patients were  
2 treated with 3 years of grass SLIT vs placebo with 2 years of follow up. The SLIT group had a significantly  
3 reduced risk of experiencing asthma symptoms or using asthma medication during the treatment and at  
4 the end of the 5-year period.<sup>768</sup>

5

6 Clinicians should be aware that there is a subset of patients for whom AIT is not an option. Absolute and  
7 relative contraindications for AIT are addressed in *Section XI.D.3 Contraindications to Allergen*  
8 *Immunotherapy*.

9

10 There is limited evidence for the efficacy of AIT for the treatment of AR in children younger than 5.  
11 However, there is data to show the efficacy and safety of both SLIT and SCIT in children 5 years and  
12 older.<sup>769,770</sup> Patient adherence with AIT can be challenging, so consideration of risks and benefits, QOL  
13 impairment, financial concerns, and patient preference are important in treatment selection.

14

15

#### 16 [XI.D.2. Benefits of allergen immunotherapy for allergic rhinitis](#)

17

18 SCIT is the best studied form of AIT and is effective for AR and rhinoconjunctivitis, allergic asthma, and  
19 Hymenoptera venom allergy.<sup>771</sup> SCIT has been practiced for over a century using aqueous extracts of the  
20 naturally occurring allergens; its effectiveness and safety have improved over time with the advent of  
21 extract standardization and research into mechanisms of action.<sup>772</sup> SCIT involves the repeated  
22 subcutaneous injection of the allergen extract in question, beginning with very small doses of allergen  
23 and gradually increasing to higher doses. This is followed by repeated injections of the highest or  
24 maintenance dose for periods of 3-5 years, to reduce symptoms upon exposure to that allergen. Clinical  
25 and physiological improvement can be demonstrated shortly after the patient reaches a maintenance  
26 dose.<sup>758</sup> AIT can also be provided in the sublingual form [SLIT]; dissolvable tablets are FDA approved for  
27 a limited number of allergens.<sup>773</sup>

28

29 In contrast to other treatment options for allergic disease, AIT helps achieve sustained immunological  
30 changes, by altering the immune system's response and inducing long-lasting immune tolerance to  
31 allergens. Despite extensive experience with this therapy and decades of research, the mechanisms  
32 underlying clinical improvement have not been fully elucidated. Although less mechanistic research  
33 exists for SLIT compared with SCIT, data suggest that both forms of AIT induce similar immunologic

1 changes. These include a reduction in mast cell and basophil degranulation; an initial increase then  
2 decrease in sIgE and increase in allergen-specific IgG blocking antibodies; generation of allergen-specific  
3 regulatory T and B cells and suppression of allergen-specific effector T cell subsets and innate lymphoid  
4 cells; and reduction in tissue mast cells and eosinophils accompanied by a decrease in type I skin test  
5 reactivity.<sup>774,775</sup> The clinically evident changes occur earlier with SCIT, and more pronounced allergen-  
6 specific IgG4 responses are observed compared with SLIT.<sup>776</sup>

7

8 The effectiveness of AIT for the treatment of AR is supported by an extensive body of evidence and is  
9 generally measured via improvement in allergy symptoms and reduction in allergy medication use.<sup>777-779</sup>

10 Although meta-analyses conclude that AIT is effective, this positive judgment of efficacy (and safety)  
11 should be limited to products tested in the clinical trials. It is incorrect to make a general assumption  
12 that all forms of AIT are effective since this may lead to the clinical use of products that have not been  
13 properly studied.<sup>308</sup>

14

15 The severity and duration of AR symptoms, as well as coexisting medical conditions such as asthma,  
16 should be considered in assessing the need for AIT.<sup>758</sup> The decision to initiate AIT depends on a number of  
17 factors, including but not limited to patient's preference, adherence, response to avoidance measures,  
18 medication requirements and adverse effects of medications. Patients should be evaluated at least  
19 every 12 months while receiving AIT.<sup>65</sup> While many patients experience sustained clinical remission of  
20 their allergic disease after discontinuing AIT, others may relapse. A decision about continuation of  
21 effective AIT should generally be made after the initial period of 3-5 years of treatment.<sup>65</sup>

22

23 As noted in the preceding section, a 2017 meta-analysis evaluating the preventative effects of AIT (SCIT  
24 and SLIT) found evidence of a reduction in the short-term (<2 years) risk of developing asthma among  
25 patients with AR.<sup>765</sup> The analysis also examined the longer term risk of asthma development, as well as  
26 the ability of AIT to prevent the occurrence of a first allergic disease in sensitized but asymptomatic  
27 individuals or to prevent sensitization to new allergens. There were trends toward benefit but  
28 inconclusive findings regarding these measures.

29

30

31 [XI.D.3. Contraindications to allergen immunotherapy](#)

32

1 Contraindications to AIT are uncommon but must be reviewed in all patients prior to initiating  
2 treatment. For both SLIT and SCIT, the adverse event of greatest severity is anaphylaxis. Therefore,  
3 many of the absolute and relative contraindications to AIT are directly related to this risk, including  
4 uncontrolled asthma, concomitant beta blocker use, contraindication to injectable epinephrine, and  
5 pregnancy.

6  
7 Uncontrolled asthma may be the single most important risk factor. There were fewer severe injection  
8 reactions reported among practices that routinely screened for and withheld injections from patients  
9 with asthma that was not controlled.<sup>780</sup> Most fatal reactions were associated with bronchospasm and/or  
10 respiratory failure.<sup>780,781</sup>

11  
12 Due to the inability to engage the  $\beta$ -adrenergic receptor with injectable epinephrine,  $\beta$ -blocker use is  
13 considered a relative contraindication for AIT. Since approximately 0.1% of allergy injections may lead to  
14 systemic symptoms, and 0.003% can be considered severe, the ability to emergently treat these  
15 reactions with epinephrine when indicated is essential.<sup>782</sup>  $\beta$ -blocker use does not appear to increase the  
16 likelihood of systemic reactions but, although not consistently observed, may be associated with higher  
17 anaphylaxis severity.<sup>783,784</sup> Thus, the lack of effect of typical subcutaneous epinephrine dosing in a  $\beta$ -  
18 blocked patient creates the treatment dilemma.

19  
20 Although there is some variability, many guidelines generally consider active systemic autoimmune  
21 diseases and active malignancy as contraindications to AIT.<sup>785</sup> This is based on case reports and case  
22 series and generally lower quality evidence that the risk of anaphylaxis from AIT is greater in patients  
23 with these conditions or that the immunomodulatory effect might negatively affect the underlying  
24 disease process. Successful AIT has been reported in several patients with malignancy.<sup>786</sup> Similarly, the  
25 theoretical concerns in autoimmune disease are offset by several case series demonstrating relative  
26 safety and effectiveness.<sup>787</sup> Furthermore, in a large observational study of 1888 patients, there was no  
27 increase in the development of autoimmune disease in AR treated with AIT over a 20 year observation  
28 period.<sup>788</sup>

29  
30 Initiating AIT during pregnancy is contraindicated although most consensus documents state that  
31 continuing maintenance immunotherapy during pregnancy is not contraindicated.<sup>757,758</sup> Avoiding the  
32 initiation of AIT is presumably based on the concern that severe anaphylaxis is more likely to occur

1 during buildup immunotherapy and that anaphylaxis, or treatment thereof, could harm the developing  
2 fetus. There are limited data to guide decision making, but in a cohort of 102 pregnancies during AIT,  
3 there were no increased fetal complications compared with untreated pregnancies. Three patients had  
4 systemic reactions requiring epinephrine – none resulting in pregnancy complication.<sup>789</sup> A more recent  
5 study demonstrated the relative safety of SLIT initiated during pregnancy.<sup>790</sup>

6  
7 SLIT is available for several allergens as an FDA approved tablet. Contraindications for this therapy  
8 include unstable or uncontrolled asthma. Therapy should not be initiated in a patient with a medical  
9 condition impairing recovery from anaphylaxis, or in those for whom epinephrine or  $\beta$ -agonist therapy  
10 might be less effective.<sup>791</sup> SLIT tablets are also contraindicated in patients with EoE.<sup>791-794</sup>

11  
12 There are a variety of relative contraindications that merit shared decision making. Cardiovascular  
13 disease, systemic autoimmune diseases in remission, severe psychiatric disorders, poor adherence,  
14 primary and secondary immunodeficiencies and a history of serious systemic reactions to AIT have all  
15 been considered as relative contraindications. A 2019 EAACI task force summary also reviews some  
16 additional considerations. ACEI therapy in venom immunotherapy is a relative contraindication, but not  
17 for AIT.<sup>785</sup> Inability to communicate symptoms that might herald the beginning of anaphylaxis are a  
18 potential contraindication and might be especially challenging in very young children (less than 5 years  
19 old). Human immunodeficiency virus (HIV) is usually not considered a contraindication unless the  
20 patient has acquired immunodeficiency syndrome (AIDS)<sup>794</sup>. This and other chronic infections should be  
21 factored into the overall risk/benefit evaluation.

#### 22 23 [XI.D.4. Allergen extracts](#)

##### 24 [XI.D.4.a. Overview, units, and standardization](#)

25  
26 **Overview.** Allergy testing began with pollen grains placed on the conjunctiva.<sup>795,796</sup> As skin testing and  
27 SCIT evolved, injectable allergen extracts were required. Inhaled allergenic particles are composed of a  
28 heterogeneous mixture of allergenic and non-allergenic proteins and macromolecules. Allergen extracts  
29 are created by refining raw materials and extracting proteins in a solution.<sup>797</sup>

30  
31 There are multiple sources of variance in allergen extracts. The composition of allergenic proteins can  
32 vary, conferring different degrees of total antigenicity through genetic or epigenetic mechanisms.<sup>798,799</sup>  
33 Impurities in the source materials, such as mold growing on pollen granules or bacteria on cat pelts, may

1 affect immunogenicity.<sup>800</sup> Variation also occurs in the raw material collection<sup>799</sup> and in the extraction  
2 process.<sup>797,798,801,802</sup> Additionally, there is biologic variation in individual sensitizations to major and minor  
3 allergens within a source. Only a very small fraction of the proteins extracted are allergenic.<sup>797</sup> Given  
4 that the antigenic composition of allergen extracts is not uniformly assessed, assuring extracts are both  
5 safe and effective is challenging.

6

7 **Units and potency.** Allergen extracts are labeled with a variety of units, many of which do not convey  
8 information about allergenic content or allergenic potency. Potency can refer to the qualitative  
9 allergenicity of a source material's proteins or the quantitative concentration of allergens in an extract.  
10 Measures of an allergen extract may refer to quantity of extracted material in the solution (a  
11 concentration) or be standardized to the biologic activity in allergic individuals. The different techniques  
12 of assessing allergen extracts leads to multiple types of units, which can be grouped into non-  
13 standardized, standardized, and proprietary.

14

15 **Non-standardized allergen extracts.** The majority of allergen extracts available in the US are non-  
16 standardized. Allergen extracts are regulated by the Center for Biologics Evaluation and Research (CBER)  
17 under the US FDA.<sup>803</sup> The FDA requires that allergen extracts list the biologic source, a potency unit, and  
18 an expiration date. This labeling allows for significant variation between manufacturers and between  
19 lots produced by the same manufacturer.

20

21 There are two US non-standardized units, weight/volume (w/v) and protein nitrogen units (PNU).  
22 Weight/volume refers to the ratio of grams of dry raw material to milliliters of extract solvent. An  
23 allergen extract labeled 1:20 w/v indicates for every 1 gram of raw material (e.g., pollen) 20 mL of  
24 extract solvent was used. This does not provide direct information about the amount of allergenic  
25 protein in the extract nor its reactivity in allergic individuals. However, it implies a reproducible  
26 extraction methodology was employed.<sup>797</sup> PNU is the second most common non-standardized unit  
27 currently used in the US. PNU refers to an assay of the precipitable protein nitrogen by phosphotungstic  
28 acid that correlates with the total protein in the extract. While most of the protein is non-allergenic, the  
29 total protein is another method to quantitate an allergen extract's content.<sup>797</sup>

30

31 In Europe, many manufactures use proprietary units and internal quality controls which must utilize a  
32 validated assay.<sup>798</sup> This European manufacturer based quality control is known as "In House Reference

1 Preparation” or “IHRP”.<sup>799</sup> However, the European Medical Agency has been developing a standardized  
2 framework based on protein homology rather than source species.<sup>804</sup> The European Union is also  
3 developing additional allergen standards with the WHO starting with Bet v 1 and Phl p 5a.<sup>804</sup> Extract  
4 units in Europe, the US, and other countries vary without agreed upon references available for  
5 conversion.

6  
7 **Standardized allergen extracts.** Standardized allergen extracts in the US are tested by the manufacturer  
8 to be within a reference range (70-140%) when compared to a standard provided by the FDA’s CBER.  
9 Standardized inhalant allergens within the US include cat, *Dermatophatoides pteronyssinus*,  
10 *Dermatophagoides farinae*, short ragweed, and multiple grass species.<sup>804</sup>

11  
12 The CBER creates the reference standardized extract through skin testing in known “highly allergic”  
13 individuals. They use serial intradermal skin testing with three-fold titrations and measure potency by  
14 how many dilutions are needed to produce a flare reaction measured by adding the largest diameter  
15 and its 90-degree (orthogonal) diameter. The orthogonal sums are plotted for each dilution and a best-  
16 fit line drawn. The concentration that corresponds to where the orthogonal sum of the flare totals  
17 50mm (ID<sub>50</sub>EAL) determines the units listed in either allergy units (AU) or biologic allergy units (BAU). AU  
18 is used for HDM historically. A mean ID<sub>50</sub>EAL of fourteen 3-fold dilutions is defined as 100,000 BAUs/mL  
19 and twelve 3-fold dilutions 10,000 BAUs/mL.<sup>804</sup> Manufactures then compare their extract lots to the  
20 CBER allergen standard through competition ELISA using pooled serum IgE from known allergic subjects.

21  
22 The process is different for extracts where the major allergen reactivity strongly correlates with overall  
23 allergen reactivity (cat and ragweed). A major allergen is defined as a specific protein that elicits an  
24 allergic reaction in more than 50% of individuals allergic to that species. If there is a major allergen that  
25 correlates strongly with the population’s clinical reactivity, the manufacturer compares their extract to  
26 the CBER’s standard by gel electrophoresis employing monoclonal IgG antibodies to the major allergen  
27 protein.<sup>803</sup> When standardized by major allergen, the units are listed in µg/mL (Fel d 1 for cat; Antigen E  
28 or Amb a 1 for ragweed). For cat extracts, the presence of Fel d 2 is also required. Also, cat extract with  
29 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  
30 designated as 100,000 BAU/mL.<sup>800</sup>

31



1 Some allergen extracts in Europe use the Nordic method where 10,000 biologically standardized  
2 units/mL is comparable to a skin prick test response elicited by 10 mg/mL of histamine.<sup>804</sup> Most allergen  
3 extracts in Europe are proprietary; however, the European effort to develop cross-product comparability  
4 is summarized nicely by Zimmer et al.<sup>800</sup> The WHO has identified allergen standardization as a problem  
5 and the European Union funds a project known as CREATE to “develop certified reference materials for  
6 allergenic products and validation of methods for their quantification”.<sup>805,806</sup>

7

8 In summary, there is not an international consensus on allergen units or standardization for allergen  
9 extracts. While cross-manufacturer standardization and biologic potency labeling increase  
10 manufacturing costs, it is widely agreed that greater standardization would benefit patient efficacy and  
11 safety. Variations in allergen extracts between manufacturers may discourage medical providers from  
12 changing vendors, thus reducing competition’s effect on price. Non-standardized and proprietary units  
13 also complicate the interpretation of published efficacy and safety studies. As of 2022, multiple  
14 opaquely referenced allergen units remain in use worldwide. (*See Section XI.D.11.a.i. Allergen*  
15 *Standardization and Heterogeneity for additional information on this topic.*)

16

17

#### 18 XI.D.4.b. Allergen extract adjuvants

19

20 Although AIT is an effective treatment for AR, it is not without limitations including cumbersome-up-  
21 dosing regimens, systemic reactions, and variable efficacy.<sup>807</sup> Adjuvants are chemicals and proteins that  
22 may enhance the safety, convenience and immunological effects of AIT.<sup>808-814</sup> Effective AIT attenuates  
23 pro-inflammatory Th2 responses in favor of tolerogenic T reg responses. This immunological  
24 transformation can be enhanced with adjuvants that are subdivided into several broad categories.

#### 25 [TABLE XI.D.4.b.]

26

27 Of the potential adjuvants listed, several have reached Phase 1 or Phase 2 clinical trials for treating AR.  
28 Some have already received FDA approval for use in modern infectious disease vaccines. Next  
29 generation AIT products may very well incorporate adjuvants in combination with peptides and other  
30 allergenic molecules. A few adjuvants deserve specific mention.

31

32 **Mineral salts and crystalline molecules.** Alum (aluminum hydroxide salt) was the first adjuvant to be  
33 tested in AIT and has recently been considered for COVID-19 vaccines.<sup>815,816</sup> Early studies with alum-

1 precipitated extracts demonstrated an augmented immunologic response but with some undesirable IgE  
2 mediated response that hindered its therapeutic application.<sup>815,817</sup> Microcrystalline tyrosine has been  
3 tested as an alternative with less IgE production.<sup>810,816</sup> Alum formulations are currently being considered  
4 for certain allergen peptide vaccines.

5  
6 ***Toll like receptor constructs.*** It has been proposed that danger signal molecules synthesized from virus,  
7 parasites, and bacteria and used in combination with allergens could help induce tolerance by  
8 augmenting TLR mediated innate immune responses.<sup>813,818-820</sup> Tversky et al<sup>821,822</sup> showed that traditional  
9 SCIT alone results in a partial restoration in the impaired TLR function demonstrated among AR sufferers  
10 and that this effect could potentially be augmented with certain adjuvants.

11  
12 Among the specific TLR targeted clinical studies, Creticos et al<sup>823</sup> first reported a study using synthetic  
13 bacterial derived DNA (CpG oligodeoxynucleotide) bound to ragweed protein Amb a 1 designed to  
14 upregulate the immunostimulatory responses via TLR-9. This TLR-9 agonist bound to Amb a 1  
15 (Tolamba™) was administered in a double-blind, placebo-controlled study of ragweed-allergic subjects  
16 with a single season 6-injection regimen. Efficacy was observed over two ragweed seasons indicating  
17 that the vaccine conferred some clinical tolerance. A follow-up study did not reach statistical  
18 significance.<sup>824</sup> In 2021, Leonard et al<sup>825</sup> reported on the use of CpG and a Fel d 1 specific mouse  
19 immunotherapy model to elucidate important signaling elements that may be capitalized upon moving  
20 forward.

21  
22 CYT003-QbG10 is another TLR targeted immunotherapeutic product in development for the treatment  
23 of AR and asthma. It is based on Cytos Biotechnology's modified Immunodrug™ platform, which  
24 incorporates virus-like particle Qb, a TLR-9 immunostimulatory DNA sequence to induce targeted T cell  
25 responses. In a Phase 2b double-blind, placebo-controlled study of 300 patients with allergic  
26 rhinoconjunctivitis, QbG10 was shown to be safe, well-tolerated and efficacious.<sup>826</sup>

27  
28 A TLR-4 adjuvant has also been in clinical development (Pollinex Quattro™, Allergy Therapeutics).<sup>827</sup> This  
29 construct is comprised of monophosphoryl lipid A and formulated with pollen allergoids. A large grass  
30 study showed significant improvement in symptom and medication scores versus placebo.<sup>828</sup> A brief  
31 ragweed trial also showed positive clinical effect.<sup>829</sup>

32

1 **Nanoparticle based constructs.** Synthetic nanoparticles have been proffered since 1959 to deliver a host  
 2 physiologically active substances including vaccines.<sup>830,831</sup> A successful recent example of this is the use  
 3 of liposomes to deliver mRNA encoded spike protein instructions in the Pfizer and Moderna COVID-19  
 4 vaccines. This same approach has been proposed to deliver genetic instructions encoding allergenic  
 5 proteins for immunotherapy. These so-called allergen “vaccines” have the potential to synergistically  
 6 activate TLR receptors while simultaneously encoding allergenic proteins.

7  
 8 **Naturally occurring adjuvants.** Certain naturally occurring immune modulators have been shown to act  
 9 as potential adjuvants. Nutritional compounds and probiotics may be ingested directly or administered  
 10 subcutaneously in tandem with allergen.<sup>832,833</sup> One example is vitamin D3 which has been shown to  
 11 reduce effector T cell stimulation and cytokine production and promote the effect of AIT in both mice  
 12 and humans.<sup>834-836</sup> One mouse immunotherapy study successfully employed the use of Fel d 1 covalently  
 13 bound to vitamin D3.<sup>837</sup> (See Section VI.H. Vitamin D for additional information on this topic.)

14  
 15 Components isolated from Ganoderma Lucidum, a Chinese herb contained in Anti-Asthma Simplified  
 16 Herbal Medicine Intervention (ASHMI), induces levels of IL-10, IFN-γ and Foxp3 in response to  
 17 environmental allergens.<sup>838</sup> Like TLR ligands, ASHMI has shown some limited effectiveness in treating  
 18 certain allergic diseases by itself without the presence of an allergen.<sup>839</sup> However, because of its unique  
 19 tolerogenic cytokine profile, ASHMI and other naturally occurring herb combinations may also prove to  
 20 be advantageous when used as an adjuvant for AIT.

21  
 22 In summary, various adjuvants have been proposed and studied in animal models and tested in humans,  
 23 but there is currently no adjuvant FDA approved for use in AIT. Improving the immunologic profiles of  
 24 immunotherapies while maintaining safety standards remains challenging. Recent Phase 1 and Phase 2  
 25 studies have been reported for select adjuvants, and there is promise for future AIT protocols to  
 26 incorporate adjuvants which outperform traditional therapies.

27  
 28 **TABLE XI.D.4.b. Potential adjuvants for allergen immunotherapy**

Category	Adjuvant	Examples and comments
Salts and crystals	Aluminum hydroxide (Alum)	Early studies showed augmented immune responses
	Calcium phosphate	Shown to have some immunogenicity enhancement with less IgE stimulation

Category	Adjuvant	Examples and comments
	Microcrystalline structures	Microcrystalline tyrosine
<b>Transfer vehicles</b>	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.
<b>Immunostimulatory</b>	TLR 9 agonists	CpG oligodeoxynucleotide (CpG-ODN) has been employed in several direct disease modifying and allergen immunotherapy approaches by increasing tolerogenic cytokines including interferons. QbG10 is a synthetic virus like particle derived from bacterial DNA.
	TLR 7 agonists	Virus like particles; single stranded viral RNA stimulates TLR-7 and stimulates the production of type I interferons can be used singly or in combination with allergens.
	TLR 4 agonists	Monophosphoryl Lipid A fraction derived from bacterial lipopolysaccharide works as a TLR-4 agonist. Monophosphoryl lipid derived from bacterial DNA or RNA stimulate dendritic cells and other antigen-presenting cells to increase Th1 cytokines.
	C-type lectin receptors	Mannan mannose polysaccharide that acts as C-type lectin 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.
<b>Natural derived</b>	Probiotics	Ingested microbial products have shown some limited benefit in reducing eczema and other atopic disease. Microbial adjuncts proposed to enhance the efficacy of food allergen immunotherapy.

Category	Adjuvant	Examples and comments
	Vitamin D	Vitamin D3 has been shown to reduce effector T cell stimulation and cytokine production and promote the effect of allergoid in mice.
	Amino acids	L-tyrosine bound to allergen acts a short-depot forming adjuvant and indirectly increases IgG production.
	Chinese herbs	ASHMI

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

### 5 XI.D.4.c. Modified allergen extracts

7 Traditionally the disease-modifying capability and potential for long-lasting therapeutic effect of AIT has  
 8 been accomplished via SCIT or SLIT with native, unmodified extracts. However, reliance on native  
 9 extracts has limitations for widespread use including production costs and availability, as well as  
 10 consistency and comparability among extracts.<sup>840</sup> Furthermore, while generally safe, AIT with natural  
 11 extracts has the potential for inducing hypersensitivity reactions that can rarely be life-threatening. The  
 12 use of modified allergen extracts has been studied as an alternative to native extracts as a means of  
 13 providing improved AIT efficacy, safety, and reliability. This section discussed several approaches of  
 14 modified allergen extracts.

16 **Recombinant allergen extracts.** Recombinant-derived allergens rely on recombinant DNA technology to  
 17 produce clones of natural allergens in the case of wild type recombinant allergens, or clones of partial  
 18 allergen sequences in hypoallergenic recombinant allergens. For wild type recombinant allergens, this  
 19 technique produces consistent structures that preserve allergenic epitopes and potencies.<sup>841</sup> However,  
 20 the disadvantage is that as a clone, there is potential for inducing hypersensitivity reactions.

21 Hypoallergenic recombinant extracts, on the other hand, maintain certain T cell epitopes but may  
 22 induce less IgE driven responses.<sup>842</sup> Immunotherapy trials using recombinant birch and Timothy grass  
 23 allergens have been reported. Timothy grass AIT with recombinant allergen induced immunologic  
 24 changes, including increased IgG4 and down trending sIgE while decreasing symptoms and medication  
 25 use compared to placebo.<sup>843,844</sup> Similarly for birch AIT, recombinant allergen use resulted in reduced  
 26 rhinoconjunctivitis symptoms and rescue medication use, with symptom improvement similar to  
 27 treatment with natural extract; immunological changes included increased IgG levels compared to  
 28 placebo.<sup>845,846</sup> Together, these studies show potential for comparable performance of recombinant

1 allergen extracts, with the advantage over natural extract of using a more consistent, pure allergen that  
2 could be precisely dosed.

3

4 **Synthetic peptides.** These are linear fragments of amino acids derived from T cell epitopes of allergens.  
5 Peptides do not induce early phase responses because they lack the conformational structure to bind to  
6 IgE receptors. When used for AIT, they do not generate a robust blocking IgG but do have the capability  
7 of inducing immunologic T cell changes. AIT with synthetic peptides has been studied for several  
8 allergens including cat, grass, HDM, ragweed, and birch with somewhat inconsistent efficacy. Grass  
9 allergen peptides were effective in reducing rhinoconjunctivitis symptom scores when injected at 2-  
10 week intervals over a brief trial,<sup>847</sup> and ragweed peptide therapy improved symptom scores compared to  
11 natural extract and placebo.<sup>848</sup> Birch pollen pre-seasonal treatment induced immunologic changes, but  
12 clinical symptoms were not significantly improved.<sup>849</sup> Cat peptide AIT in particular had promising initial  
13 results reducing symptoms in sensitized individuals, but Phase 3 data of one product did not significantly  
14 outperform the placebo group.<sup>850-853</sup> Longer sequences, termed contiguous overlapping peptides, have  
15 been alternatively used in an attempt to generate a more robust immunogenic response; birch AIT  
16 resulted in improved symptom scores and medication use as well as induction of IgG antibodies.<sup>854-856</sup>

17

18 **Allergoids.** These involve native allergens that have been modified or denatured with the use of  
19 additional chemical agents, such as aldehydes and polyethylene glycol. These modified structures have  
20 the potential to retain immunogenicity, largely via T cell responses, but also decrease the risk for IgE-  
21 mediated reactions. In addition to improved safety, this may offer ability to decrease the number of  
22 injections required during a build-up period.<sup>857</sup> While immediate hypersensitivity reactions are reduced,  
23 late phase adverse reactions can still occur.<sup>858</sup> Allergoid preparations have been evaluated to several  
24 different allergens. Initially utilized in ragweed allergic patients, allergoid preparations reduced  
25 symptom scores and increased blocking antibodies.<sup>859,860</sup> Subsequent studies with grass pollen allergoid  
26 also showed effectiveness in reducing clinical symptom scores and medication use.<sup>817,861,862</sup> Allergoids in  
27 HDM allergic patients also demonstrated improved symptom scores, in both subcutaneous and  
28 sublingual routes.<sup>863,864</sup> More recently, in an open label study a glutaraldehyde-modified allergoid in  
29 birch pollen allergic patients induced initial humoral responses as well as T cell augmentation of IL-10  
30 production.<sup>865</sup> While allergoids are commercially available in Europe, standardization criteria have been  
31 a limiting factor in receiving regulatory approval in the US.

32

1 **Encapsulated allergens.** Encapsulation of allergens involves use of nanoparticles or microparticles to  
2 envelop allergens of interest which can then be injected or ingested orally. This process has the  
3 potential to decrease the dose required for immunologic responses, protect the allergen from  
4 degradation, and improve uptake of allergen while limiting adverse reactions.<sup>866</sup> Encapsulation can be  
5 accomplished with biodegradable nanoparticles including synthetic or natural polymers, liposomes, and  
6 virus-like particles, or with nonbiodegradable nanoparticles such as dendrimers or carbon-based  
7 particles.<sup>867</sup> Most of the research involving encapsulated allergens has yet to be evaluated in human  
8 trials.<sup>809</sup> In one study, a liposome encapsulated HDM extract was evaluated in patients with asthma, who  
9 had improved symptom scores over a 12-month period compared to placebo.<sup>868</sup> Separately, an oral  
10 microencapsulated form of Timothy grass allergen was used to treat patients with AR over a period of  
11 10 weeks; patients in the active treatment group experienced decreased symptom scores compared to  
12 placebo.<sup>869</sup> Limited human trial data suggest that encapsulated allergens may induce immune responses  
13 but further understanding of their role in AIT is needed.<sup>814</sup>

14

15 Overall, a variety of modified allergen extracts hold promising clinical and immunologic findings. Further  
16 research is needed involving larger clinical groups to study the efficacy and safety of these agents as  
17 compared to the native allergen extracts.

18

19

## 20 [XI.D.5. Subcutaneous immunotherapy for allergic rhinitis](#)

### 21 [XI.D.5.a. Conventional subcutaneous immunotherapy for allergic rhinitis](#)

22

23 **Efficacy.** Over the past 68 years,<sup>870</sup> multiple RCTs have supported the therapeutic efficacy of SCIT for  
24 AR.<sup>758</sup> SCIT efficacy is contingent upon an appropriate treatment duration and dose, with an optimal  
25 target maintenance dose between 5-20µg of major allergen for each clinically relevant aeroallergen.<sup>758</sup>  
26 SCIT has been associated with effective symptom amelioration and potential disease modification that  
27 can persist after stopping treatment.<sup>758</sup>

28

29 Evidence suggests that a SCIT treatment duration of 3-5 years is appropriate.<sup>758</sup> A clinically significant  
30 relapse rate has been observed with SCIT discontinuation prior to 3 years.<sup>871</sup> Currently, there are no  
31 validated biomarkers to reliably identify when SCIT can be discontinued and clinical remission sustained.  
32 The determination to discontinue SCIT in patients who have responded should balance the potential for  
33 benefit with the potential for harm and burden, in an open discussion with patient participation in the  
34 medical decision-making process.

1

2 High-quality data have substantiated the therapeutic utility of SCIT for AR patients with particular  
3 aeroallergens and certain formulations. Therefore, SCIT efficacy for AR treatment is contextual, and  
4 should not be interpreted as an “umbrella” description based on favorable outcomes observed in RCTs  
5 focused on a limited number of products.<sup>872</sup>

6

7 SCIT is efficacious for AR sensitive to pollen, mold, HDM, and animal allergens.<sup>758,872-878</sup> Such efficacy has  
8 been demonstrated based on rigorous RCTs for pollens (e.g., ragweed, grass, birch), cat, and HDM  
9 (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), where a standardized extract target  
10 concentration is available and was studied. However, these data cannot be interpreted as a “class  
11 effect” that necessarily extends to other aeroallergens. Data supporting the SCIT efficacy for dog,  
12 cockroach, and mold spores (particularly *Alternaria* and *Cladosporium*) are encouraging, but limited, and  
13 additional studies are needed to substantiate the therapeutic efficacy of SCIT for AR related to these  
14 inhalant allergens.<sup>758,873-877</sup>

15

16 The majority of RCTs supporting SCIT for AR have been studies of single aeroallergens.<sup>758</sup> There have  
17 been very few studies of multi-allergen SCIT, which are heterogeneous and suffer from methodological  
18 shortcomings. While multi-allergen SCIT is a mainstay of clinical practice in the US, and patients report  
19 favorable treatment benefits, additional high-quality studies are needed to provide rigorous support for  
20 the efficacy of multi-allergen SCIT in treating AR.

21

22 **Safety.** SCIT is associated with localized reactions occurring in the majority of patients.<sup>758</sup> Evidence  
23 indicates local reactions do not reliably predict occurrence of subsequent systemic reactions; dosage  
24 adjustment is not typically required after their occurrence.<sup>758</sup> While there is a low risk for systemic  
25 reactions from SCIT, potentially life-threatening and fatal reactions may occur. Non-fatal systemic  
26 reactions occur at a rate of approximately 2 per 1000 injections in patients receiving SCIT.<sup>758</sup> Severe  
27 grade 4 anaphylactic reactions occur in approximately 1 per million injections, and fatal reactions in  
28 approximately 1 in 23 million injection visits.<sup>879,880</sup>

29

30 Risk factors for systemic reactions from SCIT include poorly-controlled asthma, exquisite aeroallergen  
31 sensitivity, concomitant  $\beta$ -blocker use, rush SCIT protocols, prior systemic reaction, high dose SCIT,  
32 injection from a new SCIT vial (i.e., higher potency), and dosing error.<sup>758,879-881</sup> A recent decline in fatal



1 systemic reaction rate has been observed, which has been attributed to greater awareness and  
2 identification of patients with risk factors.<sup>880</sup>

3  
4 **Cost-effectiveness.** Data support SCIT as a cost-effective intervention, in large part due to the potential  
5 for reductions in long-term symptom burden, disease complications, disease progression, and  
6 medication costs. US studies demonstrate SCIT superiority over alternative approaches – providing  
7 clinical benefit while improving health outcomes.<sup>882,883</sup> However, practice variation may produce cost  
8 disparities. As an example, some physicians may require SCIT patients to be provided a self-injectable  
9 epinephrine prescription, which has not been shown to be cost-effective (incremental cost-effectiveness  
10 ratio \$669,327,730 per QALY [quality adjusted life year]).<sup>884</sup>

11  
12 **Evidence.** Dhami et al,<sup>777</sup> undertook a systematic review appraising SCIT efficacy for AR, with 61 robustly  
13 conducted double-blind RCTs of SCIT satisfying inclusion criteria. [TABLE XI.D.5.a.] Study quality was  
14 high, with the majority of RCTs having low risk of bias. Significant improvements were seen in symptom  
15 scores (standardized mean difference (SMD) -0.65 [95% CI -0.86, -0.43]), medication use (SMD -0.52  
16 [95% CI -0.75, -0.29]), combined symptom/medication score (SMD -0.51 [95% CI -0.77, -0.26]), and QOL  
17 (SMD -0.35 [95% CI -0.74, -0.04]; 6 trials). Analysis of safety was obfuscated by variation in reporting of  
18 adverse effects. In 19 RCTs, the overall relative risk of adverse events was 1.58 (95% CI 1.13, 2.20). Local  
19 adverse event relative risk was 2.21 (95% CI 1.43-3.41, 9 RCTs). Systemic adverse event relative risk was  
20 1.15 (95% CI 0.67-2.00, 15 RCTs). This systematic review provides evidence for short-term benefit in  
21 symptoms and medication reliance, as well as a limited effect on disease specific QOL.

22  
23 Several studies imply SCIT for AR is associated with continued benefit after stopping treatment,  
24 including a reduced risk for developing asthma<sup>885,886</sup> and new allergen sensitivities.<sup>887,888</sup> However, data  
25 meta-analyzed by Dhami et al<sup>777</sup> are more limited in terms of persistence of benefit in symptoms scores  
26 after treatment discontinuation. Additional studies are required to support this important and desirable  
27 outcome of SCIT treatment.

28  
29 An updated systematic review of RCTs of SCIT for AR was performed from January 1, 2015, through  
30 October 1, 2021. All studies did not evaluate clinical endpoints, heterogeneity between studies was  
31 significant, and there was variable risk of bias. In general, studies demonstrated significant SCIT  
32 treatment benefit across age groups.<sup>889-891</sup> Arroabarren et al<sup>764</sup> evaluated children 5-15 years old in a

1 prospective study comparing a 3-year versus a 5-year course of SCIT, demonstrating a 44% reduction in  
2 symptom and medication scores from baseline after 3 years of therapy ( $p=0.002$ ) and a 50% decrease  
3 after 5 years of therapy ( $p=0.001$ ). Wang and Shi<sup>892</sup> reported 77% reduction in TNSS in children with a  
4 similar decrease in medication scores. In an elderly cohort, Bozek et al<sup>893</sup> evaluated subjects 65-75 years  
5 old with moderate or severe intermittent AR, comparing 3 years of grass SCIT to placebo and finding a  
6 41% decrease in combined symptom and medication scores versus baseline ( $p=0.004$ ).

7

8 Recent evidence demonstrates SCIT benefit for HDM and grass allergens.<sup>764,893-897</sup> Kim et al<sup>896</sup>  
9 demonstrated through network meta-analysis that efficacy of SCIT for HDM was greater than SLIT drops  
10 or tablets.

11

12 Recent studies support the safety of SCIT; however, the rate of SCIT-associated hypersensitivity  
13 reactions has shown a wide range. In the study by Arroabarren et al,<sup>764</sup> systemic adverse effects were  
14 noted in 2.5% of patients overall, while Scadding et al<sup>889</sup> reported hypersensitivity events (mostly mild)  
15 in 47.2% of subjects with grade 3 systemic reactions in 5.5%.

16

17 **Values and preferences.** While the recommendation for AIT is strong with high certainty evidence, given  
18 the potential for harm associated with potentially life-threatening anaphylaxis (with very rare SCIT  
19 associated fatality), and the burden associated with receiving SCIT, patient preference is important.  
20 Comparatively, the potential for harm and burden associated with medications is lower; the potential  
21 for benefit is also lower, with no potential for disease-modifying immunomodulation. Some patients  
22 may prefer safety and a reduced risk of therapy-associated anaphylaxis, despite reduced therapeutic  
23 efficacy. Patient motivation and choice are important considerations in AR treatment.

24

25 **Summary.** ICAR-Allergic Rhinitis 2018<sup>308</sup> recommended SCIT for AR with an Aggregate Grade of Evidence  
26 "A". Recently, evidence has continued to accrue in support of the therapeutic efficacy of SCIT in properly  
27 selected patients with AR, across age ranges and with selected standardized allergens. SCIT carries a  
28 strong recommendation and high certainty of evidence. The data concerning safety support a favorable  
29 potential for benefit with SCIT in patients with AR compared with the potential for harm or burden,  
30 though patients started and continued on SCIT must be counseled on the risk of anaphylaxis and  
31 potential fatality and presented treatment alternatives that may be safer though less efficacious. It  
32 should be noted that while SCIT remains the predominant method for AIT administration in the US, in

1 the past two decades SLIT became the dominant approach for AIT in several European countries;<sup>898</sup>  
 2 recommendations for SLIT in Europe include tablet formulations and sublingual drops.<sup>757</sup> Additional  
 3 studies are required to substantiate the long-term effectiveness of SCIT for AR, including its potential for  
 4 reducing risk for future development of asthma and sensitization to novel antigens in monosensitized  
 5 patients treated with SCIT, and the safety and efficacy of multi-allergen SCIT.

6  
 7 **Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 46 studies, level 3: 29 studies; **TABLE**  
 8 **XI.D.5.a.**)

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

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

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

17 **Benefits-harm assessment:** For patients with symptoms lasting longer than a few weeks per year and  
 18 for those who cannot obtain adequate relief with symptomatic treatment or who prefer an  
 19 immunomodulation option, benefits of SCIT outweigh harm. The potential benefit of secondary disease-  
 20 modifying effects, especially in children and adolescents, should be considered.

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

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

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

30 Option for SCIT over SLIT for the treatment of AR.

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

35

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

				-Dupilumab -Placebo		-Fewer dupilumab patients required epinephrine
Shamji et al <sup>899</sup>	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 <sup>891</sup>	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 <sup>890</sup>	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 <sup>894</sup>	2017	2	DBRCT	-HDM SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Pfaar et al <sup>895</sup>	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 <sup>889</sup>	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 <sup>900</sup>	2016	2	DBRCT	-HDM SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Kleine-Tebbe et al <sup>901</sup>	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 <sup>902</sup>	2014	2	DBRCT	-Grass pollen SCIT -Placebo	Combined symptom and medication scores	SCIT group had improvement in symptom and medication scores
Tworek et al <sup>903</sup>	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 <sup>850</sup>	2012	2	DBRCT	-Fel d 1 antigen SCIT -Placebo	Symptom scores	SCIT group had improvement in symptom scores
James et al <sup>904</sup>	2011	2	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptoms

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

					-Skin test response -FEV <sub>1</sub>	
Frew et al <sup>938</sup>	2006	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Jutel et al <sup>843</sup>	2005	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Rak et al <sup>939</sup>	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 <sup>940</sup>	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 <sup>941</sup>	1997	3*	DBRCT	-Parietaria pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Dolz et al <sup>942</sup>	1996	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use -Conjunctival and bronchial challenge -End-point cutaneous tests -slg	SCIT group had improvement in symptom and medication scores
Brunet et al <sup>943</sup>	1992	3*	DBRCT	-Ragweed pollen SCIT -Placebo	-Symptoms -Nasal provocation -slgE and slgG -Basophil histamine release	SCIT group had reduced symptom scores
Bousquet et al <sup>944</sup>	1991	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Iliopoulos et al <sup>945</sup>	1991	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Medication use -slgE and slgG	SCIT group had improvement in symptoms, but epinephrine was used in 19% of subjects
Bousquet et al <sup>861</sup>	1990	3*	DBRCT	-Grass pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Fell & Brostoff <sup>946</sup>	1990	3*	DBRCT	-Pollen SCIT -Placebo	-Symptoms -Nasal challenge	SCIT group had improvement in symptom scores
Horst et al <sup>947</sup>	1990	3*	DBRCT	- <i>Alternaria</i> SCIT -Placebo	-Global symptom and medication scores -Skin tests -slgG	SCIT group had improvement in symptom and medication scores
Juniper et al <sup>948</sup>	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 <sup>862</sup>	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 <sup>949</sup>	1988	3*	DBRCT	-HDM SCIT -Placebo	-Symptoms -Nasal challenge -Skin test response	SCIT group had improvement in symptom scores
Bousquet et al <sup>950</sup>	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 <sup>951</sup>	1987	3*	DBRCT	-Ragweed pollen SCIT -Placebo	-Symptoms -Medication use	SCIT group had improvement in symptom and medication scores
Grammer et al <sup>952</sup>	1984	3	Placebo-controlled study	-Ragweed pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptoms
Metzger et al <sup>953</sup>	1981	3*	DBRCT	-Ragweed pollen SCIT -Placebo	Clinical symptoms	SCIT group had improvement in symptoms

1 LOE=level of evidence; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; AIT=allergen  
2 immunotherapy; SRMA=systematic review and meta-analysis; DBRCT=double-blind randomized controlled trial;  
3 s=antigen-specific; Ig=immunoglobulin; HDM=house dust mite; RCT=randomized controlled trial; QOL=quality of  
4 life; SPT=skin prick test; FEV<sub>1</sub>=forced expiratory volume in 1 second  
5 \*LOE downgraded for placebo- or comparator-controlled studies due to loss to follow-up, insufficient description  
6 of blinding or protocol adherence, selective outcome reporting, use of unvalidated outcome measures, selective  
7 recruitment, or indirectness of outcome measures  
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#### 10 XI.D.5.b. Rush subcutaneous immunotherapy for allergic rhinitis

11  
12 Rush SCIT rapidly reaches the target therapeutic dose by administering incremental allergen doses over  
13 a much shorter period compared to conventional SCIT. Rush SCIT has successfully been implemented for  
14 venom immunotherapy.<sup>954</sup> Evaluating rush SCIT for aeroallergen immunotherapy is difficult due to study  
15 heterogeneity with escalation protocols, target doses, premedication regimens, and extracts utilized.  
16 Furthermore, there remains a lack of standardization of what constitutes rush SCIT versus other  
17 immunotherapy protocols.

18  
19 The main benefit of rush SCIT is the expedited build-up phase, decreasing the time to reach  
20 maintenance dosing and office visits required. Patient convenience is improved, but evidence has not  
21 yet determined if the expedited process leads to more rapid clinical improvement. Potential  
22 disadvantages include increased risk of systemic reactions, higher staff/resource utilization, and

1 decreased long-term compliance with one study at a military medical center citing a decrease from 80%  
2 (conventional schedule) to 48% (rush schedule).<sup>955</sup>

3

4 **Efficacy and safety.** Aeroallergen rush SCIT has demonstrated effectiveness for AR and asthma.<sup>954</sup> The  
5 majority of double-blind RCTs utilized single-allergen extracts, primarily grass pollen.<sup>934,942,950,956</sup> Other  
6 allergens investigated include ragweed, various tree pollens, *Alternaria*, cat, dog, and HDM.<sup>414,944,947,957-</sup>  
7 <sup>961</sup> These studies report significant benefit over placebo in clinical outcomes (most commonly reported  
8 with combined symptom-medication scores), SPT, and provocation challenges. [TABLE XI.D.5.b.]

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10 Safety remains a limiting factor for aeroallergen rush SCIT due to a greater risk of systemic reactions,  
11 which range 15-100% of patients without premedication for standardized extracts, depot preparations,  
12 and allergoids.<sup>954</sup> This improves to 12-38% when using routine premedication.<sup>962</sup> Depigmented-  
13 polymerized extracts have a significantly better safety profile with systemic reactions occurring in less  
14 than 2% of patients.<sup>934,956,958,963</sup> Local reactions do not appear to predict systemic reactions and delayed  
15 systemic reactions are reported rarely with rush SCIT.<sup>958</sup> Only one double-blind RCT specifically  
16 evaluated safety and efficacy of rush versus conventional SCIT.<sup>959</sup> In this small Der p 1 trial (n=18), the  
17 efficacy was similar, but the rush SCIT group had significantly higher side effect scores without any  
18 severe systemic reactions. One retrospective observational study found an increase in systemic  
19 reactions on subsequent doses following initial rush SCIT, although additional studies are needed due to  
20 the variability in rush SCIT protocols.<sup>964</sup>

21

22 **Rush, ultra-rush, and modified rush.** Rush SCIT has traditionally been defined as achieving target  
23 therapeutic dose within 1 to 3 days;<sup>308,758</sup> however, lack of universal standardization has led to variations  
24 of rush SCIT schedules. Modified rush designates accelerated SCIT protocols that reach a target dose  
25 within 3 days, then follow a more conventional build-up to reach maintenance. Ultra-rush classifies  
26 those that attain maintenance dose within several hours.

27

28 Due to the increased risk of systemic reactions with ultra-rush, traditional extracts have not generally  
29 been used. Depigmented-polymerized extracts, which are approved and commercially available in  
30 several regions of Europe, have been utilized via an ultra-rush protocol with good efficacy in adults and  
31 children.<sup>934,956,958,963</sup> Local reactions occurred in 21-70.4% of patients, while systemic reactions ranged 2-  
32 12.7%; all considered non-severe (no grade 3 or 4 reactions).

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**Pre-medication for rush SCIT.** Limited studies specifically evaluated the effects of premedication on aeroallergen rush SCIT.<sup>965,966</sup> Premedication regimens varied, including H<sub>1</sub> and H<sub>2</sub> 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).<sup>965</sup> 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.<sup>966</sup> 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.<sup>414,957</sup> 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.

- 1 **Cost:** Direct costs may be similar or slightly less compared to conventional SCIT, which includes cost of  
 2 extract preparation and injection visits. Indirect costs are improved due to the reduced number of  
 3 appointment visits, which reduces work and school absenteeism.  
 4 **Benefits-harm assessment:** Balance of benefit and harm.  
 5 **Value judgments:** Careful patient selection and shared decision making would reduce risks.  
 6 Heterogeneity of protocols, extract types and dosing across studies makes quantification of risk difficult.  
 7 **Policy level:** Option.  
 8 **Intervention:** Aeroallergen rush SCIT is an option for AR in appropriately selected patients that do not  
 9 have adequate control of their symptoms with symptomatic therapies. If available at practice location,  
 10 the use of depigmented-polymerized allergen extracts for rush SCIT has a better safety profile compared  
 11 with standard extracts.  
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**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 <sup>956</sup>	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 <sup>934</sup>	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 <sup>957</sup>	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 <sup>414</sup>	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 <sup>954</sup>	2006	2	Systematic review	-AR, asthma, Hymenoptera, imported fire ant	-Combined symptom-medication score	-SR rate significantly higher for rush SCIT (27-100%)

				-Adults and children -RCTs, observational cohorts, case series	-SR rate -Cutaneous testing -Provocation challenges -sIgE and sIgG	-Baseline FEV <sub>1</sub> <80% and high skin test reactivity are predictive of SR -Premedication reduced risk of SRs with rush SCIT
Akmanlar et al <sup>959</sup>	2000	2	RCT	-Der P 1 rush SCIT -Der P 1 conventional SCIT	-Combined symptom and medication score -Lung function -Side effect score -Cutaneous testing -Bronchial provocation -sIgE and sIgG4	-Similar efficacy between rush and conventional SCIT -Significantly higher side effect score was seen in the rush SCIT group -3 had mild SRs -No severe reactions
Dolz et al <sup>942</sup>	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 <sup>965</sup>	1994	2	DBRCT	-Combination H <sub>1</sub> and H <sub>2</sub> 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 <sup>944</sup>	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 <sup>947</sup>	1990	2	DBRCT	- <i>Alternaria</i> rush SCIT -Placebo	-Symptom-medication scores -Nasal provocation challenge -Skin end-point titration - <i>Alternaria</i> sIgE and sIgG	-Rush SCIT with <i>Alternaria</i> 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 <sup>960</sup>	1989	2	DBRCT	-Animal-dander rush SCIT -Placebo (transferred to active arm after 1 year)	-Skin prick test -Allergen and histamine	Improvement in skin prick test and bronchial challenges for treatment

					bronchial challenges	group at 1 year and 2 year follow up periods
Bousquet et al <sup>950</sup>	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 <sup>958</sup>	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 <sup>963</sup>	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 <sup>966</sup>	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 <sup>961</sup>	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 <sup>962</sup>	2018	4	Case series	-AR and asthma -Adults and children	SR rate and severity	Per-patient incidence of SRs was 4-fold higher in rush SCIT patients compared to conventional and cluster protocols despite premedication use
Cook et al <sup>964</sup>	2017	4	Case series	Rush SCIT	SR rate	Increased rate of SRs on subsequent doses after initial rush SCIT
Cox et al <sup>758</sup>	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 <sup>955</sup>	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

1 LOE=level of evidence; DBRCT=double-blind randomized controlled trial; SCIT=subcutaneous immunotherapy;  
2 SR=systemic reaction; IgE=immunoglobulin E; mAb=monoclonal antibody; s=antigen-specific; IgG=immunoglobulin  
3 G; AIT=allergen immunotherapy; AR=allergic rhinitis; RCT=randomized controlled trial; FEV<sub>1</sub>=forced expiratory  
4 volume in 1 second; HDM=house dust mite  
5 \*Upgraded from LOE 5 due to established methodology, several rounds of review, long history of evidence-based  
6 guideline development  
7  
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### 9 XI.D.5.c. Cluster subcutaneous immunotherapy for allergic rhinitis

10  
11 Cluster SCIT is a method to shorten the build-up phase for SCIT. Cluster schedules entail 2 or more  
12 injections during each visit on non-consecutive days. Typically, target maintenance dosing can be  
13 reached in 4-8 weeks. This improves convenience for patients and may lead to more rapid symptom  
14 improvement, without a significant rise in systemic reactions when premedication is used.<sup>967-969</sup>  
15

16 **Efficacy and safety.** Like rush SCIT, cluster SCIT is difficult to study due to the heterogeneity of study  
17 protocols, extract types, target maintenance dosing, and predication regimens. One SRMA evaluated the  
18 cluster SCIT efficacy for single allergen extracts and included 8 RCTs comparing cluster SCIT to  
19 conventional SCIT or placebo.<sup>967</sup> While no differences were found between cluster SCIT and placebo for  
20 symptom and medication scores, the high level of heterogeneity between the studies creates difficulty  
21 with interpretation. Several individual RCTs showed benefit in symptom, medication, and QOL benefit,  
22 consistent with other forms of SCIT.<sup>970,971</sup> Two additional RCTs not included in the meta-analysis show  
23 improvement in symptom/medication scores for cluster SCIT over placebo using depot or polymerized  
24 pollen extracts.<sup>902,921</sup> Compared to conventional SCIT, cluster SCIT demonstrates similar efficacy for  
25 multiple extracts including pollens and HDM.<sup>915,967,972-974</sup> Cluster and rush SCIT have not been directly  
26 compared in RCTs. [TABLE XI.D.5.c.]  
27

28 Two meta-analyses of RCTs and observational studies have assessed cluster SCIT safety.<sup>967,968</sup> When  
29 evaluating for local and systemic adverse reactions by number of patients, no difference was found with  
30 cluster versus conventional SCIT. The meta-analysis by Jiang et al<sup>968</sup> showed a lower rate of grade 1

1 systemic and local adverse reactions if analysis is done per injection. Additional studies are needed to  
2 further explore these findings, as non-randomized designed studies may favor inclusion of less  
3 vulnerable patient populations in the cluster cohort. High heterogeneity was noted which limits study  
4 conclusions.

5  
6 A more recent RCT from China and large retrospective study of a multiple-physician practice in the US  
7 with over 2.5 million injections given during the study period showed no difference in systemic reactions  
8 between cluster and conventional SCIT on a per-patient basis, but the retrospective trial did show a  
9 slightly increased risk on a per-injection basis.<sup>962,973</sup> Minimal data is available on delayed reactions with  
10 cluster SCIT and no conclusions can be drawn.<sup>968,975</sup>

11  
12 **Factors that affect systemic reactions with cluster SCIT.** Only one RCT specifically assessed the use of  
13 premedication in cluster SCIT with standardized pollen extracts.<sup>976</sup> Use of loratadine prior to cluster  
14 dosing showed a decline in systemic reactions from 79% of patients to 33% for the study duration.<sup>976</sup>  
15 While no life-threatening systemic reactions occurred, there was a reduction in severity of systemic  
16 reactions with premedication. Other RCTs and observational studies had high variability in  
17 premedication regimens (e.g., oral antihistamines, oral systemic steroids, and leukotriene modifying  
18 agents) and most do not provide relevant information. Timing of the premedication has not been  
19 directly studied.<sup>954</sup>

20  
21 Other factors may affect the frequency and severity of systemic reactions during cluster SCIT including  
22 dosing frequency, extract formulation (standardized, depot, polymerized), number of injections  
23 administered during a cluster session, and number of clusters given to reach maintenance.<sup>954</sup> Currently  
24 there is insufficient data to draw any conclusions, but this should be an area of emphasis for future  
25 research.

26  
27 In summary, cluster SCIT has a similar safety profile as conventional SCIT and fewer systemic reactions  
28 than rush SCIT.<sup>962,968,972</sup> Importantly, the safety of cluster SCIT is comparable to standard regimens  
29 overall because the number of injections required for buildup can be less, not because the per injection  
30 risk is necessarily lower. Additionally, premedication use appears to be necessary to reach this  
31 comparable safety profile for cluster SCIT. Some practices may translate this as the need to observe  
32 patients during cluster sessions more closely and for longer periods. Efficacy remains difficult to



1 investigate due to the significant study heterogeneity but does appear to be similar to conventional  
 2 SCIT, which is strongly recommended to manage refractory AR. Standardization of cluster protocols  
 3 through additional large-scale RCTs should be a key area of research as there remain many understudied  
 4 topics including dosing frequency, number of injections per visit, and the optimal duration of the build-  
 5 up phase.

6  
 7 **Aggregate grade of evidence:** B (Level 1: 1 study, level 2: 12 studies, level 4: 2 studies; **TABLE XI.D.5.c.**)

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

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

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

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

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

22 **Policy level:** Option.

23 **Intervention:** Cluster SCIT can be safely implemented in clinical practice and offered to those patients  
 24 eligible for SCIT that may prefer this protocol compared to conventional build-up protocols due to  
 25 convenience. Premedication should be strongly considered.

26

27 **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 <sup>968</sup>	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 <sup>972</sup>	2021	2	RCT	-Children and adults -Mixed allergen conventional SCIT -Mixed allergen cluster SCIT	-Symptom scores -SPT -Adverse reactions	Conventional and cluster SCIT have similar efficacies and no significant difference in SRs
Fan et al <sup>969</sup>	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 <sup>967</sup>	2014	2*	SRMA	Efficacy and safety of cluster SCIT vs	Not applicable	-Similar efficacy and safety of cluster SCIT vs conventional SCIT

				conventional SCIT or placebo		-Improved QOL for cluster SCIT versus placebo -Nonsignificant trend for improved symptom and medication scores
Klimek et al <sup>902</sup>	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 <sup>974</sup>	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 <sup>973</sup>	2009	2	RCT	-HDM cluster SCIT -HDM conventional SCIT	-QOL -Cutaneous reactivity -slgE 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 <sup>971</sup>	2008	2	RCT	-Grass mix cluster SCIT -Placebo	Nasal provocation test	Significant increase in threshold concentration for positive provocation
Cox <sup>954</sup>	2006	2**	Systematic review	-Adults & children -AR, asthma, Hymenoptera, imported fire ant -RCTs, observation cohorts, case series	-Combined symptom-medication score -SR rate -Cutaneous testing -Provocation challenges -slgE and slgG	Similar risk of SRs for cluster SCIT vs conventional SCIT
Tabar et al <sup>915</sup>	2005	2	DBRCT	-Der p cluster SCIT -Der p conventional SCIT	-Adverse reactions -Symptom-medication scores -Peak flow -SPT -slgE	-Reduction in time to maintenance dose by 47% using cluster SCIT -Similar efficacy and SR rate in both groups
Nanda et al <sup>970</sup>	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 -slgE and slgG4 -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 <sup>921</sup>	2002	2	DBRCT	Depot birch extract: -Cluster SCIT -Placebo	-Symptom score -Medication score -Conjunctival sensitivity -SPT	Treatment group showed improvement in all categories versus placebo,

					-SRs	with similar rates of adverse events
Nielsen et al <sup>976</sup>	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 <sup>962</sup>	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 <sup>975</sup>	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

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; SCIT=subcutaneous immunotherapy; SPT=skin  
2 prick test; RCT=randomized controlled trial; SR=systemic reaction; HDM=house dust mite; QOL=quality of life;  
3 DBRCT=double-blind randomized controlled trial; Ig=immunoglobulin; s=antigen-specific; AR=allergic rhinitis;  
4 TGF=transforming growth factor; IL=interleukin; IFN=interferon  
5 \*LOE downgraded due to heterogeneity of included studies included  
6 \*\*LOE downgraded due to inconsistency of results  
7  
8

## 9 XI.D.6. Sublingual immunotherapy for allergic rhinitis

### 10 XI.D.6.a. Sublingual immunotherapy for allergic rhinitis – general efficacy

11 While SCIT was first practiced over a century ago by Noon et al,<sup>796,977</sup> the first double-blind placebo-  
12 controlled trial of SLIT dates from 1986 by Scadding and Brostoff.<sup>978</sup> Over the next two decades several  
13 small trials were conducted. From 2006 onward, the ‘big trials’ finally demonstrated the clinical efficacy  
14 and safety of SLIT.<sup>979,980</sup> Since then, a wealth of high-quality SLIT trials have been conducted.<sup>981</sup>  
15  
16

17 In ICAR-Allergic Rhinitis 2018,<sup>308</sup> the joint outcomes of the best quality trials gathered in over two dozen  
18 SRMAs on SLIT were presented. Since then, further trials have been conducted taking better care to  
19 define the exact dosing, focus on specific allergens, and separate the two different sublingual  
20 administration routes: aqueous or tablets. In this section, evidence for SLIT efficacy in general is  
21 reviewed, and subsections on aqueous and tablet SLIT follow. SRMAs were primarily analyzed. Several  
22 RCT that have been published since ICAR-Allergic Rhinitis 2018 were added as well. For the  
23 interpretation of the SMD of meta-analyses, an effect size between 0.3-0.5 indicates mild effect, 0.5-0.8  
24 moderate effect, and above 0.8 a large effect of the intervention on the disease.<sup>982</sup>  
25

26 **TABLE XI.D.6.a.-1** shows the cumulative recent evidence from SRMAs, primarily over the past 5 years.

27 Additional notable studies prior to ICAR-Allergic Rhinitis 2018 are also listed. Combined evidence

1 previously published in ICAR-Allergic Rhinitis 2018 is presented in **TABLE XI.D.6.a.-2** for an Aggregate  
2 Grade of Evidence of SLIT efficacy in general.

3  
4 **Efficacy in adults.** The majority of the SRMAs show mild-to-moderate symptom and medication  
5 reduction in patients on SLIT compared to placebo. Symptom score improvements have also been  
6 demonstrated to be higher with longer treatment duration (greater than 12 months treatment,  
7 SMD=0.70).<sup>760</sup> All subjects, both those in the SLIT and in the placebo arms, had open access to rescue  
8 medication. As such, symptom reduction with SLIT comes on top of the symptom improvement obtained  
9 with rescue medication. SLIT efficacy in adults is judged to be grade A, with mild-to-moderate impact.

10

11 **Efficacy in children.** Studies on SLIT efficacy in children were previously limited by the heterogeneity of  
12 trials and the considerable risk of bias.<sup>983</sup> In addition to the ICAR-Allergic Rhinitis 2018 evidence  
13 demonstrating moderate efficacy for symptom relief in pollen and HDM liquid SLIT<sup>984</sup> and grass pollen  
14 tablet SLIT,<sup>985</sup> there is additional evidence for a moderate reduction in symptoms and medication scores  
15 in pediatric perennial AR.<sup>986,987</sup> SLIT efficacy in children is judged to be grade A, with moderate impact.

16

17 **Efficacy of SLIT over pharmacotherapy.** For perennial AR, HDM SLIT tablets are more effective than  
18 antihistamines, LTRAs, and INCS. For seasonal AR, grass pollen and ragweed tablet SLIT are almost as  
19 effective as INCS and more effective than the other pharmacotherapies.<sup>313</sup> An additional study showed  
20 that the 5-grass tablet had the highest relative clinical impact on symptom score over all other  
21 pharmacotherapy treatments.<sup>322</sup> SLIT efficacy over pharmacotherapy is judged to be grade B.

22

23 **Efficacy of SLIT compared to SCIT.** Several investigators have tried to compare the efficacy of SLIT  
24 against that of SCIT.<sup>988-993</sup> Most meta-analyses show superiority of SCIT over SLIT, but they are of low  
25 grade evidence as they are based on indirect comparisons.<sup>994</sup> There are very few direct head-to-head  
26 randomized trials comparing both treatments. One recent head-to-head study was powered for the  
27 comparison against the placebo-group, but not for SCIT versus SLIT.<sup>889</sup> In children, SCIT seems more  
28 effective than SLIT, but the quality of evidence is low.<sup>984</sup> SLIT efficacy compared to SCIT is judged to be  
29 grade B, with low grade evidence of SCIT superiority.

30

31 **Short-term preventative effects of SLIT.** There is moderate grade evidence for a high impact of SLIT in  
32 patients with AR to prevent them from developing asthma, during three years of treatment and within

1 the first two years off-treatment.<sup>765</sup> However, there is no evidence for primary prevention with SLIT, nor  
2 for long-term secondary preventive effects. For the development of new sensitizations, there are a few  
3 systematic reviews. The most comprehensive meta-analysis showed only a tendency for SLIT, and the  
4 effect did not withstand the sensitivity analysis,<sup>765</sup> while another systematic review found only low-  
5 grade evidence.<sup>995</sup> Evidence for short-term preventative effects of SLIT is judged to be grade B.

6  
7 **SLIT safety.** Rare systemic and serious adverse events have been reported with SLIT. In general, meta-  
8 analyses, including the most recent in 2019,<sup>994</sup> found SLIT to be safer than SCIT. In the complete dataset  
9 of systemic reviews, there were 7 reports of the use of epinephrine in the SLIT group.<sup>996</sup> There was no  
10 administration of epinephrine in trials outside of the US. There were several reports of symptoms  
11 suggestive of anaphylaxis with the first grass pollen tablet<sup>997,998</sup> and three with the first HDM tablet; this  
12 supports the recommendation in the package insert for administration under the supervision of a  
13 physician with experience in the diagnosis and treatment of allergic diseases and observation in the  
14 office for at least 30 minutes following the initial dose.<sup>999</sup> Starting SLIT in-season seemed to be safe.  
15 Although there were 2 serious treatment related adverse events with co-seasonal SLIT initiation, none  
16 needed epinephrine administration.<sup>1000</sup>

17  
18 Grass pollen SLIT tablets were noted to be equally safe in AR patients with and without mild asthma.<sup>1001</sup>  
19 Dropout rates have been raised as a concern for trial safety, but there is no evidence of differences in  
20 drop-out rates between SLIT and placebo groups.<sup>1002</sup> There have been a few case-reports of eosinophilic  
21 esophagitis after a course of grass pollen SLIT tablets.<sup>1003</sup> Continuing SLIT during pregnancy did not  
22 increase the incidence of adverse outcomes during delivery nor alter the risk of developing atopic  
23 disease in the offspring. However, there is insufficient data to draw conclusions about safety and  
24 efficacy in pregnant women.<sup>1004</sup>

25  
26 Evidence that SLIT is generally safe is judged to be grade A. Evidence that SLIT is safer than SCIT is judged  
27 to be grade B.

28  
29 **Cost-effectiveness of SLIT.** The meta-analysis comparing the efficacy and cost-savings of the 5-grass SLIT  
30 tablet versus the Timothy grass tablet has several flaws, making direct comparison of outcomes not  
31 possible.<sup>1005,1006</sup> The 5-grass tablet was associated with cost savings against year-round SCIT, seasonal  
32 SCIT, and the Timothy grass tablet during the first year of therapy, which persisted during the second

1 and third year of treatment. The higher costs for SCIT were due to elevated indirect costs from missing  
 2 working hours and transportation costs related to in-office SCIT administration. The higher costs for the  
 3 Timothy grass tablet are due to the year-round dosing versus the pre- and co-seasonal 6-month total  
 4 dosing of the 5-grass tablet.

5

6 After a previous positive UK meta-analysis on costs,<sup>1007</sup> a more recent one also concluded that the body  
 7 of evidence suggests that SLIT and SCIT could be considered cost-effective using the National Institute  
 8 for Health and Clinical Excellence cost-effectiveness threshold of £20,000 per QALY.<sup>1008</sup>

9

10 **Additional data not included in systematic reviews.** Investigators showed after a 3-year course of  
 11 Japanese cedar pollen tablet SLIT, there was a reduction in symptom-medication score of 45.3% one  
 12 year post-treatment and 34.0% two years post-treatment ( $p < 0.001$ ).<sup>1009</sup> A post-hoc analysis  
 13 demonstrated symptom and medication reduction with the birch SLIT tablet during the oak pollen  
 14 season in adults with allergic rhinoconjunctivitis.<sup>1010</sup>

15

16 There have been several studies on immunologic changes and biomarkers for AIT. There seems to be a  
 17 differential induction of allergen-specific antibody responses after grass pollen AIT, with SCIT primarily  
 18 inducing sIgG4 and SLIT inducing sIgA.<sup>899</sup>

19

20 **Aggregate grade of evidence for SLIT overall:** A (Level 1: 17 studies, level 2: 12 studies, level 4: 1 study;  
 21 TABLES XI.D.6.a.-1 and XI.D.6.a.-2)

22 Due to heterogeneity of SLIT study reporting, it is difficult to separate out overall vs aqueous SLIT vs  
 23 tablet SLIT.

24 **Benefit:** SLIT improves patient symptom scores, even as add-on treatment with rescue medication. SLIT  
 25 reduces medication use. The effect of SLIT lasts for at least 2 years after a 3-year course of therapy. In  
 26 AR patients, there is some evidence that SLIT reduces the frequency of onset of asthma and the  
 27 development of new sensitizations up to 2 years after treatment termination. Benefit is generally higher  
 28 than with single-drug pharmacotherapy, however, it may be less than with SCIT (low quality evidence).

29 **Harm:** Minimal harm with very frequent, but mild local adverse events, and very rare systemic adverse  
 30 events. SLIT seems to be safer than SCIT. See TABLE II.C.

31 **Cost:** Intermediate. SLIT becomes cost-effective compared to pharmacotherapy after several years of  
 32 administration. Total costs seem to be lower than with SCIT.

33 **Benefits-harm assessment:** Benefit of treatment over placebo is small but tangible and occurs in  
 34 addition to improvement with medication. There is a lasting effect at least 2 years off treatment.  
 35 Minimal harm with SLIT, greater risk for SCIT.

36 **Value judgments:** SLIT improved patient symptoms with low risk for adverse events.

37 **Policy level:** Strong recommendation for use of SLIT grass pollen tablet, ragweed tablet, HDM tablet,  
 38 and tree pollen aqueous solution. Recommendation for SLIT for *Alternaria* allergy. Option for SLIT for  
 39 animal allergy. Recommendation for dual-therapy SLIT in bi-allergic patients.

1 **Intervention:** Recommend tablet or aqueous SLIT in patients (adults and children) with seasonal and/or  
 2 perennial AR who wish to reduce their symptoms and medication use, as well as possibly reduce the  
 3 propensity to develop asthma or new allergen sensitizations.  
 4

5 **TABLE XI.D.6.a.-1. Evidence table – Recent high-level studies of sublingual immunotherapy for allergic**  
 6 **rhinitis (aqueous and tablet formulations)**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Aqueous and tablet SLIT reported together						
Kim et al <sup>1011</sup>	2021	1	SR	-SLIT aqueous and tablet HDM for mono- or poly-sensitized AR -9 RCTs	-Primary: symptoms -Secondary: QOL, medication scores	-Effective in mono- and poly-sensitized subjects -No significant difference in efficacy of single allergen SLIT for mono- vs poly-sensitized AR
Chen et al <sup>986</sup>	2020	1	SRMA	-SLIT for HDM tablet vs placebo in children with perennial AR -16 RCTs	-Symptoms -Medication use -Adverse events	-Improved symptom (p=0.0001) and medication (p<0.00001) scores -More frequent adverse events (1.08-1.68 times more)
Dhami et al <sup>777</sup>	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. <i>(For aqueous and tablet separately, see below)</i>
Feng et al <sup>987</sup>	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 <sup>765</sup>	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)
Boldovjácová et al <sup>1012</sup>	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 <sup>994</sup>	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 <sup>1013</sup>	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 <sup>896</sup>	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 <sup>777</sup>	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 <sup>989</sup>	2015	1	Network meta-analysis of RCTs	Grass pollen allergy: -SLIT tablets vs placebo -SLIT aqueous vs placebo -SCIT vs placebo	ARC symptoms & medication use	Symptom and medication scores with SCIT, SLIT aqueous and tablets all reduced vs. placebo, except for symptom score with SLIT aqueous
Di Bona et al <sup>988</sup>	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 <sup>1014</sup>	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 <sup>1015</sup>	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 <sup>1016</sup>	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 <sup>1017</sup>	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 <sup>1018</sup>	2014	2	RCT	SLIT for mono- or poly-sensitized HDM AR	-Symptoms -Medication use	Significant benefit of SLIT over placebo in mono- and poly-sensitized HDM AR without significant difference in symptom or medication scores
Kim et al <sup>984</sup>	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 <sup>1019</sup>	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 <sup>1020</sup>	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 <sup>1021</sup>	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 <sup>309</sup>	2021	1	SRMA of DBRCT	Seasonal or perennial AR in adults & adolescents: -INCS -INCS + INAH -oral AH -LTRA -Tablet-SLIT	-TNSS -Random effect MA versus placebo	SEASONAL AR: TNSS reduction (95% CI; T = number of trials) -INCS 1.38 (1.18-1.58; T39) -INCS-INAH 1.34 (1.15-1.54; T4) -INAH 0.72 (0.56-0.89; T13) -Oral AH 0.62 (0.35-0.90; T18) -SLIT tablets 0.57 (0.41-0.73; T4) -LTRA 0.48 (0.36-0.60; T10)

				-Placebo-controlled		PERENNIAL AR: TNSS reduction (95% CI; T = number of trials) -INCS 0.82 (0.66-0.97; T14) -SLIT tablet 0.65 (0.42-0.88; T3) -Oral AH 0.27 (0.11-0.42; T3)
Chen et al <sup>986</sup>	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 ( <i>See aqueous and tablet SLIT reported together</i> )
Li et al <sup>1022</sup>	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 <sup>996</sup>	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 <sup>322</sup>	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 <sup>875</sup>	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 <sup>313</sup>	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 <sup>1001</sup>	2015	2	Pooled analysis from RCTs	-Grass SLIT tablet vs placebo -Grass SLIT in AR patients with (24%) and without (76%) mild asthma	-TEAEs -Local and systemic allergic reactions -Asthma related TRAEs	-Severe asthma-related TRAE in 6/120 SLIT and 2/60 placebo -No difference in TRAE in SLIT-treated with or without asthma -Adults and children were included.
Dranitsaris & Ellis <sup>990</sup>	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

1 LOE=level of evidence; SR=systematic review; SLIT=sublingual immunotherapy; HDM=house dust mite; AR=allergic  
 2 rhinitis; RCT=randomized controlled trial; QOL=quality of life; SRMA=systematic review and meta-analysis;  
 3 AIT=allergen immunotherapy; ARC=allergic rhinoconjunctivitis; SCIT=subcutaneous immunotherapy;  
 4 SMD=standardized mean difference; MA=meta-analysis; VAS=visual analog scale; CI=confidence interval;  
 5 DBRCT=double-blind randomized controlled trial; PFT=pulmonary function test; INCS=intranasal corticosteroid;  
 6 IAH=intranasal antihistamine; AH=antihistamine; LTRA=leukotriene receptor antagonist; TNSS=Total Nasal  
 7 Symptom Score; TMS=Total Medication Score; IgE=immunoglobulin E; MFNS=mometasone furoate nasal spray;  
 8 TEAS=treatment emergent adverse events; TRAE=treatment related adverse event  
 9 \*LOE downgraded due to no meta-analysis, not limited to SLIT or AR alone  
 10 \*\*Antihistamines, montelukast, mometasone furoate nasal spray  
 11  
 12

**TABLE XI.D.6.a.-2 Established aggregate grade of evidence from ICAR-Allergic Rhinitis 2018<sup>308</sup>**

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

<b>It is safe to continue SLIT during pregnancy</b>	B	No added risk	Moderate evidence	Recommendation
	Oykhman <sup>1004</sup>			
<b>It is safe to start SLIT during the season</b>	B	Slightly added risk	Moderate evidence	Option
	Creticos <sup>1000</sup>			
<b>Tablet SLIT is more effective than pharmacotherapy</b>	A	Yes	-Moderate: antihistamines, montelukast -Weak: INCS	Recommendation
	-Devillier (pollen tablet SLIT), <sup>322</sup> Durham (grass pollen or ragweed tablet SLIT) <sup>313</sup> -Exception: in seasonal AR; INCS as efficacious as tablet SLIT			
<b>SLIT is cost-effective in the first year</b>	B	No	Moderate evidence	Option (considering its long-term benefit)
	Meadows, <sup>1007</sup> Dranitsaris <sup>990</sup>			
<b>SLIT is cost-effective after several years of treatment</b>	B	Yes	Weak-moderate evidence	Recommendation
	Meadows, <sup>1007</sup> Dranitsaris <sup>990</sup>			
<b>SLIT has a long-term effect beyond 3-years' application</b>	B	Yes	Moderate evidence	Recommendation
	Durham, <sup>1025</sup> Didier <sup>1026</sup>			
<b>SLIT has a preventive effect; reduces the development of asthma in patients with AR 2 years after a 3-year treatment course</b>	B	Yes	Weak effect	Recommendation
	Kristiansen <sup>765</sup> (New evidence since ICAR-Allergic Rhinitis 2018)			
<b>SLIT with grass pollen is effective for seasonal AR</b>	A	Yes	Low impact	Strong recommendation**
	Di Bona, <sup>996,1015</sup> Nelson, <sup>989</sup> Durham <sup>313</sup>			
<b>SLIT with tree pollen is effective for seasonal AR</b>	A	Yes	Moderate effect	Strong recommendation**
	Valovirta <sup>1027</sup>			
	A	Yes	Moderate effect	Strong recommendation**

<b>SLIT with ragweed pollen is effective for seasonal AR</b>	Durham, <sup>313</sup> Nolte, <sup>1028</sup> Creticos, <sup>1029</sup> Skoner <sup>1030</sup>			
<b>SLIT with HDM is effective for AR</b>	A	Yes	Low impact	Strong recommendation**
	Nolte, <sup>1031</sup> Bergmann, <sup>1032</sup> Mosbech, <sup>1033</sup> Calderon <sup>993</sup>			
<b>SLIT with animals is effective for AR</b>	X	No data	No data	Option
	No separate data in SRMAs; no recent trials			
<b>SLIT with fungi is effective for AR</b>	B	Yes	Weak evidence	Option
	No separate data in SRMAs; Cortellini <sup>1034</sup>			

1 SLIT=sublingual immunotherapy; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy; INCS=intranasal  
 2 corticosteroid; HDM=house dust mite; SRMA=systematic review and meta-analysis  
 3 \*For those variables with meta-analysis: according to Cohen’s classification: low impact SMD 0.2-0.5,  
 4 moderate 0.5-0.8, high above 0.8. For those with only systematic review: strength of evidence.  
 5 \*\*Considering the added long-term post-treatment effect and the possible preventive effects on the  
 6 development of asthma and new sensitizations.  
 7  
 8

9 **XI.D.6.b. Sublingual immunotherapy for allergic rhinitis – tablets**  
 10

11 SLIT tablets have been studied for HDM, as well as short ragweed, grass, birch, and Japanese cedar  
 12 pollens. US FDA-approved tablets encompass Timothy grass, short ragweed, a 5-grass combination, and  
 13 HDM allergens. Administration schedules and age ranges of approved use vary based on the specific  
 14 tablet prescribed.  
 15

16 Since 2017, numerous SRMAs were identified for SLIT tablets. **[TABLE XI.D.6.a.-1]** Eight reported both  
 17 aqueous and tablet SLIT,<sup>765,777,986,987,994,1011-1013</sup> six presented aqueous and tablet SLIT  
 18 separately,<sup>777,896,988,989,1014,1015</sup> and nine reported on tablet SLIT alone.<sup>309,313,322,875,986,990,996,1001,1022</sup> All  
 19 studies reported outcomes for HDM, grass pollen, and/or ragweed pollen. There were no SRMAs for  
 20 birch or Japanese cedar pollen tablets. Studies focusing only on SLIT tablets demonstrated safety and  
 21 efficacy for HDM, grass pollen, and ragweed pollen. Improvement in symptom scores, medication  
 22 scores, and QOL metrics are evident with minimal adverse reactions.  
 23

24 Meltzer et al<sup>309</sup> published a meta-analysis evaluating the efficacy of pharmacotherapies and SLIT tablets  
 25 versus placebo on nasal symptoms in seasonal and perennial AR. Active treatments significantly  
 26 improved nasal symptoms versus placebo. Trial heterogeneity and publication bias limited comparison

1 of treatment classes. Of note, comparison groups were not equally matched. SLIT is generally used for  
2 pharmacotherapy-recalcitrant patients, resulting in a more severe group using SLIT. Additionally,  
3 patients often use supplement SLIT with rescue medications, confounding individual comparison of  
4 medical treatments.

5

6 Analysis of pediatric studies demonstrated that HDM SLIT reduced symptoms and medication scores  
7 versus placebo, with a slight increase in adverse reactions.<sup>986</sup> A similar study of HDM SLIT tablets in  
8 adults<sup>1022</sup> showed improvement in symptom scores and QOL compared to placebo. Nelson et al<sup>875</sup>  
9 published a systematic review of 12 double-blind RCTs for HDM SLIT tablets and concluded that efficacy  
10 was established with all twelve studies, with statistically significant symptom score improvement.

11

12 SRMAs including SLIT tablet and aqueous preparations also reported favorable outcomes for symptoms  
13 scores, medications, and QOL. Findings for aqueous SLIT are discussed in the next section.

14 Examples of dose-response studies for grass pollen and HDM tablets include those by Didier et al,<sup>980</sup>  
15 Horak et al,<sup>1035</sup> Malling et al,<sup>1036</sup> and Bergmann et al.<sup>1032</sup> Dose-finding studies aim to identify effective  
16 therapeutic doses while minimizing adverse effects.

17 The efficacy findings from 2017-2022 SLIT tablet studies are consistent with the findings reported in the  
18 first ICAR-Allergic Rhinitis 2018.<sup>308</sup> The majority of the SRMAs show mild-to-moderate efficacy of SLIT  
19 tablets over placebo. There is strong evidence that grass pollen SLIT tablets and HDM tablets in children  
20 reduce symptoms of AR.

21

22 Rare systemic and serious adverse events have been reported with SLIT, but in general, meta-analyses  
23 found SLIT to be safer than SCIT. One study found 7 of 2259 patients on grass pollen SLIT tablets were  
24 given epinephrine for treatment related adverse effects.<sup>996</sup> Presence of mild asthma did not affect  
25 adverse reactions for grass pollen SLIT tablets.<sup>1001</sup> Starting SLIT in-season is generally deemed to be safe;  
26 although there were 2 serious treatment related adverse events with co-season SLIT initiation, none  
27 needed epinephrine.<sup>1000</sup>

28

29 SLIT tablet options are limited compared to off-label aqueous SLIT extracts. Since HDM is the only tablet  
30 approved for patients with non-seasonal AR, data regarding polysensitized patients is important. Kim et  
31 al<sup>1011</sup> reported a meta-analysis of HDM AIT in mono- or polysensitized patients. Nine studies, five SLIT

1 and four SCIT, revealed no differences for nasal symptom score, medication use, and QOL scores  
2 between mono- and polysensitized patients.

3

4 The use of multiple concurrent SLIT tablets (Timothy grass and short ragweed) has been studied by  
5 Maloney et al.<sup>1001</sup> Simultaneous co-administration within 5 minutes did not result in severe swelling,  
6 systemic allergic reactions, asthma attacks, or reactions requiring epinephrine. Gotoh et al<sup>1037</sup> reported  
7 the first study of dual administration of SLIT tablets for perennial and seasonal AR using HDM and  
8 Japanese cedar pollen tablets administered alone and as dual therapy. The percentage of subjects with  
9 adverse events and reactions was similar between the two groups and between the two periods of  
10 monotherapy and dual therapy. There were no serious events and immunologic marker responses were  
11 not altered by co-administration of tablets. These studies provide support for the contention that co-  
12 administration of tablets does not adversely affect the safety or efficacy of tablet SLIT.

13

14 **Aggregate grade of evidence:** A (Level 1: 11 studies, level 2: 4 studies; **TABLE XI.D.6.a.-1**)

15 **Benefit:** Improvement of symptoms, rescue medication and QOL.

16 **Harm:** Local reaction at oral administration site and low risk of anaphylaxis.

17 **Cost:** Intermediate. More expensive than standard pharmacotherapy, but persistent benefit may result  
18 in cost-saving in the long-term.

19 **Benefits-harm assessment:** Benefit outweighs harm.

20 **Value judgments:** Useful for patients with severe or refractory symptoms of AR.

21 **Policy level:** Strong recommendation.

22 **Intervention:** SLIT tablets are recommended for patients with severe or refractory AR). Epinephrine  
23 auto-injector is recommended in the FDA labeling for approved tablets due to the rare but serious risk of  
24 anaphylaxis. Tablets for select antigens are available in various countries.

25

26

### 27 [XI.D.6.c. Sublingual immunotherapy for allergic rhinitis – aqueous](#)

28

29 SLIT can be administered via tablets or aqueous drops. Like sublingual tablets, this offers easy at-home  
30 administration with a similar safety profile. While some aqueous extracts are approved for use in  
31 Europe, aqueous SLIT products are not FDA approved in the US; many providers currently use  
32 subcutaneous allergen extracts off-label for sublingual desensitization.<sup>1038</sup>

33

34 Aqueous SLIT has a mild to moderate effect on improving patient symptoms and reducing medication  
35 usage.<sup>777,984,988,1015,1016</sup> Although it is difficult to compare studies due to methodologic or extract  
36 differences, improvement in symptom/medication outcomes is prevalent across most studies. The FDA  
37 has approved SLIT tablets for HDM, grass pollen, and ragweed pollen allergy -- these antigens have

1 standardized dosages; however, many allergens cannot be treated with the limited number of available  
2 tablets. Additionally, there is currently no head-to-head data comparing aqueous SLIT to tablet SLIT.  
3 Some meta-analyses have undertaken subgroup analysis between aqueous SLIT and tablet SLIT and  
4 found both to be effective without clear superiority of one over the other.<sup>777,989</sup>

5  
6 Aqueous SLIT seems to be efficacious for adults and children. An earlier meta-analysis noted no  
7 significant improvement in symptom score for children treated with SLIT.<sup>1015</sup> However, most of the  
8 included studies included had a low monthly allergen dose that has been shown to be ineffective in  
9 subsequent meta-analyses.<sup>777,988,989,1016</sup> Lack of dosing standardization across multiple studies in different  
10 countries using extracts from various manufacturers has led to heterogeneity in aqueous SLIT data.<sup>1039</sup>

#### 11 **[TABLE XI.D.6.a.-1]**

12  
13 Leatherman et al<sup>1038</sup> provided recommendations for effective doses of aqueous SLIT based on  
14 micrograms per day administered in RCTs that demonstrated efficacy. Published and recommended  
15 dosing ranges for common allergens are shown in **TABLE XI.D.6.c.** However, many allergens such as cat,  
16 dog, mold/fungi, and cockroach did not have enough data to provide specific recommendations.<sup>1038</sup>  
17 There is expert opinion that for allergens without current effective ranges, daily SLIT dose equal to the  
18 monthly SCIT dose may be in the effective dose range; further studies should validate this.<sup>758</sup>

19  
20 While single allergen SLIT has been shown to be effective in both monosensitized and polysensitized  
21 patients,<sup>1011,1018,1021</sup> there is equivocal evidence on added benefit of multi-allergen immunotherapy in  
22 the polyallergic patient. This is pertinent to tablet SLIT as well because of the limited number of antigens  
23 available as tablets. Most RCTs demonstrate significant benefit over placebo with multi-allergen SLIT but  
24 have not compared monotherapy to polytherapy. One open-label, controlled trial in patients with grass  
25 and birch sensitization randomized patients to treatment with grass pollen, birch pollen, grass and birch  
26 pollen, or placebo.<sup>1040</sup> Monotherapy with grass or birch showed clinically significant improvement and  
27 nasal eosinophil reduction versus baseline, but polytherapy with grass and birch showed improvement  
28 over the monotherapy groups. Alternatively, comparing Timothy extract alone or with 9 additional  
29 pollen extracts against a placebo group demonstrated secondary outcome efficacy (e.g., SPT reactivity,  
30 nasal challenge, sIgE) in favor of the mono-Timothy group, though neither treatment group showed  
31 symptom/medication improvement over placebo, as the grass pollen season was too mild.<sup>1019</sup> Another  
32 study randomized polysensitized patients to single, pauci, or multi-allergen SLIT.<sup>1017</sup> Symptom scores



1 significantly improved in all groups, yet there was no significant efficacy difference shown for single vs  
 2 pauci- vs multi-allergen SLIT. Of note, this study had only 16 patients total and follow up was 9 months.  
 3 Further study is needed to determine the role of monotherapy or polytherapy SLIT on specific seasonal  
 4 symptoms and QOL measures over several seasons.

5

6 Safety of aqueous SLIT is comparable to its SCIT and tablet SLIT counterparts. There is no standardized  
 7 mechanism of reporting safety outcomes across RCTs but reported adverse outcomes have been  
 8 modest. Local reactions range 0.2-97%. Life-threatening reactions or anaphylaxis were largely absent  
 9 from most meta-analyses<sup>1014,1016</sup> except for one meta-analysis of SCIT and SLIT for grass allergens<sup>988</sup>  
 10 which found one case of anaphylaxis in the SLIT group. Notably the SCIT group had 12 cases of  
 11 anaphylaxis and the placebo group had two cases, suggesting that the risk of anaphylaxis in SLIT is  
 12 significantly lower than in SCIT.<sup>988</sup> There were no cases of anaphylaxis or life-threatening events in  
 13 children.<sup>984</sup> [TABLE II.C.]

14

15 **Aggregate grade of evidence:** B (Level 1: 7 studies, level 2: 5 studies, level 4: 1 study; TABLE XI.D.6.a-1)

16 **Benefit:** Aqueous SLIT improves patient symptom scores and decreases rescue medication use. There is  
 17 some indication of less benefit from aqueous versus tablet SLIT, but the lack of standardized dosing  
 18 across multiple trials does not allow for adequate comparison.

19 **Harm:** Common mild to moderate local adverse events. Very rare cases of systemic adverse events. No  
 20 reported cases of life-threatening reactions. See TABLE II.C.

21 **Cost:** Intermediate. More expensive than standard pharmacotherapy, but there are indications of lasting  
 22 benefit and cost-saving in the long-term.

23 **Benefits-harm assessment:** Appreciable benefit in patient symptoms and minimal harm.

24 **Value judgments:** Aqueous SLIT improves patient symptoms and rescue medication usage with minimal  
 25 risk of serious adverse events but common local mild adverse events. Single allergen therapy has been  
 26 extensively tested. Multiallergen AIT requires future studies to validate its use.

27 **Policy level:** Recommendation.

28 **Intervention:** High-dose aqueous SLIT is recommended for those patients who wish to reduce their  
 29 symptoms and rescue medication use.

30

31 **TABLE XI.D.6.c. Recommended SLIT dosing ( $\mu\text{g}/\text{day}$ )<sup>1038</sup>**

Allergen	Published dosing range ( $\mu\text{g}/\text{day}$ )	Recommended daily dose range ( $\mu\text{g}/\text{day}$ )
<i>D. pteronyssinus</i>	0.32-47	16 (10-28)
<i>D. farinae</i>	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
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1  
2  
3  
4  
5  
6

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
<b>Efficacy</b>	Significant efficacy over placebo <sup>829,909,923,1041</sup>	Significant efficacy over placebo <sup>1042-1044</sup>
	-Both demonstrate efficacy over placebo for allergic rhinoconjunctivitis and other allergic conditions, but head-to-head data are lacking <sup>761,984,994,1024,1045-1048, a</sup> -Low grade evidence for SCIT superiority	
<b>Side effects [TABLE II.C.]</b>	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
<b>Safety</b>	-Increased risk of systemic reactions compared with SLIT -Prescription of epinephrine autoinjector for delayed reactions at physician’s discretion <sup>758</sup>	-Decreased risk of systemic reactions compared with SCIT -Epinephrine autoinjector mandated in the US by the FDA for tablet SLIT <sup>1049, b</sup>
	At office visits, consider peak expiratory flow tests or spirometry in patients with asthma (no treatment or testing if exacerbation) <sup>758</sup>	
<b>Cost<sup>c</sup></b>	-Lower direct cost to patient, but may be comparable or higher in total (e.g., indirect) costs <sup>990,1050,1051, d</sup> -Lower initial ICER (e.g., first 6 years) <sup>1007</sup>	-Higher direct cost to patient, but may be comparable or lower in total (e.g., indirect) costs <sup>990,1050,1051, d</sup> -Higher initial ICER (e.g., first 6 years) <sup>1007</sup>
	Cost-effectiveness threshold: £20,000-30,000 / QALY by year 6 <sup>1007,1008</sup>	
<b>Covered by insurance?<sup>1050, c</sup></b>	Yes	-Aqueous: no -Tablet: yes
<b>Convenience</b>	Less convenient (recurring office visits for injections: weekly during build-up phase, every 2-4 weeks during maintenance phase) <sup>758</sup>	-More convenient (self-administered daily at home) -Preferable for those opposed to injections (e.g., children)
<b>Testing considerations</b>	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 <sup>e</sup>	
<b>Equipment considerations<sup>758</sup></b>	-May need supplies for IDT or MQT depending on treatment paradigm -Needs vial preparation supplies for serial dilutions -Need injection supplies	-May be performed with SPT results only -Substantially more antigen needed for aqueous SLIT preparations -Need antigen delivery device (dropper)

		-For SLIT tablets essentially no administration supplies needed
	Appropriate equipment and medications for anaphylaxis treatment <sup>f</sup>	
<b>Length of therapy</b>	Longer build up phase with conventional SCIT and cluster protocols	Shorter build up phase
	Maintenance: ≥3 years, up to 5 years <sup>1046,1052-1055</sup>	
<b>Adherence to therapy</b>	-More easily monitored (in office) -Most common reason for discontinuation is inconvenience <sup>1056</sup>	-Less easily monitored (at home) -Adherence may be improved with more frequent clinic visits, improving therapy availability, and mitigating concerns about clinical efficacy <sup>1057,1058</sup>
	-Overall adherence rates are similar, but conflicting data depends on how adherence is measured <sup>1056,1059-1061, g</sup> - Patients should be re-evaluated at least every 6-12 months while receiving immunotherapy <sup>758, h</sup>	
<b>Mechanism of action</b>	-Subcutaneous (systemic) injection -IgG, IgG4 antibody induction <sup>899</sup>	-Sublingual (local) administration <sup>1062</sup> -IgA1, IgA2 antibody induction <sup>899</sup>
	Allergen extracts presented to immune system induce allergen desensitization and immunologic tolerance <sup>1046,1052,1053</sup>	
<b>FDA-approved allergens</b> <sup>1063,1064, c, i</sup>	-Animal dander (e.g., cat) -Insect venom (e.g., honeybee, wasp, hornet, yellow jacket, mixed vespid) -Pollen (e.g., grass, ragweed) -House dust mite ( <i>Dermatophagoides pteronyssinus</i> , <i>D. farinae</i> )	-Pollen (grass, ragweed) -House dust mite
<b>Indications</b> <sup>1046,1053</sup>	-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	
<b>Contraindications</b> <sup>1046,1053</sup>	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 <sup>l</sup> -Pregnancy <sup>k</sup> -Preparation-specific contraindications (see product information leaflet)	

1 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;  
 2  
 3 IDT=intradermal dilutional test; MQT=modified quantitative test; Ig=immunoglobulin  
 4 <sup>a</sup>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  
 5

1 SLIT,<sup>988,991</sup> but the most recent meta-analyses did not demonstrate superiority of one over the other.<sup>761,994</sup> Overall  
2 there is a lack of RCTs directly comparing the efficacy of SCIT to SLIT.

3 <sup>b</sup>This is not a requirement for SLIT prescribed in Europe.<sup>1060</sup> Controversy exists regarding whether epinephrine  
4 autoinjectors are warranted for patients on SLIT due to factors such as the rarity of systemic allergic reactions,<sup>1065</sup>  
5 costs exceeding that of SLIT therapy, and poor compliance with purchasing/carrying autoinjectors.<sup>1049,1066</sup> Patients  
6 should be educated specifically regarding when and how to use epinephrine.

7 <sup>c</sup>May vary by geographic region. Examples provided in the table refer to the US unless otherwise stated.

8 <sup>d</sup>Indirect costs include travel expenses and loss of productivity. Some studies found that overall SLIT was more cost  
9 effective than SCIT.<sup>990</sup>

10 <sup>e</sup>Some tests, such as titrated SPT, titrated nasal allergen challenge, and sIgG4 measurement, have been shown to  
11 correlate with clinical efficacy or predict future response.<sup>970,1067,1068</sup>

12 <sup>f</sup>Required for all office administrations (e.g., all SCIT, first dose SLIT). Example equipment: stethoscope and  
13 sphygmomanometer; aqueous epinephrine 1:1000 weight/volume (i.e., the primary treatment for anaphylaxis);  
14 tourniquet, syringes, large bore (14 gauge) needles, and intravenous catheters; equipment to administer oxygen by  
15 mask; intravenous fluid set-up; antihistamine for injection (second-line treatment); glucocorticoids for  
16 intramuscular or intravenous administration (second-line treatment); equipment to maintain an airway  
17 appropriate for the supervising clinician's expertise and skill; glucagon kit for patients on b-blockers.

18 <sup>g</sup>Conflicting studies have shown SCIT to have higher adherence,<sup>1069,1070</sup> SLIT to have higher adherence,<sup>1071,1072</sup> or  
19 both to have comparable compliance.<sup>1061,1073</sup>

20 <sup>h</sup>To assess efficacy and compliance, reinforce safe administration, and determine whether treatment adjustments  
21 or discontinuations are warranted.

22 <sup>i</sup>SCIT allergens listed are standardized (compared to a US reference standard for potency). Other SCIT allergens  
23 demonstrated to be effective in placebo-controlled studies include molds (e.g., *Alternaria*, *Cladosporium*), insects  
24 (e.g., cockroach, imported fire ant), dog dander, and tree pollen.<sup>1074,1075</sup> May use SCIT extracts off label for SLIT.

25 <sup>j</sup>Contraindication for SLIT. Limited evidence suggests SCIT should not be typically recommended for patients with  
26 eosinophilic esophagitis. However, SCIT may benefit some patients with eosinophilic esophagitis.<sup>1076</sup>

27 <sup>k</sup>Considered a contraindication for initiating AIT, though it may be continued during pregnancy at  
28 stable/maintenance doses. Only in isolated cases may SCIT be initiated during pregnancy.<sup>758,1053</sup>

### 31 XI.D.7. Epicutaneous/transcutaneous immunotherapy

32  
33 Epicutaneous or transcutaneous immunotherapy is a non-invasive form of AIT that consists of the  
34 application of allergens to the skin without involving injections. Allergen is applied through patches kept  
35 on the skin for several hours. The epidermal barrier is usually impermeable to molecules larger than 500  
36 Da.<sup>1077</sup> In order to increase/improve antigen delivery to the immune cells of the epidermis and dermis,  
37 different techniques have been used including adhesive tape stripping, abrasion of the skin, and sweat  
38 accumulation through patch application.<sup>809,1078</sup> Newly engineered techniques are being evaluated for the  
39 delivery of powder-based AIT into the epidermis with minimal skin reaction, including microneedle  
40 arrays and laser-mediated microporation; these have primarily been studied in food allergy (peanut).<sup>1079</sup>  
41 To date, four clinical trials of aeroallergen epicutaneous AIT have been published (three of them by the  
42 same group of investigators) reporting the efficacy of grass pollen extract coated patches in varying  
43 doses, numbers of weekly patches, and duration in contact with the skin.<sup>1080</sup> [TABLE XI.D.7.]

44

1 The first pilot study of aeroallergen epicutaneous AIT was a monocentric, placebo-controlled, double-  
2 blind trial of 37 adults with positive SPT and nasal challenge tests to grass pollen randomized to  
3 treatment with allergen or placebo patches.<sup>1081</sup> Symptom scores after NPT scores showed notable  
4 reduction in the grass-treated patients, but the difference was not statistically significant. Grass-treated  
5 patients had improved subjective symptom scores, both after the pollen seasons of 2006 ( $p=0.02$ ) and  
6 2007 ( $p=0.005$ ). Eczema at application sites was significantly higher in the treatment arm; there were no  
7 serious adverse events.

8  
9 A second monocentric double-blind study randomized 15 children to grass epicutaneous AIT versus  
10 placebo.<sup>1082</sup> There were no significant differences in skin test wheal size between groups before and  
11 after treatment. Both groups had an increase in symptoms, but the treatment group had lower  
12 rhinorrhea, nasal obstruction, dyspnea, and ocular tearing. The treatment group had a significant  
13 reduction in antihistamine use ( $p=0.019$ ). There were no systemic or local reactions.

14  
15 A third monocentric trial randomized 132 adults to placebo, low, medium, or high dose grass extract  
16 patches. Significant improvement in rhinoconjunctivitis symptoms was found only in the high dose  
17 treated patients one year later ( $p=0.017$ ).<sup>1083</sup> There were no differences in conjunctival provocation test,  
18 SPT, or rescue medication use. Local reactions were more frequent in high dose treated patients and  
19 decreased with subsequent applications. Systemic reactions treated with intravenous antihistamines  
20 and corticosteroids occurred in 8.3% of patients.

21  
22 A fourth monocentric double-blind RCT randomized 98 adults to grass patches or placebo.<sup>1084</sup> There was  
23 a 48% improvement in seasonal symptom scores in the first year (placebo 10%) but no significant  
24 differences in combined treatment and medication scores. CPT scores improved after the first year in  
25 the active treatment group. Allergen-specific IgG4 was significantly increased in the active treatment  
26 group only during the first pollen season; sIgE did not show any variation. Local adverse events occurred  
27 in 18%; eight systemic reactions led to study exclusion.

28  
29 A systematic review of the efficacy and safety of epicutaneous AIT for food and pollen allergy; the four  
30 clinical trials above on grass allergy were included.<sup>1085</sup> Given the lack of original data on means and  
31 standard deviation of symptom scores, a meta-analysis on the efficacy was not possible and the authors  
32 concluded that the effectiveness of epicutaneous AIT for grass pollen allergy is unclear. Subgroup

1 analyses concluded that epicutaneous grass pollen AIT significantly increased the risk of local (RR  
 2 [relative risk] 2.29; 95% 1.05-4.96) and systemic (RR 4.65; 95% CI 1.10-19.64) adverse reactions. It is  
 3 interesting to note that the cited clinical trials were conducted more than 10 years ago suggesting little  
 4 progress in this area for AR.

5  
 6 **Aggregate grade of evidence:** B (Level 2: 5 studies; **TABLE XI.D.7.**)

7 **Benefit:** Epicutaneous AIT to grass pollen resulted in limited and variable improvement in symptoms,  
 8 medication use, and allergen provocation tests in patients with AR or conjunctivitis.

9 **Harm:** Epicutaneous AIT resulted in systemic and local reactions, with a RR of 4.65 and 2.29,  
 10 respectively. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous AIT.

11 **Cost:** Unknown.

12 **Benefits-harm assessment:** There is limited and inconsistent data on benefit of the treatment, while  
 13 there is a concerning rate of adverse effects. Three out of 4 studies on this topic were published by the  
 14 same investigators from 2009-2015.

15 **Value judgments:** Epicutaneous AIT could offer a potential alternative to SCIT and SLIT, but further  
 16 research is needed.

17 **Policy level:** Recommendation against.

18 **Intervention:** While epicutaneous AIT may potentially have a future clinical application in the treatment  
 19 of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a  
 20 significant rate of adverse reactions. Given the above and the availability of alternative treatments,  
 21 epicutaneous AIT is not recommended at this time.

22  
 23 **TABLE XI.D.7. Evidence table – Epicutaneous/transcutaneous immunotherapy for the treatment of**  
 24 **allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Xiong et al <sup>1085</sup>	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 <sup>1084</sup>	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 <sup>1083</sup>	2012	2	DBRCT	Adults, 6 weekly patches kept on for 8 hours: -Placebo patches, n=33 -Low dose grass patches, n=33 -Medium dose grass patches, n=33	-Symptoms -Medication use -SPT -CPT	-Symptoms improved only in highest dose group -No difference in medication use, SPT, or CPT -Local reactions common -Systemic reactions occurred in 8.3%

				-High dose grass patches, n=33		
Agostinis et al <sup>1082</sup>	2010	2	DBRCT	Children, 12 weekly patches kept on for 24 hours: -Grass patches, n=15 -Placebo patches, n=15	-Symptoms -Antihistamine use -Skin test wheal size	-No difference in skin wheal size at study end -Treatment group had less symptoms and antihistamine use
Senti et al <sup>1081</sup>	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

1 LOE=level of evidence; SR=systematic review; RR=relative risk; DBRCT=double-blind randomized controlled trial;  
2 CPT=conjunctival provocation test; SPT=skin prick test; NPT=nasal provocation test  
3 \*LOE downgraded due to lack of consistency in study inclusion and heterogeneity of outcome measurements  
4 (symptom scores)  
5  
6

#### 7 XI.D.8. Intralymphatic immunotherapy

8  
9 Notwithstanding the long-term benefits to AR patients by AIT, the recommended treatment duration of  
10 3-5 years is time consuming, expensive, and demands strict adherence from patients.<sup>871</sup> SCIT requires  
11 monthly maintenance injections, and SLIT requires daily oral intake. Intralymphatic immunotherapy  
12 (ILIT) was introduced to address these concerns. ILIT involves the application of low dose allergens via  
13 ultrasound-guided injection into the lymph nodes, mainly the inguinal nodes. The treatment protocol of  
14 ILIT has a shorter duration, usually comprising three injections over a period of eight weeks.<sup>1086</sup> The  
15 cumulative dose for ILIT is dramatically lower than that used for conventional AIT and there are  
16 significantly fewer adverse events.<sup>1087</sup>  
17

18 Thus far, two systematic reviews are available. **[TABLE XI.D.8.]** The first systematic review included  
19 eleven trials and two cohorts in a qualitative and quantitative analyses of 483 participants with the  
20 average age of 33 years.<sup>1087</sup> The second systematic review involved quantitative analysis of eleven trials  
21 with 452 participants aged 15 years and above.<sup>1088</sup> The outcomes assessed in both reviews include the  
22 combined symptom-medication score, symptom score, VAS, medication score, overall improvement  
23 score, medication reduction, QOL, sIgE level, sIgG level, and adverse events. The overall level of  
24 evidence of the included trials ranged from very low to moderate.  
25

26 ILIT was administered by injecting aluminum hydroxide-adsorbed antigen vaccine into inguinal lymph  
27 nodes for all patients under ultrasound guidance.<sup>1089-1099</sup> In one pilot study, the cervical lymph nodes

1 were used as the injected site.<sup>1100</sup> Single allergen was evaluated in seven trials,<sup>1090-1093,1097-1099</sup> two  
2 different allergens assessed simultaneously in four trials,<sup>1089,1094-1096</sup> and one trial assessed two different  
3 allergens individually.<sup>1095</sup> Grass pollen extract was injected in eight trials,<sup>1089,1090,1092-1097</sup> cedar pollen  
4 extract in two trials,<sup>1098,1099</sup> birch pollen extract in four trials,<sup>1089,1094-1096</sup> and cat dander allergen extract  
5 (MAT-Fel d 1) in one trial.<sup>1091</sup> Placebo injections were used in all but two trials<sup>1089,1090</sup> which used SCIT as  
6 control groups.

7  
8 All trials performed three injections at four-week intervals except for one trial which used a two-week  
9 interval. Short-term relief of the combined symptoms and medication score was achieved in the four-  
10 week but not for the two-week interval.<sup>1087</sup> Increased sIgG4 levels have been associated with the  
11 effectiveness of AIT.<sup>1101</sup> While a short-term increase of sIgG4 level has been documented following ILIT,  
12 there has not been any medium-term or long-term effects.<sup>1087</sup> The reduction of sIgE in the short,  
13 medium, and long-term is frequently reported with SCIT; however, this has been notably absent with  
14 ILIT.<sup>1087,1090</sup>

15  
16 ILIT was shown to confer short-term relief of AR symptoms in one review.<sup>1087</sup> Despite being safe and well  
17 tolerated, both meta-analyses determined that the efficacy of ILIT for long-term relief of AR symptoms  
18 was inconclusive.<sup>1087,1088</sup> The safety of ILIT and reported adverse events were investigated in all eleven  
19 trials. While more local reactions were noted from ILIT compared to placebo, systemic adverse events  
20 were similar in both the ILIT and placebo groups.<sup>1087</sup> The major advantage in favor of ILIT compared to  
21 SCIT is fewer adverse effects of local and systemic reactions<sup>1090</sup> compared to SCIT. At present, there is no  
22 trial comparing ILIT vs SLIT with regard to adverse effects. Overall, two anaphylactic events have been  
23 reported for ILIT but no deaths.<sup>1102</sup> The anaphylaxis following ILIT transpired following the first injection  
24 in one patient and following the second injection in another patient, both patients receiving non-  
25 standardized aqueous allergen extract compared to aluminum-based extract used in most trials.

26  
27 ILIT trials varied as to the dose of allergen administered and the interval between injections. Increased  
28 efficacy was associated with a four-week (vs. two-week) interval, and future trials should use and  
29 establish a standard treatment regimen. Another shortcoming is a lack of standardization of clinical  
30 endpoints. The use of standardized assessment such as combined symptoms-medication score could  
31 better reflect the actual potential of ILIT. The high heterogeneity among the trials could be due, in part,  
32 to the use of different allergens. The immunogenicity effect may differ between allergens when



1 administered as a single or multiple allergens. One trial used both grass and birch allergen to treat  
 2 polysensitized patients and found elevated sIgE and sIgG4 levels for grass pollen but not for birch  
 3 pollen.<sup>1095</sup> ILIT could be beneficial as an alternative to other forms of AIT due to its shorter treatment  
 4 period, reduced number of injections and fewer adverse events; however, the long-term efficacy has to  
 5 be supported by more studies prior to its incorporation into clinical practice.

6  
 7 **Aggregate grade of evidence:** A (Level 1: 2 studies, level 2: 11 studies, level 4: 3 studies; **TABLE XI.D.8.**)

8 **Benefit:** Shorter treatment period, decreased number of injections, smaller amount of allergen, lower  
 9 risk of adverse events versus SCIT.

10 **Harm:** Local reaction at injection site and risk of anaphylaxis.

11 **Cost:** Cost savings due to shorter treatment duration and fewer injections. Additional cost for training  
 12 required.

13 **Benefits-harm assessment:** Benefit outweighs harm.

14 **Value judgments:** Apparent short-term favorable effect, but long-term effect is lacking.

15 **Policy level:** Option.

16 **Intervention:** More studies are essential to establish the long-term effects of ILIT.

17

18 **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 <sup>1088</sup>	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 <sup>1087</sup>	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 <sup>1096</sup>	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 <sup>1097</sup>	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 <sup>1099</sup>	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 <sup>1098</sup>	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 <sup>1095</sup>	2018	2	RCT, blinded	Birch and grass pollen induced AR, n=60: -Aluminum hydroxide adsorbed, birch- or grass-pollen vaccine -Placebo	-Total nasal symptom score -NPT -Serum IgG4/IgE level -Rescue medication use -Adverse events	-Improvement in symptoms -Reduction in nasal reactivity -Increased IgG4 level -Transient increase in IgE level -Safe to inject two different allergens concurrently
Hylander et al <sup>1094</sup>	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 <sup>1093</sup>	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 <sup>1089</sup>	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 <sup>1092</sup>	2013	2	RCT, blinded	Grass pollen induced AR, n=45: -Six injections of 1000 SQU of depot grass pollen extract at a minimal interval of 14 days -Three injections of 1000 SQU followed by three injections of placebo -Six injections of placebo	-CSMS -Global seasonal assessment -RQLQ	ILIT produced immunological changes but no improvement in symptoms
Senti et al <sup>1091</sup>	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 <sup>1090</sup>	2008	2	RCT, open	Grass pollen induced AR, n=165: -Three 0.1-ml injections with 1000 SQU of aluminum hydroxide-adsorbed grass pollen extract injected into lymph node at day 0 and after 4 and 8 weeks	-Seasonal allergic symptoms by VAS -Adverse events -Safety of injections -Rescue medication use -SPT -Grass-specific IgE levels	ILIT enhanced safety and efficacy of immunotherapy and reduced treatment time from 3 years to 8 weeks

				-54 subcutaneous injections over 3 years (cumulative dose of 4,031,540 SQU).		
Wang et al <sup>1100</sup>	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 <sup>1102</sup>	2017	4	Pilot study, open, no control group	House dust mite, cat, and dog induced AR, n=11: -Aluminum hydroxide adsorbed, <i>D. farinae</i> , <i>D. pteronyssinus</i> , 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 <sup>1103</sup>	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

1 LOE=level of evidence; SRMA-systematic review and meta-analysis; ILIT=intralymphatic immunotherapy;  
2 SCIT=subcutaneous immunotherapy; CSMS=combined symptom-medication score; VAS=visual analog scale;  
3 QOL=quality of life; IgE=immunoglobulin E; IgG4=immunoglobulin G4; RCT=randomized controlled trial; NPT=nasal  
4 provocation test; AR=allergic rhinitis; SQU=standardized quality units; RQLQ=Rhinoconjunctivitis Quality of Life  
5 Questionnaire; SPT=skin prick test; SNOT-20=Sinonasal Outcome Test

6  
7

#### 8 XI.D.9. Other forms of immunotherapy – oral, nasal, inhaled

9

10 Oral, nasal, and inhaled (intra-bronchial) routes of AIT administration for AR to bypass some challenges  
11 of SCIT, including resource utilization and discomfort. Today, SCIT remains commonly used while these  
12 alternative techniques have been largely supplanted by SLIT and are relegated to primarily historical  
13 significance.<sup>758</sup>

14

15 Oral, nasal, and inhaled AIT involve the topical absorption of allergen extracts via the oral  
16 cavity/gastrointestinal tract, nasal cavity, or bronchial mucosa, respectively. RCTs have evaluated  
17 oral/gastrointestinal AIT for the treatment of birch,<sup>1104</sup> cat,<sup>1105</sup> and ragweed<sup>1106</sup> allergy without a

1 significant decline in nasal symptoms, improvement in provocation testing, or reduction in medication  
2 utilization. Moreover, oral/gastrointestinal allergen administration requires extract concentrations  
3 approaching 200-times greater than SCIT, and is associated with adverse gastrointestinal side  
4 effects.<sup>758,1105</sup> In contrast to AR, the efficacy of oral/gastrointestinal immunotherapy has been  
5 demonstrated for the treatment of food hypersensitivity.<sup>1107</sup> [TABLE XI.D.9.]

6  
7 Oral mucosal immunotherapy (OMIT) is an alternative form of AIT distinct from both SLIT and  
8 oral/gastrointestinal administration. OMIT utilizes a glycerin-based toothpaste vehicle to introduce  
9 antigen to high-density antigen processing oral Langerhans cells in the oral vestibular and buccal  
10 mucosa.<sup>1108</sup> Theoretical benefits include induction of immune tolerance using lower antigen  
11 concentrations, decreased local side effects and higher adherence versus SLIT.<sup>1109</sup> Currently, OMIT has  
12 been investigated in a single pilot study versus SLIT with findings of clinically significant improvements in  
13 disease specific QOL measures and a significant rise in specific IgG4 over the first six months of  
14 treatment.<sup>1110</sup> No adverse events were reported, and there were no significant differences between  
15 outcome measures for both treatment arms.<sup>1110</sup> Further study is needed to define the role of OMIT in  
16 the treatment of AR.

17  
18 Local nasal AIT has been established as an effective and well-tolerated approach for the treatment of  
19 pollen and HDM hypersensitivity in adults.<sup>1111,1112</sup> However, high rates of local adverse reactions have  
20 been identified in pediatric patients and may limit patient compliance, with one study finding that 43.9%  
21 of children abandoned this treatment option within the first year of therapy.<sup>1069</sup> No high quality studies  
22 of inhaled/intra-bronchial AIT exist for the treatment of AR, with current studies limited to the  
23 treatment of allergic asthma.<sup>1113</sup>

24  
25 Current evidence suggests limited utility of oral/gastrointestinal, nasal, and inhaled AIT in the treatment  
26 of AR due to limited efficacy, increased adverse events, and poor treatment compliance. However, OMIT  
27 represents a possible alternative to SCIT/SLIT warranting further study.

28  
29 **Aggregate grade of evidence:** B (Level 2: 3 studies, level 3: 3 studies; TABLE XI.D.9.)

30 **Benefit:** OMIT and local nasal AIT represent alternative AIT administration methods for individuals who  
31 are unable to comply with SCIT or SLIT treatment regimens. Oral AIT has not consistently shown benefit  
32 for the treatment of AR. Inhaled AIT has not demonstrated benefit for the treatment of AR.

33 **Harm:** OMIT may be associated with increased cost to patients due to non-standard preparation  
34 methods. Oral AIT is associated with increased risk of gastrointestinal side effects and treatment

1 noncompliance and has not consistently demonstrated benefit for AR symptoms. Inhaled AIT has not  
 2 shown benefit for AR.  
 3 **Cost:** Moderate.  
 4 **Benefits-harm assessment:** OMIT equivocal to SLIT; possible benefit for local nasal AIT with low risk for  
 5 harm; balance of harm over benefit for oral AIT and inhaled AIT.  
 6 **Value judgments:** While a single study has demonstrated OMIT to be non-inferior to SLIT in objective  
 7 and subjective patient outcomes, further study of OMIT is needed to substantiate these results prior to  
 8 widespread clinical use. Local nasal AIT may have utility for the treatment of AR not associated with  
 9 additional atopic symptoms; however, further study is needed to demonstrate clinical efficacy. Oral AIT  
 10 and inhaled IT do not appear to be beneficial for the treatment of AR.  
 11 **Policy level:** Option for OMIT as an alternative to SCIT or SLIT, pending additional studies. Local nasal AIT  
 12 has not shown benefit as alternative to SCIT or SLIT at present, further study may find benefit for  
 13 patients with AR without additional atopic symptoms. Recommend against oral AIT. Recommend against  
 14 inhaled AIT.  
 15 **Intervention:** OMIT may be presented as an option for the administration of AIT in patients unable to  
 16 tolerate SCIT or SLIT; further study is encouraged. Local nasal AIT has not yet shown clinical efficacy for  
 17 the treatment of AR relative to conventional forms of immunotherapy; further study may yet find  
 18 benefit. Oral AIT and inhaled AIT do not appear to be effective for the treatment of AR.  
 19

20 **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 <sup>1106</sup>	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 <sup>1105</sup>	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 <sup>1104</sup>	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 <sup>1110</sup>	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 <sup>1111</sup>	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 <sup>1112</sup>	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

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; AIT=allergen-specific immunotherapy;  
 2 NPT=nasal provocation test; sIgG=specific immunoglobulin G; SPT=skin prick test; sIgE=specific immunoglobulin E;  
 3 CPT=conjunctival provocation test; OMIT=oral mucosal immunotherapy; SLIT=sublingual immunotherapy;  
 4 IgE=immunoglobulin E; QOL=quality of life; ICAM=intracellular adhesion molecule; ECP=eosinophil cationic protein  
 5 \*LOE downgraded due to small sample size  
 6  
 7

8 **XI.D.10. Combination therapy – monoclonal antibody (biologic) therapy and subcutaneous**  
 9 **immunotherapy**

10  
 11 There are currently six biologics/monoclonal antibodies approved by the US FDA for the treatment of  
 12 asthma and allergic diseases: omalizumab (anti-IgE), mepolizumab (anti-IL5), reslizumab (anti-IL5),  
 13 benralizumab (anti-IL5 $\alpha$ ), dupilumab (anti-IL4R $\alpha$ ) and tezepelumab (anti-TSLP). Omalizumab,  
 14 mepolizumab, and dupilumab are also approved for the treatment of CRSwNP, and benralizumab is  
 15 pending approval for this indication.<sup>1114</sup>

16  
 17 None of the six biologics are approved as an adjunctive therapy to AIT. However, there have been  
 18 several studies examining the concomitant use of AIT with omalizumab. The only other biologic to be  
 19 studied in this manner is dupilumab, and only in a single study. In a Phase 2a, multicenter, double-blind,  
 20 placebo-controlled, parallel-group study conducted in 103 adults with grass pollen-induced seasonal AR,  
 21 patients were randomized 1:1:1:1 to SCIT, dupilumab (300 mg every 2 weeks), SCIT plus dupilumab, or

1 placebo. SCIT was administered using an 8-week cluster protocol (escalating doses of 1 to 3 SCIT  
2 injections weekly to approximately 20µg Phl p 5) followed by 8 weeks of maintenance injections. The  
3 investigators found that 16 weeks of SCIT plus dupilumab may improve SCIT tolerability but did not  
4 incrementally reduce post-allergen challenge nasal symptoms compared with SCIT alone.<sup>413</sup> [TABLE  
5 **XI.D.10.**]  
6

7 The remainder of this section will focus on the efficacy and safety of the combination of omalizumab  
8 plus AIT. Prior to many of the studies examining the combination, omalizumab as a standalone therapy  
9 was shown to be effective for the treatment of seasonal and perennial AR.<sup>403,404</sup>  
10

11 The first clinical trial that investigated the effects of omalizumab plus AIT was conducted by Kuehr et  
12 al.<sup>415</sup> In this double-blind placebo-controlled multisite RCT, 221 patients aged 6-17 years with moderate  
13 to severe AR and sensitization to birch and grass pollen were randomized to one of four different  
14 treatments: SCIT (either grass or birch pollen), starting at least 14 weeks before the local birch pollen  
15 season and after the 12-week SCIT titration phase, and either omalizumab or placebo therapy was  
16 added. This combination therapy with SCIT and omalizumab or placebo lasted 24 weeks. Combination  
17 therapy with omalizumab reduced symptom load over the 2 pollen seasons (birch and grass) by 48%  
18 over SCIT alone ( $p < 0.001$ ). Combination therapy also reduced the need for rescue medication, days with  
19 allergy symptoms and symptom severity compared with SCIT alone ( $p < 0.001$ ). A safety analyses of these  
20 data indicated that redness and swelling at the SCIT injection sites appeared significantly more often in  
21 the placebo group versus the omalizumab group ( $p < 0.05$ ) suggesting a positive effect of omalizumab on  
22 local reactions induced by SCIT.<sup>1115</sup> Subgroup analysis of grass allergic patients confirmed the primary  
23 study results.<sup>1116</sup>  
24

25 Because omalizumab reduces free IgE resulting in a decrease in the high affinity IgE receptor, FcεR1,  
26 pretreatment with omalizumab should allow for safer and more effective AIT.<sup>1117,1118</sup> Casale et al<sup>414</sup>  
27 conducted a 3-center, double-blind placebo-controlled RCT in patients with ragweed-induced seasonal  
28 AR to examine whether omalizumab given 9 weeks before rush SCIT (1-day rush, maximal dose 1.2-  
29 4.0µg Amb a 1), followed by 12 weeks of dual omalizumab and SCIT, is safer and more effective than  
30 AIT alone. Patients receiving both omalizumab and SCIT showed a significant improvement in severity  
31 scores during the ragweed season compared with those receiving SCIT alone (0.69 vs 0.86;  $p = 0.044$ ).  
32 Omalizumab pretreatment resulted in fewer adverse events during rush SCIT, and a post hoc analysis



1 found a five-fold decrease in risk of anaphylaxis caused by ragweed SCIT (SCIT alone 25.6% vs SCIT with  
 2 omalizumab 5.6%;  $p=0.03$ ). The combination also resulted in prolonged inhibition of allergen-IgE binding  
 3 compared with either treatment alone, events that might contribute to enhanced efficacy.<sup>957</sup>

4  
 5 Kopp et al performed a double-blind, placebo-controlled, multicenter RCT of omalizumab vs placebo in  
 6 combination with depigmented SCIT during the grass pollen season in patients with seasonal AR and co-  
 7 morbid seasonal allergic asthma. Omalizumab or placebo was started 2 weeks before SCIT, and the  
 8 entire treatment lasted 18 weeks. Combination therapy reduced daily symptom load by 39% ( $p<0.05$ ),  
 9 improved control of rhinoconjunctivitis and asthma, and improved QOL, but no significant  
 10 improvements in SCIT safety were observed.<sup>1119,1120</sup>

11  
 12 Massanari et al<sup>1121</sup> conducted a study to evaluate the efficacy of omalizumab in improving the safety and  
 13 tolerability of SCIT given to a high-risk population of adults with persistent asthma uncontrolled on  
 14 inhaled corticosteroids. This multicenter, double-blind, parallel-group study randomized patients to  
 15 treatment with omalizumab or placebo for eight weeks, after which they received SCIT to at least 1 of 3  
 16 perennial aeroallergens (cat, dog, HDM) according to a 4-week, 18-injection cluster regimen, followed  
 17 by 7 weeks of maintenance therapy. Use of omalizumab was associated with 50% fewer systemic allergic  
 18 reactions to AIT and enabled more patients to achieve the target immunotherapy maintenance dose.

19  
 20 **Aggregate grade of evidence:** B (Level 2: 5 studies; **TABLE XI.D.10.**)

21 **Benefit:** Improved safety of accelerated cluster and rush SCIT protocols, with decreased symptom and  
 22 rescue medication scores among a carefully selected population.

23 **Harm:** Financial cost and low risk of anaphylactic reactions to omalizumab.

24 **Cost:** Moderate to high.

25 **Benefits-harm assessment:** Preponderance of benefit over harm.

26 **Value judgments:** Combination therapy increases the safety of SCIT, with decreased systemic reactions  
 27 following cluster and rush protocols. Associated treatment cost benefits must be considered. While two  
 28 high-quality RCTs have demonstrated improved symptom control with combination therapy over SCIT or  
 29 anti-IgE alone, not all patients will require this approach. Rather, an individualized approach to patient  
 30 management must be considered, with evaluation of alternative causes for persistent symptoms, such  
 31 as unidentified allergen sensitivity. Also, the studies did not compare optimal medical treatment of AR  
 32 (INCS + antihistamine with allergen avoidance measures) to combination therapy versus SCIT alone. The  
 33 current evidence does not support the utilization of combination therapy for all patients failing to  
 34 benefit from SCIT alone.

35 **Policy level:** Option

36 **Intervention:** Current evidence supports that anti-IgE may be beneficial as a premedication prior to  
 37 induction of cluster or rush SCIT protocols, and combination therapy may be advantageous as an option  
 38 for carefully selected patients with persistent symptomatic AR following AIT. However, at the time of

1 this writing, biologic therapies are not approved by the US FDA for AR alone. An individualized approach  
 2 to patient management must be considered.

3

4 **TABLE XI.D.10. Evidence table – Combination monoclonal antibody (biologic) therapy and**  
 5 **subcutaneous immunotherapy for allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Corren et al <sup>413</sup>	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 <sup>1121</sup>	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 <sup>1119,1120</sup>	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 <sup>414</sup>	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 <sup>415</sup>	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

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy;  
2 AUC=area under the curve; TNSS=Total Nasal Symptom Score; QOL=quality of life

### 5 XI.D.11. Efficacy considerations for immunotherapy

#### 6 XI.D.11.a. Extract factors

##### 7 XI.D.11.a.i. Allergen standardization and heterogeneity

8  
9 Although the efficacy of AIT is well-established, one factor that limits its widespread application is the  
10 heterogeneity of natural allergen extracts. Maintenance of product-specific standardization (or batch-to-  
11 batch consistency) and cross-product standardization (or consistency among products from different  
12 manufacturers) both pose unique challenges. This is due, in large part, to the natural origin of allergen  
13 product from biologic sources.<sup>799,800</sup>

14  
15 Traditionally, the active ingredients of AIT extracts have been mixtures of crude proteins and allergens  
16 extracted from biological sources, such as pollens, animal dander or HDM. In fact, prior to the 1970s it  
17 was common practice for allergists to manufacture their own extracts using allergen materials provided  
18 by regional suppliers.<sup>840</sup> Understandably, this resulted in a high degree of variability among allergen  
19 extracts.

20  
21 Even now with extraction methods subject to regulatory standards, allergen extracts remain  
22 heterogeneous. Today, allergens are still manufactured by extracting mixtures of allergen and other  
23 proteins from biological sources. Impurities in source materials may exist, and there is biologic variability  
24 in the raw material. While there is inherent variance in the product related to the sourcing and  
25 collection of allergenic materials, the extraction process has become more standardized across the  
26 industry.<sup>1122</sup> Extraction typically occurs using Coca solution (physiologic saline, bicarbonate buffer and  
27 phenol) with or without glycerin. All allergen extracts must be sterilized and must contain bacteriostatic  
28 and fungistatic preservative. In the US, manufacturers typically use phenol at 0.2% to 0.5% with or  
29 without 50% glycerin. These extracts may then be used unmodified, as is the case with most US extracts,  
30 or they may be treated with aldehydes and then processed with or without an adjuvant, such as  
31 aluminum hydroxide, as is the case with a majority of European SCIT extracts.<sup>799,840</sup>

32  
33 In the US, the CBER is responsible for the regulation of allergenic extracts. Two important features of  
34 CBER's regulatory program have focused on the establishment of safe, consistent allergen  
35 manufacturing processes, as well as allergen standardization. The primary purpose of allergen

1 standardization is to characterize the biologic potency of allergen extracts in a consistent manner. CBER  
2 mandates which test defines potency and the unitage by which potency is assigned. For example, one  
3 allergen may have potency determined by ELISA, while another may be determined by IDT (ID<sub>50</sub>EAL).  
4 These standardization practices then result in potency measurements in either BAU or AU. This aids in  
5 decreasing variability among lots as well as across manufacturers. In the US, 19 allergen extracts are  
6 currently standardized. These include HDM, cat pelt and cat hair, grasses, ragweed, and venoms. A  
7 majority of allergens in the US remain non-standardized and carry labeled units (PNU or weight/volume)  
8 that do not correlate with biologic activity or potency.<sup>800</sup> One caveat to CBER's standardization effort is  
9 the fact that potency units are typically assigned based on only one or two major allergen proteins, such  
10 as Fel d 1 for cat or Amb a 1 for ragweed. Even with strides made toward standardization, limitations  
11 persist and CBER continues to investigate novel approaches toward determining extract potency.

12  
13 Further complicating efforts to minimize antigen heterogeneity and facilitate intercontinental evidence-  
14 based recommendations, US standardization efforts are difficult to compare with European and other  
15 global standardization practices. In fact, standardization in Europe is largely based on in-house  
16 references, and different units based on biological activity are utilized.<sup>840</sup> Since no international  
17 consensus is established for the standardization of extracts, comparison of different products is difficult,  
18 and this variability interferes with intelligent interpretation of published studies across the continents.  
19 The CREATE project aimed to support the introduction of major allergen-based standardization using  
20 recombinant or purified natural allergens as reference materials, as well as to validate existing ELISA  
21 tests for the measurement of major allergens.<sup>806</sup>

22  
23 One additional evolving challenge is the practice (more widespread in Europe) of modifying aeroallergen  
24 extracts via formulation with adjuvants or allergoids, as well as the use of recombinant allergens. While  
25 these novel approaches to allergen preparation may ultimately lead to improved safety and efficacy of  
26 AIT, there is currently no sufficient evidence to show clear advantage over the use of crude allergen  
27 extract in a majority of cases.<sup>809</sup> These modifications further contribute to questions regarding the  
28 impact on efficacy of AIT, as well as allergen standardization and heterogeneity. (*See Section XI.D.4.*  
29 *Allergen Extracts for additional information on this topic.*)

30  
31 [XI.D.11.a.ii. Multi-allergen immunotherapy](#)  
32

1 The approach to treatment of polysensitized patients has been the subject of international debate. In  
2 the US, it is common practice for allergists to first characterize a sensitization profile, and subsequently  
3 provide multi-allergen immunotherapy, whereby several allergen extracts are administered  
4 simultaneously throughout the treatment course. Conversely, a common practice in Europe entails  
5 identification of the most clinically problematic allergen followed by single-allergen  
6 administration.<sup>758,1123</sup> If a single allergen cannot be identified as the predominant culprit for allergic  
7 symptoms, additional extracts may be given so long as they are administered at separate sites with at  
8 least 30-minute intervals.<sup>1124,1125</sup> The Allermix survey conducted across 16 countries in 2016 revealed  
9 that 98% of providers reported management of polyallergic patients. Approximately 58% of these  
10 providers used single-allergen immunotherapy while the remaining 42% used multi-allergen  
11 immunotherapy.<sup>1126</sup>

12  
13 Given that polysensitized patients are not necessarily polyallergic, the overuse and efficacy of multi-  
14 allergen immunotherapy has been questioned. Skin testing or sIgE blood tests may be positive but may  
15 not correlate with clinical symptoms or disease. Furthermore, positive testing may reflect cross-  
16 reactivity with proteins within other allergens that are not associated with symptoms. CRD may play an  
17 important role in clarifying the primary sensitizations but is not widely available.<sup>1127</sup> The multi-allergen  
18 approach is scientifically supported by four double-blind placebo-controlled RCTs from the 1960s to  
19 1980s (2 studies with AR). These trials demonstrated significant improvement in patients who received  
20 mixtures of multiple, unrelated allergen extracts, but these studies were done prior to better  
21 standardization of extracts.<sup>1128-1131</sup> More recent studies based in Spain have also supported multi-  
22 allergen immunotherapy.<sup>1132,1133</sup> A SR in 2009 evaluated 13 multi-allergen immunotherapy studies (11  
23 SCIT, 1 SLIT and 1 both) and corroborated that co-administration of two extracts is in fact clinically  
24 effective.<sup>1134</sup> Nevertheless, the results were less clear when more than two extracts were administered  
25 contemporaneously, a practice often used by US allergists. In fact, a survey comprising 670 patients  
26 across 6 US and Canadian practices reported a mean of 18 extracts in their mixtures.<sup>1135,1136</sup>

27  
28 Although few prior studies have directly evaluated multi-allergen immunotherapy compared to single-  
29 allergen immunotherapy in polysensitized AR patients, there is growing evidence that the efficacy of  
30 these two strategies may not differ. Potential limitations in multi-allergen SLIT were highlighted in a  
31 previous double-blind placebo-controlled RCT in which efficacy outcomes were suboptimal compared to  
32 single-allergen SLIT.<sup>1019</sup> Ortiz et al<sup>1017</sup> recently demonstrated that despite significant improvement in

1 allergic symptoms across all subject groups, there was no significant difference observed in efficacy of  
2 single-allergen SLIT versus pauci-allergen (3-6 antigens) or multi-allergen SLIT in polysensitized patients.  
3 Additionally, Wang and Shi<sup>892</sup> concluded that single-allergen SLIT response is comparable to multi-  
4 allergen SCIT in children with AR secondary to HDM.<sup>20</sup> On the other hand, several studies, including a  
5 meta-analysis for HDM, have substantiated comparable efficacy of single-allergen immunotherapy in  
6 monosensitized and polysensitized AR patients.<sup>1011,1018,1021,1036,1137-1139</sup>

7

8 A clear knowledge gap is the need for further evidence to support the use of multi-allergen  
9 immunotherapy in polysensitized patients.<sup>1123</sup> Unfortunately, well-controlled studies in the  
10 polysensitized population are difficult to design and conduct. Sensitization profiles can vary drastically  
11 among patients, resulting in a heterogeneous population that is difficult to investigate. Moreover,  
12 comparison of single-allergen immunotherapy versus multi-allergen immunotherapy is challenging as  
13 each unique polysensitization profile contains a different single dominant allergen to target which in  
14 turn may be difficult to distinguish clinically. At the time of this writing, there were 11 active or  
15 recruiting clinical trials investigating efficacy of AIT in AR patients (5 SCIT, 2 SLIT, 1 both SCIT and SLIT  
16 and 3 ILIT).<sup>1140</sup> None of the studies compare single-allergen to multi-allergen IT.

17

18 If multi-allergen SCIT is administered, several considerations must be accounted for prior to the mixing  
19 process.<sup>1125,1141</sup> First, one must be careful to maintain therapeutic amounts of each allergen in the  
20 mixture. Second, the chosen preservative must be compatible with all allergens in the mixture.  
21 Moreover, attention must be paid to the proteolytic activity of fungal and some insect body extracts.  
22 When extracts with greater proteolytic activity are mixed with certain allergens susceptible to  
23 proteolysis such as pollen, mite, and animal dander allergens, the effective concentrations in the extract  
24 mixture may be reduced.<sup>1142,1143</sup>

25

26 Given the widely varied practice patterns and challenges inherent in the study of polysensitized  
27 individuals, the evidence supporting multi-allergen immunotherapy is not as strong as that supporting  
28 single-antigen immunotherapy strategies. Although it is difficult to directly compare multi-allergen and  
29 single-allergen treatment strategies, the literature strongly supports the efficacy of single-antigen  
30 immunotherapy even in polysensitized patients, while there remains a need for more careful analysis of  
31 the efficacy of multi-allergen immunotherapy. (*See Section XI.D.11.b.ii. Polysensitization for additional*  
32 *information on this topic.*)

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## 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<sub>4</sub> levels.<sup>893,894,1042,1144</sup> These effects remained durable 3 years after completing a 3-year course of SCIT.<sup>1145</sup>

In children, several studies have demonstrated AIT has short-term and long-term effectiveness, including decreasing the dose of inhaled corticosteroids in asthmatic patients.<sup>1146-1151</sup> Literature supports the efficacy of both SCIT and SLIT in the pediatric population.<sup>777</sup> 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.<sup>1152,1153</sup> SLIT using a grass tablet was shown to have a similar asthma prevention effect in the GAP [Grass immunotherapy tablet Asthma Prevention] trial.<sup>768</sup> 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.<sup>1154</sup> 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.<sup>765</sup>

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

1 was higher in children (0.2%) but not when adjusted for asthma, gender and phase of SCIT.<sup>1155</sup> In a  
2 Chinese population, systemic reactions were more common in younger children (3.28% of injections)  
3 compared with adolescents (1.47% of injections) but were treatable without requiring  
4 hospitalization.<sup>1156</sup> AIT is not customarily initiated in infants and toddlers given fears of the child not  
5 being able to communicate symptoms, in particular those of systemic reactions, and concerns that  
6 injections may be poorly tolerated in very young children.<sup>758</sup> Every potential pediatric AIT case merits  
7 consideration of balancing the potential benefits versus risks and inviting child and parent to participate  
8 in shared decision-making to express their values and preferences regarding the trade-offs of AIT, which  
9 are likely quite individualized. Similar processes and considerations are recommended for older adults.

10

#### 11 [XI.D.11.b.ii. Polysensitization](#)

12

13 Polysensitization, or sensitization to more than one allergen, is common in the general population, and a  
14 factor which potentially challenges AIT efficacy. In an effort to identify the prevalence of sensitization in  
15 the general population, a 2010 study showed that among 11,355 participants in the first ECRHS, 57-  
16 67.8% of the population was not sensitized to any test allergens, 16.2-19.6% were monosensitized, and  
17 23.8-25.3% were polysensitized.<sup>1157</sup> Similarly, the National Health and Nutrition Examination Survey III  
18 (NHANES) studied skin sensitization to common aeroallergens in the US general population. Among the  
19 10,863 participants 45.7% were not sensitized to any test allergens, 15.5% were monosensitized, and  
20 38.8% were polysensitized.<sup>1158</sup> Hence, polysensitization appears to be more prevalent than  
21 monosensitization in the general population. More recent evidence suggests that polysensitization may  
22 be an entirely distinct phenotype compared to monosensitization, possibly predictive of more severe  
23 comorbid allergic disease expression.<sup>1125,1159,1160</sup>

24

25 Once polysensitization is established via skin testing or sIgE testing, the conundrum facing allergists is  
26 whether this polysensitization represents true polyallergy. To have polyallergy, the individual must have  
27 relevant symptoms upon exposure to 2 or more specific, sensitizing allergens.

28

29 In some patients showing positive test responses to multiple allergens, this may be caused by cross-  
30 reactivity to highly conserved proteins, or panallergens. These related proteins, which have highly  
31 conserved sequence regions and structures, trigger IgE cross-recognition. Separating the clinical  
32 relevance of positive test responses to pollens known to demonstrate cross-reactivity can be challenging  
33 because the seasonality of symptoms may overlap.<sup>1161</sup> New technologies focused on component



1 resolved diagnostics may prove useful in determining whether cross-reactive allergens are the cause of  
2 polysensitization, and may help to direct AIT decisions.<sup>1162</sup>

3  
4 The issue of whether the polyallergic patient is best treated with more than one (or even several)  
5 clinically relevant allergens versus a single allergen deemed most responsible for the patient's  
6 symptoms, is a subject of debate, and one characterized by trans-continental practice variations. The  
7 predominant approach in the US is to treat the polyallergic patient with multiple allergens  
8 simultaneously, while the European approach is to focus AIT on one, or at most two, clinically significant  
9 allergens.<sup>1123</sup>

10  
11 While the published literature comparing the efficacy of single- or multi-allergen immunotherapy in the  
12 polysensitized patient continues to evolve, there are published guidelines which can help to direct  
13 practical decision making. Not unexpectedly, these guidelines reflect regional bias. The 2018 EAACI  
14 Guidelines on Allergen Immunotherapy specify that polysensitized patients who are monoallergic  
15 receive AIT only for the specific allergen driving their symptoms. The EAACI guidelines further specify  
16 that for the polyallergic patient sensitized to two homologous allergens (i.e., two grass pollens), a single  
17 allergen preparation or a mixture of 2 homologous allergens may be used, and for the polyallergic  
18 patient sensitized to allergens which are not homologous, AIT should be limited to 1 or 2 of the clinically  
19 most important allergens administered separately at distinct anatomic locations and separated by 30-60  
20 minutes.<sup>757</sup> Similarly, the 2010 Global Allergy and Asthma European Network (GA<sup>2</sup>LEN)/EAACI pocket  
21 guide does not recommend the use of allergen mixtures in AIT.<sup>1124</sup> The Practice Parameter Third Update  
22 guidelines developed by the Joint Task Force<sup>758</sup> acknowledges that there have been few studies  
23 investigating the efficacy of multiallergen SCIT, and that these studies have considerable heterogeneity,  
24 yielding conflicting results. The Practice Parameter emphasizes the importance of treating patients with  
25 only *relevant* allergens but does not discourage prescribing multi-allergen immunotherapy in properly  
26 selected patients. (*See Section XI.D.11.a.ii. Multi-allergen Immunotherapy for additional information on*  
27 *this topic.*)

#### 28 29 [XI.D.11.b.iii. Adherence to therapy](#)

30  
31 Adherence to AIT is variable and dependent upon route of administration, SLIT versus SCIT, dosing  
32 frequency/regimen, patient characteristics, and AIT-associated adverse events. A review of the literature  
33 indicates no reported prospective double-blind, placebo-controlled RCT examining and/or comparing

1 the adherence of SLIT versus SCIT as the primary endpoint. However, there are data on the adherence of  
2 AIT in prospective double-blind, placebo-controlled RCT of clinical efficacy, but these data are somewhat  
3 artificial in that adherence is closely monitored and patients are selected based on criteria that would  
4 promote better compliance to therapy. Furthermore, since optimal efficacy of either SLIT or SCIT is not  
5 appreciated until a minimum of two and optimally three years of therapy, adherence rates must be  
6 determined over a prolonged period. AIT adherence is reported to be much lower in real-life studies  
7 versus clinical trials. For example, in an analysis of sales figures from two SLIT manufacturers in Italy that  
8 account for more than 60% of the Italian immunotherapy market, sales decreased from 100% at the  
9 start to approximately 44% in the first year, 28% in the second year and 13% in the third year. This  
10 indicates that less than 20% of patients were adherent to the prescribed SLIT regimen.<sup>1163</sup>

11  
12 A non-interventional, prospective, observational, multicenter, open label study examined the adherence  
13 of 399 patients (236 adults and 163 children) with moderate-to-severe grass-induced allergic  
14 rhinoconjunctivitis to a three-year regimen of grass SLIT tablets. The authors found that only 55% of  
15 patients completed the three-year treatment period.<sup>1164</sup> These data are similar to many retrospective  
16 analyses of adherence to SLIT at the end of a 3-year regimen, ranging 10-61%<sup>1165-1167</sup> and illustrate that  
17 even though self-administration of AIT could be advantageous over injections requiring office visits,  
18 adherence is a significant problem.

19  
20 The adherence rate to SCIT regimens have also been studied in retrospective and a few prospective  
21 uncontrolled studies. In a real-world study examining claims data, 103,207 patients were reported to  
22 have at least one AIT claim, but only approximately 44% of these patients reached maintenance AIT.  
23 There was no follow-up of these patients to determine how many of the 56% that reached maintenance  
24 continued AIT for a full three years.<sup>1168</sup> A retrospective cohort analysis of a German longitudinal  
25 prescription database indicated that at the end of three years, adherence to SCIT was 35-37%, and  
26 higher than that reported for SLIT (10-18%).<sup>1169</sup> A data management retrospective study compared  
27 adherence to SCIT and SLIT at the end of three years and found that SLIT patients had a higher dropout  
28 rate (39%) versus SCIT (32.4%).<sup>1167</sup> In a retrospective analysis of a community pharmacy database, only  
29 18% of 6486 patients starting AIT reached a minimal duration of three years, 23% for SCIT and 7% for  
30 SLIT.<sup>1070</sup> A retrospective analysis compared attrition rates in patients prescribed SCIT or SLIT found at the  
31 end of the prescribed period, attrition rates were similar, 45% and 41%, respectively.<sup>1170</sup> Another

1 retrospective analysis comparing SLIT versus SCIT adherence found that only about 30% of patients  
2 completed a three-year course of either therapy.<sup>1171</sup>

3  
4 Overall, the strength of evidence is low since most studies involved retrospective analyses and none  
5 reported efficacy outcomes. However, data strongly suggest that adherence to either regimen of AIT is  
6 very low which likely results in poorer efficacy. Reasons for the poor adherence are many and include  
7 inconvenience of taking a daily medication (SLIT) or frequent office visits (SCIT), adverse events  
8 especially during the first months of therapy, cost, and perceived lack of benefit.

#### 9 10 [XI.D.11.b.iv. Pregnancy](#)

11  
12 AR and asthma affect 20-30% of women of childbearing age and are considered two of the most  
13 common medical conditions that can affect pregnancy.<sup>1172</sup> One-third of these women will suffer from  
14 worsening symptoms during pregnancy<sup>1173</sup> and up to 20% will experience exacerbations of asthma  
15 resulting in hospitalization or even death.<sup>1174</sup> AIT is an effective treatment option for AR, and its role in  
16 pregnancy continues to be investigated. The evidence regarding the efficacy and safety of AIT during  
17 pregnancy is scarce with a single large-scale prospective study published to date. In the most recent  
18 Practice Parameter update, it is stated that AIT can be continued, but not initiated, in the pregnant  
19 patient. Furthermore, if pregnancy occurs during the build-up phase and the patient has not reached a  
20 therapeutic dose, discontinuation of AIT should be considered.<sup>758</sup>

21  
22 The first study to assess the safety of AIT in pregnancy was published in 1978 by Metzger et al.<sup>1175</sup> This  
23 retrospective study analyzed the incidence of prematurity, toxemia, abortion, neonatal death, and  
24 congenital malformation in 90 atopic women who received SCIT during their pregnancy compared to a  
25 group of 147 untreated atopic mothers. No significant difference in these outcomes was found between  
26 the two groups suggesting that continuation of AIT during pregnancy was safe.

27  
28 Over the next 10 years questions regarding the safety of AIT during pregnancy continued. In a 1993  
29 study, Shaikh et al<sup>789</sup> published a retrospective study that investigated 81 atopic women who underwent  
30 SCIT during pregnancy, for a total of 109 pregnancies. Similar variables as the Metzger et al<sup>1175</sup> study  
31 were analyzed, and when compared to the control group of 60 patients (82 pregnancies) who refused  
32 AIT, the incidence of prematurity, gestational hypertension, and proteinuria were actually lower. Of  
33 note, only 7 of the 109 pregnancies initiated SCIT for the first-time during pregnancy. This study

1 supported that SCIT was not only safe during pregnancy, but control of allergies and asthma during  
2 pregnancy may decrease adverse perinatal outcomes.

3

4 To date, only one RCT has been performed to demonstrate the safety of starting SLIT in the pregnant  
5 population. Shaikh et al<sup>790</sup> separated 280 atopic women (326 total pregnancies) into one of three  
6 groups: 155 patients received SLIT during 185 pregnancies (with 24 patients receiving SLIT for the first  
7 time during pregnancy). The remaining patients were separated into two control groups, receiving  
8 either daily budesonide (group A) or rescue inhaled salbutamol (group B). The study showed no  
9 significant differences in perinatal outcomes, suggesting that both initiation and continuation of SLIT  
10 was safe during pregnancy. Although this study concludes that initiation of SLIT during pregnancy is safe,  
11 it is important to note that only 24 patients, 13% of the treatment group, fell into the initiation arm of  
12 the study.

13

14 Continuation of AIT during pregnancy has not shown to be harmful to either the mother or the fetus.  
15 There is limited data, however, to draw conclusions regarding the safety of first-time initiation of AIT  
16 during pregnancy. Lastly, no conclusion can be made regarding the effects of pregnancy on efficacy of  
17 AIT due to lack of literature.<sup>898</sup>

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## 1 XII. Pediatric considerations in allergic rhinitis

### 2 3 XII.A. History and physical exam

4  
5 As repeated exposure to allergens is required, AR takes a few years to develop in children. Food and  
6 indoor allergies are more common in children under the age of 3, with seasonal outdoor allergy risk  
7 increasing after the age of 3.<sup>1</sup> A family history of AR, atopy, or asthma is important to assess as children  
8 may be at an increased risk of developing AR or other allergic diseases.<sup>2</sup> The future development of AR  
9 should be considered in children exhibiting signs of the “allergic march”.<sup>3</sup> Certain risk factors may have a  
10 link to the development of AR in children. (*See Sections VIII. A-B. Risk Factors for Allergic Rhinitis for*  
11 *additional information on this topic.*)

12  
13 Common findings consistent with AR in children include nasal congestion, sneezing, postnasal drip,  
14 cough, sniffing, throat clearing, palatal click, and mouth breathing.<sup>4-8</sup> Defining a seasonal timeline or  
15 triggers for symptoms can help identify a cause and help determine if rhinitis is allergic or non-allergic in  
16 nature.<sup>2</sup>

17  
18 Although evidence is conflicting and variable, there are several conditions possibly associated with AR in  
19 children, which should be assessed during clinical evaluation. The most common comorbidities  
20 associated with childhood AR are asthma, conjunctivitis and AD.<sup>7</sup> Other comorbidities include  
21 rhinosinusitis, SDB, ETD, otitis media, and oral allergy syndrome.<sup>1,9-11</sup> Oral allergy syndrome may be  
22 suspected in patients with mouth itching or swelling after eating raw fruits or vegetables.<sup>9</sup>

23  
24 There is data to suggest that AR is more common in children with otitis media with effusion (OME) than  
25 those without. While the results vary based on the age of the children studied, this highlights the  
26 importance of ear evaluation during the physical exam.<sup>10,12,13</sup> (*See Section XIII.G.2. Otitis Media for*  
27 *additional information on this topic.*) Similarly, the association of adenoid hypertrophy (AH) with AR is  
28 debated, but some studies have suggested the importance of the correlation between these two  
29 diseases.<sup>10,11,14-16</sup> (*See Section XIII.F. Adenoid Hypertrophy for additional information on this topic.*) This  
30 may help to explain the association between AR and OSA in children.

31  
32 Diagnosing AR in the pediatric population may be challenging due to difficulty clearly communicating  
33 symptoms. There is also overlap of symptoms with frequent illnesses experienced in childhood, for

1 example upper respiratory infection. Diagnostic clues, which may be reported by a parent or caregiver  
2 include chapped lips from mouth breathing, fatigue, irritability, poor appetite, and attention issues.<sup>2,4</sup>

3  
4 After a complete history, there are several elements of the physical exam that may aid in diagnosis. An  
5 important aspect of the physical exam is to rule out other etiologies of nasal obstruction and rhinitis  
6 such as nasal foreign body or choanal atresia.<sup>2</sup> Some physical exam findings are similar to the adult  
7 population including posterior pharyngeal cobblestoning, clear drainage, serous middle ear effusions,  
8 and enlarged/boggy ITs.<sup>2,4</sup> Specifically in the pediatric population, “allergic” or “adenoid facies” may be  
9 present, characterized by mouth breathing, high-arched palate and dental malocclusion. Additionally,  
10 the “allergic salute” is defined as repeated rubbing of the nose, which can lead to a transverse nasal  
11 crease or “allergic crease.”<sup>17</sup> “Allergic shiners” are caused by infraorbital venous stasis and “Dennie-  
12 Morgan lines” are folds below the lower eyelids suggesting allergic conjunctivitis.<sup>2-4,6,18</sup> Voice changes  
13 including hoarseness and hyponasality are common in pediatric AR.<sup>5</sup> Anterior rhinoscopy can reveal IT  
14 bogginess, paleness and/or hypertrophy.<sup>2</sup> Nasal endoscopy has been evaluated as a tool for diagnosis in  
15 pediatric AR, with IT and MT contact with other nasal structures as predictive factors for positive SPT  
16 results.<sup>19</sup> There are no specific recommendations for the use of nasal endoscopy in children with  
17 suspected AR, but this assessment may be important in ruling out other, less common, causes of nasal  
18 obstruction or rhinitis.

19  
20 Of note, one important goal of early diagnosis of AR is to identify young children at risk of developing  
21 other allergic disorders.<sup>20</sup> Non-allergic rhinitis, viral URI, and anatomical causes of nasal obstruction  
22 should be on the differential diagnosis in children evaluated for AR.<sup>4</sup>

## 23 24 25 XII.B. Diagnostic techniques

26  
27 Allergy testing recommendations for the pediatric population are similar to those for adults. Allergy  
28 testing should be considered in children with insufficient response to medical treatment.<sup>21</sup> The EAACI  
29 Section on Pediatrics recommends that allergy testing be considered in children presenting with AR  
30 clinical symptoms and signs in order to initiate treatment and lifestyle changes, such as avoidance of  
31 allergens. Clinical practice guidelines exclude children younger than 2 years of age as causes of rhinitis  
32 may be different in this population. However, there are no age limits for allergy testing and young  
33 children are eligible.<sup>22</sup>



1  
2 The diagnosis of AR in children should be based on both clinical history and testing. Allergy testing  
3 without clinical suspicion has been shown to lead to false-positive SPT results over 50% of the time.<sup>10</sup>  
4 SPT is generally accepted as the preferred method of testing in children; it is faster and less painful than  
5 intradermal testing, and it is less expensive than in vitro serum testing.<sup>18</sup> Although intradermal testing or  
6 SPT may be considered in the pediatric population, SPT is often considered superior due to ease,  
7 minimal discomfort and timeliness of results. There are indications for in vitro testing in children as  
8 there are in adults, including skin disorders (e.g., dermatographism, dermatitis at the proposed testing  
9 site) and medication usage (e.g., inability to hold antihistamines for testing). It is also important to note  
10 that a positive SPT in a young child will result in a smaller wheal size than in an older child or adult due  
11 to relatively lower circulating IgE levels.<sup>2</sup>

12  
13 There is limited data regarding nasal eosinophil and basophil levels for the purpose of AR diagnosis.  
14 Nasal eosinophilia has been associated with AR in children but is not widely used to diagnose AR.<sup>23-26</sup>  
15 Additionally, nasal basophilic metachromic cells have shown high sensitivity for AR.<sup>2,27</sup> While there is  
16 limited data on BAT in general, and it is considered an option for AR diagnosis in adults; one small  
17 pediatric study has shown that BAT has sensitivity and specificity of 90% and 73%, respectively.<sup>28</sup>

## 18 19 XII.C. Pharmacotherapy

20  
21 Most patients with symptoms of AR will use some form of pharmacotherapy for satisfactory symptom  
22 control. The specific management of each patient is influenced by the frequency and intensity of  
23 symptoms, response to treatment, the presence of comorbid conditions as well as the patient's age and  
24 preference. Current pharmacologic options in the treatment of AR include INCS, intranasal and oral  
25 antihistamines, decongestants, mast cell stabilizers, intranasal anticholinergics and LTRAs.<sup>6,29,30</sup>

26  
27 **Children less than 2 years of age.** In this age group AR is less prevalent, but children may have frequent  
28 bouts of allergy-type symptoms including rhinorrhea, sneezing, itchy eyes, etc. which could be due to  
29 other, more common triggers, such as recurrent viral illness, AH, or rhinosinusitis. Before treating a  
30 young child for AR, other causes should be investigated and ruled out.

31  
32 The pharmacologic options for AR in children under 2 years old are limited. Second- and third-  
33 generation antihistamines such as cetirizine, levocetirizine and desloratadine, have indications down to

1 six months of age and are an option in the treatment of the young patient with AR. First-generation  
2 antihistamines (diphenhydramine, chlorpheniramine) have the disadvantage of being lipophilic and  
3 cross the brain blood barrier. Unwanted side effects of these medications make them difficult and  
4 dangerous to use and not indicated in children less than 2 years old. [TABLE II.C.]

5

6 **Children 2 years old and older.** For the older child, treatment of AR is very similar to that in the adult  
7 patient and depends largely on the frequency and severity of symptoms.

8

9 *Mild or episodic symptoms* may be treated with medications aimed at addressing the specific  
10 symptom(s). A second- or third-generation antihistamine may be used on an as needed basis for rhinitis,  
11 sneezing, and itchy watery eyes. Intranasal antihistamine preparations are another option in children  
12 over the age of 5 (azelastine 0.1%) and 6 years old (olapatadine); benefits include targeted delivery,  
13 decreased side effects, and rapid onset of action.<sup>29-32</sup> Intranasal antihistamines have been recommended  
14 over oral antihistamines in the appropriate patient population.<sup>22,29</sup>

15

16 *For persistent or moderate-to-severe symptoms*, INCS are recommended as the best single therapy in  
17 the treatment of allergic symptoms affecting QOL.<sup>6,22,29,30</sup> The effectiveness of INCS in the reduction of  
18 nasal symptoms including sneezing, itching, rhinorrhea, and congestion in children with AR has been  
19 demonstrated.<sup>33-36</sup> INCS are usually well tolerated; however, because adverse effects are possible,  
20 growth in children using INCS should be monitored and dosages should be tapered to the lowest  
21 effective dose in all patients.

22

23 INCS preparations approved for children aged 2 years and older include mometasone furoate,  
24 triamcinolone acetonide and fluticasone furoate. Most others are indicated for children aged 6 years  
25 and older, except for fluticasone propionate and beclomethasone dipropionate, which are indicated  
26 down to age 4 years.

27

28 *When response to initial INCS is suboptimal*, a second agent can be considered. Options include  
29 intranasal or oral antihistamines, combination intranasal INCS/antihistamine, or  
30 antihistamine/decongestant products. The choice should be made based on the persistent symptoms  
31 being addressed, patient preference, possible side effects and coexistent conditions. [TABLE II.C.]

32

1 LTRAs, such as montelukast, have been used in the management of AR and asthma. LTRA efficacy has  
2 been shown to be less effective than INCS, but more effective than placebo.<sup>6,29,30,37-39</sup> Due to its potential  
3 for neuropsychiatric effects, the US FDA has recommended against the use of montelukast in patients  
4 with AR in favor of other treatment options. In the latest Clinical Practice Guideline on AR published by  
5 the AAO-HNSF, montelukast is not recommended as first line therapy.<sup>22</sup>

6  
7 Cromolyn nasal spray is a mast cell stabilizer that can inhibit the allergic response. It is most effective  
8 when used as a preventive measure when allergy exposure is anticipated. It has a low side effect profile  
9 (sneezing, bad taste, etc.), but due to its short half-life must be administered 3-6 times daily. It has been  
10 approved for use in children as young as 2 years old. Though less effective than INCS or second-  
11 generation antihistamines, some parents and clinicians prefer it due to its excellent safety profile.<sup>30,40,41</sup>

12  
13 Ipratropium bromide nasal spray has been shown to decrease rhinorrhea. It has a quick but short-lasting  
14 onset of action and must be used frequently. It is not recommended as a first-line drug in AR but has  
15 had some success in patients with profuse rhinorrhea not otherwise controlled with INCS. It has been  
16 shown to be more effective when combined with a nasal steroid than when either medication is used  
17 alone in the treatment of chronic rhinitis.<sup>42</sup> It is indicated down to age 5 years.

18  
19 Oral decongestants are also a consideration in the treatment of AR, but due to their side effect profile  
20 and potential for central nervous system stimulation in the pediatric population, the risk/benefit ratio  
21 should be carefully considered when used in children between the ages of 2 and 6 year old.<sup>30,43,44</sup> Oral  
22 decongestants are not recommended in younger children. **[TABLE II.C.]**

## 23 24 XII.D. Immunotherapy

25 AIT is a treatment option when other strategies, such as avoidance and pharmacotherapy, have failed.  
27 It may also be considered for patients who cannot tolerate standard therapies, those who want to avoid  
28 prolonged used of medications, and those wishing to obtain a lasting response by modifying the  
29 immunologic process.<sup>45</sup> Consideration for AIT should only be undertaken in patients with documented  
30 sIgE response to aeroallergens correlating with the patient's allergic symptoms. As long as these  
31 recommendations are followed, AIT is an option for allergic patients regardless of age. However, due to  
32 the required environmental exposure for the development of clinically relevant sensitization(s) to  
33 aeroallergens, combined with the limited evidence for the efficacy of AIT for AR in children under 5

1 years of age, the decision to provide AIT should consider the above factors along with a discussion with  
2 the family regarding its limitations and safety concerns.

3  
4 Modalities for AIT administration include SCIT and SLIT (available in the form of a dissolvable tablet or as  
5 a liquid extract). Both options are available for adults and children, with specific age indications of SLIT  
6 tablets variable depending on the individual tablet. Usually patient demographics, preference, and  
7 treatment goals are used to guide the choice of AIT modality. For example, in young children who may  
8 be traumatized by or unable to tolerate repeated injections, and who may be unable to report early  
9 symptoms of an allergic reaction, SLIT may be considered due to its ease of administration and superior  
10 safety profile.<sup>46</sup>

11  
12 Dosing of SCIT and SLIT liquid extract is the same in the adult and pediatric populations. SLIT tablets  
13 currently available in the United States for use in children include a single grass (Timothy) tablet, a multi-  
14 grass (sweet vernal, orchard, perennial rye, Timothy, Kentucky bluegrass) tablet, and a short ragweed  
15 tablet, all indicated down to age 5 years. The HDM tablet available for adults has not received approval  
16 for pediatric use as of this writing.

17  
18 Though the literature regarding efficacy of AIT is less robust in the pediatric population, it has been  
19 shown to be effective in the treatment of AR,<sup>47-49</sup> and both SCIT and SLIT have resulted in improved  
20 control of comorbid conditions such as asthma and allergic conjunctivitis.<sup>22</sup> Of particular importance is  
21 the research that has demonstrated that AIT has the potential added benefit of decreasing the  
22 development of asthma in pediatric patients with AR, as well as reducing the onset of new allergen  
23 sensitizations.<sup>50-52</sup>

24  
25 In all populations, absolute contraindications to AIT (SCIT and SLIT) include uncontrolled or poorly  
26 controlled asthma, active autoimmune disorders, and malignancy.<sup>53</sup> EoE is also a contraindication to  
27 SLIT.<sup>54-57</sup> Special consideration should be given when treating patients with cardiovascular disease, those  
28 on  $\beta$ -blocker medications, and those with partially controlled asthma due to their impaired ability to  
29 respond to resuscitation efforts should an allergic reaction occur.<sup>45</sup>

30  
31 Challenges systematically being addressed in the practice of adult AIT extend to the pediatric  
32 population. These include the use of one or multiple allergens in the treatment of AR; whether mixtures

1 of multiple allergens can compromise efficacy; the standardization of the allergen extracts for  
 2 consistency, quality, and potency; and effective dose ranges for the pertinent allergens used.<sup>58</sup>

3  
 4

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## 1 XIII. Associated conditions

### 2 XIII.A. Asthma

#### 3 XIII.A.1. Asthma definition

4 Asthma is a common chronic lung disease comprising a heterogeneous group of phenotypes, including  
5 allergic and non-allergic, and further subtypes based on demographic, clinical and/or pathophysiological  
6 characteristics.<sup>1</sup> The definition of asthma has appreciably changed over time.<sup>2</sup> The latest Global Initiative  
7 for Asthma (GINA) Guidelines define asthma as *'a heterogeneous disease, usually characterized by chronic*  
8 *airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of*  
9 *breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory*  
10 *airflow limitation'*.<sup>3</sup>

11  
12  
13 In addition to the aforementioned respiratory symptoms, a diagnosis of asthma typically requires  
14 evidence of variable obstruction of expiratory airflow, by bronchodilator reversibility testing or bronchial  
15 hyperreactivity tests.<sup>3</sup> In clinical practice patients have a variety of clinical presentations, and when  
16 patients are well, most tests show no abnormalities.<sup>4</sup> Increasingly, asthma is being recognized as a  
17 disease of airway inflammation and disordered immunology, as well as aberrant physiology, with  
18 combinations of 'treatable traits' in different patients.<sup>5</sup> Most patients have mild or moderate disease. A  
19 small proportion (up to 10%) have severe disease that is refractory to standard inhaled medications.  
20 These patients have more severe symptoms, frequent exacerbations and need more intensive treatment  
21 regimens.<sup>6</sup>

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#### 25 XIII.A.2. Asthma association with allergic and non-allergic rhinitis

27 AR and non-allergic rhinitis have been established as important comorbidities of asthma. Increasingly,  
28 there has been a shift towards conceptualizing multimorbid chronic upper airway inflammation and  
29 asthma as a single 'unified airway' pathology affecting both the upper and lower airway.

30

31 The prevalence of comorbid AR and asthma varies. Recent population-based studies have shown rates  
32 between 20.3% and 93.5%.<sup>7-12</sup> In one study, AR was found to be an independent determinant of current  
33 asthma among adults (OR 7.72; 95% CI 6.56-9.09, p<0.001).<sup>12</sup> Some studies have shown that patients  
34 with comorbid AR tend to have poorer asthma control, a greater number of exacerbations per year, and

1 more visits to the emergency department.<sup>13-16</sup> Interestingly, the association of allergy with asthma  
 2 weakens with more severe asthma.<sup>17</sup> [TABLE XIII.A.2.]

3  
 4 Non-allergic rhinitis is also commonly associated with comorbid asthma.<sup>18,19</sup> Increasingly, asthma is  
 5 being considered a multifactorial disease with variable endotype and phenotypic presentations,  
 6 particularly with regards to aberrant type 2 inflammation, which may or may not be allergic.<sup>20,21</sup> The  
 7 functional relevance of this upper airway association can be summarized as follows:

- 8 i. In line with the unified airway hypothesis, allergen and irritant challenge to the nose and upper  
 9 airway elicits lower airway inflammation through shared immunological and neurogenic  
 10 pathways.<sup>22</sup>
- 11 ii. Nasal obstruction results in mouth breathing, which leads to reduced filtration and  
 12 humidification of inspired air, facilitating reactive lower airways.<sup>23</sup>
- 13 iii. Nasal blockage resulting in mouth breathing can be associated with breathing pattern disorders  
 14 and increased breathlessness in patients with asthma.<sup>22,23</sup>

15  
 16 Several recent molecular studies have shed light on the mechanisms underlying the phenomenon of this  
 17 multimorbidity. GWAS studies have demonstrated independent risk variants, which are common  
 18 between asthma, AR and eczema.<sup>24</sup> Moreover, gene expression analyses suggest that type 2 mediated  
 19 inflammation has a similar molecular basis across disease types.<sup>25</sup> These findings underscore the  
 20 proposed ‘one airway’ model, which recognizes similar disease mechanisms occurring in both the upper  
 21 airway and the lower airway.<sup>26</sup>

22  
 23 In summary, upper airway symptoms can impact asthma disease control and patient QOL.<sup>27</sup> Assessment  
 24 and treatment via a multidisciplinary approach, encompassing pulmonologists, allergists, immunologists,  
 25 otolaryngologists/rhinologists, should be considered.

26  
 27 **Aggregate grade of evidence:** B (Level 1: 3 studies, level 2: 3 studies, level 3: 3 studies, level 4: 8 studies;  
 28 **TABLE XIII.A.2.)**

29  
 30 **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 <sup>28</sup>	2019	1	Meta-analysis of cross-	General public, asthma patients, n=3182	Asthma+AR prevalence	-Asthma and AR are often comorbid diseases

			sectional studies			-Asthma+AR prevalence 39%
Tohinidik et al <sup>8</sup>	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 <sup>29</sup>	2018	1	Meta-analysis of cross-sectional studies	General public	Prevalence of AR in pediatric asthma patients	-54.9% prevalence of AR in pediatric asthma -Prevalence of AR higher in children with asthma than prevalence of asthma in children with AR
Machluf et al <sup>9</sup>	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 <sup>10</sup>	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 <sup>11</sup>	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 <sup>30</sup>	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 <sup>18</sup>	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 <sup>31</sup>	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 <sup>32</sup>	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 <sup>7</sup>	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 <sup>33</sup>	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 <sup>34</sup>	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 <sup>35</sup>	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 <sup>12</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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

1 Relevant studies prior to 2017 are included in the listed meta-analyses.  
2 LOE=level of evidence; AR=allergic rhinitis; OR=odds ratio; NAR=non-allergic rhinitis

3  
4

### 5 XIII.A.3. Allergic rhinitis and asthma – association of risk factors

6

7 Up to 30% of patients with AR develop asthma.<sup>38</sup> Indeed, several large epidemiological studies have  
8 demonstrated that AR is an independent risk factor for developing asthma. Specifically, persistent AR  
9 appears to portend a significantly greater risk for development of asthma compared to intermittent  
10 AR.<sup>39</sup> [TABLE XIII.A.3.]

11

12 The Children’s Respiratory Study showed that there is a doubling of the risk of developing asthma by age  
13 11 when AR is diagnosed by a physician during infancy.<sup>40</sup> Rhinitis is also a significant risk factor for adult-  
14 onset asthma whether patients are atopic or non-atopic.<sup>41-44</sup> In contrast, in childhood, asthma is  
15 frequently associated with allergy.<sup>40,45</sup> Limited data fail to demonstrate a relationship between a  
16 diagnosis of AR and severity of comorbid asthma.<sup>46</sup> Nevertheless, data on whether the severity of AR  
17 itself impacts the prevalence of comorbid asthma remains conflicting.<sup>47,48</sup>

18

19 Asthma and AR have overlapping risk factors. Aeroallergen sensitization may be the most important and  
20 has been demonstrated among adults and children across different geographic regions and populations  
21 around the world.<sup>39,49,50</sup> Indeed, most inhaled allergens are associated with both nasal and bronchial  
22 hyperresponsiveness.<sup>51</sup> Occupational rhinitis is also a risk factor for occupational asthma caused by high-  
23 molecular-weight agents.<sup>52</sup> Genetic polymorphisms common to AR and asthma, such as unique subtypes  
24 of deregulated circulating microRNAs, may also provide a mechanistic link between the two disease  
25 processes.<sup>53</sup>

26

27 There is growing evidence that exposure to traffic related air pollutants, (i.e., black carbon, NO<sub>2</sub>, NO,  
28 SO<sub>2</sub>, CO, CO<sub>2</sub>, PM) may increase the risk of developing both asthma and AR. Nevertheless, additional  
29 studies with improved study designs incorporating confounder variables (e.g., allergens), and  
30 standardized definitions of traffic related air pollutants are needed.<sup>54-56</sup> (*See Section VIII.B.3. Pollution for  
31 additional information on this topic.*)

32

33 Similarly, a cross-sectional study of 325 non-asthmatic AR patients suggest that cigarette smoking may  
34 be an independent risk factor for the development of new asthma among patients with AR, although

1 confirmatory studies are still needed.<sup>57</sup> (see Section VIII.B.4. Tobacco Smoke for additional information  
2 on this topic.)

3  
4 In summary, AR is a significant risk factor for asthma. However, there is currently limited evidence for  
5 the role of traffic related air pollutants and smoking as additional risk factors in the development of  
6 asthma among patients with AR.

7

8 **Aggregate grade of evidence:** C (Level 2: 3 studies, level 3: 19 studies; **TABLE XIII.A.3.**)

9

10 **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 <sup>42</sup>	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 <sup>50</sup>	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 <sup>40</sup>	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 <sup>58</sup>	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 <sup>56</sup>	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 <sup>49</sup>	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 <sup>55</sup>	2021	3	Cross-sectional	General population of young adults (China)	Impact of health and home environment on risk of developing asthma and AR	Exposure to NO <sub>2</sub> , urbanization and traffic exhaust increased risk of developing asthma and AR

Lipiec et al <sup>39</sup>	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 <sup>54</sup>	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 <sup>53</sup>	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 <sup>59</sup>	2013	3	Cross-sectional	Children with AR	Associated diseases	Asthma present in 49.5% of AR patients
Jarvis et al <sup>60</sup>	2012	3	Cross-sectional	General population	Self-reported current asthma	Asthma associated with chronic rhinosinusitis
Rochat et al <sup>45</sup>	2010	3	Cohort	Birth cohort	Development of wheezing	AR is a predictor for subsequent wheezing onset
Polosa et al <sup>57</sup>	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 <sup>19</sup>	2008	3	Cohort	Population-based study	Frequency of asthma	Rhinitis (+/- atopy) is a powerful predictor of adult-onset asthma
Burgess et al <sup>61</sup>	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 <sup>44</sup>	2007	3	Cohort	General population	Changes in bronchial hyperresponsiveness in non-asthmatic subjects	AR associated with increased onset bronchial hyperresponsiveness
Bodtger et al <sup>62</sup>	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 <sup>63</sup>	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 <sup>43</sup>	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 <sup>64</sup>	2000	3	Cohort	Random sample	Risk factors and onset or remission of AR and asthma	AR, sensitization to pets, and smoking were risk factors for onset of asthma
Settipane et al <sup>41</sup>	2000	3	Cohort	University students	Asthma development	Allergic asthma depends on elevated IgE, eosinophilia, airway hyperresponsiveness, exposure to allergens, and the predominance of the Th2 pathway of immunologic reactions

1 LOE=level of evidence; AR=allergic rhinitis; OR=odds ratio; CI=confidence interval; RHINESSA=Respiratory Health in  
2 Northern Europe, Spain and Australia study; NO<sub>2</sub>=nitrogen dioxide; TRAP=traffic related air pollutants;  
3 IgE=immunoglobulin E

#### 6 XIII.A.4. Treatment of allergic rhinitis and its effect on asthma

8 AR and asthma are linked both epidemiologically and pathophysiologically along one common airway.<sup>65-</sup>

9 <sup>69</sup> Indeed, there is a body of evidence to suggest that the following AR therapies may benefit both  
10 conditions: INCS,<sup>70-73</sup> intranasal antihistamine,<sup>74</sup> oral antihistamines,<sup>75,76</sup> LTRAs,<sup>77</sup> and AIT.<sup>78-80</sup> AIT has  
11 shown promising results in altering the course of the allergic inflammation seen in both AR and  
12 asthma.<sup>81-83</sup> There is extensive literature in this area; therefore, this section focuses primarily on  
13 prospective randomized trials and systematic reviews to minimize inherent biases and weaknesses of  
14 retrospective studies.<sup>84</sup>

#### 16 **Allergen avoidance**

17 Allergen avoidance is often recommended for allergies, specifically for AR and allergic asthma.<sup>85-87</sup>

18 Despite being intuitive and having reasonable biological plausibility, the actual evidence for benefit in AR  
19 and asthma is limited. No benefit was identified for chemical or physical methods to reduce HDM  
20 methods in a 2008 Cochrane review examining randomized trials of subjects with asthma.<sup>88</sup> Similarly,  
21 single allergen avoidance or elimination plans such as removing or washing pets, mattress coverings,  
22 removing carpeting, and use of HEPA filters have not shown strong evidence-based clinical benefit for  
23 reducing asthma and/or AR symptoms, although there are some exceptions (e.g., acaricides for HDM



1 allergy).<sup>88-90</sup> Nevertheless, there is theoretical benefit of reducing allergen exposure, a paucity of data on  
2 multimodality approaches to reduce allergen load, and minimal downside to attempting these various  
3 techniques. (See Section XI.A. Allergen Avoidance for additional information on this topic.) Allergen  
4 avoidance is mentioned here for completeness in discussing treatment modalities for AR with an effect  
5 on asthma, but given poor evidence of effect, an aggregate grade of evidence and literature summary  
6 table are deferred.

7

## 8 **Pharmacotherapy**

9 **Oral H<sub>1</sub> antihistamines.** Six RCTs were identified that specifically evaluated H<sub>1</sub> antihistamines for the  
10 treatment of asthma in the context of coexistent AR.<sup>91-96</sup> Cetirizine and loratadine are the two most  
11 highly studied second generation antihistamines used concomitantly in AR and asthma. Elevated  
12 histamine levels after allergen challenge are associated with bronchoconstriction responses in acute  
13 asthma episodes. Cetirizine also has bronchodilatory effects which are significant both as monotherapy  
14 and in combination with albuterol.<sup>97</sup> Despite biological plausibility of antihistamines as effective  
15 treatment and improvement in subjective asthma symptoms, objective measures using PFT and PEF  
16 have failed to demonstrate significant improvements.<sup>95,98,99</sup> Antihistamines may also have a preventive  
17 effect on the development of asthma in atopic patients.<sup>100</sup> In a subgroup analysis, the Early Treatment of  
18 the Atopic Child trial found a near 50% reduced risk of developing asthma among cetirizine-treated  
19 patients with grass pollen and HDM sensitivities. (See Section XI.B.1. Antihistamines for additional  
20 information on this topic.) [TABLE XIII.A.4.-1]

21

22 **Oral corticosteroids.** Oral corticosteroids are commonly used in asthma patients who are inadequately  
23 controlled with bronchodilators and inhaled corticosteroids.<sup>101</sup> They are also effective for symptoms of  
24 rhinitis.<sup>102</sup> Due to the side-effect profile associated with these medications, especially with increasing  
25 duration of use,<sup>103</sup> oral steroids are not recommended for the routine treatment of AR. For these  
26 reasons, an aggregate grade of evidence and evidence summary table are deferred. (See Section  
27 XI.B.2.a. Oral Corticosteroids for additional information on this topic.)

28

29 **Intranasal corticosteroids.** In the 1980s, INCS were reported to improve asthma symptoms in patients  
30 with coexistent AR and asthma.<sup>104,105</sup> Two meta-analyses and 12 RCTs address the potential “unified  
31 airway” effect of INCS on asthma, and a single historical cohort study evaluates the impact of  
32 combination INCS and intranasal antihistamine on asthma outcomes in patients with both AR and

1 asthma.<sup>70,71,73,74,106-116</sup> A 2003 Cochrane review evaluated the efficacy of INCS on asthma outcomes in  
 2 patients with coexistent rhinitis, finding no significant improvement in asthma outcomes with INCS.<sup>106</sup>  
 3 Heterogeneity in study designs may have limited the findings of this meta-analysis and explain the  
 4 discrepancy of the results compared to high-quality RCTs. Alternatively, a 2013 SRMA demonstrated  
 5 improvements in asthma outcomes with the use of INCS compared to placebo in patients with asthma  
 6 and AR, although the addition of INCS to inhaled corticosteroids was not associated with improved  
 7 asthma outcomes.<sup>71</sup> Patient education was noted to be important as patients with concomitant AR and  
 8 asthma who received training on the proper use of INCS and education on the relationship of AR and  
 9 asthma demonstrated significant reductions in asthma symptoms and albuterol use compared to  
 10 patients receiving INCS without additional education.<sup>117</sup> Finally, intranasal azelastine-fluticasone  
 11 propionate spray is a known effective treatment for AR alone. Recently, a pre-post historical cohort also  
 12 demonstrated its potential utility in asthmatics with AR, demonstrating a significant reduction in acute  
 13 respiratory events and rescue inhaler medication usage, as well as an increase in the overall number of  
 14 well-controlled asthmatics.<sup>74</sup> (See Section XI.B.2.b. *Intranasal Corticosteroids for additional information*  
 15 *on this topic.*) [TABLE XIII.A.4.-2]

16  
 17 **Leukotriene receptor antagonists.** LTRAs (montelukast and zafirlukast), often in combination with  
 18 topical corticosteroids, have demonstrated benefit for the treatment of both asthma and AR, consistent  
 19 with efficacy in addressing inflammation in the “unified airway”.<sup>118</sup> ARIA 2008 guidelines supported the  
 20 effectiveness of montelukast in treating patients with asthma and AR, finding improvement of both  
 21 nasal and bronchial symptoms as well as reduction of beta agonist use.<sup>89</sup> The 2010 ARIA update  
 22 specified that LTRAs are not recommended over other first-line therapies for the respective conditions,  
 23 recommending treatment of asthma and AR with a nasal and inhaled corticosteroid as first-line  
 24 therapies, rather than an LTRA to treat both conditions.<sup>119</sup> A more recent review in 2015 also identified  
 25 some utility of LTRAs for patients with concomitant AR and asthma.<sup>120</sup> However, the limited additional  
 26 benefit must be weighed against added cost and an FDA boxed warning regarding serious  
 27 neuropsychiatric events when comparing inhaled corticosteroids to LTRAs for single-modality treatment  
 28 of asthma in patients with comorbid AR.<sup>119</sup> (See Section XI.B.4. *Leukotriene Receptor Antagonists for*  
 29 *additional information on this topic*) [TABLE XIII.A.4.-3]

30

31 **Aggregate grade of evidence for pharmacotherapy treatment of AR and its effect on asthma:** A  
 32 -Oral H<sub>1</sub> antihistamines (Level 2: 4 studies, level 3: 2 studies; TABLE XIII.A.4.-1)  
 33 -Intranasal corticosteroids (Level 1: 2 studies, level 2: 5 studies, level 3: 8 studies; TABLE XIII.A.4.-2)

1 -Leukotriene receptor antagonists (Level 2: 7 studies; **TABLE XIII.A.4.-3**)

2  
3 **Biologics**

4 ***Omalizumab.*** Omalizumab is a monoclonal anti-IgE antibody which binds free-IgE, preventing  
5 interactions with high-affinity IgE receptors and resulting in receptor downregulation on inflammatory  
6 cells.<sup>121</sup> Omalizumab has demonstrated effectiveness separately for asthma as well as AR.<sup>121-125</sup> There  
7 are several published studies evaluating omalizumab in AR or asthma,<sup>121,126</sup> with one RCT specifically  
8 evaluating the efficacy of omalizumab in patients with concomitant moderate-to-severe asthma and  
9 persistent AR.<sup>127</sup> Omalizumab as an adjunct to SCIT has also been evaluated.<sup>128</sup> Both studies show a  
10 reduction in symptoms as well as an improvement in QOL measures.<sup>127,128</sup> Additional biologics are  
11 currently in varying stages of development/emergence with further evaluation needed to determine  
12 their role for the treatment of coexistent AR and asthma. (*See Sections XI.B.7. Biologics and XI.D.10.*  
13 *Combination Biologic Therapy and Subcutaneous Immunotherapy for additional information on this*  
14 *topic.*) [**TABLE XIII.A.4.-4**]

15  
16 **Aggregate grade of evidence for biologic treatment of AR and its effect on asthma:** B (Level 2: 2  
17 studies; **TABLE XIII.A.4.-4**)

18 **\*\*Note:** There is high level evidence with multiple RCTs and reviews for asthma individually, but only  
19 one RCT specifically evaluating omalizumab versus placebo in patients with concurrent conditions.  
20

21 **Allergen immunotherapy**

22 Both SCIT and SLIT improve control of AR and comorbid asthma.<sup>129-133</sup> Several studies indicate that AIT,  
23 often in addition to traditional antihistamine pharmacotherapies, may help halt the progression of  
24 allergic disease, including preventing new allergic sensitivities and the development of asthma.<sup>81-83,134-139</sup>  
25 However, several systematic reviews have concluded that the evidence for AIT preventing further  
26 allergic sensitization is low, due to limited analyses of asthma exacerbations, mixed population  
27 recruitment, and a focus on mild disease only.<sup>140-142</sup> Further evaluation is required to assess safety in  
28 patients with uncontrolled asthma.<sup>142</sup> Of note, the 2010 ARIA statement recommended both SCIT and  
29 SLIT for the treatment of asthma in patients with AR and asthma.<sup>119</sup> The 2019 GINA guidelines  
30 recommend adding HDM SLIT for adult patients with AR and FEV<sub>1</sub> >70% who are suboptimally controlled  
31 on high dose inhaled corticosteroids.<sup>143</sup> Finally, the National Heart Lung and Blood Institute Expert Panel  
32 conditionally recommends SCIT as an adjunct treatment to standard pharmacotherapy for those 5 years  
33 and older with mild to moderate persistent asthma who show clear evidence of a relationship between

1 symptoms and exposure to an allergen to which the individual is sensitive.<sup>144</sup> (See Section XI.D. Allergen  
2 Immunotherapy for additional information on this topic.) [TABLE XIII.A.4.-5]

3

4 **Aggregate grade of evidence:** A (Level 1: 7 studies, level 2: 3 studies, level 3: 3 studies; TABLE XIII.A.4.-  
5 5)

6

7 **TABLE XIII.A.4.-1 Evidence table – Antihistamines for asthma treatment in coexistent asthma and**  
8 **allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Pasquali et al <sup>91</sup>	2006	2	RCT	Persistent AR and asthma, n=50: -Levocetirizine 5mg -Placebo	-Daily rhinitis and asthma symptoms -QOL by Rhinasthma questionnaire -QOL by SF-36	-Rhinitis and asthma symptoms reduced with levocetirizine -Rhinasthma QOL score reduced with levocetirizine -No differences in SF-36
Baena-Cagnani et al <sup>92</sup>	2003	2	RCT	Seasonal AR and asthma, n=924: -Desloratadine 5mg -Montelukast 10mg -Placebo	-TASS -FEV <sub>1</sub> -β-agonist use	-Desloratadine versus placebo: reduction in mean TASS, improvement in FEV <sub>1</sub> , reduction in β-agonist use -Desloratadine versus montelukast: no difference
Berger et al <sup>93</sup>	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 <sup>94</sup>	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 <sup>95</sup>	2001	3*	RCT	Seasonal AR and asthma, n=12: -Cetirizine crossover to placebo -Placebo crossover to cetirizine	-BHR <sup>a</sup> -NBI <sup>b</sup>	-Cetirizine increased BHR -Cetirizine reduced NBI vs placebo at 6 hours
Aaronson <sup>96</sup>	1996	3*	RCT	AR and perennial asthma, n=28: -Cetirizine 20mg -Placebo	-Daily rhinitis and asthma symptoms -Medication use -PEFR, PC <sub>20</sub> , PFTs -Asthma management	-Cetirizine reduced asthma and rhinitis symptoms -No difference in albuterol use -No difference in PFTs, PC <sub>20</sub> , PEFR -No difference in asthma management

9 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; QOL=quality of life; SF-36=Short Form  
10 Health Survey; TASS= Total Asthma Symptom Score; FEV<sub>1</sub>= forced expiratory volume in 1 second; TSS=Total  
11 Symptom Score; BHR=bronchial hyperresponsiveness; NBI=nasal blocking index; PEFR=peak expiratory flow rate;  
12 PC<sub>20</sub> and PD<sub>20</sub>= provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV<sub>1</sub>;  
13 PFT=pulmonary function test

14 <sup>a</sup>BHR measured as methacholine PD<sub>20</sub>

15 <sup>b</sup>NBI measured using peak expiratory flow meter and calculated as (oral peak flow – nasal peak flow) / (oral peak  
16 flow)

1 \*LOE downgraded due to small sample size, no power analysis or power calculation, which limits interpretation of  
 2 negative findings

3

4 **TABLE XIII.A.4.-2 Evidence table – Intranasal corticosteroids for asthma treatment in coexistent**  
 5 **asthma and allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lohia et al <sup>71</sup>	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 <sub>1</sub> , PEF, PC <sub>20</sub> -QOL	-INCS improved FEV <sub>1</sub> , PC <sub>20</sub> , 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 <sup>106</sup>	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 <sub>1</sub> , PEF, PC <sub>20</sub> , PD <sub>20</sub> -Inflammatory markers	-Non-significant symptom improvement INCS vs placebo -No difference in FEV <sub>1</sub> , PEF, PC <sub>20</sub> , PD <sub>20</sub>
Jindal et al <sup>107</sup>	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 <sup>108</sup>	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 <sub>1</sub> higher with IHFP -Increased BHR with INFP; no increase with IHFP
Nathan et al <sup>109</sup>	2005	2	RCT	Seasonal AR and persistent asthma, n=863; all received FSC: -INFP 200µg and FSC daily -MON 10mg + FSC -Placebo + FSC	-Daily PEF -Daily asthma and AR symptoms -Rescue albuterol use	-INFP added to FSC improved nasal symptoms -No asthma outcome improvement with INFP addition to FSC
Stelmach et al <sup>110</sup>	2005	2	RCT	Perennial AR and mild-to-moderate persistent asthma, n=59: -Nasal Bdp 400µg + placebo MDI	-Asthma and AR symptom scores -PEF -FEV <sub>1</sub> and BHR (PC <sub>20</sub> ) -Proxy indicators of asthma-related	-Reductions of AR and asthma symptoms in all groups -No change PEF or BHR

				-Placebo nasal spray + Bdp MDI 1000µg -Bdp nasal spray 400µg + Bdp MDI 1000µg daily	morbidity (work absence, emergency visits, etc)	-Increased FEV <sub>1</sub> with nasal Bdp alone and for Bdp MDI alone -Asthma morbidity reduced for all
Thio et al <sup>111</sup>	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 <sub>20</sub> FEV <sub>1</sub>	-No difference in asthma scores or as-needed salbutamol for all groups -PD <sub>20</sub> not significantly different -FEV <sub>1</sub> increased with FP and BDP in season 2
De Jong et al <sup>74</sup>	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 β <sub>2</sub> -agonists
Kersten et al <sup>70</sup>	2012	3*	RCT	AR and mild-to-moderate exercise exacerbated asthma, n=32: -Fluticasone furoate nasal spray -Placebo nasal spray	-Exercise induced FEV <sub>1</sub> change -AUC of FEV <sub>1</sub> curve -ACQ score -PAQLQ score -FeNO	-Exercise-induced decrease in FEV <sub>1</sub> reduced with FP -No difference in FEV <sub>1</sub> , ACQ, PAQLQ, FeNO
Baiardini et al <sup>112</sup>	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 <sup>a</sup> -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 <sup>113</sup>	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 <sub>20</sub> -FeNO -PNIF -FEV <sub>1</sub> -Asthma and rhinitis QOL	-PC <sub>20</sub> improvement in all groups -No PC <sub>20</sub> 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 <sup>114</sup>	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 <sup>115</sup>	2008	3*	RCT	Perennial rhinitis and allergic asthma, n=40: -MFNS -Placebo	-FeNO -ECP in nasal lavage -PEF -FEV <sub>1</sub>	-No difference in FeNO for MFNS vs placebo -Nasal ECP reduced -No difference in PEF or FEV <sub>1</sub>
Watson et al <sup>116</sup>	1993	3*	RCT	AR and controlled asthma, n=21: -Intranasal Bdp 100µg twice daily, then placebo -Placebo nasal spray, then intranasal Bdp 100µg twice daily	-Asthma and rhinitis symptoms -PC <sub>20</sub> -Bdp deposition**	-No difference in asthma symptoms with Bdp -PC <sub>20</sub> improved with Bdp -Evening asthma symptoms reduced with Bdp
Corren et al <sup>73</sup>	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 <sub>20</sub> )	-PC <sub>20</sub> decreased over pollen season with placebo, not Bdp -AM NBI decreased with placebo, improved with Bdp -No difference in symptoms

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; RCT=randomized controlled trial;  
2 INCS=intranasal corticosteroid; ICS=inhaled corticosteroid; INH=inhaled; FEV<sub>1</sub>=forced expiratory volume in 1  
3 second; PEF=peak expiratory flow; PC<sub>20</sub> and PD<sub>20</sub>= provocation 'concentration' or 'dose' of methacholine causing a  
4 20% decrease in FEV<sub>1</sub>; QOL=quality of life; AR=allergic rhinitis; FP=fluticasone propionate; BID=twice daily;  
5 MON=montelukast; PO=per os (taken orally); QHS=each night; INFP=inhaled fluticasone propionate;  
6 PFT=pulmonary function test; BHR=bronchial hyperresponsiveness; FSC=inhaled fluticasone propionate and  
7 salmeterol; Bdp=beclomethasone dipropionate; MDI=metered dose inhaler; AUC=area under the curve;  
8 ACQ=Asthma Control Questionnaire; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; FeNO=fraction of  
9 exhaled nitric oxide; MFNS=mometasone furoate nasal spray; GS=Rhinasthma global summary; RAI=respiratory  
10 allergy impact; LA=lower airway; UA=upper airway; PNIF=peak nasal inspiratory flow; ECP=eosinophil cationic  
11 protein; NBI=nasal blocking index (based on PEF and calculated as (oral peak flow – nasal peak flow) / (oral peak  
12 flow))

13 \*LOE downgraded due to small sample size

14 \*\*Radiolabeled Bdp < 2% deposition in lungs, 20%-50% in nasal cavity, and 48%-78% swallowed

15

16 **TABLE XIII.A.4.-3 Evidence table – Leukotriene receptor antagonists for asthma treatment in**  
17 **coexistent asthma and allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim et al <sup>145</sup>	2018	2	RCT	Perennial AR and mild to moderate asthma, n=228: -MON 10mg -MON 10mg + levocetirizine 5mg	-Mean daytime and nighttime nasal symptom score -Mean composite symptom score -Overall assessment AR -FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC -Asthma Control Test -Rescue medication usage	MON-levocetirizine safe and more effective than MON alone across all observed endpoints

Jindal et al <sup>107</sup>	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 <sup>146</sup>	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 <sup>147</sup>	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 <sup>109</sup>	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 <sup>148</sup>	2004	2	RCT	Seasonal AR and asthma, n=831: -MON 10mg daily -Placebo	-Rhinitis symptoms -RQLQ -Global evaluations of asthma -β-agonist use	-Global evaluation of asthma by patients and physicians improved with MON -Reduction in β-agonist use with MON
Baena-Cagnani et al <sup>92</sup>	2003	2	RCT	Seasonal AR and asthma, n=924: -Desloratadine 5mg -MON 10mg -placebo	-TASS -FEV <sub>1</sub> -β-agonist use	Desloratadine vs placebo: -Reduction in mean TASS -Improvement in FEV <sub>1</sub> -Reduction in β-agonist use -Desloratadine versus montelukast: No differences

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; MON=montelukast; FEV<sub>1</sub>=forced  
 2 expiratory volume in 1 second; FVC=forced vital capacity; FP=fluticasone propionate; INCS=inhaled corticosteroid;  
 3 BID=twice daily; PO=per os (by mouth); QHS=each night; PEF=peak expiratory flow; FSC= inhaled fluticasone  
 4 propionate and salmeterol; FPNS=fluticasone propionate nasal spray; ICS=inhaled corticosteroid; INFP= inhaled  
 5 fluticasone propionate; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; TASS=Total Asthma Symptom  
 6 Score  
 7

8 **TABLE XIII.A.4.-4 Evidence table – Omalizumab for asthma treatment in coexistent asthma and allergic**  
 9 **rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
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Kopp et al <sup>128</sup>	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 <sub>1</sub> or mean PEF
Vignola et al <sup>127</sup>	2004	2	RCT	Moderate-to-severe persistent AR and allergic asthma, n=405: -Omalizumab -Placebo	-Asthma exacerbations -AQLQ score -RQLQ score -Rescue medication use -Symptom scores -Patient and investigator GETE -ICS use -FEV <sub>1</sub> , FVC, AM PEF	Omalizumab: -Reduced asthma exacerbations -Increased AQLQ and RQLQ -Reduced asthma symptoms -Increased FEV <sub>1</sub> , FVC, PEF -No difference in $\beta$ -agonist use

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; SCIT=subcutaneous immunotherapy;  
 2 PEF=peak expiratory flow; GETE=global evaluation of treatment effectiveness; ACQ=Asthma Control  
 3 Questionnaire; QOL=quality of life; AQLQ=Asthma Quality of Life Questionnaire; RQLQ=Rhinoconjunctivitis Quality  
 4 of Life Questionnaire; PFT=pulmonary function test; FEV<sub>1</sub>=forced expiratory volume in 1 second; ICS=inhaled  
 5 corticosteroid; FVC=forced vital capacity

6

7 **TABLE XIII.A.4.-5 Evidence table – Evidence for allergen immunotherapy for asthma treatment in**  
 8 **coexistent asthma and allergic rhinitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Fortescue et al <sup>142</sup>	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 <sup>132</sup>	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 <sup>140</sup>	2017	1	Systematic review	Systematic review of 18 studies (4 RCT, 10 prospective, 2 retrospective, 2 observational): mono- or polysensitized AR patients +/- asthma, treated with AIT vs not treated with AIT	New allergic sensitization	Low evidence that AIT prevents further allergic sensitization among mono- and polysensitized patients with AR
Di Lorenzo et al <sup>141</sup>	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 <sup>139</sup>	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 <math>\leq 2</math> years after completion AIT (short-term) and <math>\geq 2</math> 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 <sup>129</sup>	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 <sup>a</sup> -Most adverse reactions mild
Lin et al <sup>149</sup>	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 <sup>b</sup> -Medication plus symptom scores reduced with SLIT <sup>b</sup>
Marogna et al <sup>81</sup>	2008	2	RCT	Rhinitis +/- intermittent asthma, n=216: -Standard drug therapy control group -Standard drug therapy plus SLIT*	-Development of persistent asthma (not at baseline) -Symptom and medication scores of allergic symptoms -Daily medication use -New sensitization	-Persistent asthma incidence lower with SLIT vs control -Methacholine-positive patients after 3 years reduced with SLIT -Lower symptom and medication scores with SLIT

Novembre et al <sup>83</sup>	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 <sup>82</sup>	2002	2	RCT	RC with or without asthma, n=191: -SCIT -Control	-Development of asthma (if none at trial start) -BHR by PC <sub>20</sub> -VAS of symptoms	-Asthma incidence greater in controls -BHR improved with SCIT after 1 year pollen season
Sidenius et al <sup>133</sup>	2021	3	Non-interventional, prospective, multicenter, observational study	AR with (n=83) or without asthma (n=115), 1 year treatment SQ <sup>®</sup> HDM SLIT	-Adverse events -AR symptoms -Asthma symptoms -Asthma control	-SQ <sup>®</sup> HDM SLIT is safe and well tolerated -SQ <sup>®</sup> HDM SLIT decreases AR and asthma symptoms and medication usage -SQ <sup>®</sup> HDM SLIT improves asthma control
Inal et al <sup>135</sup>	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 <sup>78</sup>	2000	3**	RCT	AR and BHR to methacholine, HDM allergy, n=44: -SCIT (HDM allergen extract) -Placebo	-BHR by PD <sub>20</sub> -Serum IgE levels -Rescue medication use -Additional visits for symptoms -Development of asthma	-BHR increased with SCIT -No HDM IgE difference -Increased med use and visits with placebo -No difference in asthma incidence

1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; QOL=quality of life; SLIT=sublingual  
2 immunotherapy; ICS=inhaled corticosteroid; AIT=allergen immunotherapy; HDM=house dust mite;  
3 SCIT=subcutaneous immunotherapy; RC=rhinoconjunctivitis; BHR=bronchial hyperreactivity; PC<sub>20</sub> and PD<sub>20</sub>=  
4 provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV<sub>1</sub>; VAS=visual analog scale;  
5 IgE=immunoglobulin E

6 <sup>a</sup>Strength of evidence moderate to high, for asthma-focused studies and rhinitis-focused studies, respectively

7 <sup>b</sup>Strength of evidence is moderate for both comparisons

8 \*SLIT administered as sublingual drops of standardized allergen for a build-up phase and then continued for  
9 maintenance phase

10 \*\*LOE downgraded due to small sample size

11

12

### 13 XIII.B. Rhinosinusitis

#### 14 XIII.B.1. General association of allergic rhinitis with chronic rhinosinusitis

15

1 AR may be associated with CRS in several clinical settings.<sup>150</sup> CRS is a condition of the sinonasal cavity  
2 characterized by persistent inflammation. While the causes of inflammation vary, CRSwNP is generally  
3 associated with type 2 mediated inflammation, while CRSsNP tends to have less predominance of type 2  
4 inflammation.<sup>150,151</sup> AR is predominantly driven by type 2 mediated inflammation and is thought to  
5 potentially be an inciting factor in the development of CRS, though the relationship remains  
6 unclear.<sup>152,153</sup> This section will discuss the overall association between AR and CRSsNP as well as  
7 CRSwNP.

8  
9 ***Allergic rhinitis and chronic rhinosinusitis without nasal polyposis.*** Since the previous iteration of ICAR-  
10 AR, there have been no new studies examining CRSsNP and AR.<sup>152,153</sup> There are no controlled studies  
11 examining the role of AR in the development of CRSsNP and no studies showing that the treatment of  
12 allergic disease alters the progression of CRSsNP, or vice versa.<sup>150,154</sup> The Wilson et al<sup>155</sup> review continues  
13 to provide the most robust assessment of the relationship between allergy and CRSsNP, reporting four  
14 studies that supported an association between allergy and CRSsNP and five that do not. Because the  
15 correlation remains unclear, allergy testing is listed as an option in CRSsNP patients based on the  
16 theoretical benefit of identifying and treating comorbid allergic disease.<sup>150,155</sup> **[TABLE XIII.B.1.-1]**

17  
18 **Aggregate grade of evidence (AR and CRSsNP):** D (Level 2: 1 study, level 3: 1 study, level 4: 8 studies,  
19 conflicting evidence; **TABLE XIII.B.1.-1**) Table adapted from Wilson et al.<sup>155</sup>

20  
21 ***Allergic rhinitis and chronic rhinosinusitis with nasal polyposis.*** The pathogenesis of CRSwNP is strongly  
22 associated with type 2 inflammation.<sup>150,151</sup> Additionally, nasal polyps have high levels of tissue  
23 eosinophils, as well as mast cells and basophils.<sup>150,151</sup> AR follows a similar inflammatory pathway and this  
24 suggests there may be a pathophysiologic similarities between CRSwNP and AR.<sup>150,151,154</sup> However, the  
25 clinical evidence for or against an association between AR and CRSwNP has been mixed.<sup>150,154</sup> Similar to  
26 CRSsNP, there have been no new studies specifically examining CRSwNP and AR since ICAR-Allergic  
27 Rhinitis 2018.<sup>154</sup> There is an expanding area of research on CCAD. (*See Section XIII.B.3. Central*  
28 *Compartment Atopic Disease for additional information on this topic.*) The evidence for a relationship  
29 between AR and CRSwNP remains conflicted. Ten studies support an association while ten do not, or  
30 have equivocal findings.<sup>155</sup> Hypersensitivity to HDM, cockroach, and *Candida* have been associated with  
31 CRSwNP. Despite the overlapping pathophysiologic features between allergy and CRSwNP, conflicting  
32 evidence exists regarding and association between AR and CRSwNP. Allergy testing remains an option in

1 CRSwNP patients based on the theoretical benefit of identifying and treating comorbid allergic disease,  
 2 especially since allergy may be seen in these patients.<sup>150,155</sup> [TABLE XIII.B.1.-2]

3

4 **Aggregate grade of evidence (AR and CRSwNP):** D (Level 3: 5 studies, level 4: 16 studies, conflicting  
 5 evidence; TABLE XIII.B.1.-2) Table adapted from Wilson et al.<sup>155</sup>

6

7 In summary, the association between AR and CRSwNP or CRSsNP remains unclear, with conflicting  
 8 evidence. The available literature is limited by varying definitions of allergy versus AR as well as a failure  
 9 to separate CRSwNP and CRSsNP. Studies that combined CRSwNP and CRSsNP in their evaluation of a  
 10 potential CRS-AR association were excluded from the Wilson et al<sup>155</sup> review and the ICAR-Allergic  
 11 Rhinitis 2018<sup>154</sup> and are not included here. As our understanding of CRS endotypes and inflammatory  
 12 patterns evolves, it becomes more pertinent to specify the relationship of AR with specific CRS disease  
 13 processes (allergic fungal rhinosinusitis [AFRS], CCAD, AERD), which are discussed in the following  
 14 sections.

15

16 Despite the unclear relationship, the diagnosis and treatment of comorbid allergy is an option in  
 17 rhinosinusitis patients balancing the cost and low evidence with the low risk of allergic rhinosinusitis  
 18 treatment and the theoretical benefits of reducing allergic sinonasal inflammation.<sup>150</sup>

19

20 **TABLE XIII.B.1.-1 Evidence table – Association between allergic rhinitis and chronic rhinosinusitis**  
 21 **without nasal polyposis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Baroody et al <sup>156</sup>	2008	2	RCT	CRSsNP with or without ragweed allergy, n=18	Reactivity in ragweed season determined by symptoms and sinus inflammation	Allergic patients have increased reactivity and sinonasal inflammation in ragweed season
Wilson et al <sup>155</sup>	2014	3	Systematic review	CRSsNP with or without allergy	Association between CRSsNP and allergy	Conflicting evidence, no clear association
Tan et al <sup>157</sup>	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 <sup>158</sup>	2009	4	Prospective case series	CRSsNP with or without allergy, n=115	CT scores	No difference in CT scores
Gelincik et al <sup>159</sup>	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 <sup>160</sup>	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 <sup>161</sup>	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 <sup>162</sup>	2004	4	Prospective case series	CRSsNP with or without allergy, n=48	-CT findings during viral URTI -Incidence of <i>S. aureus</i> sensitization	Allergic patients had higher CT scores and higher incidences of <i>S. aureus</i> sensitization
Van Zele et al <sup>163</sup>	2004	4	Prospective case-control	CRSsNP with or without allergy, n=31	Rates of <i>S. aureus</i> colonization	No difference in colonization rates
Berrettini et al <sup>164</sup>	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

1 LOE=level of evidence; RCT=randomized controlled trial; CRSsNP=chronic rhinosinusitis without nasal polyps;  
2 CT=computed tomography; URTI=upper respiratory tract infection  
3  
4

5 **TABLE XIII.B.1.-2 Evidence table – Association between allergic rhinitis and chronic rhinosinusitis with**  
6 **nasal polyposis**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Al-Qudah <sup>165</sup>	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 <sup>166</sup>	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 <sup>155</sup>	2014	3	Systematic review	CRSwNP with or without allergy	Association between CRSwNP and allergy	Conflicting evidence, no clear association
Houser & Keen <sup>167</sup>	2008	3	Retrospective case series	CRSwNP with or without allergy, n=373	Nasal polyposis	AR associated with the development of nasal polyposis
Kirtsreesakul <sup>168</sup>	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 <sup>169</sup>	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 <sup>170</sup>	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 <sup>157</sup>	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 <sup>171</sup>	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 <sup>158</sup>	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 <sup>172</sup>	2008	4	Prospective case series	CRSwNP with or without allergy, n=63	-Postoperative course -Recurrence	No difference between allergic and non-allergic patients
Erbek et al <sup>173</sup>	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 <sup>174</sup>	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 <sup>175</sup>	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 <sup>163</sup>	2004	4	Prospective case-control	CRSwNP compared to CRSsNP and controls, n=55	Rates of <i>S. aureus</i> colonization	Higher rates of colonization in CRSwNP
Asero & Bottazzi <sup>176</sup>	2001	4	Prospective case-control	CRSwNP compared to non-polyp controls, n=68	Rates of <i>Candida</i> and house dust sensitivity	Higher rates of sensitivity in CRSwNP
Vogels et al <sup>177</sup>	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 <sup>178</sup>	2000	4	Prospective case-control	CRSwNP compared to allergic controls, n=20	Rates of <i>Candida</i> sensitivity	Higher rates of sensitivity in CRSwNP
Pang et al <sup>179</sup>	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 <sup>180</sup>	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 <sup>181</sup>	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

1 LOE=level of evidence; CRSwNP=chronic rhinosinusitis with nasal polyps; CT=computed tomography

2 AR=allergic rhinitis

3

4

5

### XIII.B.2. Allergic fungal rhinosinusitis

1  
2 AFRS is a non-invasive, chronic, hypertrophic form of rhinosinusitis that affects immunocompetent hosts  
3 and is associated with an IgE-mediated local inflammatory response to extramucosal fungi present in the  
4 sinonasal cavities.<sup>182,183</sup> The Bent and Kuhn criteria are the most commonly cited diagnostic criteria for  
5 AFRS and include type I IgE-mediated hypersensitivity, recognizing that the diagnosis of AFRS requires a  
6 positive allergy history<sup>184</sup> and that type I hypersensitivity can be used to distinguish IgE-mediated forms  
7 of rhinosinusitis, such as AFRS and CCAD, from other forms of non-IgE-mediated rhinosinusitis.<sup>185</sup>

8  
9 Various studies have demonstrated the importance of IgE in the pathophysiology of AFRS, with both  
10 systemic and local IgE and fungal sIgE production consistently shown to be elevated in this disease  
11 process.<sup>186-188</sup> Additionally, it has been determined that most AFRS patients have detectable fungal sIgE  
12 in their allergic mucin.<sup>189,190</sup> Wise et al<sup>191</sup> further established that there is a significant increase in  
13 localized IgE staining of the sinus epithelium and subepithelium in AFRS patients compared to controls  
14 and CRSsNP patients. The role of type 1 hypersensitivity in AFRS, even in the absence of positive serum  
15 sIgE to fungal allergens, has also been demonstrated.<sup>192,193</sup> **[TABLE XIII.B.2.]**

16  
17 Although generally both CRSsNP and CRSwNP have been found to have an equivocal association with  
18 allergy,<sup>155</sup> 100% of AFRS patients in a study by Marcus et al<sup>194</sup> demonstrated positive allergy testing.  
19 Allergy testing and treatment is not recommended in CRS unless there are concurrent AR symptoms and  
20 sensitivities, respectively,<sup>195</sup> but some data support a role for AIT in improving AFRS patient outcomes in  
21 terms of reliance on systemic or topical corticosteroids, need for revision surgery, sinonasal crusting,  
22 QOL scores, and objective endoscopy scores.<sup>196,197</sup> Still, a systematic review by Gan et al<sup>198</sup> reported a  
23 grade C in quality of evidence for AIT in AFRS, so it is considered an option in refractory AFRS cases.

24  
25 The exact role of allergy and fungal hypersensitivity in the pathogenesis of AFRS has long been debated,  
26 partially due to a vague understanding of eosinophilic mucin CRS subtypes, including those classified as  
27 CRS with eosinophilic mucin but without the presence of fungi. Furthermore, eosinophilic mucin and  
28 polyps, which must be present to diagnose AFRS, can occur in the absence of allergy.<sup>199,200</sup> Pant et al<sup>200</sup>  
29 showed that elevated IgG3 levels specific to *Alternaria alternata* and *Aspergillus fumigatus* could  
30 distinguish eosinophilic mucin CRS from control groups, which suggests a possible fungal-specific non-  
31 allergic immune response in AFRS, and Clark et al<sup>201</sup> found significantly higher levels of *Staphylococcus*  
32 *aureus* in AFRS patients as compared to non-AFRS patients, again suggesting a different type of immune



1 mechanism in the pathophysiology of AFRS. In addition, with improved fungal culture techniques, some  
 2 studies report the presence of fungi in nearly 100% of non-AFRS CRS patients and control subjects,  
 3 further complicating the true role of fungi in AFRS.<sup>199,202-204</sup> Despite these debates, there is evidence  
 4 demonstrating the important role allergy and type 2 inflammation play in the pathophysiology,  
 5 diagnosis, and treatment of AFRS.<sup>205</sup>

7 **Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 9 studies, level 4: 5 studies; **TABLE XIII.B.2.**)  
 8

9 **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 <sup>198</sup>	2014	2*	Systematic review	Adults, AFRS (Bent and Kuhn <sup>184</sup> 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 <sup>192</sup>	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 <i>Aspergillus</i> -85.7% had tissue sIgE to <i>Aspergillus</i>
Wise et al <sup>191</sup>	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 <sup>185</sup>	2006	3	Prospective comparative	70 consecutive patients with CRS +/- polyps: -M+F+ (likely AFRS, n=36) -M+F- (likely EMCRS, n=12) -M-F+ (likely sinus mycetoma, n=4) -M-F- (CRS from other causes, n=18)	-Skin test against aspergillin antigen, n=47 -Histopathologic monitoring for the presence of mucin -Mycologic monitoring for the presence of fungus	Type 1 hypersensitivity was significantly associated with the AFRS group (p<0.05)

Pant et al <sup>200</sup>	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	<i>Alternaria alternata</i> and <i>Aspergillus fumigatus</i> -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 <sup>190</sup>	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 <sup>188</sup>	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 <sup>202</sup>	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 <sup>197</sup>	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 <sup>196</sup>	1998	3	Prospective cohort	-AFRS patients post-sinus surgery had allergy testing for 11 fungal and 12 nonfungal antigens, then AIT for 1-36 months (n=23; 15 still on AIT at publication) -Patients with early discontinuation of AIT	-Need for systemic or topical nasal steroids -Nasal crusting, accumulation of allergic mucin or debris in the sinus cavities, mucosal edema, or reformation of polyps -Need for repeat surgery	-No adverse events or deleterious effects of AIT -Treatment group: revision surgery (2 patients), methylprednisone (1 patient) -Control group: 2 patients with frequent use of oral steroids and recommendation for revision surgery, 1 patient with recurrent disease at 4 months post-op
Marcus et al <sup>194</sup>	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 <sup>201</sup>	2013	4	Retrospective case series	-AFRS patients, n=19 -CRSwNP patients, n=21	-Bacterial cultures -Fungal cultures	<i>S. aureus</i> more prevalent in the AFRS group vs non-AFRS group (63.2% vs 24.1%, p = 0.005)
Hutcheson et al <sup>186</sup>	2010	4	Case-control	-AFRS patients, n=64 -CRS patients, n=35	-Serum total IgE -IgG anti- <i>Alternaria</i> -specific antibodies -IgE antifungal antibodies	Mean serum total IgE, IgG anti- <i>Alternaria</i> -specific antibodies, and IgE antifungal bands increased in AFRS vs CRS patients
Cody et al <sup>203</sup>	1994	4	Retrospective cohort	789 histologic specimens, 44 had allergic mucin: -AFRS based on fungal hyphae in mucin or positive fungal culture, n=26	Culture results of 31 of the 44 AFRS patients	19 of the 31 had negative culture results

				-AFRS-like mucin, n=18		
Manning et al <sup>187</sup>	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

1 LOE=level of evidence; AFRS=allergic fungal rhinosinusitis; AIT=allergen immunotherapy; INCS=intranasal  
2 corticosteroid; CRSwNP=chronic rhinosinusitis with nasal polyps; CRS=chronic rhinosinusitis; sIgE=specific  
3 immunoglobulin E; CRSsNP=chronic rhinosinusitis without nasal polyps; Ig=immunoglobulin; M=allergic mucin;  
4 F=fungal/mycelial element; EMCRS= eosinophilic mucin chronic rhinosinusitis; CRP=C-reactive protein;  
5 ECP=eosinophilic cationic protein; RAST=radioallergosorbent test; EMSS=endoscopic mucosal staging system;  
6 QOL=quality of life; CSS=Chronic Sinusitis Survey; AERD=aspirin exacerbated respiratory disease; CCAD=central  
7 compartment atopic disease; NOS=not otherwise specified; CC=central compartment

8 \*LOE downgraded due to inclusion of cohort studies primarily

### 11 XIII.B.3. Central compartment atopic disease

13 CCAD is a distinct variant of CRS described as polypoid changes of central compartment (CC) structures  
14 where airflow is most prominent, including the MT, superior turbinate, and or/posterosuperior nasal  
15 septum. There is relative disease sparing of the peripheral sinus cavities, and studies suggest a strong  
16 association with allergy.<sup>206</sup> In 2014 White et al<sup>207</sup> first described the association between allergy and  
17 isolated MT polypoid edema, with 16/16 patients having allergen sensitization. Hamizan et al<sup>208</sup> found  
18 that MT edema/polyposis has a high specificity and positive predictive value for the presence of inhalant  
19 allergy, with the highest grades of MT edema having the strongest association. In comparing patients  
20 with isolated MT polyposis to those with paranasal sinus polyposis, Brunner et al<sup>209</sup> found clinically  
21 distinct features as patients with isolated MT polyposis were more commonly younger, female, had  
22 lower Lund-Mackay CT scores, and had a significantly higher association with AR compared to those with  
23 diffuse polyposis ( $p<0.001$ ). [TABLE XIII.B.3.]

25 In 2017, DelGaudio et al<sup>206</sup> introduced the term CCAD to describe this distinct variant of sinonasal  
26 disease. Further progression of CCAD results in involvement of the sinuses by lateralization or polypoid  
27 changes of the MT causing secondary obstruction of the sinuses in a medial to lateral progression. In a  
28 multi-institutional case series including 15 patients, all patients had symptoms consistent with AR and  
29 allergen sensitization was seen in the 14 patients who underwent allergy testing. Based on

1 computational fluid dynamics, the proposed pathophysiology is a local immune response related to  
 2 antigen deposition in CC structures exposed to inhaled allergens.<sup>206</sup> To further characterize CCAD,  
 3 Roland et al<sup>210</sup> described radiologic features that differentiate CCAD from other CRSwNP subtypes,  
 4 including oblique MT orientation, septal involvement, and lower Lund-Mackay score.

5  
 6 While there is conflicting data regarding the association between allergy and CRS in general, there is  
 7 evidence to support an association between allergy and CCAD. In a subtype analysis of patients with  
 8 CRSwNP, Marcus et al<sup>194</sup> reported significantly higher allergy prevalence in patients with CCAD  
 9 compared with CRSwNP not otherwise specified ( $p < 0.001$ ). In patients with radiologic features of CCAD,  
 10 Hamizan et al<sup>211</sup> noted a significantly higher association with allergen sensitization compared to the non-  
 11 CCAD group ( $p = 0.03$ ). Abdullah et al<sup>212</sup> reported similar results with 100% of patients with CCAD having  
 12 sensitization to HDM, compared to only 13.6% of non-CCAD patients ( $p = 0.00$ ). Additionally, Lee et al<sup>213</sup>  
 13 found higher blood eosinophil and serum IgE levels, and higher prevalence of allergen sensitization in  
 14 pediatric patients with CCAD compared to non-CCAD ( $p = 0.008$ ). While no association between CCAD  
 15 and allergy sensitization was noted in CRS patients in East Asia, patients with CCAD had significantly  
 16 higher peripheral eosinophils ( $p = 0.001$ ), tissue eosinophils ( $p = 0.005$ ), and IL-13 ( $p < 0.05$ ) and IL-5 levels  
 17 ( $p < 0.05$ ) in MT tissue compared to the non-CCAD group, suggesting an eosinophilic/type 2 inflammatory  
 18 response.<sup>214</sup> Radiologic features can be predictive of CCAD, but edema/polyposis of the CC on  
 19 endoscopy remains the current diagnostic standard. In a study by Lin et al,<sup>214</sup> patients with minor CC  
 20 radiologic findings and essentially normal endoscopy were included in the CC-CRSsNP group, which may  
 21 not meet the definition of CCAD according to DelGaudio et al.<sup>206</sup> While CCAD is a distinct variant of  
 22 sinonasal disease, CC disease can be found in other processes such as AERD and respiratory epithelial  
 23 adenomatoid hamartoma, with studies reporting a positive association with AR.<sup>215-217</sup>

24  
 25 **Aggregate grade of evidence:** C (Level 3: 2 studies, level 4: 11 studies; **TABLE XIII.B.3.**)  
 26

27 **TABLE XIII.B.3. Evidence table – Association between allergic rhinitis and central compartment atopic**  
 28 **disease**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Lee et al <sup>213</sup>	2021	3	Cross-sectional	Pediatric CRS subtypes, n=82	-Allergen sensitivity -Peripheral eos -tIgE -CT and endoscopy pattern of disease	-Increased peripheral eos ( $p = 0.020$ ), serum IgE ( $p = 0.23$ ) in CCAD vs non-CCAD -Higher prevalence of allergen sensitization in

						CCAD (87.1%) vs non-CCAD (62.4%) (p=0.008)
Hamizan et al <sup>208</sup>	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 <sup>214</sup>	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 <sup>216</sup>	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 <sup>212</sup>	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 <sup>194</sup>	2020	4	Case-control	CRSwNP subtypes, n=356: -AFRS -AERD -CCAD -CRSwNP NOS	Allergy and asthma prevalence by subtype	-Allergen sensitivity increased in CCAD, AERD and AFRS compared with CRSwNP NOS (p<0.001) -CCAD significantly higher association with allergy (p<0.001) than CRSwNP NOS
Roland et al <sup>210</sup>	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 <sup>217</sup>	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 <sup>215</sup>	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 <sup>211</sup>	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 <sup>209</sup>	2017	4	Case series	n=67 -Diffuse sinonasal polyposis -Isolated MT polypoid change	-Demographics -Presence of CRS, AR, asthma -SNOT-22, NOSE L-M score -Eos, tlgE	-Isolated MT polypoid patients had greater association with AR vs diffuse paranasal sinus polyposis (83% vs. 34%, p<0.001) -Isolated MT polypoid patients: more commonly female, younger, lower L-M score, lower incidence of CRS
DelGaudio et al <sup>206</sup>	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 <sup>207</sup>	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

1 LOE=level of evidence; CRS=chronic rhinosinusitis; eos=eosinophils; tlgE=total immunoglobulin E; CT=computed  
2 tomography; IgE=immunoglobulin E; CCAD=central compartment atopic disease; MT=middle turbinate;  
3 ROC=receiver-operating characteristic curve; CC=central compartment; SNOT=Sinonasal Outcome Test; L-M=Lund-  
4 Mackay CT score; IL=interleukin; AERD=aspirin exacerbated respiratory disease; AFRS=allergic fungal rhinosinusitis;  
5 eCRSwNP=eosinophilic chronic rhinosinusitis with nasal polyps; CRSwNP=chronic rhinosinusitis with nasal polyps;  
6 NOS=not otherwise specified; REAH=respiratory epithelioid adenomatous hamartoma; PPV=positive predictive  
7 value; AR=allergic rhinitis; NOSE=Nasal Obstruction Symptom Evaluation

8  
9

#### 10 XIII.B.4. Aspirin exacerbated respiratory disease

11

12 AERD is a chronic inflammatory condition that includes the tetrad of asthma, nasal polyposis,

13 eosinophilic rhinosinusitis, and a non-IgE-mediated reaction to inhibitors of the COX-1 enzyme.<sup>218</sup>

1 Although considered an inflammatory disease that results from dysregulation of arachidonic acid  
2 metabolism leading to an overproduction of leukotrienes and not a true allergic condition, there are  
3 data that suggest an association between AERD and IgE-mediated allergy.

4

5 Historically, Samter and Beers reported the prevalence of atopy in AERD as less than 3% (n=182) using  
6 the criteria of positive SPT, and either a family history of atopy or a correlation between allergen  
7 exposure and clinical symptoms.<sup>219</sup> However, recent evidence supports a higher atopic rate in AERD.<sup>220-</sup>  
8 <sup>223</sup> In one cohort, 200 of 300 (66%) AERD subjects had a history of positive SPT,<sup>221</sup> and in a latent class  
9 analysis of AERD sub-phenotypes, 105 of 201 (52.2%) patients had positive aeroallergen SPT  
10 responses,<sup>220</sup> with the most common allergen being HDM (29.6%).<sup>223</sup> In another study that evaluated  
11 personal atopic history, SPT, and elevated total and specific IgE, AERD subjects had a higher rate of  
12 atopy than controls (53.9% versus 14%, p<0.001).<sup>224</sup> **[TABLE XIII.B.4.]**

13

14 When compared to other forms of CRS, greater rates of physician diagnosed AR and positive SPT were  
15 found in AERD subjects when compared with CRSwNP subjects (80% vs 66%, p<0.001).<sup>225</sup> Recently, a  
16 retrospective study investigated the prevalence of atopy in patients with various CRS phenotypes  
17 (n=380) and found that a significantly higher percentage of atopic CRS patients had AERD (9.4% atopic  
18 versus 1.1% non-atopic subjects).<sup>226</sup>

19

20 Although the aforementioned studies demonstrate a higher rate of atopy in AERD compared to other  
21 forms of CRS, it should be noted that AERD is not driven by sIgE-mediated reactions. Even though local  
22 IgE levels within AERD nasal polyps are significantly elevated when compared with nasal tissue from  
23 other CRSwNP patients and healthy controls, this does not reflect atopic status.<sup>227</sup> Similarly, serum tIgE  
24 is often elevated in AERD patients but does not discriminate atopic from non-atopic AERD  
25 populations.<sup>220</sup>

26

27 The understanding that AERD is not driven by traditional atopic mechanisms has important ramifications  
28 regarding treatment. In a survey of 190 patients with AERD, 86 (45%) of respondents had concomitant  
29 AR treated with AIT.<sup>228</sup> More than half did not perceive any clinical benefit, and only 8% reported  
30 significant efficacy. This contrasts with non-AERD patients with AR, in whom rates of improvement with  
31 AIT are greater than 80%.<sup>229</sup> The high failure rate of AIT in AERD suggests that amelioration of any atopic



1 component of their symptoms is overwhelmed by the non-allergic AERD mechanisms. Although it is  
 2 important to note that AIT has not been properly studied as a treatment option for AERD.

3  
 4 In summary, despite the high rate of concomitant atopy in AERD, symptoms related to inhalant  
 5 sensitization are not responsible for the majority of AERD symptoms. Therefore, allergen-directed  
 6 therapies, such as standard AIT, are unlikely to be efficacious for most AERD patients. Nevertheless,  
 7 clinicians should elicit atopic histories for contributory comorbid AR, as recent expert guidance suggests  
 8 routine allergy testing in AERD for sensitization to inhalant allergens.<sup>230</sup> However, AIT may only be  
 9 highest yield for candidates with obvious seasonal variation to their symptoms and identifiable  
 10 environmental triggers.

11

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

13

14 **TABLE XIII.B.4. Evidence table – Association between allergic rhinitis and aspirin exacerbated**  
 15 **respiratory disease**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Brown et al <sup>226</sup>	2021	3	Retrospective cohort	380 CRS patients, including 28 patients with comorbid AERD	-Prevalence of atopy in CRS subtypes -Clinical characteristics, histopathology, serum IgE, symptom and radiographic scores -Atopy defined by clinical symptoms + SPT	-75.3% of CRS patients were atopic -Polysensitization in 76.2% -27/28 AERD patients atopic
Stevens et al <sup>225</sup>	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 <sup>224</sup>	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 <sup>222</sup>	2021	4*	Observational cohort	Polish cohort: -AERD, n=22 -NSAID-tolerant asthma, n=22 -Controls, n=11	-Distinguish inflammatory sub-endotypes of lower airway inflammation in AERD	-36% of AERD patients with positive SPT -SPT positivity did not differ

					-SPT, spirometry, nasal lavage, bronchoscopy -Cytokine and eicosanoid levels in bronchoalveolar lavage	between eosinophilic and non-eosinophilic AERD endotypes of AERD
DelGaudio et al <sup>215</sup>	2019	4	Retrospective cohort	US cohort, 72 AERD patients	-Describe CC involvement and association with atopic status in AERD -Atopy defined based on personal history of AR and positive SPT	-80.6% of AERD subjects had CC disease -100% of CC-AERD patients had atopic history, 93.8% had positive SPT -Lower rate of atopy in non-CC patients (p<0.0001)
Dona et al <sup>223</sup>	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%)

1 LOE=level of evidence; CRS=chronic rhinosinusitis; AERD=aspirin exacerbated respiratory disease;  
2 IgE=immunoglobulin E; SPT=skin prick test; CRSwNP=chronic rhinosinusitis with nasal polyposis; AR=allergic  
3 rhinitis; NSAID=non-steroidal anti-inflammatory drug; tIgE=total immunoglobulin E; sIgE=specific immunoglobulin  
4 E; US=United States; CC=central compartment  
5 \*LOE downgraded due to very limited study sample  
6 \*\*LOE downgraded due to poor inclusion criteria  
7  
8

### 9 XIII.C. Conjunctivitis

10  
11 Although the association between AR and allergic conjunctivitis (AC) is well recognized, accurate insight  
12 into ocular allergy prevalence is complicated by multiple factors.<sup>231,232</sup> Most prevalence studies use  
13 variable definitions of AC and may employ several different assessment questionnaires. Additionally,  
14 most studies do not distinguish specifically between AR and AC symptoms. Rather, AC is considered a  
15 secondary manifestation of AR.<sup>233,234</sup> There is phenotypic diversity of both AR and AC, with very few  
16 studies adequately characterizing the phenotypes of their study samples. Further, many epidemiologic  
17 studies are based solely on subjective questionnaires rather than incorporating objective evidence of  
18 allergic sensitization. [TABLE XIII.C.]

19

1 Overall, there is a significant burden of associated AC in patients with AR. In the US, the 1988-1994  
2 NHANES III survey (n=33,994) found a 30% prevalence of concomitant AR and AC.<sup>235</sup> Isolated ocular  
3 symptoms were reported by 6%, more frequently in patients over 50 years old – which may be  
4 attributable to dry eye and concomitant ocular conditions contributing to symptom severity. AC was  
5 associated with skin test positivity to all allergen classes except mold.

6  
7 Similar AC prevalence trends are echoed globally,<sup>236-241</sup> with higher rates noted in some studies. In one  
8 report, 95% of 187 Australian patients with allergist-diagnosed AR reported ocular allergy.<sup>242</sup> A Swiss  
9 survey of hay fever patients showed 85% prevalence of concomitant nasal and eye symptoms.<sup>243</sup> A  
10 cross-sectional Italian study of 2150 adolescents determined that more than half of the respondents  
11 with AR also had AC.<sup>240</sup> Comorbid AC also conferred an increased risk of asthma (OR 5.23) versus AR  
12 alone (OR 2.28).<sup>240</sup>

13  
14 The largest global data source regarding the AR-AC association derives from the ISAAC investigations, a  
15 series of worldwide studies established in 1991 with the aim of investigating the epidemiology of allergic  
16 diseases. ISAAC used a standardized questionnaire and obtained unified assessments of the time trends  
17 of the global prevalence in different regions or countries. Current rhinoconjunctivitis was defined as self-  
18 reported “current rhinitis” along with a positive answer to “In the past 12 months, has this nose problem  
19 been accompanied by itchy-watery eyes?”

20  
21 ISAAC Phase 1 reported AC prevalence in 257,800 children aged 6-7 years in 91 centers (38 countries)  
22 and 463,801 children aged 13-14 years in 155 centers (56 countries). Although the ISAAC survey was not  
23 validated for the diagnosis of AC, ISAAC studies support the frequent association of AR with itchy/watery  
24 eyes; Phase I results revealed that ocular symptoms affect 33-50% of children with AR.<sup>244</sup> ISAAC Phase 3  
25 analyzed temporal trends in prevalence of allergic rhinoconjunctivitis over 7 years in the two age groups  
26 (n=498,083). There was a global increase in rhinoconjunctivitis prevalence, with considerable  
27 heterogeneity between test centers. The average overall prevalence of allergic rhinoconjunctivitis was  
28 14.6% for adolescents.<sup>233</sup>

29  
30 Recently, the Global Asthma Network used ISAAC methodology to update the prevalence of pediatric  
31 atopic diseases.<sup>234</sup> The study surveyed 74,361 adolescents and 45,434 6-7-year-olds from 27 centers (14  
32 countries). Overall, the prevalence of current rhinoconjunctivitis had decreased slightly from ISAAC

1 Phase 3 among young children (-0.44%) and adolescents (-1.32%). Additionally, an analysis of 2914  
 2 patients from the Alergológica 2015 study revealed AC in one-third of participants, and AC was  
 3 associated with AR in 88%.<sup>245</sup> The duration and severity of AC was also associated with that of AR  
 4 ( $p<0.001$ ).

5  
 6 Underreporting of ocular allergy may be attributable to symptom variability and increased attention to  
 7 non-ocular allergy symptoms. Although the burden of illness (i.e., QOL impairment) associated with AC is  
 8 established,<sup>246</sup> AC is often underrecognized and undertreated except when severe.<sup>231</sup> More than half of  
 9 AR patients endorsed that red/itchy/watery eyes were moderately to extremely bothersome in the  
 10 Allergies in America Survey.<sup>247</sup> Another survey of allergic rhinoconjunctivitis patients (n=2765) ranked  
 11 red/itchy eyes as the second most bothersome symptom after nasal obstruction.<sup>248</sup>

12  
 13 Ocular allergy symptoms also contribute significantly to QOL impairment associated with AR. Ocular  
 14 symptoms of allergic rhinoconjunctivitis are among the most common symptoms which cause patients  
 15 to seek allergy treatment.<sup>248</sup> When assessing AR patients, one should evaluate ocular symptoms and  
 16 consider treatment specific to AC. AIT may have a role in AC management; however, most studies  
 17 investigating AIT efficacy have studied allergic rhinoconjunctivitis rather than AC alone.<sup>249</sup> In a  
 18 prospective study of patients with AC receiving SCIT or SLIT, both groups had similar rates of clinical  
 19 improvement in terms of decreased symptoms, medications, IgE and skin test wheal diameters after 1  
 20 year.<sup>250</sup>

21  
 22 **Aggregate grade of evidence:** C (Level 2: 4 studies, level 3: 8 studies; **TABLE XIII.C.**)  
 23  
 24

**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 <sup>234</sup>	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 <sup>238</sup>	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 <sup>239</sup>	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 <sup>235</sup>	2010	2*	Cross-sectional survey	NHANES III participants (n=33,994), 1988-1994	Describe the epidemiology of AC in the United States	-40% adults with AC -Isolated ocular symptoms reported by 6% -30% prevalence of concomitant AR and AC
Sanchez-Hernandez et al <sup>245</sup>	2021	3	Retrospective cohort analysis	Patients referred for allergy evaluation, n=2914	-History -Skin test -sIgE -Provocation tests	-33% diagnosed with AC - AC associated with AR in 88% of cases -Duration and severity of AC associated with that of AR (p<0.001)
Williams et al <sup>242</sup>	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 <sup>251</sup>	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 <sup>252</sup>	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 <sup>236</sup>	2009	3	Cross-sectional	Patients referred for allergy evaluation (n=4991), <i>Alergologica</i> 2005	Characteristics of patients with AR	55% of patients diagnosed with AR, 65% had associated AC
Gradman & Wolthers <sup>241</sup>	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
Kosrirkvongs et al <sup>237</sup>	2001	3	Observational cohort	445 patients (24.5 +/- 16.3 years old), history of itching, foreign body sensation, lacrimation, red eyes	-Physical examination -Skin prick test	-73.8% of patients with perennial AC had associated AR -Most common sensitization was house dust mite
Wuthrich et al <sup>243</sup>	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%
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1 LOE=level of evidence; RC=rhinoconjunctivitis; ISAAC=International Study of Asthma and Allergies in Childhood;  
2 AR=allergic rhinitis; AC=allergic conjunctivitis; OR=odds ratio; CI=confidence interval; sIgE=specific immunoglobulin  
3 E; NHANES=National Health and Nutrition Examination Survey  
4 \*LOE upgraded due to very large sample size

5

6

### 7 XIII.D. Atopic dermatitis

8

9 AD is a chronic/relapsing, inflammatory skin disorder characterized by recurrent eczematous lesions and  
10 pruritis that affects all ages and ethnicities.<sup>253</sup> AD is the leading cause of the global burden from skin  
11 disease.<sup>254</sup> AD is associated with increased risk of multiple allergic comorbidities, including food allergy,  
12 asthma, and AR.<sup>253,255</sup> AD that starts in infancy usually precedes the development of other atopic  
13 diseases, and therefore, is considered the first step of the “atopic march,” or an early marker of the  
14 predisposition toward type I hypersensitivity.<sup>256,257</sup>

15

16 AD and AR are the most prevalent allergic diseases, but many epidemiological studies focus on asthma;  
17 only 15.7% and 24.5% of epidemiological studies provide data on AD and AR, respectively.<sup>255</sup> Studying  
18 the epidemiology of AR and its comorbidities, in particular AD, is complicated by different disease  
19 definitions and reporting, and different testing to confirm diagnoses. In one study, for example, less  
20 than half of all patients reporting AR had a physician-confirmed diagnosis of AR.<sup>258</sup> Therefore, the link  
21 between AR and AD remains poorly defined due to methodologic differences and limitations of the  
22 studies that have examined this association.<sup>7,259-270</sup> **[TABLE XIII.D.]**

23

24 The largest study to assess the association between AR and AD was based on data collected in the ISAAC  
25 study, which started in 1991 and aimed to investigate the epidemiology and etiology of asthma, rhinitis  
26 and AD in each country using standard questionnaires, SPT, and flexural dermatitis examination.<sup>271</sup> The  
27 study involved 256,410 children age 6-7 years in 90 centers from 37 countries, and 458,623 children age  
28 13-14 years in 153 centers from 56 countries, demonstrating a prevalence of AD between 5-20%.<sup>271</sup>  
29 Several longitudinal studies show improvement or resolution of AD with age, but children often remain  
30 atopic for the rest of their lives with a prevalence of AR among those with AD ranging from 15-61%.<sup>272-275</sup>

31

32 Multiple studies performed in different countries and age groups, using a variety of methodologies,  
33 conclude that there is a disease association between AR and AD. The available evidence suggests that

1 there is a 2-4-fold increase in AR among people with AD.<sup>7,259-269,276</sup> For example, in the cross-sectional  
 2 multicenter study titled “Epidemiology of Allergic Diseases in Poland” conducted in children age 6-7 and  
 3 13-14 years and adults aged 20-44 years, allergic diseases were common in children and young adults.  
 4 Single disease AR occurred in 29.3% and AD in 7.2%. A single disease (asthma, AR, or AD) was observed  
 5 in 27.7% of the subjects and allergic multimorbidity was noted in 9.3%. Allergic multimorbidity was more  
 6 common in children (10.7-10.9%) than in adults. There was an increasing risk of multimorbidity  
 7 depending on the number of positive SPTs.<sup>269</sup>

8  
 9 High prevalences of AR and AD were also shown in an independent Phase 3 follow-up study of  
 10 unselected 8<sup>th</sup>-grade school children in Denmark participating in the Odense Adolescence Cohort Study.  
 11 The participating children were reassessed after reaching 28-30 years of age. The lifetime prevalence of  
 12 atopic diseases increased significantly from adolescence (31%) to adulthood (57%), particularly AR  
 13 (incidence 17.5/1000 person-years). The lifetime prevalence of AD was 34.1%. Childhood predictors for  
 14 adult AR were AR, asthma, asymptomatic sensitization to pollen and AD (OR 1.7; 95% CI 1.1-2.5,  
 15 p=0.021). Seven percent of subjects with AD developed AR.<sup>263</sup>

16  
 17 The Canadian Healthy Infant Longitudinal Development study recruited pregnant women from the  
 18 general population across four Canadian provinces and followed them until their children were 5 years  
 19 old. The authors defined five distinct classes of individuals: healthy (81.8%), AD (7.6%), inhalant  
 20 sensitization (3.5%), transient sensitization (4.1%), and persistent sensitization (3.2%). Children in the AD  
 21 groups were at increased risk of developing AR (OR 2.36; 95% CI 2.13-2.62).<sup>265</sup>

22  
 23 The increased risk of AR in patients with AD has been seen in multiple studies using different research  
 24 strategies (i.e., prospective, population-based, cross-sectional) in different age groups and in different  
 25 continents (Asia, Europe). This supports the notion that AR and AD are related diseases.<sup>7,259-269</sup>

26  
 27 **Aggregate grade of evidence:** C (Level 2: 16 studies, level 3: 12 studies, level 4: 3 studies; **TABLE XIII.D.**)

28

29 **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 <sup>267</sup>	2021	2	Prospective longitudinal cohort	Children with AD/eczema in Cincinnati	-SPT -Symptoms upon allergen exposure	AD associated with AR (-asthma) in White (3x risk) and Black (6x risk) children

				enrolled $\leq 2$ years old, n=601		
Schoos et al <sup>262</sup>	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 ( $\leq 1$ year) and more severe AD associated with aeroallergen sensitization and AR in childhood
Pedersen et al <sup>7</sup>	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 <sup>259</sup>	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 <sup>263</sup>	2019	2	Observational cohort	Follow-up cohort of 8 <sup>th</sup> 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 <sup>265</sup>	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)
Schneider et al <sup>275</sup>	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 <sup>276</sup>	2015	2	Cohort	Follow-up cohort of 8 <sup>th</sup> 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 <sup>277</sup>	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 <sup>278</sup>	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 <sup>279</sup>	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 <sup>280</sup>	2006	2	Cross-sectional	Students in 3 <sup>rd</sup> , 4 <sup>th</sup> , 5 <sup>th</sup> 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 <sup>281</sup>	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 <sup>282</sup>	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 <sup>283</sup>	2001	2	Cross-sectional	Otolaryngology patients in Korea, n=71,120	-Questionnaire -Rhiniologic exam -SPT -slgE	-Prevalence of perennial AR 3.93% -AD associated with perennial AR in 20.9%
Leung & Ho <sup>284</sup>	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 <sup>261</sup>	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 <sup>264</sup>	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 <sup>266</sup>	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 <sup>285</sup>	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 <sup>286</sup>	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 <sup>287</sup>	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 <sup>288</sup>	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 <sup>289</sup>	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 <sup>273</sup>	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 <sup>274</sup>	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 <sup>290</sup>	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 <sup>291</sup>	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 <sup>270</sup>	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 <sup>260</sup>	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 <sup>268</sup>	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%)

1 LOE=level of evidence; AD=atopic dermatitis; SPT=skin prick test; AR=allergic rhinitis; ISAAC= International Study  
2 of Asthma and Allergies in Childhood; sIgE=specific immunoglobulin E; OR=odds ratio; tIgE=total immunoglobulin  
3 E; HDM=house dust mite; RR=relative risk; UK=United Kingdom  
4  
5

### 6 XIII.E. Food allergy

#### 7 XIII.E.1. Pollen food allergy syndrome

8  
9 Immune responses to foods may produce a spectrum of symptoms and disorders including pollen food  
10 allergy syndrome (PFAS; also known as oral allergy syndrome [OAS]).<sup>292,293</sup> PFAS is an IgE-mediated  
11 allergy which localizes to the oral mucosa, leading to transient itching, perioral hives, angioedema, and  
12 rarely systemic symptoms. Patients with pollen allergies may have allergic reactions confined to the oral  
13 cavity after consuming specific fruits, vegetables, nuts, or spices. PFAS symptoms manifest as a result of  
14 cross-reactivity of IgE specific for an offending pollen with highly homologous proteins found in a variety  
15 of fruits, vegetables, and nuts. The most common example of this cross-reactivity in Western  
16 populations is birch pollen and apples, which is due to the high degree of sequence homology between  
17 Bet v 1 (major allergen of birch pollen) and Mal d 1 (major allergen of apple), leading to IgE-mediated  
18 cross-reactivity.<sup>294</sup> **TABLE XIII.E.1.-1** lists common pollen allergens with plant-derived foods that may  
19 demonstrate cross-reactivity.<sup>295</sup> A 2018 review by Carlson et al<sup>296</sup> reported PFAS prevalence ranged from  
20 4.7% to over 20% among children and 13-58% among adults, with prevalence varying widely by  
21 geographic region. A study conducted in 1360 Italian children with pollen-related AR noted that a longer  
22 duration of AR symptoms was related to developing PFAS, suggesting that individuals living in areas with  
23 more pollen seasons have a higher rate of PFAS, possibly reflecting the higher range of prevalence in  
24 adults.<sup>297,298</sup> **TABLE XIII.E.1.-2** summarizes the evidence link between PFAS and AR.

25  
26 The diagnosis of PFAS is typically established by a detailed history and physical exam that explores a  
27 given patient's underlying allergy to pollen and raw foods with shared homologous proteins. As per the

1 Joint Task Force Practice Parameters, sIgE testing to pollens is recommended in patients with a  
2 suggestive clinical history.<sup>299</sup> The estimated rates of systemic and anaphylactic reactions from a pollen-  
3 food allergy are 10% and 2-10%,<sup>300,301</sup> respectively, and such a history must be thoroughly elicited. The  
4 gold standard for establishing a diagnosis of PFAS is a double-blind food challenge, but this can still be  
5 confounded by biases inherent to the appearance, texture, and taste of foods.<sup>302</sup> It is important to note  
6 that skin testing using commercially available fruit or vegetable extracts may not be useful as the  
7 allergens are heat labile.<sup>303</sup> Oral food challenge, SPT, and food sIgE levels have also been used to  
8 diagnose PFAS or food allergy.<sup>296,304-306</sup> Another technique that has also shown promise in accurate  
9 diagnosis of PFAS and food allergy is component-resolved testing utilizing pure and potentially cross-  
10 reactive allergenic components in certain foods.<sup>307</sup> This has been demonstrated in refining diagnosis of  
11 true peanut allergy, where the component Ara h 2 has been identified as a better predictor of clinical  
12 allergy.<sup>308</sup>

13

14 The standard recommendation for the treatment of PFAS has been to identify and eliminate offending  
15 foods from the diet. There is no consensus on whether patients should be provided auto-injectable  
16 epinephrine.<sup>301</sup> Some pollen-associated foods may lose their cross-reactivity potential once the often-  
17 labile proteins are denatured by heat. In one study, food challenges were performed with cooked apple,  
18 carrot, or celery in patients with AD and birch pollen allergy, who reported OAS and dermatologic  
19 symptoms upon ingestion of the raw foods.<sup>309</sup> Cooked versions of the offending foods did not cause oral  
20 allergy symptoms.

21

22 Several studies have evaluated the effect of targeted AIT for pollen allergy at reducing PFAS symptoms  
23 with mixed results. There has been some published evidence of pollen-specific AIT resulting in increased  
24 tolerance to the PFAS-associated offending foods.<sup>309-312</sup> However, one RCT failed to demonstrate any  
25 improved tolerance to apple in birch allergic patients treated with birch specific AIT compared to  
26 placebo.<sup>302</sup> One study evaluating the persistence of tolerance for apple after birch AIT demonstrated  
27 that AIT resulted in increased apple tolerance for some patients up to 30 months; however, there was  
28 no difference between the AIT and control groups.<sup>311</sup> Currently, AIT is not recommended for the sole  
29 purpose of treating PFAS, although patients receiving AIT should be counseled on the potential benefit  
30 of improved food tolerance. **[TABLE XIII.E.1.-3]**

31

1 **Aggregate grade of evidence:** C (Level 3: 3 studies, level 4: 5 studies, Level 5: 5 studies; **TABLE XIII.E.1.-**  
 2 **2)** for link between AR and PFAS, including cross-reactivity; C (Level 2: 2 studies, Level 3: 2 studies;  
 3 **TABLE XIII.E.1.-3)** for AIT in treatment of PFAS

4  
 5 **TABLE XIII.E.1.-1 Pollen-food allergy cross-reactivity<sup>313</sup>**

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

6  
 7 **TABLE XIII. E.1.-2 Evidence table – Association between allergic rhinitis and pollen-food allergy**  
 8 **syndrome**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
de Jong et al <sup>304</sup>	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 <sup>297</sup>	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 <sup>302</sup>	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 <sup>314</sup>	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 <sup>305</sup>	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 <sup>315</sup>	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 <sup>300</sup>	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 <sup>294</sup>	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 <sup>316</sup>	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 <sup>317</sup>	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 <sup>318</sup>	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 <sup>296</sup>	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
Katellaris <sup>293</sup>	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

1 LOE=level of evidence; AR=allergic rhinitis; PFAS=pollen-food allergy syndrome; IgE=immunoglobulin E; FA=food  
2 allergy; OR=odds ratio; CI=confidence interval  
3

1 **TABLE XIII. E.1.-3 Evidence table – Allergen immunotherapy as a treatment for pollen-food allergy**  
 2 **syndrome**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Mauro et al <sup>312</sup>	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 <sup>309</sup>	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 <sup>310</sup>	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 <sup>311</sup>	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

3 LOE=level of evidence; RCT=randomized controlled trial; AIT=allergen immunotherapy; AR=allergic rhinitis;  
 4 SCIT=subcutaneous immunotherapy; PFAS=pollen-food allergy syndrome

### 7 XIII.E.2. Anaphylactic food allergy

8  
 9 Like AR, food allergy may be driven by an IgE-mediated response and as a result may sometimes lead to  
 10 anaphylactic reactions.<sup>319</sup> There is an abundance of consistent evidence, largely in the form of large  
 11 sample cross-sectional and retrospective analyses, that the occurrence of food allergy is independently  
 12 associated with AR.<sup>314,317,318,320-332</sup> [TABLE XIII.E.2.] In an analysis of over 8000 families, Alm et al<sup>327</sup> found  
 13 a strong, independent association between the development of food allergy and AR (OR 10.21; 95% CI  
 14 4.22-24.73). A separate analysis of more than 300,000 children by Hill et al<sup>326</sup> found that a diagnosis of  
 15 FA was highly associated with later development of AR (OR 2.72; 95% CI 2.45-3.03).

16  
 17 Peanut allergy is one of the most common and well-studied food allergies, and its prevalence has been  
 18 linked to AR in the existing literature.<sup>326,333-335</sup> Similarly, AR is a relatively more common atopic condition  
 19 among people with allergies to shellfish,<sup>315,326,336,337</sup> and specifically shrimp.<sup>315,336,338</sup> Identifying infants at  
 20 high risk of peanut allergy and introducing peanuts to them early can significantly decrease the  
 21 frequency of developing peanut allergy;<sup>339,340</sup> however, it is currently unclear whether such measures

1 can have a protective effect on developing AR in the future.<sup>341</sup> There is reported low- to very low-  
 2 certainty evidence that early fish introduction to the diet before age 6-12 months can be associated with  
 3 reduced AR before age 14.<sup>342</sup>

4  
 5 Long-term management of food allergies mainly includes identification and avoidance of each food item  
 6 and provision of counseling regarding food-related systemic or anaphylactic reactions; in some  
 7 circumstances, oral immunotherapy may be an option. Epinephrine auto-injectors with associated  
 8 instructions for use should be provided to patients who are at risk for anaphylactic reactions.<sup>343,344</sup>  
 9 Finally, there are ongoing studies investigating several possible type 2 targeted biologics in treatment of  
 10 food allergy.

11  
 12 It is suggested that AIT is perhaps the only possible disease-modifying treatment for allergic diseases by  
 13 inducing long-term tolerance against specific allergens.<sup>345</sup> AIT prompts the inhibition of early and late-  
 14 phase allergic responses and induction of immunological tolerance of AR and food allergy via diverse  
 15 mechanisms on T cells (e.g., Th1/2, T reg), regulatory B cells, innate lymphoid cells, dendritic cells, mast  
 16 cells, eosinophils, and basophils.<sup>345</sup> When studied separately, AIT treatment has been shown to lead to  
 17 several years of symptomatic remission in AR<sup>346,347</sup> or sustained responsiveness for various food  
 18 allergies.<sup>348,349</sup>

19  
 20 **Aggregate grade of evidence:** C (Level 1: 1 study, level 2: 3 studies, level 3: 6 studies, level 4: 9 studies,  
 21 level 5: 1 study; **TABLE XIII.E.2.**)

22  
 23 **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 <sup>342</sup>	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 $\leq 4$ 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 <sup>334</sup>	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 <sup>323</sup>	2020	2	Cross-sectional survey	Nationally representative sample	Prevalence of shellfish food	History of AR independently associated



				of US children, n=38,408	allergy, associated factors	with shellfish allergy (OR 2.0; 95% CI 1.4-2.9)
Alm et al <sup>327</sup>	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 <sup>338</sup>	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 <sup>331</sup>	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 <sup>329</sup>	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 <sup>325</sup>	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 <sup>335</sup>	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 <sup>337</sup>	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 <sup>320</sup>	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 <sup>333</sup>	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 <sup>328</sup>	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 <sup>322</sup>	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 <sup>324</sup>	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 <sup>332</sup>	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 <sup>330</sup>	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 <sup>326</sup>	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 <sup>321</sup>	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 <sup>336</sup>	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
--------------------------------------	------	---	-----------------	---	---	--

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; OR=odds ratio; CI-  
2 confidence interval; US=United States; HDM=house dust mite; IgE=immunoglobulin E; RR=relative risk; FPIES= food  
3 protein-induced enterocolitis syndrome

4 \*LOE downgraded due to peripheral focus of study

### 7 XIII.F. Adenoid hypertrophy

8  
9 Children with AH and AR may exhibit similar symptoms including nasal obstruction and rhinorrhea.

10 Adenoids commonly enlarge through the preschool years but typically involute with puberty.<sup>350,351</sup>

11  
12 Literature evaluating the relationship between AH and allergic sensitization draws from two  
13 populations. The first is allergic children assessed for AH. Several studies assessing allergic children  
14 found an association with AH. In one study, the prevalence of AH in 1322 allergic children (12.4%) was  
15 higher than in 100 age-matched non-allergic controls (3%),  $p < 0.0001$ .<sup>352</sup> Similarly, Dogru et al<sup>353</sup> found a  
16 relatively high rate (21.2%) of AH amongst 566 children with AR. Modrynksi and Zawisza<sup>354</sup> reported that  
17 seasonal adenoid enlargement in birch pollen allergic children was more frequent than in controls but  
18 the increased adenoid size resolved after pollen season. However, this study was small (n=67) and did  
19 not comment on blinding. **[TABLE XIII.F.]**

20  
21 Three cohort studies have assessed the relationship of mold sensitivity and AH with mixed results. Atan  
22 Sahin et al<sup>355</sup> compared 242 children living in an arid environment to 142 children living on the coast and  
23 found no correlation between mold and pollen sensitization with AH. However, HDM-sensitive children  
24 in the coastal group had an increased prevalence of AH ( $p=0.01$ ). Huang and Giovanni<sup>356</sup> compared 315  
25 children who had AH with AR to age-matched controls with AR alone and found a higher prevalence of  
26 mold sensitivity in AH with AR versus AR alone ( $p=0.013$  to  $p < 0.0001$ ). Dogru et al<sup>353</sup> also reported an  
27 increased sensitization to *Alternaria* in the AH with AR group compared to AR alone ( $p=0.032$ ).

28  
29 The second population studied is children suspected of AH who are assessed for allergic sensitization;  
30 these studies also have mixed results. Cassano et al<sup>351</sup> reported that inhalant allergen sensitization  
31 decreased as AH size increased. Karaca et al<sup>357</sup> compared allergy sensitization to radiographic adenoid

1 size in 82 children and found no association. Ameli et al<sup>358</sup> assessed 205 children with nasal endoscopy  
2 and SPT and found a negative association between SPT positivity and adenoid volume ( $p < 0.0001$ ).  
3 Conversely, Sadeghi-Shabestari et al<sup>359</sup> compared SPT results and IgE levels amongst 117 children with  
4 adenotonsillar hypertrophy (ATH) and 100 controls. Over 70% of the ATH group had a positive SPT  
5 versus 10% of the control group ( $p = 0.04$ ), but this study is limited by the inclusion of SPT for foods  
6 (highest positive allergen subgroup) and latex.

7  
8 In two additional studies, children referred from allergy practices were assessed for both AH with nasal  
9 endoscopy and SPT sensitivity. Both studies excluded children on allergy medication and observed a  
10 significant negative correlation between AH and SPT positivity ( $r = -0.208$ ,  $p = 0.009$ )<sup>360</sup> and ( $p = 0.04$ ).<sup>361</sup> The  
11 variability in study population recruitment and age range may explain the mixed findings.

12  
13 Several studies have found immunologic evidence of allergic physiology in adenoid tissue. Ni et al<sup>362</sup>  
14 found a higher Th17/Treg ratio in adenoid tissue from children with AR versus non-allergic controls.  
15 Masieri et al<sup>363</sup> reported Th1 gene expression in non-allergic adenoid tissue, Th1 and Th2 gene  
16 expression in adenoid tissue of children with AH and AR, and downregulation of Th1 and Th2 gene  
17 expression in adenoid tissue during SLIT. Zhu et al<sup>364</sup> found increased tissue eosinophilia and markers of  
18 Th2 inflammation in the adenoid tissue of children with AH with AR, compared to AH alone. Local allergy  
19 may also play a role. One cohort of 102 children with ATH showing 53.9% sero-atopy and 68.6% with  
20 sIgE detected in their adenotonsillar tissue. sIgE positive adenoid tissue was found in 36.2% of the sero-  
21 negative children.<sup>365</sup> Independently, Shin et al<sup>366,367</sup> detected HDM and *Alternaria* local sIgE in adenoid  
22 tissue. Therefore, studies of allergic markers in adenoid tissue are present more often in atopic children,  
23 and there is some evidence of local allergic sensitization in children testing negative for sero-atopy.

24  
25 The effect of INCS on reducing nasal obstruction in the setting of AH has been demonstrated in  
26 systematic reviews and is independent of allergy.<sup>368,369</sup> Whether INCS reduce adenoid size is unclear.<sup>370</sup>  
27 One retrospective study ( $n = 47$ ) reported improvement in rhinitis symptoms in similar percentages of AR  
28 (86%) and non-allergic rhinitis (76%) after adenoidectomy.<sup>371</sup> At least one study suggests that AR is a risk  
29 factor for refractory nasal symptoms after adenoidectomy.<sup>372</sup>

30  
31 In summary, AH occurs in allergic children more often than non-allergic controls.<sup>352-354</sup> A recent  
32 systematic review concluded that clinical and biomarker evidence favored an association between

1 allergy and AH.<sup>373</sup> However, in children referred to otolaryngology for nasal obstruction, the association  
 2 between allergic sensitivity and AH is inconsistent.<sup>351,357,358,360,361</sup> One possible explanation for this  
 3 discrepancy is that symptomatic AH peaks earlier in childhood than AR. This is supported in the  
 4 literature by Pagella et al,<sup>374</sup> who reviewed records of children referred to otolaryngology for nasal  
 5 symptoms (n=795) and found no association between AR and AH in children aged 1-7 years (p=0.34), but  
 6 noted an association for children aged 8-14 years (p=0.0043).

7  
 8 **Aggregate grade of evidence:** C (Level 2: 1 study, level 4: 12 studies; **TABLE XIII.F.**)  
 9

10 **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 <sup>373</sup>	2021	2*	Systematic review	-Allergy -Adenotonsillar disease	-Clinical evidence -Biomarkers	Qualitative link between allergy and AH/ATH
Karabulut et al <sup>361</sup>	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 <sup>353</sup>	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 <sup>355</sup>	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 <sup>360</sup>	2015	4	Consecutive cohort	Children referred from pediatric allergy to otolaryngology	-Endoscopic adenoid size -SPT	AH negatively correlated with (+) allergy testing
Evcimik et al <sup>352</sup>	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 <sup>374</sup>	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 <sup>358</sup>	2013	4	Consecutive cohort	Children with persistent upper airway obstruction	-Endoscopic adenoid size -SPT	Adenoid volume and % not associated with allergy
Karaca et al <sup>357</sup>	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 <sup>359</sup>	2011	4	Retrospective cohort	-ATH -No ATH	SPT for food, inhalant, and latex	-ATH & positive SPT 70.3% -No ATH & positive SPT 10%
Mordzynski & Zawisza <sup>354</sup>	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 <sup>351</sup>	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 <sup>356</sup>	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

1 LOE=level of evidence; AH=adenoid hypertrophy; ATH=adenotonsillar hypertrophy; SPT=skin prick test; AR=allergic  
2 rhinitis; IgE=immunoglobulin E; RAST=radioallergosorbent test; LRTI=lower respiratory tract infection

3 \*LOE downgraded due to low quality of included studies

4

5

### 6 XIII.G. Otologic conditions

#### 7 XIII.G.1. Eustachian tube dysfunction

8

9 The Eustachian tube (ET) is a bony and cartilaginous canal that connects the middle ear to the

10 nasopharynx and functions to equalize pressure between the middle ear and the environment, protect

11 the middle ear from harmful sounds and nasopharyngeal pathogens, and provide mucociliary clearance

12 of middle ear secretions.<sup>375,376</sup> Obstructive ETD refers primarily to ventilatory dysfunction and is

13 considered to have multifactorial etiologies including inflammation around the ET orifice (e.g., upper

1 respiratory tract infection, rhinosinusitis, reflux), pressure dysregulation (e.g., air travel, scuba diving),  
2 and obstructive lesions (e.g., nasopharyngeal tumor, AH). Evidence suggests a causal role of AR in the  
3 etiology of ETD due to allergic secretions, nasal mucosa edema, and hypersecretion of nasal cavity  
4 seromucous glands, all resulting in obstruction of the ET lumen.<sup>377-379</sup>

5

6 Data supporting a causal role of AR in the development of ETD comes from experimental studies using  
7 intranasal and transtympanic allergen challenges. Multiple studies have demonstrated transient ETD  
8 following allergen challenges in adult and pediatric subjects with<sup>380-383</sup> and without AR,<sup>378</sup> as well as in  
9 animal models,<sup>384-386</sup> although ET responses have not been found to correlate with IgE levels.<sup>379</sup> [TABLE

#### 10 **XIII.G.1.]**

11

12 In addition to experimental evidence suggesting a link between AR and ETD, observational data also  
13 supports this association. For example, ET obstruction is observed during natural exposure to allergens  
14 during pollen season, even without subjects being intranasally or transtympanically challenged.<sup>387,388</sup>

15 Furthermore, in a representative adult cohort from the NHANES data, odds of reporting allergies was  
16 1.71 times higher in subjects with ETD compared to those without ETD.<sup>389</sup> Similarly, a pediatric  
17 population study found that significantly more children with AR had abnormal tympanograms compared  
18 to those without AR.<sup>390</sup> Histologically, increased levels of allergic cytokines such as IL-4, IL-5, and  
19 eosinophils have been found at both ends of the ET,<sup>376</sup> suggesting that an allergic response could be  
20 activated at the ET in sensitized patients.

21

22 However, despite both experimental and observational data supporting an association between allergy  
23 and ETD, studies have failed to consistently demonstrate improvement in ETD and its associated  
24 symptoms with allergy treatment. Gluth et al<sup>391</sup> found no significant normalization of abnormal  
25 tympanometric signs and no improvement in ETD symptoms between patients treated with INCS and  
26 those in placebo groups, and a clinical consensus statement found no role for systemic decongestants,  
27 antihistamines, nasal topical decongestants, or INCS in the diagnosis or treatment of patients with  
28 ETD.<sup>392</sup> On the other hand, Pollock et al<sup>393</sup> found that ETD could be prevented in sensitized rats when  
29 pre-treated with IL-4 receptor decoys, and Derebery et al<sup>394</sup> reported improvement in the ETD symptom  
30 of ear fullness in allergic patients treated with AIT in a retrospective case series (although the presence  
31 of reported food allergy in this group may confound the results).

32

1 Overall, there is experimental and observational evidence to support a causal role of allergy in the  
 2 development of ETD. However, the exact pathophysiologic mechanism behind this association is unclear  
 3 since not all patients with ETD have AR, and traditional allergy treatment has not consistently shown  
 4 benefit in reducing symptoms of ETD.

5

6 **Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 12 studies, level 4: 3 studies; **TABLE XIII.G.1.**)

7

8 **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 <sup>391</sup>	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 <sup>385</sup>	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 <sup>393</sup>	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 <sup>384</sup>	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 groups)



Hardy et al <sup>386</sup>	2001	3*	Randomized observational	Rats randomly assigned to receive: -SC injection of OVA followed by transtympanic injection of OVA, n=7 -No SC injection of OVA followed by OVA in PBS, n=5 -No SC injection of OVA followed by PBS only, n=5	-Passive opening and closing pressures of the ET -Active clearance of positive and negative pressure -MCTT	Sensitized rats had significant increases in passive and active opening pressures, decreased ability to actively clear middle ear pressure, and impaired MCTT
Knight et al <sup>388</sup>	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 <sup>378</sup>	1991	3	Cohort	Intranasal challenge of increasing doses of histamine, methacholine, bradykinin, PGD <sub>2</sub> , and PGE <sub>2</sub> 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 PGD <sub>2</sub> , 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 <sup>387</sup>	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 <sup>379</sup>	1989	3	Cohort	Intranasal challenge of increasing doses of ragweed and histamine in subjects with ragweed AR before, during, and after ragweed season; n=8	-Rhinomanometry for nasal patency -Sonotubometry for ET function	-Mean ET obstruction dose for histamine decreased during and up to 6 weeks after ragweed season vs preseason and 3–5 months postseason doses -ET hyperresponsiveness to ragweed limited to the ragweed season Responses did not correlate with serum IgE
Skoner et al <sup>382</sup>	1987	3**	Double-blind crossover	-Adults with AR, n=5 -Adults without AR, n=5	-Nine-step tympanometric ET function test	-All AR subjects had ET obstruction after histamine provocation (56% at 0.1mg, 100% at 0.5mg) -Two non-AR subjects developed ET obstruction following a much higher dose (20% at 5mg) -Remainder did not develop ET obstruction (up to 10mg)

Skoner et al <sup>381</sup>	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 <sup>383</sup>	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 <sup>380</sup>	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 <sup>389</sup>	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 <sup>390</sup>	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 -Palma criteria <sup>395</sup> for children younger than 11 months	-Adults with AR demonstrated a significant difference in tympanogram peak admittance vs controls -15.5% of children with AR and 0% of controls had abnormal tympanograms (p=0.03)
Derebery et al <sup>394</sup>	1997	4	Retrospective case series	Patients with ETD and positive allergy testing (100% reactivity to inhalants and 92.3% positivity to one or more foods) who had undergone allergy treatment with immunotherapy and diet (n=151)	Ratings of fullness, allergy symptoms, and well-being as "improved", "no change", or "worse"	Majority improved on all three symptoms - fullness 70.9%, allergy symptoms 82.8%, and well-being 80.2%

1 LOE=level of evidence; RDBPCT=randomized double-blind placebo-controlled trial; TAA-AQ=triamcinolone  
2 acetonide aqueous; ETD=Eustachian tube dysfunction; PBS=phosphate buffered saline; ET=Eustachian tube;  
3 MCTT=mucociliary clearance time of the tubotympanum; IL=interleukin; OVA=ovalbumin; OME=otitis media with  
4 effusion; SC=subcutaneous; AR=allergic rhinitis; PG=prostaglandin; IgE=immunoglobulin E; OR=odds ratio  
5 \*LOE downgraded due to animal study  
6 \*\*LOE downgraded due to small sample size  
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### XIII.G.2. Otitis media

1 OME is a common pediatric condition characterized by pressure changes and inflammation in the middle  
2 ear resulting in serous or mucoid fluid buildup behind the tympanic membrane.<sup>396</sup> A relationship  
3 between middle ear effusion (MEE) and allergy and has long been a subject of epidemiologic study. The  
4 reported prevalence of allergy amongst patients with OME has varied widely, from essentially no  
5 difference compared to controls,<sup>397,398</sup> to varying degrees of difference,<sup>399-406</sup> to a near universal  
6 association.<sup>407-412</sup> However, cross-sectional studies and one recent SRMA have reported that AR and  
7 atopy are independent risk factors for OME.<sup>413-415</sup> The inconsistencies of findings in these observational  
8 studies likely represent differences between highly selected populations and OME diagnostic criteria,  
9 variability of allergy testing methods and sensitivities and the challenges of accounting for cofounders,  
10 such as age<sup>416</sup> or OME phenotype.<sup>417</sup> **[TABLE XIII.G.2.]**

11  
12 Proposed pathogenic mechanisms of the development of OME center around Eustachian tube  
13 dysfunction,<sup>418</sup> and theories regarding causal mechanisms that directly link allergy and otitis media  
14 without concurrent Eustachian tube dysfunction are controversial. (*See Section XIII.G.1. Eustachian Tube*  
15 *Dysfunction for additional information on this topic.*) Some have proposed that the middle ear itself can  
16 be a site of targeted allergic reaction.<sup>419</sup> Several cohort studies suggest that the middle ear is capable of  
17 developing a local IgE-mediated inflammatory reaction irrespective of a systemic inflammatory  
18 reaction.<sup>420-423</sup> Additionally, type 2 inflammatory patterns, such as eosinophil growth, mucus production  
19 and mast cell presence, have been found in effusions of atopic patients when compared to non-atopic  
20 patients.<sup>424-426</sup> Furthermore, the chemoattractant cytokine RANTES, ECP, IL-4, IL-5 and MBP were found  
21 to be higher in effusions of atopic children than non-atopic children.<sup>425,427-430</sup> Arguably the strongest  
22 evidence to date directly establishing the middle ear as an allergic target and linking it with the upper  
23 airway is the presence of similar cytokine expression patterns from biopsies of middle ear and  
24 nasopharyngeal specimens in atopic patients with OME.<sup>430</sup>

25  
26 Despite evidence suggesting that the middle ear is a site of allergic inflammation in patients with OME,  
27 high quality evidence has failed to demonstrate significant improvement or resolution of effusions after  
28 traditional allergy treatments. Placebo-controlled RCTs have shown that INCS do not improve OME  
29 outcomes.<sup>431,432</sup> Two Cochrane reviews have demonstrated the statistical ineffectiveness of  
30 antihistamines, decongestants, antihistamine/decongestant combinations, and INCS in resolution of  
31 OME.<sup>433,434</sup> In two RCTs of children with OME, LTRAs provided no benefit over placebo in resolution of  
32 effusions.<sup>435,436</sup> Finally, though one prospective cohort demonstrated a significant improvement in OME

1 after targeted SCIT compared to a group of controls self-selected to avoid AIT, some aspects of the study  
 2 design are flawed, including significant selection bias and inclusion of a generally older population than  
 3 that most affected by OME.<sup>411</sup>

4

5 In summary, observational studies provide low grade evidence of an association between allergy and  
 6 OME. Nevertheless, moderate grade evidence from histologic studies suggest that the middle ear could  
 7 be a primary site of allergy. Additionally, a high level of evidence suggests that traditional allergy  
 8 treatment is not effective in resolving OME.

9

10 **Aggregate grade of evidence:** C (Level 1: 3 studies, level 2: 8 studies, level 3: 1 study, level 4: 24 studies;  
 11 **TABLE XIII.G.2.)**

12

13

**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 <sup>414</sup>	2017	1	SRMA	Comparison of AR between: -OME patients, n=630 -Controls, n=380  Comparison of allergy between: -OME patients, n=1233 -Controls, n=4504	-Prevalence of AR -Prevalence of allergy	OME patients are more likely to have AR (OR 3.06; 95% CI 2.01-4.66) and allergy (OR 3.94; 95% CI 1.60-9.72) than controls
Griffin & Flynn <sup>433</sup>	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 <sup>434</sup>	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 <sup>412</sup>	2020	2	Cross-sectional	Children with OME, n=130	-Prevalence of AR at baseline -Prevalence of AR for pts with	Prevalence of AR in OME children was 52.3% and 80.3% for those with persistent OME

					persistent OME after 3 months	
Byeon <sup>415</sup>	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 <sup>416</sup>	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 <sup>436</sup>	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 <sup>403</sup>	2010	2	Cross-sectional	Primary school-aged children, n=1740	-Prevalence of OME -Prevalence of OME risk factors	-8.7% prevalence of OME -History of allergy was significant OME risk factor
Schoem et al <sup>435</sup>	2010	2	RCT	Children with OME, n=38	Clearance of effusion at 1 month after montelukast or placebo	Montelukast is no more effective than placebo in eliminating effusion
Williamson et al <sup>432</sup>	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 <sup>431</sup>	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 <sup>406</sup>	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 <sup>405</sup>	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 <sup>417</sup>	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 <sup>404</sup>	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 <sup>413</sup>	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 <sup>411</sup>	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 <sup>398</sup>	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 <sup>402</sup>	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 <sup>430</sup>	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 <sup>429</sup>	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 <sup>428</sup>	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- $\alpha$ in effusions of allergy positive group than allergy negative group
Sobol et al <sup>425</sup>	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 <sup>410</sup>	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 <sup>424</sup>	2000	4	Cohort	Patients with OME, n=97	-In vitro allergy tests -Effusion levels of ECP, MPO, tryptase -Serum tIgE	-Atopic patients had higher levels of ECP, MPO and tryptase in effusions vs non-atopic -No difference in serum tIgE
Wright et al <sup>427</sup>	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 <sup>423</sup>	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 <sup>397</sup>	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 <sup>409</sup>	1996	4	Cohort	-Patients with OME, n=73 -Controls, n=16	-Allergy tests -Effusion ECP	Positive allergies in 97% of COME
Corey et al <sup>401</sup>	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 <sup>400</sup>	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 <sup>422</sup>	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 <sup>421</sup>	1983	4	Cohort	Children with OME and history of myringotomy tubes, n=77	-Allergy evaluation -Serum tIgE -Nasal IgE -MEE IgE	Higher levels of IgE in MEE of allergic children than non-allergic children
Borge <sup>399</sup>	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 <sup>420</sup>	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 <sup>407</sup>	1981	4	Case series	Patients with COME, n=119	-RAST	93% of COME patients tested positive to inhalants

1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; OME= otitis media with  
2 effusion; OR=odds ratio; CI=confidence interval; CHL=conductive hearing loss; INCS=intranasal corticosteroid;  
3 MEE=middle ear effusion; tIgE=total immunoglobulin E; RAOM=recurrent acute otitis media; IgE=immunoglobulin  
4 E; AIT=allergen immunotherapy; IL=interleukin; RANTES= regulated upon activation, normal T cell expressed and  
5 secreted; ECP=eosinophil cationic protein; TNF=tumor necrosis factor; MPO=myeloperoxidase; CD=cluster of  
6 differentiation; MBP=major basic protein; sIgE=specific immunoglobulin E; COME=chronic otitis media with  
7 effusion; RAST=radioallergosorbent test; SOM=serous otitis media

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### 10 XIII.G.3. Meniere's and inner ear disease

11

12 Meniere's disease is a chronic condition that occurs almost exclusively in adults and is characterized by  
13 aural fullness, tinnitus, fluctuating sensorineural hearing loss (SNHL), and episodic vertigo. While the  
14 underlying pathophysiologic mechanism of Meniere's disease remains uncertain, it is associated with a  
15 dysregulation of inner ear fluid volume resulting in endolymphatic hydrops.<sup>437</sup> Theories linking allergy to

1 Meniere's disease have centered on the role of the endolymphatic sac in the development of hydrops  
2 and clinical symptoms through its release of allergic mediators or its susceptibility to circulating immune  
3 complexes and dormant viral antigens.<sup>438</sup> A causal relationship between allergy and Meniere's disease is  
4 supported by limited studies, though there have been a number of observations of association between  
5 Meniere's disease and allergic conditions. Patient-reported and physician-reported data suggest that  
6 Meniere's disease patients have higher rates of concurrent AR than expected in the general  
7 population<sup>439</sup> and have increased odds of allergies versus controls.<sup>440</sup> Similar patient-reported data  
8 suggests higher rates of allergy and migraine in Meniere's disease patients.<sup>441</sup> Overall, these studies  
9 generally provide low grade evidence. **[TABLE XIII.G.3.]**

10  
11 Objective evidence of heightened immunopathologic profiles and reactivity in Meniere's disease  
12 patients has been mixed. Higher rates of serum IgE levels were observed in Meniere's disease patients  
13 versus controls,<sup>442,443</sup> as well as in patients with acute low frequency SNHL compared to those with  
14 sudden SNHL.<sup>444</sup> However, in another small study, there was no difference in serum tIgE levels between  
15 Meniere's disease and controls.<sup>445</sup> In two small studies, electrocochleographic summation  
16 potential/action potential [SP/AP] ratios increased in response to allergen challenge in Meniere's  
17 disease patients,<sup>446,447</sup> suggesting that allergy may worsen endolymphatic hydrops. Likewise, serum IgE  
18 levels were found to correlate with elevated SP/AP ratios in patients with low frequency SNHL.<sup>444</sup>  
19 Overall, studies on IgE levels and electrocochleography are of low-grade evidence with significant  
20 shortcomings in design.

21  
22 Lastly, there have been two studies on the treatment of allergies in Meniere's disease patients, both of  
23 low-grade evidence, suggesting that AIT results in improvement of Meniere's disease symptoms in  
24 patients with concurrent allergies (although potentially confounded by inclusion of non-IgE mediated  
25 food allergy).<sup>448,449</sup> However, a double-blind RCT, expected to conclude in April 2022, is being conducted  
26 to investigate the efficacy of a leukotriene inhibitor in reducing vertigo and hearing loss in Meniere's  
27 disease patients.<sup>450</sup> In conclusion, though observational studies have found associations between  
28 Meniere's disease and allergy, no data to date supports reflexive allergy testing and treatment in  
29 Meniere's disease patients without a concurrent history of allergies.

30  
31 **Aggregate grade of evidence:** C (Level 2: 1 study, level 3: 1 study, level 4: 10 studies; **TABLE XIII.G.3.**)

32



1 **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 <sup>440</sup>	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 <sup>449</sup>	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 <sup>444</sup>	2021	4	Case-control	-Sudden SNHL patients, n=127 -Acute low frequency SNHL patients, n=115	-Serum tIgE -Serum sIgE -ECoG SP/AP ratio	-Patients with acute low frequency SNHL have higher serum tIgE and sIgE -High IgE levels correlate with increased SP/AP amplitudes
Roomiani et al <sup>443</sup>	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 <sup>451</sup>	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 <sup>441</sup>	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 <sup>442</sup>	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 <sup>439</sup>	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 <sup>447</sup>	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 <sup>448</sup>	1992	4	Cohort	MD patients with suspected allergy, n=93	-Allergy skin test -In vitro allergy tests -Serum IgE	-82% had normal serum IgE -AIT improved vertigo in 62%

					-Provocative food testing -AIT response	
Viscomi & Bojrab <sup>446</sup>	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 <sup>445</sup>	1990	4	Case-control	-MD patients, n=42 -Controls, n=18	-Serum tIgE	No difference in serum tIgE between groups

1 LOE=level of evidence; MD=Meniere's disease; OR=odds ratio; AIT=allergen immunotherapy; SNHL=sensorineural  
2 hearing loss; tIgE=total immunoglobulin E; sIgE=specific IgE; ECoG=electrocochleography; SP/AP=summation  
3 potential/action potential ratio; IgE=immunoglobulin E; AR=allergic rhinitis; OAE=otoacoustic emissions;  
4 ABR=auditory brainstem response  
5  
6

### 7 XIII.H. Cough

8  
9 Cough clears the lower airways of irritants. Vagal afferent nerves regulate involuntary cough, yet there is  
10 cortical control of the overall visceral cough reflex.<sup>452</sup> AR has been associated with cough. Allergens may  
11 stimulate the nasal mucosa, resulting in the rhinobronchial reflex and bronchospasm.<sup>453</sup> Inflammation in  
12 the upper airways with eosinophil activation and cytokine release may also lead to inflammation of the  
13 lower airways and cough. There is a complex interplay between cells and inflammatory cytokines, and  
14 the upper and lower airways can be considered a single functional unit.<sup>453</sup> The exact pathways and  
15 mechanisms of this unified airway model continue to unfold.  
16

17 Patients with AR and concomitant cough may have asthma and/or a nonspecific bronchial hyper-  
18 reactivity, and generalized inflammation of the upper and lower airways can be present.<sup>119</sup> Patients with  
19 cough and AR may cough due to their underlying asthma. However, many patients with AR and cough  
20 do not have the diagnostic airflow obstruction or bronchodilator-associated FEV<sub>1</sub> reversibility that is  
21 necessary to meet asthma diagnostic criteria.<sup>119</sup> Krzych-Falta et al<sup>454</sup> performed nasal allergen challenges  
22 in AR patients and noted extra-nasal symptoms, including cough and breathlessness, especially in those  
23 with perennial AR. Additionally, Chakir et al<sup>455</sup> showed increased lymphocytes, eosinophil recruitment,  
24 and IL-5 expression in the bronchial mucosa after exposure with natural pollen in patients with AR  
25 without current or prior asthma. The same group noted deposition of type I and III collagens and  
26 fibronectin by bronchial myofibroblasts in patients with AR in a previous study, suggesting structural

1 remodeling of the lower airways in patients with AR which was similar to asthma, albeit less severe.<sup>456</sup> In  
2 an animal model, HDM-sensitized guinea pigs had a significantly enhanced cough response compared to  
3 non-sensitized animals.<sup>457</sup> These studies demonstrate that AR, independent of asthma, may result in  
4 bronchial inflammation, lower airway remodeling, and ultimately cough. [TABLE XIII.H.]

5

6 Several publications in 2016 reported results of relatively large studies evaluating the characteristics of  
7 respiratory diseases in the Asia Pacific region. In a 1000-person cross-sectional observational study, it  
8 was noted that patients with asthma and/or COPD present to physicians with a primary complaint of  
9 cough, whereas AR patients typically present with watery rhinorrhea and/or sneezing.<sup>458,459</sup> In addition,  
10 combined respiratory disease may be seen; this occurred in 33.5%, with the most common combination  
11 being AR and asthma.<sup>458,459</sup> A multi-country observational study of 5250 subjects reported that 47% of  
12 patients with AR reported cough; however, only 11% of these patients reported cough as the main  
13 reason for seeking medical care.<sup>460</sup> Interestingly, for patients with asthma, 61% reported cough, and for  
14 33% cough was the primary reason for seeing medical care. In a prospective study of 2713 patients with  
15 AR, He et al<sup>461</sup> found the prevalence of comorbidities, including cough, to gradually increase with  
16 increasing AR severity and frequency.

17

18 Publications from 2020-2021 provide additional evidence to support the association between cough and  
19 AR. In two RCTs that enrolled patients with either refractory or unexplained cough, concomitant AR was  
20 present in 15% and 20% of patients.<sup>462</sup> Kim et al<sup>463</sup> found that more patients presenting with AR for  
21 allergy testing reported cough in the 2010s (27.9%) compared to the 1990s (22%). Increasing evidence  
22 associates AR with cough or, more commonly, cough as a comorbidity of AR.<sup>455-457</sup> Therefore, diagnostic  
23 and treatment modalities for cough in patients with AR have an increasingly important role.

24

25 Recent studies have proposed FeNO as a tool to differentiate causes of cough in patients with AR.  
26 Elevated FeNO is associated with airway eosinophilia in asthma patients. Elevated FeNO may raise  
27 suspicion for AR in patients with cough variant asthma or cough predominant asthma.<sup>464,465</sup> When AR  
28 and chronic cough are both present, FeNO may be able to differentiate between chronic cough due to  
29 cough variant asthma or non-asthmatic eosinophilic bronchitis from other forms of chronic cough.<sup>466,467</sup>

30

1 It is not clear if treatment of AR with INCS improves the associated cough,<sup>463,468</sup> but an RCT by Kim et  
 2 al<sup>463</sup> suggests that nasal saline irrigations decrease cough associated with AR. Posterior nasal  
 3 neurectomy with or without pharyngeal neurectomy in patients with AR may decrease cough.<sup>469</sup>

4

5 **Aggregate grade of evidence:** C (Level 2: 3 studies, level 3: 3 studies, level 4: 11 studies, level 5: 1 study;  
 6 **TABLE XIII.H.)**

7

8 **TABLE XIII.H. Evidence table – Association between allergic rhinitis and cough**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Dicpinigiatis et al <sup>462</sup>	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 <sup>469</sup>	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 <sup>470</sup>	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 <sup>468</sup>	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 <sup>461</sup>	2016	3	Prospective, nonrandomized	Serum sIgE from patients with AR symptoms from 2011-2014, n=2713	-Questionnaire -Allergen profile -Clinical features of AR	- <i>D. pteronyssinus</i> most common allergen -Occurrence of co-morbidities, including cough, increased with AR severity
Passali et al <sup>453</sup>	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 <sup>466</sup>	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 <sup>465</sup>	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 <sup>463</sup>	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 <sup>467</sup>	2019	4	Case series	Consecutive patients with AR and chronic cough, n=316	-FeNO -FEF <sub>25-75</sub>	-FeNO can differentiate chronic cough patients with CVA or NAEB from patients with UACS or GERC -Lower FEF <sub>25-75</sub> can then be used to identify CVA patients
Tang et al <sup>464</sup>	2018	4	Case series	Consecutive newly diagnosed CVA patients, n=99	FeNO levels dichotomized as high ( $\geq 25$ 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 <sup>460</sup>	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 <sup>459</sup>	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 <sup>458</sup>	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 <sup>454</sup>	2015	4	Case-control	-Patients with allergy to common environmental allergens, n=30 -Controls, n=30	Assess safety of nasal allergen challenge, and the use of certain parameters applied in assessing the condition of the respiratory system.	Extra-nasal symptoms observed early in reaction, namely cough and breathlessness, and more common in those with perennial AR
Chakir et al <sup>455</sup>	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 <sup>456</sup>	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 <sup>457</sup>	2016	5	Bench research	30 guinea pigs: -HDM group (sensitized by HDM aerosol, then challenged, sensitization	-Symptoms of AR induced by intranasal application of 15µl 0.5 % HDM -Cough challenge with	-HDM and OVA-sensitized groups showed a significantly enhanced nasal reactivity and cough response vs controls

				confirmed via skin test) -OVA group -Control group	citric acid performed -Airway resistance measured in vivo by Pennock's method.	-Airway resistance data did not show significant differences.
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1 LOE=level of evidence; RCT=randomized controlled trial; AR=allergic rhinitis; HDM=house dust mite;  
 2 INCS=intranasal corticosteroid; sIgE=specific immunoglobulin E; CVA=cough variant asthma; FeNO=fraction of  
 3 exhaled nitric oxide; MMEF=maximum mid-expiratory flow; CPA=cough predominant asthma; FEF<sub>25-75</sub>= forced  
 4 expiratory flow at 25% to 75% of pulmonary volume; NAEB=non-asthmatic eosinophilic bronchitis; UACS=upper  
 5 airway cough syndrome; GERC=gastroesophageal reflux-related cough; OR=odds ratio; CI=confidence interval;  
 6 COPD=chronic obstructive pulmonary disease; IL=interleukin; OVA=ovalbumin  
 7 \*Downgraded due to low number of included studies, inconsistent results  
 8  
 9

### 10 XIII.I. Laryngeal disease

11  
 12 AR and inhalant allergy have been associated with laryngeal disease; however, understanding of their  
 13 precise role in laryngeal disease is limited. This section evaluates studies that examine the relationship  
 14 between inhalant allergy and laryngeal disease, including allergic laryngitis. Allergic laryngitis is  
 15 characterized by allergen-induced laryngeal inflammation and can present with dysphonia, coughing,  
 16 throat clearing, and globus.<sup>471</sup> Some studies have evaluated laryngeal symptoms in individuals with AR  
 17 while others have evaluated the direct effects of allergen exposure on the larynx. **[TABLE XIII.I.]**  
 18

19 Establishing a causal relationship between AR and laryngeal disease has proven difficult, although  
 20 associations have been reported. Lee et al<sup>472</sup> found an association between the diagnosis of chronic  
 21 laryngitis and AR in a Korean nationwide cohort. Subsequently, Wang et al<sup>473</sup> identified a strong  
 22 association between AR and developing laryngeal pathology in a Taiwanese nationwide cohort. Several  
 23 studies have reported higher Voice Handicap Index (VHI) scores in AR patients versus controls.<sup>474-477</sup>  
 24 Ohlsson et al<sup>478</sup> reported that vocal symptoms in those with AR worsen during the allergy season and  
 25 may be associated with a decrease in speech fundamental frequency. Velickovic et al<sup>479</sup> found that  
 26 overall AR is common and occurs in 44.2% of professional voice users presenting with dysphonia. Singers  
 27 with self-perceived voice issues were 15% more likely to have AR than those without vocal  
 28 complaints.<sup>480</sup> The likelihood of AR increased as the number of vocal symptoms increased.<sup>480</sup>  
 29

1 The adverse effects of AR on voice-related QOL have also been reported,<sup>474,476,481</sup> and Turley et al<sup>481</sup>  
2 supported this association by showing that patients who reported poor rhinitis-related QOL also had  
3 poor voice-related QOL and increased severity of chronic laryngeal symptoms. Furthermore, increased  
4 allergen load was associated with greater severity of vocal symptoms.<sup>477</sup> Overall, there is a higher than  
5 anticipated incidence of AR in patients with vocal dysfunction and vice versa.<sup>477,480-482</sup>

6  
7 Findings of laryngeal inflammation have largely been attributed to laryngopharyngeal reflux (LPR), but  
8 recent studies have questioned its role as the primary source of laryngeal dysfunction.<sup>476,483</sup> Allergic  
9 laryngitis associated with AR can be difficult to distinguish from other laryngeal inflammatory disorders,  
10 including LPR, due to limitations of current diagnostic methods including poor specificity and inter-rater  
11 reliability. Patients with clinically significant LPR may be more likely to report AR symptoms.<sup>484</sup> However,  
12 the opposite may be true in professional voice users presenting with dysphonia.<sup>479</sup> Randhawa et al<sup>483</sup>  
13 studied patients presenting with voice concerns and reported one-third were diagnosed with LPR,  
14 whereas two-thirds of patients were diagnosed with allergies. Laryngeal findings in LPR and allergic  
15 laryngitis and LPR may be similar; laryngeal edema, laryngeal erythema, and excessive thick mucus are  
16 often seen.<sup>485,486</sup> Eren et al<sup>486</sup> demonstrated no significant difference in laryngeal appearance between  
17 allergy-positive and LPR-positive subjects. However, thick endolaryngeal mucus may predict allergy.<sup>487</sup>

18  
19 Several studies have evaluated the direct effect of allergens on the larynx. Belafsky et al<sup>488</sup> and Mouadeb  
20 et al<sup>489</sup> examined *Dermatophagoides farinae* exposure to the laryngeal mucosa of guinea pigs and found  
21 an increase in eosinophilia compared to saline exposure, providing some support for allergens  
22 contributing to laryngeal disease. Two studies from the same voice laboratory evaluated direct laryngeal  
23 stimulation by nebulized *Dermatophagoides pteronyssinus* in allergic patients to assess laryngeal  
24 symptoms, appearance, and function.<sup>471,490</sup> In the first study, Reidy et al<sup>471</sup> did not identify a significant  
25 difference between antigen- and placebo-challenged subjects on any of the evaluated measures, such as  
26 VHI, Sinus Symptoms Questionnaire, laryngoscopy, and acoustic/aerodynamic testing. In a follow-up,  
27 Dworkin et al<sup>490</sup> used increased allergen concentration for the challenge and noted an increase in  
28 endolaryngeal mucus, throat clearing, and coughing. Roth et al<sup>491</sup> performed a similar study but isolated  
29 the larynx by utilizing a nose clip to ensure oral inhalation and eliminated patients with reactive airways  
30 based on methacholine challenge, thus demonstrating a causal relationship between allergen  
31 stimulation and impaired vocal function. Suzuki et al<sup>492</sup> also utilized a nose clip and found more laryngeal  
32 symptoms when patients were exposed to cypress pollen compared to placebo. However, there were no



1 corresponding objective changes in acoustic analysis or flexible laryngoscopy.<sup>492</sup> These studies suggest  
 2 that in subjects with inhalant allergy there can be laryngeal dysfunction due to direct allergen  
 3 stimulation of the larynx as well as possible symptoms secondary to the nasal congestion, inflammation,  
 4 and drainage of AR.

5

6 There is increasing evidence suggesting a relationship between AR, inhalant allergy, and laryngeal  
 7 disease. Although laryngeal findings specific to allergic laryngitis are not consistently demonstrated,  
 8 thick endolaryngeal mucus should raise suspicion for underlying allergy. AR should be considered in the  
 9 differential diagnosis of patients with vocal complaints. Additional studies are needed on the effect of  
 10 AR treatment on associated laryngeal disease.<sup>471</sup>

11

12 **Aggregate grade of evidence:** C (Level 2: 7 studies, level 3: 4 studies, level 4: 10 studies, level 5: 2  
 13 studies; **TABLE XIII.I.**)

14

15

**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 <sup>472</sup>	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 <i>D. farinae</i>
Roth et al <sup>491</sup>	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 <sup>477</sup>	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 <sup>490</sup>	2009	2	RCT	HDM-sensitive adults: - <i>D. pteronyssinus</i> challenge -Placebo	Effect of allergen on laryngeal findings	Laryngeal abnormalities secondary to lower respiratory stimulation
Krouse et al <sup>476</sup>	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

						<p>abnormalities</p> <ul style="list-style-type: none"> <li>-Findings present in subjects without LPR/GERD</li> <li>-VHI changes seen in HDM-sensitive patients</li> </ul>
Simberg et al <sup>482</sup>	2007	2	Cross sectional	<ul style="list-style-type: none"> <li>-Allergy patients undergoing AIT</li> <li>-Non-allergic controls</li> </ul>	Symptom prevalence	<ul style="list-style-type: none"> <li>-Allergic patients had more severe vocal symptoms</li> <li>-Patients on AIT &gt;2 years had fewer vocal symptoms</li> </ul>
Reidy et al <sup>471</sup>	2003	2	RCT	<ul style="list-style-type: none"> <li>-<i>D. pteronyssinus</i> challenge</li> <li>-Placebo challenge</li> </ul>	Effect of allergen on laryngeal findings	No significant differences between allergen and placebo exposed subjects
Wang et al <sup>473</sup>	2021	3	Nationwide cohort	<ul style="list-style-type: none"> <li>-AR patients, all ages</li> <li>-Patients without AR matched by gender, age, urbanized level, and income</li> </ul>	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 <sup>484</sup>	2018	3	Cohort	Patients presenting to otolaryngology clinic with LPR symptoms	SFAR in patients with positive and negative 24-hour oropharyngeal pH monitoring	<ul style="list-style-type: none"> <li>-LPR patients based on pH testing had higher SFAR scores</li> <li>-Higher Ryan score associated with higher SFAR score</li> </ul>
Velickovic et al <sup>479</sup>	2017	3	Cohort	Professional voice users with dysphonia presenting to an otolaryngology department	<ul style="list-style-type: none"> <li>-Prevalence of AR based on ARIA guidelines</li> <li>-Prevalence of LPR based on RSI &gt;13</li> </ul>	<ul style="list-style-type: none"> <li>-AR present in 44.2%</li> <li>-AR was less common in patients with LPR</li> </ul>
Suzuki et al <sup>492</sup>	2016	3	Placebo-controlled trial	Subjects with AR to cypress pollen, n=25	<ul style="list-style-type: none"> <li>-Subjective report of laryngeal symptoms during pollen/placebo exposure</li> <li>-Laryngeal symptom questionnaire</li> <li>-Acoustic analysis</li> <li>-Flexible laryngoscopy</li> </ul>	<ul style="list-style-type: none"> <li>-More laryngeal symptoms were reported with pollen exposure, especially when nose plugged</li> <li>-No significant findings in acoustic analysis or laryngoscopy</li> </ul>
Brook et al <sup>493</sup>	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 <sup>478</sup>	2016	4	Case-control	-Patients with AR from birch pollen, n=30 -Controls without AR, matched for gender and age, n=30	-4-question allergy questionnaire -Swedish questionnaire about voice symptoms -Acoustic analysis of voice recordings	-AR patients had more voice symptoms during allergy and non-allergy season, voice symptoms decreased during non-allergy season -Speech fundamental frequency was lower during both seasons in AR patients suggesting vocal fold edema
Brook et al <sup>494</sup>	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 <sup>486</sup>	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 <sup>475</sup>	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 <sup>481</sup>	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 <sup>483</sup>	2010	4	Case series	Patients diagnosed with primary voice disorder or globus sensation	Prevalence of AR and LPR	3 times as many patients had allergies vs LPR, not statistically significant
Hamdan et al <sup>480</sup>	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 <sup>474</sup>	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 <sup>487</sup>	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 <sup>488</sup>	2015	5	Bench research	-Guinea pigs exposed to saline (allergen control) + filtered air (pollution control) -HDMA ( <i>Dermatophyoides farinae</i> ) + 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 <sup>489</sup>	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

1 LOE=level of evidence, IgE=immunoglobulin E; VHI=Voice Handicap Index; RCT=randomized controlled trial;  
2 HDM=house dust mite; LPR=laryngopharyngeal reflux; GERD=gastroesophageal reflux disease; AIT=allergen  
3 immunotherapy; AR=allergic rhinitis; ICD=International Classification of Diseases; SFAR=Score for Allergic Rhinitis;  
4 ARIA=Allergic Rhinitis and its Impact on Asthma; RSI=Reflux Symptom Index; SPT=skin prick test; NAR=non-allergic  
5 rhinitis; HDMA=house dust mite allergen

### 7 XIII.J. Eosinophilic esophagitis

8  
9 EoE is a chronic inflammatory condition of the esophagus defined symptomatically by esophageal  
10 dysfunction and histologically by eosinophil-predominant inflammation. EoE is widely considered a type  
11 2 inflammatory disease, and patients with EoE often have other comorbid atopic conditions such as AD,  
12 asthma, food allergies and AR.<sup>495</sup>

13  
14 Several studies have examined the prevalence of clinician-diagnosed AR and aeroallergen sensitization  
15 in patients with EoE. Among both pediatric and adult patients with EoE, 50-75% have consistently been  
16 found to have AR.<sup>496-512</sup> There is also evidence for a higher prevalence of AR among EoE patients  
17 compared with the general population.<sup>495,513,514</sup> Although most studies were case series, the consistency  
18 of findings strongly suggests that a majority of patients with EoE have comorbid AR and that the  
19 presence of AR in EoE patients may be higher compared with the general population. [TABLE XIII.J.]

1 While the above associations have been well documented, the pathophysiology underpinning the  
 2 specific relationship between IgE sensitization and EoE remains unclear. Hill et al<sup>257</sup> demonstrated that  
 3 the presence of AR was associated with subsequent EoE diagnosis, suggesting that sensitization to  
 4 aeroallergens early in life may predispose to EoE development. Additionally, several case series noted an  
 5 increase in EoE diagnosis, symptoms, and/or esophageal eosinophilia during pollen season, typically  
 6 with peaks during spring and summer.<sup>515-522</sup> AIT has also demonstrated efficacy in the treatment of EoE  
 7 in one case-control study and two case reports.<sup>523-525</sup> Of note, several case reports described the  
 8 development of EoE in patients undergoing SLIT and resolution with cessation, raising the possibility that  
 9 repeated esophageal stimuli with offending allergens might elicit esophageal eosinophilia.<sup>526</sup> However  
 10 other studies, including a systematic review by Lucendo et al,<sup>527</sup> demonstrated no seasonal variation in  
 11 EoE diagnosis or exacerbations, suggesting a limited role for aeroallergens as a relevant trigger for  
 12 initiating or aggravating EoE.<sup>527-529</sup> Therefore, there is limited observational data suggesting a potential  
 13 association between aeroallergens and EoE pathogenesis, with some conflicting data.

14  
 15  
 16

**Aggregate grade of evidence:** C (Level 3: 6 studies, level 4: 29 studies; **TABLE XIII.J.**)

17 **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 <sup>497</sup>	2017	3	Population-based database	Pediatric and adult EoE patients	Demographic and clinical characteristics	45% had AR
Gonzalez-Cervera et al <sup>513</sup>	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 <sup>496</sup>	2007	3	Systematic review	Pediatric and adult EoE patients	Demographic and clinical characteristics	50-80% had AR and sensitization to aeroallergens
Ancellin et al <sup>499</sup>	2020	4	Case series	Pediatric EoE patients, n=49	Demographic and clinical characteristics	78% were atopic; 64% sensitized to aeroallergens
Azzano et al <sup>498</sup>	2020	4	Case series	Pediatric EoE patients, n=108	Demographic and clinical characteristics	63% sensitized to aeroallergens; 51% had AR
Imamura et al <sup>514</sup>	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 <sup>495</sup>	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 <sup>501</sup>	2017	4	Case series	Pediatric EoE patients, n=25	Demographic and clinical characteristics	92% sensitized to aeroallergens
Mohammad et al <sup>500</sup>	2017	4	Case series	Pediatric and adult EoE patients, n=449	Demographic and clinical characteristics	62% had AR
Olson et al <sup>502</sup>	2016	4	Case series	Adult EoE patients, n=257	Demographic and clinical characteristics	79% had AR
Castro Jimenez et al <sup>505</sup>	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 <sup>504</sup>	2014	4	Case series	Pediatric EoE patients, n=311	Demographic and clinical characteristics	86% were atopic; 67% had AR
Vernon et al <sup>503</sup>	2014	4	Case series	Pediatric and adult EoE patients, n=100	Demographic and clinical characteristics	65% had AR
Spergel et al <sup>506</sup>	2009	4	Case series	Pediatric EoE patients, n=562	Demographic and clinical characteristics	68% were atopic; 43% had AR
Roy-Ghanta et al <sup>507</sup>	2008	4	Case series	Adult EoE patients, n=23	Demographic and clinical characteristics	78% had AR; 86% sensitized to aeroallergens
Assa'ad et al <sup>508</sup>	2007	4	Case series	Pediatric EoE patients, n=89	Demographic and clinical characteristics	79% sensitized to environmental allergens
Plaza-Martin et al <sup>509</sup>	2007	4	Case series	Pediatric EoE patients, n=14	Demographic and clinical characteristics	93% had AR and sensitization to aeroallergens
Sugnanam et al <sup>510</sup>	2007	4	Case series	Pediatric EoE patients, n=45	Demographic and clinical characteristics	93% had AR
Remedios et al <sup>511</sup>	2006	4	Case series	Adult EoE patients, n=26	Demographic and clinical characteristics	77% were atopic; 54% had AR
Guajardo et al <sup>512</sup>	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 <sup>515</sup>	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 <sup>523</sup>	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 <sup>527</sup>	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 <sup>524</sup>	2021	4	Case report	Pediatric patients with EoE and multiple environmental	Clinicohistologic remission	EoE remission observed after treatment with multiallergen SCIT as monotherapy

				allergies treated with AIT		
Reed et al <sup>516</sup>	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 <sup>257</sup>	2018	4	Retrospective case-control	-Pediatric EoE patients, n=139 -Controls, n=22,272	Rate of EoE diagnosis in patients with AR	AR diagnosis associated with an increased rate of subsequent EoE diagnosis
Fahey et al <sup>517</sup>	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 <sup>528</sup>	2015	4	Case series	Adult EoE patients, n=372	Season of EoE diagnosis	Increased presentation of EoE in winter months
Ram et al <sup>518</sup>	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 <sup>529</sup>	2014	4	Retrospective cohort	Pediatric and adult EoE patients	Season of EoE diagnosis	Incidence of EoE consistent across all seasons
Ramirez & Jacobs <sup>525</sup>	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 <sup>519</sup>	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 <sup>520</sup>	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 <sup>521</sup>	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 <sup>522</sup>	2003	4	Case report	Pediatric EoE patient	Seasonal biopsy findings	Increased esophageal eosinophilia during pollen seasons

1 LOE=level of evidence; EoE=eosinophilic esophagitis; AR=allergic rhinitis; OR=odds ratio; AIT=allergen  
2 immunotherapy; SCIT=subcutaneous immunotherapy

3

4

### 5 XIII.K. Sleep disturbance and obstructive sleep apnea

6

7 AR negatively impacts sleep and is a risk factor for OSA.<sup>530</sup> Various symptoms of AR may contribute to  
8 sleep dysfunction. However, nasal obstruction, which is present in up to 90% of AR patients, seems to  
9 have the greatest impact and is a major independent contributor to poor sleep quality and SDB.<sup>531-542</sup>

10 This may be due to increased nasal obstruction during the night with a peak in the early morning.<sup>543</sup> The

11 mechanisms underlying the association between AR and sleep disturbance include inflammatory

12 cytokines causing fatigue, direct impact of AR symptoms, combination of recumbency and diurnal

13 variation in turbinate size and pathophysiologic changes, and as sequelae of autonomic dysfunction in

14 AR.<sup>544-546</sup> Histamine plays a role in the regulation of the sleep-wake cycle and arousal, and cysteinyl

15 leukotrienes are involved in sleep disruption.<sup>547,548</sup> Excessive histamine results in insomnia and

16 inadequate amounts cause hypersomnolence.<sup>547,549</sup> Cytokines released in AR patients, such as IL-1 $\beta$  and

17 IL-4, are thought to reduce sleep onset latency and increase the time to onset of rapid eye movement

18 (REM) sleep.<sup>550-552</sup> Patients with OSA also have increased mediators which activate Th2 cells, such as TNF,

19 IL-1 and IL-6, further exacerbating symptoms of AR and potentiating the severity of OSA.<sup>553</sup> Further,

20 nasal airflow stimulates respiration and improves upper airway dilatory muscle tone via the nasal-

21 ventilatory reflex and also stimulates the genioglossus muscle, resulting in tongue protrusion and

22 improved airway patency via the trigemino-hypoglossal reflex.<sup>554-559</sup> Therefore, nasal obstruction may

23 reduce the stimulation of these mechanoreceptors resulting in collapsibility of the downstream

24 pharyngeal segment of the upper airway, thereby leading to OSA.<sup>560</sup> **[TABLE XIII.K.]**

25

26 Sleep is critical for mood, cognitive function, immune function, and endocrine functions.<sup>544</sup> OSA is

27 associated with hypertension, coronary artery disease, cerebrovascular disease, arrhythmias, insulin

28 resistance, congestive heart failure, pulmonary hypertension, and behavioral problems in children.<sup>561-566</sup>

29 Further, in children, SDB may negatively impact brain development, impair psychomotor and cognitive

30 performance, and contribute to hyperactivity.<sup>567-569</sup> REM sleep is associated with memory, cognition,

31 dreams, and restorative sleep.<sup>570,571</sup> As the nasal cycle is prolonged, worsening nasal obstruction, people

32 with AR have impaired REM sleep.<sup>570-574</sup> However, as the diagnosis of SDB typically relies upon the

33 measurement of all-night AHI and RDI via polysomnography, many patients with AR and SDB have

34 normal indices by this method. By considering respiratory effort-related arousals, as well as AHI and RDI



1 measured specifically in REM sleep (REM-AHI, REM-RDI), sleep disorders in AR patients will be detected  
2 more often.<sup>575</sup>

3  
4 CPAP treatment for OSA may present a non-allergic trigger to AR patients with OSA and worsen nasal  
5 symptoms.<sup>576</sup> Further, persistent nasal symptoms are a common reason for early CPAP non-  
6 compliance.<sup>576-578</sup> However, correction of nasal obstruction can improve CPAP compliance/tolerance,<sup>579-</sup>  
7 <sup>581</sup> though there is typically no direct impact on OSA severity.<sup>582</sup>

8  
9 It is important to assess AR patients for sleep disorders due to their negative impact on health.  
10 Numerous instruments are available to assess the impact of AR on sleep. These include the Stanford  
11 Sleepiness Score, Jenkins Questionnaire, Epworth Sleepiness Score, Pittsburgh Sleep Quality Index,  
12 University of Pennsylvania Functional Outcomes of Sleep, Sleep scale from the Medical Outcome Study,  
13 Sleep Disorders Questionnaire, The Pediatric Sleep Questionnaire, and The Pediatric Daytime Sleepiness  
14 Scale.

15  
16 Treatment of nasal congestion in AR patients improves sleep quality, daytime somnolence, and QOL.<sup>583</sup>  
17 Numerous medical therapies have been investigated regarding the link between AR treatment and sleep  
18 quality. INCS and isolated nasal surgery have also been shown to improve sleep quality in AR patients,  
19 particularly those with moderate-to-severe pre-treatment obstruction.<sup>584-588</sup> INCS may improve sleep in  
20 patients with AR due to improvement in nasal obstruction, but also due to reduction in local  
21 inflammatory cytokines.<sup>547,548</sup> A recent RCT and case series found significant improvements in sleep  
22 parameters following AR treatment with HDM SLIT.<sup>589,590</sup> First generation H<sub>1</sub>-antihistamines cross the  
23 blood-brain barrier and cause sedation which may exacerbate daytime somnolence in patients with AR  
24 and SDB. Therefore, second generation H<sub>1</sub> antagonists are favored, such as fexofenadine and loratadine,  
25 which are lipophobic and do not cross the blood-brain barrier.<sup>591-593</sup> Although leukotriene antagonists  
26 have not demonstrated benefit when added to INCS in the treatment of AR, one RCT found that  
27 montelukast was more effective than cetirizine in improving sleep quality in children according to  
28 patient diaries.<sup>594,595</sup> Nasal decongestants may result in stimulatory effects causing insomnia.<sup>546</sup> Nasal  
29 decongestant sprays do not significantly improve AHI.<sup>596</sup> A cross-over RCT comparing xylometazoline to  
30 placebo in patients with OSA and nasal congestion found that xylometazoline did not improve sleep  
31 quality and resulted in a transient improvement in AHI at the time of peak effectiveness only.<sup>596</sup> As these

1 sprays carry the potential for rhinitis medicamentosa, insomnia, and palpitations, they are not  
 2 recommended for the treatment of AR in OSA patients.  
 3  
 4 Sleep disorders should be considered in any patient diagnosed with AR due to their significant  
 5 association and the negative impact that SDB has on QOL. Changes in sleep parameters should also be  
 6 considered when evaluating the impact of treatment of AR. (See Section IX.A.2. Allergic Rhinitis Disease  
 7 Burden – Sleep Disturbance for additional information on this topic)

8  
 9 **Aggregate grade of evidence:** B (Level 2: 3 studies, level 3: 4 studies, level 4: 9 studies; **TABLE XIII.K.**)  
 10

11 **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 <sup>597</sup>	2020	2 <sup>o</sup>	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 <sup>589</sup>	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 <sup>594</sup>	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 <sup>544</sup>	2020	3*	Cross-sectional	Children with snoring from adenotonsillar hypertrophy,	-PSG -Sleep questionnaire	-Prevalence of AR in SDB (25.8%), OSA (19.4%) -Regardless of OSA status, AR children had more daytime

				aged 3-14 years, n=660		hypersomnolence, behavioral symptoms, and shorter sleep time -Children with AR without OSA spent shorter time in REM -Children with AR had shorter sleep time
Na et al <sup>598</sup>	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 <sup>576</sup>	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 <sup>599</sup>	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 <sup>584</sup>	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 <sup>600</sup>	2021	4	Cross-sectional survey	Adolescents participating in national health survey, aged 12-18 years, n=1936	-Questionnaire -Examination -Serum IgE	-Higher prevalence of AR in inappropriate sleep duration group -Endoscopic findings of AR associated with inappropriate sleep duration in males
Berson et al <sup>575</sup>	2020#	4***	Retrospective case-control	Patients with AR or SDB, n=100	-STOP-BANG -ESS -PSG	-HDM AR patients more likely to have REM-RDI and REM-AHI in moderate-severe range vs controls -AR patients more likely to have REM-AHI in moderate-severe range vs controls
Bosnic-Anticevich et al <sup>601</sup>	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 <sup>602</sup>	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 <sup>530</sup>	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 <sup>603</sup>	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 <sup>571</sup>	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 <sup>590</sup>	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)

- 1 LOE=level of evidence; SRMA=systematic review and meta-analysis; AR=allergic rhinitis; RCT=randomized
- 2 controlled trial; HDM=house dust mite; SLIT=sublingual immunotherapy; RQLQ=Rhinoconjunctivitis Quality of Life
- 3 Questionnaire; TNSS=Total Nasal Symptoms Score; IgE=immunoglobulin E; ECP=eosinophil cationic protein;
- 4 PSG=polysomnography; SDB=sleep disordered breathing; OSA=obstructive sleep apnea; REM=rapid eye
- 5 movement; CPAP=continuous positive airway pressure; SFAR=Score for Allergic Rhinitis; NOSE=Nasal Obstruction
- 6 Symptom Evaluation; SNOT=Sinonasal Outcome Test; VAS=visual analog scale; IT=inferior turbinate; ESS=Epworth
- 7 Sleepiness Scale; AHI=apnea-hypopnea index; RDI=respiratory disturbance index; sIgE=specific immunoglobulin E;
- 8 STOP-BANG= Snoring, Tiredness, Observed breathing cessation, Pressure, BMI, Age, Neck circumference, Gender

1 Questionnaire; ESPRINT-15=validated health-related quality of life questionnaire for adults with AR; PSQ=Pediatric  
 2 Sleep Questionnaire; NARES=non-allergic rhinitis with eosinophilia syndrome  
 3 %LOE downgraded; not a SRMA of RCTs  
 4 \*LOE downgraded due to significant difference in group sizes  
 5 \*\*LOE downgraded due to small number of AR patients (n=8) and only 1 female patient included  
 6 \*\*\*diagnosis of AR based on skin prick or serum testing  
 7 \*\*\*\*LOE downgraded as diagnosis of AR based on symptoms only  
 8 \*\*\*\*\*LOE downgraded as OSA diagnosed on home sleep study and AHI values only  
 9 \*\*\*\*\*LOE downgraded as OSA diagnosed on questionnaires, not PSG (probability of OSA calculated)  
 10 # same patient group as 2018 study  
 11  
 12

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## 1 XIV. Special section on COVID-19

### 2 3 XIV.A. COVID-19 effect on patient presentation for allergic rhinitis evaluation

4  
5 The WHO declared COVID-19 a pandemic on March 11, 2020.<sup>1</sup> With mounting evidence of rapid spread,  
6 high morbidity and mortality, and a push to maintain the healthcare system infrastructure, routine  
7 ambulatory care for conditions like AR was often reduced.<sup>2</sup> As the pandemic endured, expert group  
8 consensus generally applied different recommendation strategies depending on case rates. When case  
9 rates were high, it was reasonable to suspend care temporarily, particularly if providers and healthcare  
10 facilities were redeployed.<sup>3,4</sup> However, as case rates fell, it was necessary to find ways to evaluate  
11 patients for AR.<sup>5,6</sup> Telemedicine, using phone or video where available, was rapidly implemented and  
12 provided significant access to specialty care while limiting exposure for patients and providers.<sup>2-4,7,8</sup>  
13 However, implementation of telemedicine practices may exacerbate gaps in access for populations  
14 already at risk for health disparities.<sup>9</sup>

15  
16 Another evident issue became the similarities in presentation between AR and COVID-19, and it was  
17 important to identify ways to differentiate the diseases.<sup>2,4</sup> AR was not a risk factor for severe COVID-19  
18 infection.<sup>10-17</sup> The consensus from a survey distributed to members of the ARIA/EAACI study group was  
19 that AR presented with runny nose, sneezing, stuffy nose, nasal pruritus, ocular pruritus and redness  
20 compared to COVID-19 which presented with more smell and taste dysfunction, dyspnea, and cough.<sup>18</sup>  
21 Patients scored validated questionnaires like the SNOT-22 and mini-RQLQ differently.<sup>19,20</sup> SNOT-22  
22 scores were higher in patients with COVID-19 infection (with more frequent cough, dizziness, loss of  
23 smell/taste, psychiatric and sleep dysfunction) compared to patients with AR (with more frequent nose  
24 blowing and sneezing).<sup>19</sup> In patients with allergic rhinoconjunctivitis with COVID-19 infection, mini-RQLQ  
25 scores were lower in COVID-19 infection compared to their allergies.<sup>20</sup> They specifically reported less  
26 sneezing, runny nose, itchy eyes, sore eyes, and watery eyes and generally noted a difference in their  
27 symptoms with COVID-19 infection compared to typical allergies.

28  
29 Changes in exposure associated with widespread lockdowns affected the clinical presentation of  
30 patients with AR. Visits for AR increased during the COVID pandemic, with patients reporting ongoing  
31 nasal symptoms as an impetus for seeking care.<sup>21,22</sup> However, in general, AR symptoms and medication  
32 use decreased.<sup>23-26</sup> The decrease in AR symptoms was attributed to reduced outdoor exposures, use of  
33 face masks, and decreased pollution as a result of COVID-19 lockdowns.<sup>2,27</sup> However, changes in

1 symptom presentation depended on sensitization pattern – patients with cypress pollen allergy  
2 reported decreased symptoms but those with dust mite allergy noted increased symptoms.<sup>25,28</sup> The  
3 COVID pandemic also led to increased exposure to indoor respiratory irritants such as tobacco, cooking  
4 smoke, and cleaning products.<sup>29</sup> And although use of face masks were reliably associated with fewer  
5 nasal symptoms compared to no mask, the effect on ocular symptoms was mixed.<sup>30,31</sup> Finally, patients  
6 who discontinued their therapies for AR due to pandemic concerns expectedly reported loss of  
7 symptom control.<sup>32</sup>

8  
9 Comorbid mental health diagnoses including depression and anxiety are commonly reported in patients  
10 with AR and positively correlated with symptom scores.<sup>33</sup> This correlation persisted during the pandemic  
11 with atopic patients reporting higher symptoms of post-traumatic stress disorder, higher depression risk  
12 scores, and higher hyperarousable subscale scores<sup>24</sup> than non-atopic patients.<sup>34</sup>

13

14

#### 15 XIV.B. Changes in allergic rhinitis diagnostic techniques related to COVID-19

16

17 Although the initial clinical evaluation of patients often could be done through telemedicine, many  
18 diagnostic techniques for AR require a face-to-face encounter with potentially aerosol generating  
19 procedures (e.g., performing spirometry on an asthmatic patient prior to allergy skin testing). Because  
20 SARS-CoV-2 viral loads are highest in the upper airway, these procedures are particularly high risk.<sup>6,35</sup> In  
21 many cases, if in-person encounters were not appropriate, diagnostic testing was deferred. In vitro  
22 serum sIgE was an alternative option to evaluate for allergen sensitization, although phlebotomy still  
23 required healthcare contact.<sup>3</sup> Additionally, there was often national, regional, and/or institutional  
24 guidance for in person visits and procedures.<sup>3,6,35-40</sup> Policies to contain and reduce spread of COVID-19  
25 are still evolving. At the time of this writing, available publications often stemmed from early pandemic  
26 practices and expert opinion. Adjustments to the recommendation with changing COVID-19 community  
27 transmission levels are ongoing but typically involved phased de-escalation of these recommendations.<sup>5</sup>

28

29 For in-person encounters, general considerations included measures to screen for COVID-19 infection,  
30 enhance social distancing, and reduce transmission. Early in the COVID-19 pandemic, screening prior to  
31 healthcare facility encounters included survey screening of symptoms suggestive of COVID-19 for  
32 patients and staff<sup>4,5,41</sup> and, in some countries, body temperature screening and epidemiologic tracking  
33 via smartphone.<sup>38,41</sup> Social distancing of at least 6 feet was recommended when possible.<sup>4,38,42</sup> This was

1 important in clinical spaces and the waiting room. Visitor limitations (with 1 adult allowed for children  
2 and none for adult patients when possible) were enacted.<sup>43,44</sup> Clinical care modifications included asking  
3 patients to fill out health information prior to visits, using telemedicine to obtain history to minimize in  
4 person time, and adjusting clinic schedule templates to allow for social distancing and room ventilation.<sup>5</sup>  
5 Finally, measures to reduce transmission included hand hygiene, appropriate personal protective  
6 equipment (generally including a mask), removing reading material to minimize indirect transmission,  
7 and enhanced cleaning of facilities.<sup>4,8,35,41,42</sup>

8  
9 For aerosol-generating procedures, additional action was recommended. There have not been clinical  
10 studies of COVID-19 transmission with any allergy or otolaryngologic procedures. As stated earlier in  
11 ICAR-Allergic Rhinitis 2023, nasal endoscopy is an option when evaluating the AR patient, used primarily  
12 to evaluate potential intranasal signs associated with allergy or to rule out alternate causes presenting  
13 symptoms. Studies of nasal endoscopy has provided conflicting reports on aerosol generation.<sup>45,46</sup> Initial  
14 studies by two research groups using cadaveric heads did not demonstrate aerosol generation during  
15 cold instrumentation<sup>47,48</sup> although further studies in live patients undergoing nasal endoscopy detected  
16 increased airborne particles.<sup>49,50</sup> Another study did not detect a significant change in particle  
17 concentration from pre-scope to scope, but there was a trend for increased particle concentrations in  
18 patients who required sinonasal debridement.<sup>51</sup> There is also concern that nasal endoscopy can induce  
19 behaviors including sneezing, breathing, speaking, and possibly coughing that are aerosol  
20 generating.<sup>47,49,52</sup> However, some modifications including nasal endoscopy using modified surgical or  
21 N95 masks could prevent aerosol generation,<sup>47,49,50</sup> as well as repositioning at the back of the patient<sup>53</sup>  
22 or using a tower with camera, screen, and light source.<sup>6</sup> Local anesthetics and decongestants could be  
23 applied with actuated pump sprays or soaked pledgets rather than atomized forms to avoid aerosol  
24 generation.<sup>37,47,52</sup> Immediate decontamination of equipment, especially the endoscope, was also  
25 recommended.<sup>35</sup> Expert groups generally recommended against certain procedures including nasal  
26 provocation, nasal cytology, anterior rhinomanometry, and PNIF.<sup>37,54,55</sup> If supplies were not constrained,  
27 rapid and accurate pre-procedural screening for SARS-CoV-2 was also recommended.<sup>5</sup> For personal  
28 protective equipment, the WHO recommended an N95 face mask, full eye protection, and full body  
29 protective clothing.<sup>4,37,54</sup> Techniques to improve donning and doffing included one-step glove and gown  
30 removal, double-gloving, spoken instructions during doffing, and glove disinfection.<sup>54</sup>

31



1 Aerosol clearance depends on ventilation and air exchange.<sup>54</sup> The Centers for Disease Control (CDC)  
2 recommended at least 12 air changes per hour and controlled direction of airflow although the WHO  
3 recommends double this. After the patient leaves the room and 5 air exchanges occur, less than 1% of  
4 airborne contaminants will remain. With at least 12 air changes per hour, this would occur in 30  
5 minutes. The COVID-19 pandemic led to changes in access to in-person healthcare and potentially  
6 aerosol-generating procedures. In making the diagnosis of AR, there were strategies employed to help  
7 contain and reduce spread of COVID-19.<sup>56,57</sup>

8  
9

#### 10 XIV.C. Changes in allergic rhinitis management related to COVID-19

11  
12 Much of the standard management of AR was recommended by expert groups to be continued during  
13 the COVID-19 pandemic. There was specific motivation to control AR symptoms given concern that  
14 sneezing increased viral spreading and poorly controlled upper airway symptoms serve as a trigger for  
15 asthma exacerbations.<sup>6,27,39,55,58</sup> In Beijing, providers made public efforts to develop pollen monitoring  
16 networks, television and online lectures, and suggested over the counter drug recommendations for all  
17 patients with AR.<sup>38</sup> In addition, AR is not a contraindication to receiving the COVID-19 vaccine. Patients  
18 with AR were able to tolerate COVID-19 vaccination without severe reactions.<sup>59-61</sup>

19

20 As always, the first step in management of AR remains allergen avoidance. The pandemic demonstrated  
21 that allergen avoidance could significantly improve symptoms. Practices like face masks and  
22 handwashing appear to be mutually beneficial for management of AR and COVID-19.<sup>27</sup> Standard  
23 therapies for AR, including INCS, oral and topical antihistamines, montelukast, and AIT, were not  
24 identified as increasing susceptibility or severity of COVID-19 infection.<sup>2,4,10,55,62</sup> Systemic corticosteroids  
25 may be a concern although this is not a standard therapy for AR.<sup>63</sup> Patients on INCS were found to have  
26 a lower risk for COVID-19 related hospitalization, admission to the intensive care unit, and in-hospital  
27 mortality compared to patients who were not on INCS.<sup>64</sup> Montelukast has also been associated with a  
28 reduction in COVID-infection in a small retrospective cohort study of elderly asthmatics.<sup>65</sup>

29

30 AIT has been shown to improve symptom control with a decrease in respiratory infections and antibiotic  
31 use.<sup>66</sup> Prior studies with viral infections including influenza, cytomegalovirus (CMV), and HIV have not  
32 shown changes in the efficacy or safety of AIT.<sup>32</sup> When COVID-19 cases were high, initiating AIT was  
33 generally not recommended. However, consideration for continuing AIT includes lengthening the

1 injection interval which minimizes healthcare visits.<sup>3,39,43,55</sup> Consensus from one expert panel  
 2 recommended lengthening the interval to every 2 weeks during the build-up phase and every 6 weeks  
 3 during maintenance. Therapy should be stopped if COVID-19 infection is suspected or diagnosed, until  
 4 resolution.<sup>4</sup> There was evidence that patients were more likely to be nonadherent and discontinue AIT  
 5 during the pandemic leading to higher symptom scores, decreased QOL, and higher medication use than  
 6 before the pandemic.<sup>7,67-70</sup> Consideration for switching patients to or starting patients on SLIT, both  
 7 tablet and aqueous forms, may be a preferred therapy since maintenance does not require in-person  
 8 administration.<sup>8,39,55</sup> In case of COVID-associated quarantine, an adequate supply of SLIT should be  
 9 maintained at home.<sup>6,32</sup> Finally, home SCIT in selected patients was cost effective under pandemic  
 10 considerations alone.<sup>2,71</sup> Of note, this is not currently approved and is not the standard of care.<sup>3</sup>  
 11  
 12 Finally, anti-IgE therapy has been approved for severe cases of Japanese cedar pollinosis.<sup>55</sup> There is no  
 13 evidence of altered susceptibility or severity of COVID-19 infection with anti-IgE therapy. In fact, clinical  
 14 studies have shown that pre-seasonal treatment with anti-IgE therapy decreases seasonal exacerbations  
 15 of asthma related to viral infections.<sup>72-74</sup> IgE has been found to suppress the ability of dendritic cells to  
 16 produce type I interferons and theorized to increase the susceptibility for respiratory viral infections.<sup>75-77</sup>  
 17 However, as there is limited evidence, physician judgment is recommended.

18  
 19

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## XV. Summary of knowledge gaps and research opportunities

Through the ICAR-Allergic Rhinitis 2023 update process, we have seen an increased number of scientific publications in many areas. We are also encouraged to see additional high-quality studies, including many SRMAs, addressing many of the individual AR topics. As highlighted in previous ICAR documents, one of the most important aspects of this process is to identify knowledge gaps and key areas where future research may further advance our knowledge in AR. The sections that follow emphasize several important areas where additional research may further expand and solidify our understanding of AR.

**Epidemiology and risk factors.** Studies have been undertaken to understand the prevalence of AR around the world. These are limited by differing methodology and reporting. Since ICAR-Allergic Rhinitis 2018, the Aggregate Grades of Evidence remain largely unchanged. However, there has been significant work evaluating the hygiene hypothesis, SES, and in utero influences on AR development. Challenges of these studies are the retrospective nature of most work evaluating risk factors. Randomization is difficult in such studies, and the confounding effects of other risk factors are difficult to assess. Several gaps in knowledge exist and may be helpful to address. The following are areas where we suggest additional study:

- Improved understanding of the incidence of AR based on geographic location
- Evaluation of climate change effects on incidence and severity of AR
- Improved understanding of the relationship between genetics and environmental factors in the development of AR
- High quality longitudinal studies evaluating risk factors for development of AR

**Evaluation and diagnosis.** Diagnosis of AR begins with history and physical exam. Classic symptoms of AR (e.g., nasal/ocular pruritis, rhinorrhea, nasal congestion) are well documented. Since the early months of the COVID-19 pandemic, awareness of hyposmia and its association with nasal pathology has been heightened, but research on the association between hyposmia and AR remains limited. Studies have suggested that AR can affect smell during pollen season,<sup>1</sup> but the cause of hyposmia in AR is unclear.<sup>2,3</sup> 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.<sup>4,5</sup> The use of this test for AR specific evaluation is currently limited, reported techniques

1 are time consuming, and human mast cells are heterogeneous. Additional understanding of mast cell  
2 activation testing and its application in AR is needed.

3

4 The following are areas in which AR evaluation and diagnosis may be improved in the future:

5

- 6 • Increased understanding of hyposmia as a symptom of AR or a marker of its severity
- 7 • Further evaluation and validation of nasal sIgE testing for AR diagnosis
- 8 • Further work evaluating the use of novel AR testing techniques, such as BAT and mast cell  
9 activation testing, provocation testing, and objective measures of nasal air flow
- 10 • Improvement of low-cost diagnostic tools

11

12 **Pediatrics.** The pediatrics section has been added for the ICAR-Allergic Rhinitis 2023 update. This section  
13 summarizes the existing literature on pediatric allergy diagnosis and treatment. We have identified  
14 areas in which more work is needed:

15

- 16 • Improved treatment options for young children
- 17 • Improved interpretation of skin testing results in young children
- 18 • Optimizing treatment strategies for children who are polysensitized
- 19 • Further work developing AIT delivery routes appropriate and safe for children

20

21 **Management.** There are several well documented strategies for AR management with high levels of  
22 evidence and effectiveness. Avoidance strategies are cost-effective, but high-level data is lacking.  
23 However, many pharmacotherapy and AIT options have been shown to be effective, and several of  
24 these treatment strategies are strongly recommended. Since ICAR-Allergic Rhinitis 2018, additional  
25 studies have been completed; however, all avoidance strategies other than reduction of occupational  
26 exposures remain as an “option” due to relatively low-quality evidence. Pharmacotherapy and AIT  
27 treatment option aggregate grades of evidence remain largely stable since ICAR-Allergic Rhinitis 2018,  
28 although there are a few notable recommendation updates including strong recommendations against  
29 oral steroids and oral decongestants for routine use in the treatment of AR. Areas of future work in AR  
30 management include:

31

- 32 • Continued investigation of combination therapy options, including topical therapies
- 33 • Studies of comparative effectiveness and cost-effectiveness for AR treatments
- 34 • Further work directly comparing SCIT to SLIT in large-scale RCTs
- 35 • Standardization of rush and cluster SCIT protocols for aeroallergen immunotherapy

36

1 **Associated conditions.** The evidence supporting the relationship between AR and other conditions is  
2 often conflicting. Since ICAR-Allergic Rhinitis 2018, the relationship of asthma to AR has been extensively  
3 studied with an increase in the Aggregate Grades of Evidence. In addition, several new sections in ICAR-  
4 Allergic Rhinitis 2023 highlight the potential relationship of allergy to various subtypes/endotypes of  
5 CRS, however the evidence remains conflicting. More research is needed in the following domains:

- 6
- 7 • Improved understanding of treatment effects of AR on specific comorbid CRSwNP
- 8 subtypes/endotypes
- 9 • Continued work to determine the relationship of AR to ear disease
- 10 • Investigation of treatment effect of AR on cough
- 11

12 **COVID-19.** One of the notable effects of the identification of the novel coronavirus disease in 2019 was a  
13 rapid expansion in research efforts, scientific publications, and dissemination of knowledge related to  
14 the transmission, health consequences, and risk to patients and healthcare workers. The work on AR  
15 and COVID-19 continues to evolve. The following are topics of interest regarding COVID-19 and AR:

- 16
- 17 • Improved understanding of the aerosolization risk during nasal endoscopy
- 18 • Improved understanding of the risks of AR treatment, including AIT, during COVID infection
- 19 • A deeper understanding of the long-term effects of COVID on allergic diseases and their
- 20 development
- 21

## 22

## 23 XVI. Conclusion

## 24

25 In this document, we summarized the available literature for AR and created recommendations based  
26 on the highest levels of evidence. Through this, we have identified several areas with robust literature  
27 and a strong evidence base. There have been many advances in the field since the publication of ICAR-  
28 Allergic Rhinitis 2018, but notable knowledge gaps remain. There are several areas of AR research which  
29 will be limited based on inherent conditions of study design. For example, it is not feasible to blind or  
30 randomize for some AR treatments, and epidemiological studies to evaluate risk factors may be  
31 inherently limited by their retrospective nature and confounding variables. Therefore, for each major  
32 content area, we have suggested practical and feasible areas of study that we believe could advance our  
33 knowledge of AR in a productive manner.

## 34

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