International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis

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List of Abbreviations Used

AAAAI	American Academy of Allergy Asthma & Immunology
AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
AC	allergic conjunctivitis
ACC	allergen challenge chamber
ACE-I	angiotensin converting enzyme inhibitor
ACTH	adrenal corticotropic hormone
AD	atopic dermatitis
AERD	aspirin exacerbated respiratory disease
AH	adenoid hypertrophy
AHI	apnea-hypopnea index
AIT	allergen immunotherapy
ANA	anti-nuclear antibody
ANCA	anti-nuclear cytoplasmic antibody
APC	antigen presenting cell
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ARS	acute rhinosinusitis
BAFF	B-cell activating factor
BAT	basophil activation test
BDNF	brain-derived neurotrophic factor
BKC	benzalkonium chloride
CARAT10	Control of Allergic Rhinitis and Asthma Test
CCAAPS	Cincinnati Childhood Allergen and Air Pollution Study
CCAD	central compartment atopic disease
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CNS	central nervous system
CO	carbon monoxide
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CPG	clinical practice guideline
CPT	conjunctival provocation test
CRD	component resolved diagnosis
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyposis
CRSwNP	chronic rhinosinusitis with nasal polyposis
CS	Combined Score
CSF	cerebrospinal fluid
CT	computed tomography
DCS	Daily Combined Score
DEP	diesel exhaust particles
DBP	diastolic blood pressure
DSCG	disodium cromoglycate
EAACI	European Academy of Allergy & Clinical Immunology
EAN	European Aeroallergen Network
EBR	evidence-based review (without recommendations)
EBRR	evidence-based review with recommendations
EC	environmental control
ECP	eosinophil cationic protein
ECRHS	European Community Respiratory Health Survey

1	EEC	environmental exposure chamber
2	EGPA	eosinophilic granulomatosis with polyangiitis
3	ENS	empty nose syndrome
4	EoE	eosinophilic esophagitis
5	EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
6	ESS	Epworth Sleepiness Scale
7	EU	European Union
8	FDA	Food and Drug Administration (US)
9	FEV1	forced expiratory volume in 1 second
10	FoxP3	forkhead box P3
11	GA^{2}LEN	Global Allergy and Asthma Network of Excellence
12	GM-CSF	granulocyte-macrophage colony stimulating factor
13	GPA	granulomatosis with polyangiitis
14	GWAS	genome-wide association study
15	HD-42	Sleep Disorders Questionnaire
16	HDM	house dust mite
17	HEPA	high efficiency particulate air
18	HFA	hydrofluoroalkane
19	HMW	high molecular weight
20	HR	heart rate
21	IAR	intermittent allergic rhinitis
22	ICAR	International Consensus Statement on Allergy and Rhinology
23	ICAR:AR	International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis
24	ICAR:RS	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
25	IDT	intradermal dilutional testing
26	IFN	interferon
27	IgE	immunoglobulin E
28	IL	interleukin
29	ILC	innate lymphoid cell
30	ILIT	intralymphatic immunotherapy
31	IND	intranasal decongestant
32	INCS	intranasal corticosteroid
33	INV	intranasal volume
34	IPB	ipratropium bromide
35	ISAAC	International Study of Asthma and Allergies in Childhood
36	JSQ	The Jenkins Questionnaire
37	LAR	local allergic rhinitis
38	LMW	low molecular weight
39	LOE	level of evidence
40	LPR	laryngopharyngeal reflux
41	LRRC32	leucine-rich repeat-containing protein 32
42	LT	leukotriene
43	LTRA	leukotriene receptor antagonist
44	mAb	monoclonal antibody
45	MAS	Multicentre Allergy Study
46	MCC	mucociliary clearance
47	MCP	macrophage/monocyte chemoattractant protein
48	MD	molecular diagnosis
49	MDC	macrophage-derived chemokine
50	MIF	macrophage migration inhibitory factor
51	MIP	macrophage inflammatory protein
52	MQT	Modified Quantitative Testing
53	NAR	non-allergic rhinitis

1	NARES	non-allergic rhinitis with eosinophilia syndrome
2	NARESMA	non-allergic rhinitis with eosinophils and mast cells
3	NARMA	non-allergic rhinitis with mast cells
4	NARNE	non-allergic rhinitis with neutrophils
5	NC	nasal cytology
6	NGF	nerve growth factor
7	NHANES	National Health and Nutrition Examination Survey
8	NO	nitric oxide
9	NO_2	nitrogen dioxide
10	NPT	nasal provocation test
11	NSAID	non-steroidal anti-inflammatory drug
12	O_3	ozone
13	OAS	oral allergy syndrome
14	OME	otitis media with effusion
15	OMIT	oral mucosal immunotherapy
16	OR	odds ratio
17	OSA	obstructive sleep apnea
18	OTC	over the counter
19	PAR	perennial allergic rhinitis
20	PARIS	Pollution and Asthma Risk: An Infant Study
21	PER	persistent allergic rhinitis
22	PDE	phosphodiesterase
23	PFAS	pollen food allergy syndrome
24	PM_{10}	particulate matter <10 microns
25	$PM_{2.5}$	particulate matter <2.5 microns
26	PNU	protein nitrogen unit
27	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
28	ppm	parts per million
29	PROM	patient reported outcome measure
30	PSG	polysomnogram
31	QOL	quality of life
32	RANTES	regulated on activation, normal T-cell expressed and secreted
33	RAP	Respiratory Allergy Prediction test
34	RARS	recurrent acute rhinosinusitis
35	RAST	radioallergosorbent test
36	RC-ACS	Rhinoconjunctivitis-Allergy Control Score
37	RCT	randomized controlled trial
38	RFA	radiofrequency ablation
39	RM	rhinitis medicamentosa
40	RMS	Rescue Medication Score
41	RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
42	rTNSS	Reflective Total Nasal Symptom Score
43	RTSS	Rhinitis Total Symptom Score
44	RUDS	reactive upper airway dysfunction syndrome
45	SAPALDIA	Swiss Study of Air Pollution and Lung Disease in Adults
46	SAR	seasonal allergic rhinitis
47	SBP	systolic blood pressure
48	SCIT	subcutaneous immunotherapy
49	SDB	sleep disordered breathing
50	SES	socioeconomic status
51	sIgE	antigen-specific immunoglobulin E
52	SLE	systemic lupus erythematosus
53	SLIT	sublingual immunotherapy

SMD	standardized mean difference
SNP	single nucleotide polymorphism
SO_2	sulfur dioxide
SPT	skin prick test
SQ-U	standardized quality units
SSRI	selective serotonin reuptake inhibitor
SSS	Stanford Sleepiness Score
TARC	thymus and activation regulated chemokine
TCRS	Total Combined Rhinitis Score
TDI	threshold, discrimination, identification
TGF-β	transforming growth factor beta
Th	T-helper cell
Th0	naïve T-helper cell
tIgE	total immunoglobulin E
TLR	toll-like receptor
TNF	tumor necrosis factor
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TOTALL	TOTal Costs of ALLergic Rhinitis in Sweden
Treg	T-regulatory cell
TSLP	thymic stromal lymphoprotein
US	United States
VAS	Visual Analog Scale
VHI	Voice Handicap Index
WHO	World Health Organization

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Abstract

Background. Critical examination of the quality and validity of available allergic rhinitis (AR) literature is necessary to improve understanding and to appropriately translate this knowledge to clinical care of the AR patient. To evaluate the existing AR literature, international multidisciplinary experts with an interest in AR have produced the International Consensus statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR).

Methods. Using previously described methodology, specific topics were developed relating to AR. Each topic was assigned a literature review, evidence-based review (EBR), or evidence-based review with recommendations (EBRR) format as dictated by available evidence and purpose within the ICAR:AR document. Following iterative reviews of each topic, the ICAR:AR document was synthesized and reviewed by all authors for consensus.

Results. The ICAR:AR document addresses over 100 individual topics related to AR, including diagnosis, pathophysiology, epidemiology, disease burden, risk factors for the development of AR, allergy testing modalities, treatment, and other conditions/comorbidities associated with AR.

Conclusion. This critical review of the AR literature has identified several strengths, where providers can be confident that treatment decisions are supported by rigorous studies. However, there are also substantial gaps in the AR literature. These knowledge gaps should be viewed as opportunities for improvement, as often the things that we teach and the medicine that we practice is not based on the best quality evidence. This document aims to highlight the strengths and weaknesses of the AR literature to identify areas for future AR research and improved understanding.

I. Introduction

The available literature on allergic rhinitis (AR) grows more quickly with each passing decade. A search of "allergic rhinitis" in the PubMed database yielded 4,135 articles published between 1945 and 1979. The next 20 years (1980-2000) saw 7,064 AR articles published. Each subsequent decade has surpassed this number with 8,143 AR articles published between 2000 and 2010, and 8,212 published from 2010 to the present day. Like many other areas of medicine, a close look at the available literature demonstrates a wide variation in the type and quality of AR publications, ranging from case reports to meta-analyses, review articles to randomized controlled trials (RCT), and large prospective studies to small retrospective case series. As a medical professional reads the literature or hears literature quoted by others, it is important that he/she understand the quality of the evidence in order to appropriately translate the findings and recommendations into daily clinical care of the AR patient. With such vast AR literature available, developing an appropriate understanding of the relevant evidence can be daunting.

This International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) was developed to summarize the best external evidence relating to AR, with the goal of gathering and critically reviewing the available literature on AR epidemiology, risk factors, diagnosis, management, and associated conditions/comorbidities. More than 100 international authors from various specialties utilized a structured review process to evaluate the evidence related to AR. Initial topic development and writing by a primary author or team of authors, followed by a stepwise anonymous iterative review process for over 100 AR topics held this process to extremely high standards. The resulting document provides a strong review of the existing AR literature. The recommendations for AR diagnostic modalities and treatment contained herein rely directly on this evidence, with a clear delineation of the benefit, harm, and cost considerations that supported each recommendation level.

Like the 2016 International Consensus statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) by Orlandi et al,[1] this ICAR:AR document places high value on the strength of the evidence in making recommendations. Therefore, for example, expert opinion receives lower value. **[Table II.A-1.]** There are limitations, however. Like ICAR:RS, this document is not a clinical practice guideline (CPG) or a meta-analysis. This document summarizes the findings of meta-analyses and other systematic reviews when those are identified in the literature for a specific AR topic area. However, a meta-analysis was not performed on the data included in this document. In addition, much of the available AR literature is not appropriate for meta-analysis due to its heterogeneous nature and inconsistent methodologies. ICAR:AR is also not a CPG, as the typical steps of a CPG (i.e. medical specialty society and patient advocate review) were not employed here.

Throughout this document, certain topic areas have very strong evidence whereas other topics demonstrate relatively weak evidence. Many of our common practices in the diagnosis and care of the AR patient are based upon weak external evidence. As practitioners, academicians, and scientists, we must examine this evidence and strive to increase the strength of the evidence in areas where gaps exist.

Within the ICAR:AR document, recommendations are given based on the evidence in a specific topic area. However, this document is a compilation of the best AR evidence, not a manual for the care of the AR patient. Evidence-based medicine requires that the clinician has the best evidence available, but also uses his/her expertise and takes the patient's values and expectations into account.[2] Therefore,

with a background of evidence-based knowledge, the practitioner must approach each patient as an individual to determine the most appropriate diagnostic and treatment modalities for that particular patient. Given the numerous potential conditions in the AR differential diagnosis, various diagnostic and treatment options available, and diverse comorbidities and associated conditions that may accompany AR, treatment of the AR patient with an evidence-based approach requires careful consideration.

As previously stated by Orlandi et al,[1] the recommendations provided in an ICAR document must be interpreted based on the strength of the evidence that forms their foundation. The recommendations in this document are evidence-based. They do not define the standard of care or medical necessity. Recommendations written in this document, or any similar document, do not dictate the specific care of an individual patient. There are numerous other factors that enter into the treatment decisions for each individual patient. Finally, it is expected that these recommendations will change with time and with new evidence. We encourage new research, especially rigorous studies that aim to fill the identified knowledge gaps. With new evidence, recommendations will undergo necessary revisions and better patient outcomes should result.

II. Methods

II. A. Topic development

In a similar fashion to the 2016 ICAR:RS document by Orlandi et al,[1] this ICAR:AR document is formulated with the utmost reliance on published evidence. With the 2011 Rudmik and Smith[3] evidence-based review with recommendations (EBRR) method as its foundation, ICAR:AR strives to analyze the existing literature on each AR topic, grading the evidence and providing literature-based recommendations where appropriate.

The subject of AR was initially divided into 103 topics or content areas. A senior author who is a recognized expert in allergy, rhinology, or the assigned topic was appointed to each topic. Authors were initially selected via online literature searches for each ICAR:AR topic. Authors of high-quality publications in each topic area were invited as ICAR:AR contributors. Other invited authors included experts in the EBRR process, experts in teaching/lecturing on specific AR topic areas, and those with knowledge of the systematic review process.

Some of the topics, such as those providing background or definitions, were assigned as literature reviews without evidence grades. Certain topics that were not appropriate for clinical recommendations were assigned as evidence-based reviews without recommendations (EBRs). Topics that had evidence to inform clinical recommendations were assigned as EBRRs.

Each topic author received specific instructions to perform a systematic review for the topic literature using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) standardized guidelines.[4] Ovid MEDLINE® (1947-September 2016), EMBASE (1974-September 2016) and Cochrane Review databases were included. The search began by identifying any previously published systematic reviews or guidelines pertaining to the assigned topic. Since clinical recommendations are best supported by high quality evidence, the search focused on identifying RCTs and meta-analyses of RCTs to provide the highest level of evidence (LOE). Reference lists of all identified studies were examined to ensure all relevant studies were captured. If the authors felt as though a non-English study should be included in the review, it was instructed that the paper be appropriately translated to minimize the risk of missing important data during the development of recommendations.[4]

To optimize transparency of the evidence, all included studies in EBR and EBRR topic sections are presented in a standardized table format and the quality of each study was evaluated to receive a level based on the Oxford LOE (level 1a to 5).[5] At the completion of the systematic review and research quality evaluation for each clinical topic, an aggregate grade of evidence was produced for the topic based on the guidelines from the American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM).[6] **[Table II.A-1.]**

After providing an aggregate grade of evidence for each EBRR topic (A to D), a recommendation using the AAP SCQIM guidelines was produced. **[Table II.A-2.]** It is important to note that each evidence-based recommendation took into account the aggregate grade of evidence along with the balance of benefit, harm, and costs. A summary of the EBRR development process is provided in **Figure II.A-1**.

II. B. Iterative review

Following the development of the initial topic text and any associated evidence tables, evidence grades, and recommendations, each section underwent a two-stage online iterative review process using two independent reviewers. **[Figure II.A-2.]** The purpose of the topic iterative review process was to evaluate the completeness of the identified literature and ensure any EBRR recommendations were appropriate. The content of the first draft from each topic section was reviewed by a first reviewer, and all changes were agreed upon by the initial author and this first reviewer. The revised topic section was then subsequently reviewed by a second reviewer. Initial authors of the topic and both assigned reviewers agreed upon all changes before each section was considered appropriate to proceed into the final ICAR statement stage.

II. C. ICAR statement development

After the content of each of topic was reviewed and consensus reached amongst the initial author and two iterative reviewers, the principal editor (SKW) compiled all topics into one ICAR:AR statement. The first draft of each large ICAR:AR portion (i.e. Evaluation and Diagnosis, Pharmacotherapy, Immunotherapy, etc.) then underwent additional reviews for consistency and understanding using a group of 6-8 authors. Finally, the draft ICAR:AR was circulated to all authors. The final ICAR:AR manuscript was produced when all authors agreed upon the literature and final recommendations. External peer review, with 20 reviewers, was also undertaken for the final ICAR:AR document. **[Figure II.A-3.]**

II. D. Limitations of methods and data presentation

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

Table II.A-1. Aggregate grade of evidence[6]

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

RCT: randomized controlled trial

Table II.A-2. American Academy of Pediatrics defined strategy for recommendation development[6]

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCT's	*Strong recommendation*	*Option*	*Strong recommendation against*
B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	*Recommendation*		
C. Observational studies (case-control and cohort design)			*Recommendation against*
D. Expert opinion; Case reports; Reasoning from first principles	*Option*	*No recommendation*	

RCT: randomized controlled trial

Figure II.A-1. Topic development

EBRR: evidence-based review with recommendation; PE: principal editor; 1^0: primary; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AAP: American Academy of Pediatrics

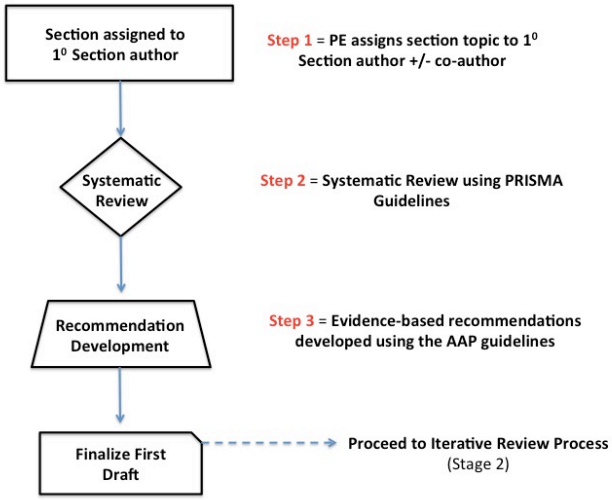


Figure II.A-2. Topic EBRR Iterative Review

PE: principal editor; 1^0: primary; 2^0: secondary; 3^0: tertiary

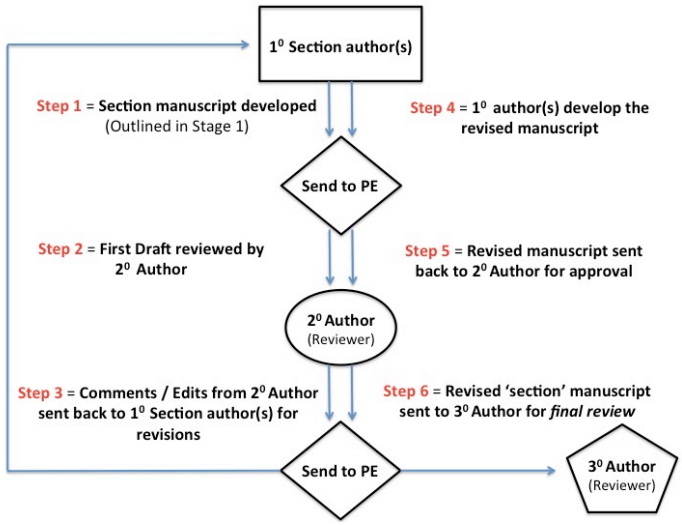
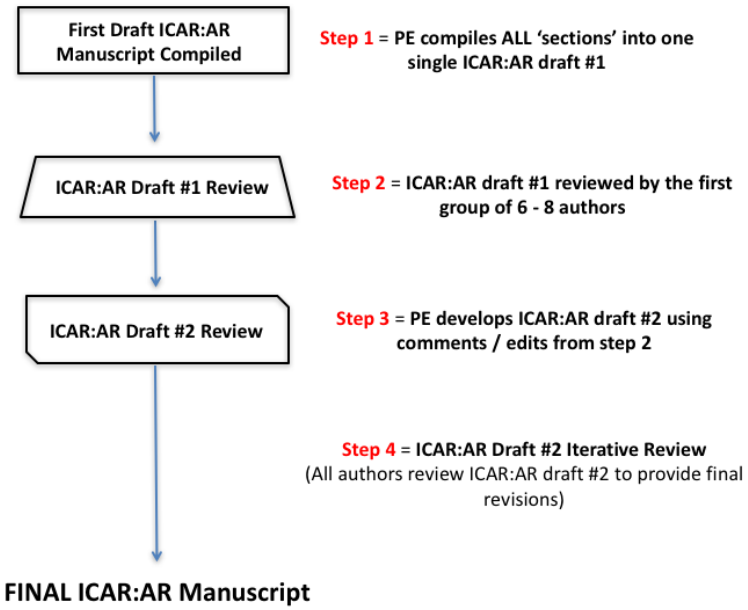


Figure II.A-3. ICAR: Allergic Rhinitis statement iterative review

PE: principal editor; ICAR:AR: International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis



III. Definition and differential diagnosis

AR is an immunoglobulin E (IgE)-mediated inflammatory nasal condition resulting from allergen introduction in a sensitized individual.[7] AR was defined in 1929 as a process which included three cardinal symptoms: sneezing, nasal obstruction, and mucus discharge.[8] Symptoms occur with allergen exposure in the allergic patient. AR is a widely prevalent condition that can result in significant physical sequelae and recurrent or persistent morbidities.[7]

The prevalence of AR is approximately 10-40%, depending on geographic location,[9] with the highest incidence occurring in children.[10] However, AR is nearly absent in infants, typically not manifesting until the second year of life at the earliest. When AR presents in children, this is likely secondary to the rapidly evolving immune system. AR often results from an overactive response of T helper (Th) 2 lymphocytes which can initiate a systemic, IgE-driven reaction which may dominate child's immune system until it is completely mature. During this time, a skin prick test (SPT) or *in vitro* antigen-specific IgE (sIgE) test can be used to confirm the diagnosis of AR.

In the atopic individual, exposure to indoor and outdoor allergens may prompt antigen-specific IgE production. Re-introduction of the allergen triggers early and late-stage reactions, leading to the clinical manifestations of AR. The early-stage reaction occurs within minutes after re-introduction of the sensitized allergen, producing nasal itching, nasal congestion, and rhinorrhea.[11] The late-stage reaction occurs during the 4-8 hour period after allergen introduction and results in nasal blockage, hyposmia, increased mucus secretion, and nasal hyper-responsiveness to the same or different allergens. Additionally, even in the absence of overt symptoms, IgE has an increased presence in the lymphoid tissue of the atopic patient, which can result in persistent mucosal inflammation.[12]

III. B. Allergic rhinitis classification

Seasonal vs. perennial AR. The Allergic Rhinitis and its Impact on Asthma (ARIA) proposals have categorized AR by presumed cause and seasonal versus perennial presentation. Classically, this has included seasonal AR (SAR; hay fever) and perennial allergic rhinitis (PAR).[7] SAR is triggered by a wide assortment of outdoor allergens, especially pollens.[7] PAR is commonly brought about by indoor allergens that are present throughout the year, such as dust mites, molds, insects (cockroaches), and animal dander.[7]

Intermittent vs. persistent AR. The classification of "seasonal" and "perennial" AR can often be in conflict, as manifestations of perennial allergy may not occur throughout the entire year. This is particularly the case for patients allergic to house dust mites (HDM), who may demonstrate mild or moderate/severe intermittent allergic rhinitis (IAR).[9,13-15] In addition, because of the priming effect on the nasal mucosa initiated by low levels of pollen allergens[16-21] and minimal persistent nasal inflammation in patients with "symptom-free rhinitis",[14,22,23] symptoms may not occur entirely in conjunction with the allergen season, therefore resulting in non-specific exacerbations. Air pollution may also contribute to alterations in allergen sensitivity, resulting in varying degrees of symptoms depending on location and air quality.[24] Furthermore, individuals sensitized to multiple pollens may have symptoms across several seasons while individuals with PAR may encounter symptoms for short periods

of time with frequent, repetitive relapses.

Because of the issues outlined above, ARIA proposed a new method of classification based on the length and recurrence of the symptom manifestations.[25] IAR is characterized by symptoms for less than 4 days per week or less than 4 consecutive weeks. Persistent AR (PER) is characterized by symptoms occurring more than 4 days per week for at least 4 consecutive weeks; therefore, PER patients are symptomatic most of the time.[26] It has been recommended that the previous categories of seasonal and perennial AR not be used along with the new classification of IAR and PER, as they don't represent the same stratification of the disease state. As such, IAR and PER are not synonymous with seasonal and perennial.[25,27-30] In describing AR, one should determine which classification scheme best conveys the message that he/she wishes to relay: seasonal/perennial or intermittent/persistent.

Severity of allergic rhinitis. AR can result in significant disturbances in quality of life (QOL), sleep, exercise tolerance, productivity, and social functioning. The ARIA guidelines have likewise proposed the stratification of severity (mild and moderate-severe) in view of these disabilities.[13] *(See Section VII. Disease Burden for additional information on this topic.)*

Sensitization vs. clinical allergy. Monosensitization is sensitization (as indicated by positive reactions on standardized SPTs or serum sIgE levels) to only one allergen, such as grass pollen, tree pollen, HDM or cat dander (even though extracts of these concentrates contain numerous diverse polypeptides).[31] Monoallergy is defined as a single sensitizing allergen causing clinical allergy symptoms. Polysensitization is sensitization to two or more allergens. Polyallergy is affirmed clinical symptoms to two or more sensitizing allergens. Findings of allergy testing, either skin testing or sIgE must be correlated with clinical symptoms to identify the allergen(s) likely responsible for the symptoms.[32] Allergen challenges (i.e. nasal provocation testing, conjunctival challenge, or allergen test chambers) can reproducibly confirm the clinical significance of a sensitized allergen, but these tests may be difficult to perform, subjective, and limited by irritant effects.[33] Allergy skin testing and sIgE titer must be carefully interpreted at the patient level, and can also be valuable at the population level when evaluating sensitization for epidemiological studies.[34] With increasing availability of component-resolved diagnosis (CRD), physicians will have a more objective means of identifying clinically relevant allergens and distinguishing true co-sensitization from polysensitization due to cross-reactivity. *(See Section VIII.F.6. Component Resolved Diagnosis for additional information on this topic.)*

III. C. Allergic rhinitis differential diagnosis

The symptoms of AR may be similar to symptoms of other types of sinonasal disease, and at times multiple types of rhinitis may coexist. It is important to correctly determine the etiology of rhinitis to appropriately treat the patient and have the best chance of resolving his or her symptoms. In the following sections, a discussion of the differential diagnosis of AR is presented, along with a description of how each rhinitis entity differs from AR. Of note, this section on AR differential diagnosis is specific to various etiologies of rhinitis. Other entities that may enter into the differential diagnosis of AR, such as

structural sinonasal conditions (i.e. deviated septum), tumors, and cerebrospinal fluid leak are not discussed here. **[Table III.C.]**

Table III.C. Differential diagnosis of allergic rhinitis*

Types of rhinitis[#]
• Drug-induced rhinitis • Rhinitis medicamentosa • Occupational rhinitis • Chemical rhinitis • Smoke-induced rhinitis • Infectious rhinitis • Rhinitis of pregnancy and hormonally-induced rhinitis • Food and alcohol-induced rhinitis • Non-allergic rhinitis with eosinophilia syndrome (NARES) • Vasomotor rhinitis (non-allergic rhinopathy) • Age-related rhinitis (i.e. elderly) • Empty nose syndrome • Atrophic rhinitis • Autoimmune, gramulomatous, and vasculitic rhinitis • Rhinosinusitis

***For each of these conditions, the similarities and difference to allergic rhinitis are discussed within each content section.

[#]This table is specific to various etiologies of rhinitis. Structural sinonasal conditions (i.e. deviated septum), tumors, and cerebrospinal fluid leak are not listed here.

III. C. 1. Drug-induced rhinitis

Rhinitis secondary to systemic medications can be classified into local inflammatory, neurogenic, and idiopathic types.[35,36] **[Table III.C.1.]** The local inflammatory type occurs when consumption of a drug causes a direct change in inflammatory mediators within the nasal mucosa. The neurogenic type occurs after use of a drug that systemically modulates neural stimulation, leading to downstream changes in the nasal mucosa. Idiopathic drug-induced rhinitis is used to classify drugs without a well-defined mechanism contributing to symptoms. Topical nasal decongestants can cause drug-induced rhinitis, known as rhinitis medicamentosa (RM). *(See Section III.C.2. Rhinitis Medicamentosa for additional information on this topic.)*

Local inflammatory type. Systemic ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with a disorder of eiconsanoid synthesis can result in rhinitis and nasal congestion, which may also be associated with chronic rhinosinusitis (CRS) and asthma.[37] In brief, NSAIDs inhibit cyclooxygenase (COX)-1 and COX-2 enzymes, shifting arachidonic acid metabolism toward the lipoxygenase pathway, with decreased production of prostaglandins and thromboxane in exchange for inflammatory leukotrienes (LT). Reduction in nasal mucosal prostaglandin E2, as well as increased LTC4, LTD4, and LTE4 causes mucus production and nasal mucosal edema, hallmarks of rhinitis.[35,38]

Neurogenic and neuromuscular type. Neurogenic type non-allergic rhinitis (NAR) is caused by drug-induced modulation of the autonomic nervous system. Antihypertensives and vasodilators are among

the many classes of drugs that cause drug-induced NAR. Other nonspecific drugs, such as psychotropics and immunosuppressants, have unknown mechanisms and are categorized as idiopathic, but can cause neuromodulatory effects as well. Modulation of the autonomic nervous system leads to downstream changes in nasal mucosa, blood vessels, and secretory glands.[39] For example, α and β-adrenergic antagonists, and presynaptic α-agonists, cause decreased sympathetic tone and unopposed parasympathetic stimulation producing mucosal engorgement, nasal congestion, and rhinorrhea.[40-42] Phosphodiesterase (PDE)-5 specific inhibitors promote penile vasodilation and erection. PDE-3 and nonselective PDE inhibitors result in vasodilation and increased extremity blood flow, relieving symptoms of peripheral artery disease. Nitric oxide (NO)/cyclic nucleotide mediated vasodilation occurs in the nasal mucosa as well, causing nasal mucosal engorgement and edema.[43-46] Finally, angiotensin converting enzyme inhibitors (ACE-I) inhibit the conversion of angiotensin I to angiotensin II in the lungs resulting in a decrease in sympathetic activity. Bradykinin is also formed. Bradykinin B1 and B2 receptors have been demonstrated in nasal mucosa;[47] bradykinin application to the nasal mucosa has been shown to increase sneezing,[44,48] suggesting a role of ACE-Is in NAR.

Illicit drug use. The nose provides a unique portal for illicit drug use, as nasal mucosa is well vascularized and easily accessible. The illicit drug user can avoid invasive intravascular or intramuscular administration of a desired product by applying a crushed solid, liquid, or aerosolized form of the product directly to the nasal cavity. For some drugs, nasal administration increases bioavailability and shortens time to onset when compared to oral ingestion.[49,50] Cocaine is most commonly associated with nasal illicit drug use and exerts its effect by modulating dopamine transporters to inhibit reuptake at the synapse, increasing dopamine available for post-synaptic stimulation.[51] Cocaine-induced rhinitis is a result of vasoconstrictive events, which can be followed by rebound nasal mucosal edema and mucous production, similar to those seen in RM.[52-55] In the repeat user, vasoconstriction, direct trauma compounded by anesthetic effects, and/or injury secondary to contaminants may result in nasal septal perforation.[56-59] Similarly, prescription narcotics,[59] antidepressants,[47] anticholinergics, and psychostimulants can be abused by intranasal administration.[47,60] Intranasal hydrocodone has been shown to induce nasal tissue necrosis and loss in a similar manner to cocaine.[59] Antidepressants such as bupropion have been used to achieve a euphoria similar to that of cocaine and may induce seizures.[47]

In summary, systemic medications and intranasal illicit drugs affect the nasal mucosa. Increased mucosal edema, vasodilation and inflammatory mediators are a consequence of systemic medications. Vasoconstriction and direct mucosal injury often accompanies illicit drug use. The physiologic response in drug-induced rhinitis differs from AR as it is not allergen-induced nor dependent on IgE mechanisms, although symptomatology may be similar.

Table III.C.1. Medications causative or contributory to drug-induced rhinitis[40,44,48]

Type of drug-induced rhinitis	General drug category	Specific drug category	Examples
Local inflammatory			- NSAIDs (ibuprofen, indomethacin, diclofenac, sulindac, ketoprofen,

			naproxen, flurbiprofen, fenoprofen, piroxicam, meclofenamate, etodolac) - Aspirin - Ketolorac (if administered via nasolacrimal duct)
Neurogenic and neuromuscular	α and β-adrenergic receptor modulators	α antagonists	- α-1: doxazosin, silodosin, prazosin, tamsulosin, alfuzosin, indoramin - α-1, α-2: phentolamine
		Presynaptic α-2 agonists	clonidine, methyldopa, guanfacine, piribedil
		Beta-antagonists	- β-1: metoprolol, atenolol, bisoprolol - β-1, β-2: pindolol - β-1, β-2, α-1: carvedilol, labetalol
		Presynaptic depletion of norepinephrine stores	guanethidine
	Phosphodiesterase inhibitors	Phosphodiesterase-3 specific	cilostazol
		Phosphodiesterase-5 specific	sildenafil, tadalafil, vardenafil
		Non-selective phosphodiesterase	pentoxifylline
	Angiotensin converting enzyme inhibitor		ramipril, captopril, lisinopril, benazepril, quinapril, enalapril
Idiopathic		Psychotropics	Chlorpromazine, thioridazine, amitriptyline, alprazolam, reserpine, risperadone, mianserin
		Immunomodulators	cyclosporine
		Hormones	estrogen, oral contraceptives
		Antihypertensives	Amiloride, chlorothiazide, hydralazine, hydrochlorothiazide
		Other	gabapentin, gingko biloba

III. C. 2. Rhinitis medicamentosa (RM)

RM, or rebound rhinitis, is a condition induced by prolonged use of topical intranasal decongestant (IND).[26,61] **[Table III.C.2.]** Although no consensus diagnostic criteria exist, RM is classically associated with the triad of prolonged IND use, constant nasal obstruction, and poor shrinkage of the nasal mucosa[61] in the setting of nasal congestion, rhinorrhea, and decreased efficacy of further INDs.[55,62,63] Physical exam findings consist of mucosal edema, erythema, and hyperemia.

The exact physiologic mechanism causing RM is unclear. Continuous IND use may decrease endogenous norepinephrine production and cause upregulation of the parasympathetic system, leading to rebound congestion once the decongestant is discontinued.[54,55] This may be further exacerbated by recurrent nasal tissue hypoxia and negative neural feedback with chronic decreased α-2 receptor responsiveness.[64] Mucosal changes include ciliary damage and loss, epithelial metaplasia and hyperplasia, dilated intercellular spaces, goblet cell hyperplasia, and edema.[65-67] Benzalkonium chloride (BKC), an antimicrobial preservative used in many nasal decongestants, has been implicated in the

mechanism of RM. Studies have suggested that BKC is toxic to nasal epithelium and may propagate RM, although the data are inconclusive.[68-71]

Neither duration, nor cumulative dose of IND needed to initiate RM is known. Rebound congestion has developed after 3-10 days of medication use,[55,66] but may not occur until after 30 days.[72,73] Other studies have demonstrated a lack of rebound after 8 weeks of continuous use.[72-75] Furthermore, doubling the dose of intranasal imidazoline did not increase the extent of rebound edema.[72] Although inconclusive, studies suggest that IND use should be discontinued after three days to avoid rebound congestion.[62,76,77]

Treatment of RM involves discontinuation of INDs. Various medications have been used to improve nasal decongestion including nasal cromolyn, sedatives, nasal saline spray, oral antihistamines, oral decongestants, and intranasal corticosteroids (INCS; sometimes used in conjunction with brief courses of systemic corticosteroids).[50,62,78-82] Only the use of INCS has been demonstrated to mitigate rebound congestion after discontinuation of topical INDs.[67,81-83] Often there is an underlying rhinitis and/or anatomic issue that initiated the decongestant use. This underlying issue should be addressed to diminish the drive to continue to use INDs.

Importantly, RM is typically associated with repeated exposure to INDs, with increasing symptoms at times when the medication is withheld. In contrast, AR is classically associated with an allergic trigger with similar symptoms increasing upon allergen exposure, and is dependent upon IgE-mediated inflammation.

Table III.C.2. Intranasal decongestants associated with rhinitis medicamentosa[26,61]

Sympathomimetic amines	phenylephrine, pseudoephedrine, ephedrine, amphetamine, benzedrine, caffeine, mescaline
Imidazoline derivatives	oxymetazoline, xylometazoline, naphazoline, clonidine

III. C. 3. Occupational rhinitis

Occupational rhinitis is an inflammatory condition of the nasal mucosa, characterized by intermittent or persistent nasal congestion, sneezing, rhinorrhea, itching and/or hypersecretion due to causes and conditions attributable to a particular work environment, and not to stimuli encountered outside the workplace.[84] Occupational rhinitis is considered a form of "work-related rhinitis", which also encompasses work-exacerbated rhinitis, which is pre-existing or concurrent rhinitis that is worsened by workplace exposures.[84,85] **[Figure III.C.3.]**

Occupational rhinitis may be allergic, consequent to exposure to a sensitising high-molecular (HMW) or low-molecular weight (LMW) compound acting through an immunological mechanism, and characterized by the presence of a latency period between beginning of exposure and symptom onset. Alternatively, occupational rhinitis may be non-allergic, mediated by and irritant or non-immunological mechanism. Symptoms occur after single or multiple exposures to irritant compounds, and usually present without a latency period. Non-allergic occupational rhinitis resulting from a single exposure to a very high concentration of irritants is also referred as reactive upper airways dysfunction syndrome (RUDS). The most severe form of irritant-induced occupational rhinitis is corrosive rhinitis, which is

characterized by permanent inflammation of the nasal mucosa sometimes associated with ulcerations and perforation of the nasal septum.[84,85]

The results of cross sectional studies in working groups show a wide range of prevalence of occupational rhinitis (3-87%),[86] lower prevalence for LMW-agent exposure and higher prevalence for HMW-agent exposure. Examples of occupations at increased risk are reported in **Table III.C.3.**[87-98] Occupational rhinitis due to HMW-agents tend to be three times more prevalent than occupational asthma,[86] with which it is often associated (up to 92% of cases).[99]

Occupational rhinitis and occupational asthma share etiologic agents and pathogenic mechanisms,[100] and can be considered in the broader context of the Unified Airway Disease model.[85,93,101,102] **[Table III.C.3.]** The severity of occupational rhinitis may also affect the severity of occupational asthma.[103] In a high proportion (20-78%) of workers exposed to sensitizers, work-related nasal symptoms tend to develop 5-6 months before the onset of bronchial symptoms.[84,86] Consequently, occupational rhinitis may be considered a marker of the likelihood of developing occupational asthma.

The clinical presentation of occupational rhinitis is nonspecific. Nasal symptoms do not differ from those of non-occupational rhinitis. An occupational origin should be sought for all rhinitis of new onset in adults, especially in subjects employed in high-risk occupations. **[Table III.C.3.]** The diagnostic assessment first includes a thorough clinical and occupational history, aimed to investigate type of symptoms and work-relatedness, and to collect information on occupational exposure. Typical nasal symptoms are often accompanied by crust formation, sporadic epistaxis, olfaction impairment, conjunctivitis, or associate with pharyngeal, laryngeal or bronchial symptoms (which should always be evaluated). The presence of a latency period between an occupational exposure and symptom onset suggests an allergic mechanism. Documentation of noxious compounds (sensitizers and irritants) in the workplace to which the worker is more directly exposed are typically posted by the employer (i.e. Material Safety Data Sheets).[84,85]

Nasal examinations by anterior rhinoscopy and nasal endoscopy, assessing nasal patency[85,104] and inflammation in nasal secretions[105] are often performed as part of the clinical evaluation. Sensitization to a suspected HMW-agent can be evaluated through SPT and/or *in vitro* sIgE assessment, when standardized and validated extracts are available. A suggestive history associated with a positive immunological test for an occupational agent could be considered as probable allergic occupational rhinitis. A definitive diagnosis is obtained by objective demonstration of the causal relationship between rhinitis and the work environment through a nasal provocation test (NPT) with the suspected agent(s) in the laboratory, which is considered the gold standard for diagnosis.[84,85] If NPT is negative, further evaluation of work-related changes in nasal parameters at the workplace is recommended, especially in the presence of a highly suggestive clinical history. In subjects exposed to HMW-agents with a suggestive history and negative immunological tests, the type of inflammatory response to NPT might demonstrate the presence of an occupational local allergic rhinitis (LAR).[106,107] Due to the relationship between the upper and lower airways, spirometry, measurement of non-specific airway responsiveness, and measurement of bronchial inflammation by means of exhaled NO may also be performed.[84,85]

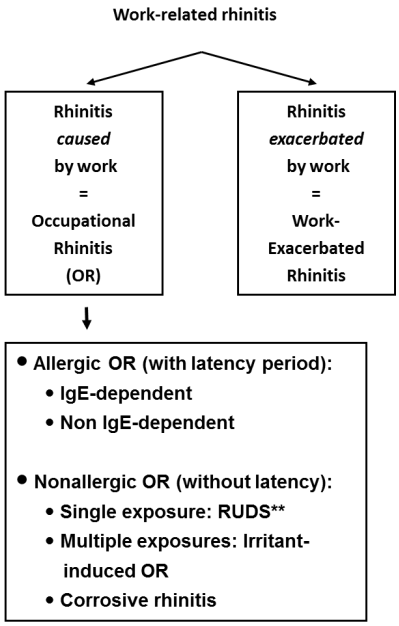
Primary treatment of allergic occupational rhinitis is avoidance or reduction of culprit exposures.[108] Pharmacologic treatment does not differ from that of non-occupational rhinitis.[101] In allergic occupational rhinitis due to HMW-sensitizers, specific immunotherapy may be proposed when validated extracts are available.[109] The prevention and early identification of occupational rhinitis during

medical surveillance of exposed workers and of young apprentices may provide an excellent opportunity to prevent the development of occupational asthma.[110,111]

Table III.C.3. Examples of high-risk occupations for occupational rhinitis and causal agents

Occupation	Agent
High molecular weight agents	
Bakers, food industry	Cereal flours[87]
Laboratory workers	Laboratory animals (rat, mouse)[88]
Health care workers	Latex[89]
Farmers	Animal-derived allergens, plant allergens, molds[90]
Seafood workers	Shellfish, bony fish[91]
Pharmaceutical & detergent industries	Biological enzymes[92]
Low molecular weight agents	
Hairdressers	Persulphates[93]
Carpentry, furniture making	Wood dust[94,95]
Pharmaceutics, health care workers	Drugs[96]
Chemical factories	Mixture of irritants[96]
Cleaners	Mixture of irritants[97,98]

Figure III.C.3. Classification of work-related rhinitis[84]
Adapted from Moscato G, et al. *Allergy* 2008;63:969-980.



III. C. 4. Chemical rhinitis

Chemical rhinitis largely falls under the category of occupational rhinitis, however there are chemical exposures that are not necessarily occupational (and vice versa). Some chemicals may cause sensory irritation which can include congestion, rhinorrhea, nasal discomfort, post-nasal drainage, headache, and even epistaxis.[112] Exposures, or exposure risk, are important elements to elicit in the history. There are many chemicals with which specific occupations are closely associated, though household chemicals and sport/leisure exposures (i.e. chlorine-induced rhinitis in swimmers[113]) may play a role as well. Larger chemical particles are typically the culprit in this form of rhinitis as smaller particles usually pass through to the lower airways. Water soluble agents such as ammonia, formaldehyde, or sulfur dioxide may readily dissolve into the mucous membrane layer.[114] These responses are non-IgE mediated by a reflex response which is often termed neurogenic inflammation.[115] A subset of these individuals involved in high-level single exposure incidents may develop persistent symptoms. This phenomenon has been described as RUDS when only rhinitis symptoms are present, and Reactive Airways Dysfunction Syndrome when asthma-like symptoms are present.[116,117]

Although chemicals are not always thought of as sensitizers, some of these compounds can induce immunologic disease. Chemicals known to cause sensitization of the respiratory tract include diisocyanates, acid anhydrides, some platinum salts, reactive dyes, glutaraldehyde, plicatic acid, and chroamine.[118-120] There is still much debate as to the exact mechanism behind sensitization to these chemicals. However, smaller chemical compounds must associate with larger protein molecules to induce an immune response. While specific IgE production toward chemicals causing respiratory allergy is seen, evidence to show symptoms related to chemical exposure without concomitant rise in IgE has also been previously documented.[121] It is possible that these findings may be due to the inability to synthesize appropriate *in vitro* conjugates for diagnostic assays to detect serum IgE that binds these chemicals.[122,123]

Typically, the differential should include causes of both AR and NAR, as well as mixed rhinitis, recurrent acute rhinosinusitis (RARS), and potentially CRS. Some symptoms of chemical rhinitis may be similar to AR with nasal discharge, congestion, sneezing, and itching all being reported. Nasal discharge may be anterior or posterior with chemical rhinitis or AR but is typically not unilateral with either of these diagnoses. Chemical-induced rhinitis may be associated with olfactory dysfunction, both temporary and long-lasting. These disturbances include hyposmia, or anosmia as well as dysosmia or agnosmia (inability to identify smells).[112] Nasal discomfort, discharge, congestion, headaches, and sometimes epistaxis may also be present.[112]

III. C. 5. Smoke-induced rhinitis

Environmental tobacco smoke exposure is associated with chronic rhinitis and in some cases, AR.[124,125] In several studies, self-reported symptoms tend to be elicited by exposure to smoke and can correlate with serum cotinine levels.[126-128] Symptoms common to both AR and smoke-induced rhinitis include rhinorrhea and congestion, but smoke-induced rhinitis does not appear to be driven by IgE-mediated hypersensitivity (which tends to exhibit a constellation of congestion, rhinorrhea, and

sneezing on exposure to a specific allergen). As AR symptoms are immunologically mediated, there must be a sensitization period prior to the exposure that elicits symptoms. In contrast, smoke induced-rhinitis typically does not require sensitization, although there has been report of potential allergenic compounds in smoke.[129] Interestingly, although active smokers are likely to have an elevated serum IgE, they exhibit a lower skin test reactivity to allergens than allergic non-smokers.[130]

In contrast to AR, smoke-induced rhinitis is likely multifactorial, and other mechanisms such as neurogenic or irritant etiologies play a more predominant role.[131,132] Neurogenic 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.[133] Patients who are reactive to tobacco exposure are identified by both subjective (congestion, rhinorrhea, sneezing) and objective response (increased nasal resistance) to controlled challenge with tobacco smoke. In a prospective study, patients were defined as demonstrating reactivity if nasal resistance on acoustic rhinometry increased by over 35% in response to tobacco smoke. Patients with less than 5% increase in nasal resistance were defined as nonreactive.[131] In addition, altered mucociliary clearance (MCC) resulting from tobacco smoke exposure has been demonstrated. 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, brief smoke exposure (45 parts per million [ppm] for 15 minutes) led to increased nasal resistance as measured by posterior rhinometry. In individuals with and without a history of smoke-induced rhinitis, prolonged exposure to moderate levels of smoke (15 ppm for 2 hours) also induced a congestive response lasting for an hour or longer.[134] Even though the objective response was short lived, patients reported symptoms lasting hours to days following exposure. Significant symptom overlap may exist, but a thorough history and allergy testing can help further differentiate smoke-induced rhinitis from AR. *(See section VI.E. Risk Factors for Allergic Rhinitis – Tobacco Smoke for additional information on this topic)*

III. C. 6. Infectious rhinitis

Infectious rhinitis may be classified into acute and chronic forms, with both bacterial and viral etiologies. Physical findings and chronicity of symptoms play an important role in differentiating between different forms of rhinitis, including infectious, allergic, and the inflammation associated with CRS. Symptoms suggestive of a non-infectious etiology include nasal itching and sneezing, while findings of mucosal inflammation and rhinorrhea may be present in either infectious or non-infectious rhinitis.[26] Taken in isolation, dark or purulent rhinorrhea is not pathognomonic for bacterial rhinitis/rhinosinusitis. Additional findings suggestive of infectious etiologies include associated pharyngeal inflammation or cervical lymphadenopathy.[135]

Viral rhinitis typically manifests in an acute form, and accounts for up to 98% of infectious rhinitis in the young child. The incidence of viral rhinitis in young children is six episodes per patient-year.[136] In adult viral rhinitis, the incidence is 2-3 episodes per year. Symptoms associated with viral rhinitis include clear rhinorrhea, nasal obstruction, and often, fever. The responsible organisms of viral rhinitis can be rhinovirus, adenovirus, influenza virus, and parainfluenza virus.[81] Most viral rhinitis is self-limiting within 4-5 days, with prolonged symptoms lasting longer than two weeks suggestive of a non-

infectious etiology or conversion to bacterial infection. There are instances when continued rhinitis beyond 10 days is felt to be due to worsening infection (i.e. possible superimposed bacterial rhinosinusitis) and these patients should be treated more aggressively.[137] Approximately 2% of viral rhinitis episodes are secondarily infected by bacterial organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis*, with subsequent presentation of acute bacterial infection.[138]

III. C. 7. Rhinitis of pregnancy and hormonally-induced rhinitis

The development of a type of rhinitis unique to the pregnant patient has been referred to as rhinitis of pregnancy or pregnancy rhinitis. It occurs in about 22% of pregnancies[139] and, although symptoms may occur at any time, it typically starts after the second month of pregnancy and is most severe in the second trimester.[26,140] Rhinitis of pregnancy has been defined as nasal congestion in the last 6 or more weeks of pregnancy, without other signs of respiratory tract infection or allergic cause, followed by complete, spontaneous resolution of symptoms within 2 weeks after delivery.[141]

The symptoms of rhinitis of pregnancy, like those of AR, include rhinorrhea and nasal congestion, which can be prominent and prolonged. Clinical history frequently elicits a prior history of chronic rhinitis, obscuring the extent to which pregnancy is a causal or aggravating factor.[139] In addition, pre-existing AR can worsen in approximately one-third of pregnant women.[142]

There are several etiologic factors potentially associated with the nasal symptoms in rhinitis of pregnancy. Hormonal changes, such as increased progesterone, estrogen, prolactin, vasoactive intestinal peptide and/or placental growth hormone have been implicated,[143,144] but there is little evidence to support this theory.[145] Other physiologic phenomena occurring during pregnancy that may contribute to increased nasal congestion or obstruction include vasodilation, progesterone-induced smooth muscle relaxation, and a massive expansion of the circulating blood volume, which may contribute to increased nasal vascular pooling.[146]

Rhinitis of pregnancy does not usually require therapy, nor does it respond well to standard allergy medications. Its management is made more difficult by the lack of high-quality studies on the efficacy of treatment and fetal outcomes. In those who seek treatment, conservative non-pharmacologic measures are suggested. These can include elevation of the head of the bed,[147] nasal dilator strips,[148] and exercise.[149,150] Saline lavage using hypertonic saline has been demonstrated to be effective without obvious deleterious effects on the fetus.[151] Several medications, including INCS, have been studied in rhinitis of pregnancy but have failed to demonstrate clear efficacy.[152] More recently, a systematic review by Kumar et al[153] identified only one RCT that failed to demonstrate any additional benefit of fluticasone compared to placebo for symptom control in this patient population. Although an extensive discussion of rhinitis of pregnancy management is beyond the scope of this document, the use of various other medications (i.e. topical and oral decongestants) is controversial and should be addressed at the individual patient level, with close involvement of the obstetrician.

Direct stimulation of the nasal mucosa by estrogen may induce mucosal gland hyperactivity resulting in increased nasal secretions/rhinorrhea.[154] As such, nasal symptoms can be associated with conditions other than pregnancy that affect hormone balance, such as hypothyroidism and

acromegaly.[155] Rhinitis may also arise as a result of changing blood hormone concentrations during puberty, menstruation and the perimenopausal years.[145] Although oral contraceptives have also been implicated as causes of nasal symptoms, a study by Wolstenholme et al[156] found no nasal physiologic effects in patients receiving oral contraceptive treatment.

In summary, there are numerous metabolic conditions with symptoms like those of AR. Accurate diagnosis can be made on history and presentation, but additional testing may be required for symptoms that are persistent or severe.

III. C. 8. Food- and alcohol-induced rhinitis

Food-induced rhinitis. Certain food ingestions may result in rhinitis based on a non-immunologic reaction, and therefore are not characterized as an allergy. For instance, in subjects with gustatory rhinitis, shortly after ingestion of hot or spicy foods, unilateral or bilateral watery rhinorrhea develops in the absence of nasal congestion, pruritus, or facial pain. This is considered a reflex response due to an adrenergic and cholinergic neural reaction of the nose.[157]

The prevalence of "food-induced rhinitis" seems to be under 1%.[157] While rhinitis may frequently be observed as part of systemic IgE-mediated food allergy reaction, it is rarely the only presenting symptom. In a double-blind, placebo-controlled food challenge study of 480 children, 185 children (39%) experienced ocular and upper respiratory symptoms, but only 5% had symptoms confined to the upper respiratory tract alone.[158]

Patients with pollen-food allergy syndrome (PFAS), also referred to as oral allergy syndrome (OAS), often experience oropharyngeal itching, tingling, and/or mild swelling of the lips, tongue, palate, and throat, and less commonly AR symptoms, after ingestion of certain raw fruits and vegetables. The assessed prevalence of this disorder ranges from 5% to 17%, and it affects up to half of pollen-allergic patients.[159-161] It occurs in individuals who are sensitized to pollen aeroallergens through the respiratory tract, which then predisposes them to clinical symptoms of PFAS after ingestion of cross-reactive, heat-labile food proteins of plant origin. Because the antigens are heat-labile, patients are usually able to tolerate cooked forms of the causative fruits and vegetables.[162] *(See Section X.E. Associated Conditions – Food Allergy and Pollen-Food Allergy Syndrome for additional information on this topic.)*

Alcohol-induced rhinitis. Nasal symptoms can also occur after alcohol consumption.[163,164] However, very little is known about the prevalence and presentation of alcohol-induced nasal symptoms. Additionally, there is a paucity of information about the relationship between alcohol-induced nasal symptoms and other diseases, such as AR, nasal polyposis, asthma, and other chronic lower airway diseases.[165]

Airway symptoms are predominantly initiated by inhaled components that contact the airway mucosal membrane. However, several forms of rhinitis and asthma may not operate through this mechanism. One such example is known as alcohol-induced asthma. In these patients, alcoholic beverages, particularly red and white wines, have been shown to trigger bronchial symptoms.[163,166,167]

Alcohol-induced nasal symptoms are about twice as common in females as in males,[165] but the basis for this predilection is not well understood.[168-170] Nasal congestion is the predominant symptom, and red wine is the most common alcoholic beverage to elicit symptoms. Additionally, wine, particularly

red, is also the most widely recognized trigger of alcohol-induced bronchial symptoms.[163] Finally, direct alcohol utilization has also been associated with a trend towards developing SPT positivity,[171] and with increased serum total IgE (tIgE) levels.[172]

III. C. 9. Non-allergic rhinitis with eosinophilia syndrome (NARES)

Non-allergic rhinitis with eosinophilia syndrome (NARES) is a clinical disorder comprising symptoms consistent with PAR in which an absence of atopy has been demonstrated, and eosinophilia is found on nasal cytology.[173] The pathophysiology of NARES is not well understood, but a key component involves chronic an eosinophilic, self-perpetuating inflammation, with non-specific histamine release. It is the most common type of inflammatory NAR, and was first described in 1981 by Jacobs et al.[174]

NARES patients report symptoms that are typical, although often more pronounced, than those of PAR. These include, nasal congestion, profuse aqueous rhinorrhea, sneezing, and nasal and ocular pruritis. A prominent feature not shared with AR is anosmia, a frequent finding in NARES patients.[175] NARES is diagnosed by careful history, findings on physical exam (pale, boggy turbinates, like those found in PAR patients), and negative skin or *in vitro* allergy testing. Cytologic examination in NARES reveals the presence of prominent eosinophilia, usually 10-20%[173] on nasal smear, with a diagnostic criterion (described by some) of more than 25% eosinophilia.[176] In addition, nasal biopsies from these patients commonly show increased numbers of mast cells and prominent mast cell degranulation.[177,178]

Research has supported the role of chronic inflammation in the development of NARES. Though there is still a lack of understanding as to the exact pathophysiology, studies have shown an increased transendothelial migration of eosinophils, attracted and activated by chemokines and cytokines.[179,180] Specifically, NARES is characterized by elevated nasal fluid levels of tryptase (also seen in PAR patients) and eosinophilic cationic protein (ECP) (markedly increased solely in NARES).[181] In addition, increased Th2 cytokines (interleukin [IL]-6 and IL-17) appear to be a factor in the remodeling process seen in NARES.[182] Other pro-inflammatory chemokines that have been implicated for their role in eosinophil chemotaxis and infiltration include macrophage/monocyte chemoattractant protein (MCP)-1 and regulated on activation, normal T-cell expressed and secreted (RANTES). Elevated RANTES concentrations have been found in the nasal fluid of patients with PAR and NARES.[183] Recently, Peric et al[184] demonstrated a correlation between the concentration of RANTES with nasal symptoms and eosinophil counts in PAR patients. However, levels of MCP-1 and RANTES were significantly higher in the nasal fluid of NARES compared to PAR subjects, which again, correlated with nasal symptom scores and density of eosinophilia in these patients. Nasal neural dysfunction has also been described as a contributing factor to the symptomatology in NARES.[185]

NARES usually occurs in isolation but may be associated with aspirin-exacerbated respiratory disease (AERD), characterized by asthma, nasal polyps, and NSAID intolerance.[173] NARES has also been identified as a risk factor for the induction or augmentation of obstructive sleep apnea (OSA).[186]

The treatment of NAR centers on its underlying cause. Given the inflammatory changes demonstrated on nasal cytology and physical exam, NARES is primarily treated with INCS sprays.[154] This method of treatment is known to decrease neutrophil and eosinophil chemotaxis, reduce mast cell and basophil mediator release, and result in decreased mucosal edema and local inflammation.[187] The

intranasal antihistamine azelastine is United States (US) Food and Drug Administration (FDA)-approved for both AR and NAR. In clinical trials, azelastine has been shown to reduce symptoms of rhinitis, including postnasal drainage, sneezing, rhinorrhea, and congestion.[188] However, these multi-centered, placebo-controlled trials studied azelastine for the treatment of vasomotor rhinitis (non-allergic rhinopathy) rather than NARES specifically.

III. C. 10. Non-allergic rhinopathy (vasomotor rhinitis)

Vasomotor rhinitis is the most common cause of NAR, and is found in 71% of cases.[189-191] The absence of an IgE-mediated immune response differentiates vasomotor from allergic forms of rhinitis.[101] Therefore, the term "non-allergic rhinopathy" is recommended to replace vasomotor rhinitis, as inflammation is not regarded as a crucial part in the pathogenesis of non-allergic rhinopathy. In Europe, "Idiopathic rhinitis" has also been used to describe this condition.

Non-allergic rhinopathy is a diagnosis of exclusion, and other etiologic factors for rhinopathy must be evaluated. These include CRS, NARES, AERD, infectious rhinitis, anatomical abnormalities, RM, drug side effects, cerebrospinal fluid (CSF) rhinorrhea, and rhinitis of pregnancy. Clinical characteristics of non-allergic rhinopathy have been summarized in a consensus paper by Kaliner et al.[40] Non-allergic rhinopathy represents a chronic disease with primary symptoms of rhinorrhea. Associated symptoms of nasal congestion, postnasal drip in the absence of acid reflux, throat clearing, cough, Eustachian tube dysfunction, sneezing, hyposmia and facial pressure/headache may also be present with non-allergic rhinopathy. These symptoms may be perennial, persistent, or seasonal, and are typically elicited by defined triggers, such as cold air, climate changes (i.e. temperature, humidity, barometric pressure), strong smells, tobacco smoke, changes in sexual hormone levels, environmental pollutants, physical exercise, and alcohol. While often associated with non-allergic rhinopathy, the lack of a defined trigger does not preclude this diagnosis. In addition, nasal hyper-reactivity to non-specific stimuli may occur in both allergic and non-allergic rhinitis.[192]

Deleted: occasionally exist but are not the primary complaint

Non-allergic rhinopathy is primarily found in adults, with a female-to-male ratio of 2:1 to 3:1. On physical exam, the nasal mucosa usually appears normal, but may show signs of erythema and clear rhinorrhea. While systemic allergy testing (skin or *in vitro* testing) is typically sufficient to differentiate between AR and non-allergic rhinopathy, a diagnosis of LAR may be considered in the setting of negative systemic testing. Individuals with LAR suffer from typical allergic symptoms upon allergen exposure, but display a lack of systemic IgE sensitization. Local provocation is necessary to definitively exclude this diagnosis.[193,194]

While the exact pathophysiology of non-allergic rhinopathy remains incompletely described, neurosensory abnormalities are thought to play a crucial role.[40] In a prior study of central responses to olfactory stimuli, subjects with non-allergic rhinopathy underwent functional magnetic resonance imaging following exposure to different odors (vanilla and hickory smoke). Findings included increased blood flow to the olfactory cortex, leading to the hypothesis of an altered neurologic response in non-allergic rhinopathy.[195,196] Patients with non-allergic rhinopathy with a predominant symptom of rhinorrhea will often respond to treatment with intranasal anticholinergics such as ipratropium bromide (IPB).

III. C. 11. Age-related rhinitis

Age-related changes occur in every organ system, including the respiratory system. Specific to the nasal cavity, the physiological process of aging results in neural, hormonal, mucosal, olfactory, and histologic alterations that cause morphological and functional changes in the aging nose.[197,198] This makes the elderly population more vulnerable to symptoms such as rhinorrhea, nasal congestion, postnasal drip, dry nose, intranasal crusting, and decreased olfaction.[199,200] A recent publication by DelGaudio and Panella reviewed the literature pertaining to intranasal findings of the aging nose, which they have termed "presbynasalis".[201]

Age-related rhinorrhea. Rhinitis of the older adult (i.e. "drippy nose" or "senile rhinorrhea") is a well-recognized entity. Rodriguez et al[202] used a questionnaire to demonstrate that clear rhinorrhea increases with age. Results showed that only 33% of the younger age group respondents (n=76, mean age 19 years) regularly reported clear anterior drainage as compared to 74% of the older age group respondents (n=82, mean age 86 years).

The physiologic reason for increased rhinorrhea with age is not entirely known. However, it is known that α and β receptors become less sensitive and autonomic function declines with age, which leads to an imbalance of sympathetic and parasympathetic tone.[202-204] It is possible that decreased sympathetic tone with unopposed parasympathetic stimulation results in a rise in glandular activity in the nasal cavity, leading to increased nasal drainage.[202,205] This mechanism is similar to vasomotor rhinitis/non-allergic rhinopathy, where the autonomic response to certain stimulants causes the nasal mucosal blood vessels to vasodilate and the mucus glands to become overactive, resulting in hypersecretion and drainage.[206] Vasomotor rhinitis/non-allergic rhinopathy is the most common type of NAR,[205] and the highest prevalence of NAR is seen in the elderly.[144,189,200,207] This would suggest an autonomic dysregulation as the reason for increased rhinorrhea in the aging population.

Age-related nasal obstruction and congestion. Factors that contribute to an increase in nasal obstruction/congestion in the aging nose include thicker mucus secondary to a decrease in body water content,[208-210] nasal airflow obstruction secondary to structural changes caused by the loss of nasal cartilage elasticity and tip support,[198,200,210] and mucus stasis secondary to less effective MCC.[200,209] Ho et al[211] demonstrated a decline in MCC effectiveness with age in 90 healthy subjects aged 11-90. Subjects over 40 years of age had a slower ciliary beat frequency, increased microtubule disarrangement, and longer MCC times on saccharin testing. Thickened mucus and a less effective MCC system may also lead to postnasal drip, which is a common nasal complaint in the elderly population.[200]

Another factor contributing to nasal obstruction/congestion in the elderly is age-related central nervous system changes that affect the physiologic nasal cycle.[208,212] Mirza et al[212] measured the relative airflow of the two nasal chambers at 15-minute intervals for 6 hours across 4 different age groups (n=60) using liquid crystal thermography. They found that the proportion of subjects exhibiting the classic nasal cycle decreased with age, being lowest in the 70-85 year-old group.

Age-related nasal dryness and intranasal crusting. Nasal dryness and intranasal crusting are more common in the elderly population. This is likely due to age-related changes of the nasal mucosa,[199] such as a decrease in mucosal blood flow and an increase in epithelial atrophy.[213] Schrodter at el[214] evaluated nasal mucosa samples from the middle turbinate of 40 healthy subjects between the ages of 5 and 75 years, and found an age-related increase in atrophic epithelium and thickened basement membranes in patients over 40.

Nasal dryness in the elderly population may also be caused by a decrease in intranasal temperature and humidity.[200] Lindemann et al[199] measured these values in 80 healthy patients and found them to be significantly lower in older patients (age 61-84 years) than in younger patients (age 20-40 years). The authors attributed the difference to an increase in intranasal volume (INV) from age-related atrophy of the nasal mucosa, with INV measured by minimal cross-sectional areas and volumes of each nasal cavity. An increase in INV with age has also been demonstrated by Loftus et al[215] using 3D-volumetric analysis of computed tomography scans from subjects without sinonasal pathology. Mean INV was 15.73mL in the 20-30 year-old age group (n=22), 17.30mL in the 40-50 year age group (n=20), and 18.38mL in the over 70 year age group (n=20).

Allergic rhinitis in the elderly. Although there is overlap between age-related rhinitis and AR in the elderly in terms of symptoms and recommended treatment with INCS,[210,216] the underlying physiologic process of each is quite different. AR is a type I IgE-mediated hypersensitivity reaction,[217,218] whereas allergy and allergens do not play a role in the symptoms and physiologic changes of age-related rhinitis. However, it has been shown that aging does not reduce the prevalence of AR and that AR in the elderly is likely underdiagnosed, so AR should be considered when diagnosing new-onset nasal symptoms in the elderly population.[210]

III. C. 12. Empty nose syndrome and atrophic rhinitis

The descriptive term “empty nose syndrome” (ENS) was originally coined in 1994 by Kern and Stenkvist to describe empty space in the region of the inferior and middle turbinates on coronal computed tomography (CT) images of patients who had partial or total inferior and middle turbinectomies.[219] Today, ENS is defined as an upper airway disorder characterized by impaired nasal airflow sensation and often involves tissue loss from nasal surgery. ENS is divided into at least three subtypes: ENS-inferior turbinate, ENS-middle turbinate, and ENS-both, which are classified based on the site of tissue loss.[219] ENS-inferior turbinate is the most common type.[220] A fourth subtype to offer is ENS-type wherein a patient has sufficient appearing turbinate tissue but suffers ENS symptoms after surgery affecting the mucosal surface of the turbinates.

ENS typically occurs following surgery in the turbinates. Most turbinate surgery has successful outcomes, with ENS occuring after a very small percentage of sinonasal procedures.[221,222] ENS occurs most frequently after total turbinate excision, but also with lesser procedures such as submucosal cautery or resection, laser therapy, and cryosurgery.[223] Patients often complain of dryness and crusting, although the hallmark complaint of ENS patients is paradoxical nasal congestion that may be so severe that they feel as if they are suffocating.[223] Recent research has validated that the primary physiological

Deleted: The onset of this condition may occur months to years postoperatively.[219]

mechanism that produces the sensation of ample nasal airflow is activation of trigeminal cool thermoreceptors, specifically TRPM8, by nasal mucosal cooling.[224-228] Beyond alterations in airflow and a reduction in surface area, aberrations in neurosensory systems likely play a major role in the abnormal sensations ENS patients experience. Not only does turbinate resection remove nasal mucosa and consequently airflow sensing thermoreceptors, such surgery causes nerve damage that if improperly healed, results in failure to return to a normal physiologic state.[221] Differences in nerve recovery after surgery may explain why only some patients develop ENS despite identical turbinate surgeries. Indeed, certain surgeons have identified patients with unilateral ENS symptoms while their normal sensing side looks like a mirror image in terms of absent IT tissue. Diagnosis is made based on history, physical exam, and the cotton test where a piece of slightly moist cotton is placed in the nasal cavity for 10 to 30 minutes with alleviation of symptoms, validating the diagnosis.[223] Other conditions that present with nasal dryness and crusting should be ruled out (i.e. atrophic rhinitis, sarcoidosis, etc). The Empty Nose Syndrome 6-Item Questionnaire has documented validity in identifying ENS patients.[229] Surgery for submucosal expansion of the internal nasal mucosa can often bring relief for patients.[223] It has also been reported that depression and anxiety are prevalent amongst ENS patients.[230]

Atrophic rhinitis is a chronic, degenerative condition characterized by inflammation and atrophy of the nasal and paranasal mucosa.[231] Primary atrophic rhinitis runs a protracted course. It can occur spontaneously with unknown etiology, but it is also associated with a bacterial infection, almost exclusively *Klebsiella ozaenae*. In a study examining 45 patients diagnosed with primary atrophic rhinitis, all nasal cultures were positive for *Klebsiella ozaenae*.[231] Mucosal injury is hypothesized to result from prolonged microvascular or ischemic injury.[231-233] Secondary atrophic rhinitis is far more common and usually develops following direct injury from trauma, irradiation, reductive nasal or sinus surgery, or in certain rare granulomatous diseases.[231,234] Secondary atrophic rhinitis is also associated with a bacterial infection, but *Staphylococcus aureus*, *Proteus mirabilis*, and *Escherichia coli* are the more common pathogens with *Klebsiella ozaenae* rarely isolated.[231]

Atrophic rhinitis presents as thick, adherent nasal crusting, nasal congestion, foul odor, and atrophy of mucosal and turbinate surfaces, with severe cases having complete absence of recognizable anatomic landmarks, septal perforations, or saddle nose deformity.[231-233] Hyposmia, epistaxis, and facial pain or pressure may also occur. Histological examination of intranasal tissue demonstrates squamous metaplasia, glandular atrophy, and diffuse endarteritis obliterans in both types of atrophic rhinitis.[231] Diagnosis is established from clinical examination, nasal biopsy, and nasal cultures for associated bacteria.

Both atrophic rhinitis and ENS patients complain of nasal congestion. For atrophic rhinitis patients, this is often a result of significant nasal crusting, although as the disease progresses and mucosa and turbinate tissue is lost, the widened nasal cavity can very closely resemble that of an ENS patient. The pathophysiology of the paradoxical sensation of nasal congestion at this point is the same in both disease states, although the origin of the inciting event differs.

In the literature, ENS has repeatedly been described erroneously as a form or subset of atrophic rhinitis. ENS results from iatrogenic removal of turbinate tissue and is not associated with a bacterial infection whereas atrophic rhinitis results from a chronic, often idiopathic inflammatory process associated with bacterial infection that progresses to resorption of turbinate tissue. Atrophic rhinitis patients suffer from heavy crusting whereas ENS patients exhibit only minor crusting or none.

To differentiate AR [allergic rhinitis] from atrophic rhinitis, it should be noted that AR is an immunological response to a benign substance, the allergen, that manifests primarily as nasal inflammation. AR is IgE-dependent[235] and characterized by sneezing, clear rhinorrhea, watery eyes, and nasal and ocular pruritus.[1] This condition has a clear distinction from ENS and atrophic rhinitis in its clinical presentation and pathophysiology.

III. C. 13. Autoimmune, granulomatous, and vasculitic rhinitis

Both the upper and lower airways can be affected by systemic disorders including vasculitic, granulomatous, and autoimmune diseases. Commonly, affected patients may present with non-specific sinonasal symptoms (nasal obstruction, rhinorrhea, facial pain, and loss of smell) mimicking AR. Allergy testing will, however, be negative or not clinically relevant. Clinicians should consider broadening the differential to consider systemic etiologies if either crusting or recurrent epistaxis is seen.[236] Oral steroids are the mainstay of treatment for the entities discussed in this section, although the recent introduction of monoclonal antibodies targeting specific biomarkers represents an important hallmark for future therapy.

Granulomatosis with polyangiitis (GPA). Previously referred to as Wegener's disease, GPA is an idiopathic disease characterized by necrotizing and granulomatous inflammation of the upper and lower airways (85%), glomerulonephritis (75%) and systemic vasculitis.[237-239] Limited forms of GPA involving only the head and neck may also be seen. GPA predominantly affects small to medium sized arteries and vein walls.[240] GPA affects both men and women in a similar proportion, being frequently diagnosed in the fourth to sixth decades of life.[240] In the US, estimated prevalence is 13 to 30 cases per-million people per 5-year period. Nasal symptoms include obstruction, rhinorrhea, recurrent epistaxis, crusting, and pain over the nasal dorsum.[237,241] Nasal mucosa disruption may lead to anosmia while tissue necrosis with secondary infection may lead to cacosmia.[236] Nasal endoscopy can reveal an erythematous, friable mucosa with crusting and granulation that is seen in the septum and inferior turbinate.[240] Patients with severe forms can present with nonvascular necrosis causing perforation or bony destruction of the nasal septum and/or other nasal structures.[242] Diagnosis is based on clinical symptoms, physical findings, radiological examinations, laboratory tests (positive c-ANCA [anti-nuclear cytoplasmic antibody] in 60-90%), and biopsy of affected tissue for pathological examination.[237,238,240] Profiling the nasal transcriptome in GPA reveals unique gene expression signatures related to innate immunity, inflammatory cell chemotaxis, extracellular matrix composition, and epithelial barrier integrity that may eventually be used clinically.[243,244] Treatment includes prednisone, cyclophosphamide or methotrexate.[237,238,245] Rituximab, anti-CD20 monoclonal antibody, may be an effective therapy in refractory or relapsing c-ANCA vasculitis,[246] although additional study is needed.

Eosinophilic granulomatosis with polyangiitis (EGPA). Previously known as Churg-Strauss Syndrome, EGPA is a rare small-sized vessel vasculitis with a prevalence of 1.3 cases per 100,000,[247] typically diagnosed in patients age 30-50 years.[236] Rhinitis (75% of patients) is one of the initial manifestations of EGPA,[248] in addition to CRS with nasal polyps, and partial/total smell loss.[249] Diagnosis should be

suspected in patients with asthma, with increased peripheral blood eosinophil count (>10%) and pulmonary manifestations.[238,248] EGPA is often associated with the presence of p-ANCA.[247] CRS with nasal polyps (CRSwNP) is present in approximately 50% of patients.[238] Nasal pain with purulent or bloody nasal discharge, nasal crusting or nasal septal perforation can be present but are less common than in GPA patients.[238,250] Treatment usually includes high doses of corticosteroids and immunosuppressants.[248,251] Anti-IL-5 therapy (mepolizumab) is a potential biological treatment offering clinical benefit and stability and reducing corticosteroid needs.[252]

Sarcoidosis. Sarcoidosis is a chronic multisystem disorder characterized by bilateral hilar adenopathy, pulmonary infiltration, ocular, and skin lesions.[238,253] More commonly seen in young and middle-aged adults,[254] females more frequently than males, and African-Americans,[255] a prevalence of 50 per 100,000 individuals has been reported.[236] The involvement of the upper respiratory tract epithelium is infrequent[236] and nasal symptoms are non-specific: obstruction, epistaxis, nasal pain, epiphora, and anosmia.[237] The most consistent findings are erythematous, edematous, friable, and hypertrophied mucosa in the septum and inferior turbinate. Submucosal yellow nodules representative of intramucosal granulomas may be identified in mucosal biopsies, while nasal polyps, rhinophyma, and septal perforations have also been reported.[238,256] Aggressive non-caseating granulomas can cause hard or soft palate erosions as well as septal perforations leading to saddle-nose deformity.[257,258] The diagnosis of sinonasal sarcoidosis is based on the clinical findings with either polypoid changes or characteristic yellowish submucosal nodularity.[238] Tissue for diagnosis is usually obtained by transbronchial-lung biopsy[254] or nasal biopsy, as well as from skin lesions, minor salivary glands, and lymph nodes.[238] The primary treatment for sarcoidosis is systemic steroids, chloroquine, immunosuppressants, and lung-transplantation.[237,238,256,257] The emergence of biological therapies has increased the therapeutic options to treat refractory organ-threatening sarcoidosis, with monoclonal anti-TNF (tumor necrosis factor) agents (infliximab) being the most promising.[259]

Systemic lupus erythematosus (SLE). SLE is an autoimmune disease that can affect any body system. SLE predominantly affects women (10:1) with an incidence of 5.6 per 100,000 people.[260] The skin of the nose and nasal vestibule can also be involved in the skin rashes.[237] Mucosal lesions are seen in 9-18% of cases with oral, nasal, and pharyngeal mucosa being commonly affected.[260] The diagnosis requires a detailed medical history, a physical examination, and laboratory tests (anti-nuclear antibody [ANA] or anti-double stranded DNA), including a complete blood count, chemistry panel, and urinalysis.[236,261] Therapy with corticosteroids, immunomodulators (prasterone, vitamin D, hydroxychloroquine) or immunosuppressants (azathioprine, cyclophosphamide, or mycophenolate) is prescribed for symptom control,[238,262] while belimumab is a recent biological (anti-BAFF [B-cell activating factor] monoclonal antibody) to potentially treat SLE.[263]

III. C. 14. Rhinosinusitis

The symptoms of AR may overlap with other forms of nasal inflammation, including rhinosinusitis. It is important to differentiate between AR and rhinosinusitis to ensure the correct

diagnosis and subsequent treatment can be pursued. AR may be associated with comorbid rhinosinusitis, although whether AR increases the risk of rhinosinusitis is debatable.[1] Identifying comorbid rhinosinusitis is essential to ensure the appropriate management of both conditions. Of note, these conditions are not mutually exclusive and there may be an association between rhinosinusitis and AR. It is possible to have concurrent AR and rhinosinusitis, and this possibility should be considered when patients meet diagnostic criteria for both independently and when patient symptomatology or response to treatment does not fit with a single diagnosis.[1] A high degree of clinical suspicion is required; however, careful consideration of these factors may help guide clinicians to the correct diagnosis or diagnoses.

Rhinosinusitis is a broad term that includes the diagnoses of acute rhinosinusitis (ARS), RARS, and CRS, demarcated as CRSwNP or CRS without nasal polyposis (CRSsNP). Symptomatically, these conditions are characterized by nasal obstruction, nasal congestion, facial pressure or pain, anterior or posterior nasal discharge and anosmia/hyposmia for varying durations of time.[1,138] AR shares several overlapping symptoms, namely rhinorrhea and nasal congestion, which may be confused with the subtypes of rhinosinusitis.[264,265] Conversely, rhinosinusitis may be mistaken for AR due to the similar symptomatology.[1] Understanding the diagnostic criteria for the subtypes of rhinosinusitis will aid clinicians in solidifying the correct diagnosis, as well as identifying comorbid conditions.

ARS is defined as the sudden onset of sinonasal symptoms with associated sinonasal inflammation that lasts less than 4 weeks.[1,137,138,266,267] Symptoms include nasal congestion, nasal obstruction or nasal discharge, and facial pressure or pain, or anosmia/hyposmia. Nasal discharge is often purulent and may be discolored, with a tendency to be unilateral although may be bilateral.[1,138] Facial pressure and pain is described as moderate to severe.[137] ARS may be viral or bacterial. In general, viral ARS is present for less than 10 days. A longer duration of illness suggests bacterial ARS.[137,138] Progressive worsening over a short period of time (i.e. 5 days) is also suggestive of bacterial ARS.[137,138] In the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) statement, fever and elevated serum markers of inflammation (C-reactive protein or erythrocyte sedimentation rate) are also included as diagnostic criteria.[138] Fever is not included in other guidelines, due to its low specificity and sensitivity.[137] RARS is defined as at least 4 episodes of ARS per year, with disease free intervals between episodes.[1,137,138,266,268]

CRS is an inflammatory condition of the sinonasal cavity persisting for more than 12 weeks with at least two symptoms of nasal obstruction and congestion, mucopurulent nasal drainage (anterior or posterior), facial pressure or pain and anosmia/hyposmia.[1,137,138,266,267] In addition, patients must have objective evidence of sinonasal inflammation on either nasal endoscopy (polyps, edema, mucopurulent rhinorrhea) or on CT scans of the sinuses.[137,138,266,267] CRS is divided into two main phenotypic groups: CRSwNP and CRSsNP.

Comparatively, AR is characterized by nasal obstruction, nasal congestion, clear watery rhinorrhea (anterior or posterior) and allergic symptoms.[264,265] The presence of these symptoms should raise suspicions of AR as either a primary or comorbid diagnosis. Conversely, AR is typically not associated with purulent or unilateral nasal discharge. Moderate to severe facial pain and/or fever would also be atypical for isolated AR and may indicate the presence of an episode of ARS or an acute exacerbation of CRS, differentiated by duration and chronicity of symptoms.[1,137,138] The timing of symptoms may also help delineate between rhinosinusitis and AR as ARS symptoms typically last days to

weeks (but no more than 4 weeks), CRS symptoms persist daily for greater than 12 weeks. In comparison, while AR symptoms are variable in duration, they tend to have seasonal or exposure-related fluctuations.[1,137,138] AR symptoms are present for at least 1 hour on most symptomatic days; however, patients may have symptom-free intervals.[264,265] AR symptoms are also exacerbated by exposure to allergens in a time dependent fashion.[264] The early reaction occurs immediately after exposure and is characterized by sneezing, nasal and ocular itching and rhinorrhea, which typically resolves within 30 minutes.[264] The late reaction takes place up to 6 hours after exposure and is characterized by nasal obstruction and congestion.[264] Superimposed late reactions may blunt the manifestation of acute phase symptoms and make the diagnosis of AR less obvious.

When attempting to determine whether a patient has AR, ARS, RARS or CRS, it is important to elicit a history of specific symptoms from the patient that includes onset and duration of symptoms. A history of allergic symptoms or allergen exposure-related symptoms support a possible diagnosis of AR, as these are not associated with rhinosinusitis and AR may or may not be seasonal in nature, which can also be elicited by history.[264,265] The development of acute, moderate to severe symptoms and nasal purulence may be consistent with ARS or RARS rather than AR.[1,137,138] A prolonged duration of symptoms (greater than 12 weeks) should raise suspicions for CRS and prompt further investigation.[1,137,138] *(See Section X.B. Associated Conditions – Rhinosinusitis for additional information on this topic.)*

IV. Pathophysiology and mechanisms of allergic rhinitis

A background understanding of the pathophysiology and underlying mechanisms of AR is necessary as we examine the clinical presentations, physical manifestations, goals of allergy testing and response to treatment. This section addresses the cellular inflammation, soluble mediators, local allergic manifestations, and systemic effects associated with AR. While this document is not intended to provide an extensive review of the pathophysiology of AR, the following short section provides a foundation for understanding the clinical expression of AR and its treatment.

IV. A. 1. Systemic mechanisms and manifestations

The immune response leading to IgE production in AR is often a systemic phenomenon, and patients with AR demonstrate evidence of systemic atopy.[269,270] One manifestation of systemic atopy in AR is the cutaneous reaction elicited during traditional allergy skin testing.[271] Further evidence for the systemic nature of the IgE response in AR includes the temporal relationship of AR to a number of other allergic diseases, including atopic dermatitis (AD), food allergy, and allergic asthma, a phenomenon known as the "atopic march".[272] This pattern of atopic disease progression is well-known and supported by prospective studies.[273]

The immunologic processes underlying IgE-mediated AR are similar to those of other atopic conditions and involve activation of the adaptive immune system. The adaptive immune response can be broadly classified into two categories based upon the predominant Th lymphocyte subtype.[274] The Th1 profile is responsible for defense against intracellular pathogens, while Th2 responses are implicated in the defense against parasitic infections as well as the IgE-mediated eosinophilic inflammation of allergy.[272] Whether AR will develop as a result of inhalant allergen exposure therefore depends largely upon the balance between Th1 and Th2 effector cells.[274]

A number of steps in the sensitization process are responsible for eliciting the Th2-predominant response. The process begins with exposure of the nasal mucosa to inhalant allergens.[275] While mucosal epithelial cells were once thought to function simply as a mechanical barrier to allergen penetration, recent research suggests that epithelial cells play a much more sophisticated role in allergy development, through the secretion of numerous inflammatory mediators including cytokines, chemokines, eicosanoids, and endopeptidases, as well as through upregulation of cellular adhesion molecules and release of matrix metalloproteinases.[276] They also provide an important early stimulus toward a Th2-weighted immune response, through the secretion of thymic stromal lymphopoetin (TSLP).[272,275,276] TSLP causes maturation of dendritic cells into Th2-promoting subtypes,[277] which secrete chemokines that attract Th2-destined T lymphocytes, foster clonal amplification of Th2 cells, and enhance survival of memory B-cells.[272] TSLP also promotes recruitment of eosinophils and enhanced activity of basophils and mast cells.[272]

Allergens are then engulfed by dendritic cells which migrate to lymphoid organs where the antigen is presented to naïve helper T (Th0) cells on MHC class II molecules.[274] Th2 differentiation also requires co-stimulation via the interaction of CD28 on T cells with CD80 and CD86 on antigen presenting cells (APCs).[278] Additionally, the presence of the cytokine IL-4 is required.[279] IL-4 binds STAT-6 on the Th0

cell, activating the master switch GATA-3.[272] This stimulates IL-4, IL-5, and IL-13 production,[274] which is characteristic of the Th2 response. These cytokines, produced by the newly differentiated Th2 cell, have several effects that further promote IgE-mediated eosinophilic inflammation and allergy.

IgE is produced by B-cells under the influence of Th2 effector cells and the cytokines they secrete.[275] Development of an IgE-secreting B cell requires the presence of IL-4 or IL-13, which induce class switching via up-regulation of ε-germline gene transcription and clonal expansion, as well as interaction between CD40 ligand on the T-cell surface and CD40 on the B-cell surface, which promotes B-cell activation and the production of IgE.[279] Allergen-specific IgE (sIgE) is then released into the circulation by plasma cells.

IgE antibodies subsequently bind high-affinity receptors (FcεRI) on the surface of mast cells and basophils, rendering them sensitized.[280] Future allergen exposure results in crosslinking of IgE on the surface of mast cells and basophils causing degranulation, release of inflammatory mediators such as histamine, and the classic symptoms of AR.

IV. A. 2. IgE-IgE receptor cascade

IgE plays a central and defining role in the pathophysiology of acute allergic reactions as well as chronic atopic disease.[281] In individuals with AR, exposure to specific allergens results in the production of allergen-specific IgE, which then binds to effector cells like mast cells and basophils via the high affinity receptor FcεRI. Although IgE in plasma is short-lived, IgE that is receptor-bound remains attached to these cells for weeks or months. Moreover, when IgE bound to FcεRI cross links with a specific allergen, it induces the release of pre-formed inflammatory mediators from mast cells and basophils, resulting in clinical manifestations of allergic diseases.

Cytokines including interleukin (IL)-4 and IL-13 released from T cells and mast cells drive the differentiation of B cells into IgE-secreting plasma cells. Several studies, both *in vivo* and *in vitro* have confirmed the production of local IgE in the nasal mucosa of patients with AR.[282-284] The locally produced IgE plays a key role in ongoing inflammation by upregulating FcεRI expression in mast cells.[283-285] The augmented expression of FcεRI allows them to bind greater numbers of IgE-antigen complexes, which in turn enhances the sensitivity of mast cells to allergen. This results in an increased production of immunomodulatory cytokines and chemical mediators, forming an important positive-feedback amplification loop involving the IgE-IgE receptor cascade, thus perpetuating ongoing inflammation.[285,286] Interestingly, the density of IgE receptors and IgE molecules in mast cells within the nasal mucosa of patients with AR have been shown to correlate with levels of serum IgE.[285] The presence of elevated levels of IgE in nasal secretions has been demonstrated in non-allergic rhinopathy as well, which potentially further highlights a significance of the IgE-IgE receptor cascade in driving the disease process of rhinitis.[287]

IV. A. 3. Local IgE production and local allergic rhinitis (LAR)

LAR is a regional inflammatory condition defined by local symptoms and sIgE-mediated inflammation without evidence of systemic hypersensitivity.[107,194,284,288] It is important to remember that

conventional allergy testing, such as SPT and the radioallergosorbent test (RAST), only indicates sensitization (atopy), but not symptomatic allergy. While it is possible for a positive allergy skin or *in vitro* test result to lack clinical relevance, the opposite is also true, as a negative allergy skin or *in vitro* test result does not exclude regional IgE-mediated sensitivity, as in the case of LAR.[194,288-290] LAR may affect more than 47% of children and adults previously classified as NAR,[290-295] and persists throughout the years with a low rate of conversion to clinical AR.[296-298] However, LAR may evolve to the development of asthma.[296,297] Diagnosis of LAR is based on demonstration of a positive response to NPT and/or the detection of nasal sIgE and/or a positive basophil activation test (BAT) in the absence of systemic atopy. The pathophysiology of LAR is complex and not completely understood. Immunologic studies have revealed the existence of a Th2 inflammatory response in the nasal mucosa of LAR patients,[177,299-301] with positive response to NPT,[291,300-302] and local production of sIgE[177,290,299-301,303-305] and inflammatory mediators.[304,306,307]

Nasal Th2 inflammatory response. Flow cytometry studies in nasal secretions have confirmed that aeroallergen exposure induces a Th2 inflammatory response in the nasal mucosa of LAR patients with increased eosinophils, basophils, mast cells, CD3+, and CD4+ T cells.[300,301] NPT studies have demonstrated the existence of characteristic immediate/early and late-phases of the allergic response in LAR patients with local production of sIgE, mast cell and eosinophil activation, with mucosal secretion of tryptase and ECP.[306,307] A recent study showed that 83% of LAR subjects sensitized to *Olea Europaea* pollen responded to NPT with nOle e 1 (the most significant allergen of *Olea Europea)* demonstrating that purified allergens can also induce an allergic response with secretion of ECP.[308]

Local sIgE production. The respiratory airway mucosa is a site of IgE production during allergic inflammation, as has been demonstrated in patients with AR[309-312] and LAR,[299-301,303-307] with both somatic hypermutation and class switching occurring in the nasal mucosa.[309,312-315] Cellular studies have confirmed the expression of ε-germline gene transcripts and mRNA for the ε heavy-chain of IgE in nasal mucosal B-cells.[310] The rate of local IgE production[316] is sufficient to saturate IgE receptors on local mast cells, and potentially spill over into the circulation.[316,317] In LAR, the presence of sIgE in nasal secretions has been confirmed after natural allergen exposure,[300,301] NPT,[300,301,303-305] and periods of non-exposure.[300,301] Furthermore, local sIgE in LAR has the capability of activating basophils via the high affinity receptor FcεRI, leading to the release of inflammatory mediators characteristic of AR.[308,318]

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

It is commonly accepted that AR is primarily an IgE-driven response.[319] However, in recent years our understanding and appreciation of the important contributions of the nasal innate immune response to the pathogenesis of AR has grown substantially.[320] The pathophysiologic mechanisms of inflammatory airway disease are related to large physiologic networks that influence host-environment interactions. The nasal epithelium is the first structure to encounter inhaled aeroallergens. Intrinsic proteolytic activity of allergens may disrupt the nasal epithelial barrier, facilitating allergen penetration and chronic inflammation.[321] Recent data provide additional evidence that epithelial barrier dysfunction

contributes to the development of inflammatory diseases like AR, but it remains to be elucidated to what extent primary (genetic) versus secondary (inflammatory) mechanisms drive this breakdown.[322] Epithelial cells do not only act as a physical barrier toward inhaled allergens, but also actively contribute to airway inflammation by detecting and responding to environmental factors. The nasal epithelium expresses pattern recognition receptors in the form of toll-like receptors (TLR) that, after activation by allergens or pathogens, lead to the production of different mediators. [323,324] These mediators affect recruitment of inflammatory cells to local tissues and create a microenvironment that affects the function of immune cells, thereby propagating local inflammatory processes.[325] In allergic disease, the nasal epithelium seems to be in a permanently activated state,[326] potentially as a consequence of the inability to switch off the activation response.[327]

An interesting recent development was the discovery of innate lymphoid cells (ILCs) as potential key players in the pathogenesis of Th2-type diseases like AR, CRSwNP, and asthma.[328-330] ILCs are a family of effector cells that are important for protection against infiltrating pathogens and restoration of tissue integrity. ILCs do not express antigen-specific T-cell receptors, but can react promptly to "danger signals" and produce an array of cytokines that direct ensuing immune responses. Three major subsets have been defined based on their phenotype and functional similarities to Th1 (ILC1), Th2 (ILC2), and Th17 (ILC3) cells. Upon exposure to environmental antigens, including viruses and allergens, airway epithelial cells rapidly release the cytokines IL-25, IL-33, and TSLP that directly activate ILC2s that then produce the prototypical type 2 cytokines IL-5 and IL-13.[331] Allergen challenge in AR subjects induces an increased number of peripheral serum ILC2s;[332,333] however, a similar increase in the nasal mucosa is yet to be demonstrated. In addition to treatments aimed at modulating IgE-mediated inflammation, novel therapies directed toward the innate immune system are in development for treatment of AR.[334,335]

IV. C. Unified airway concept

The upper and lower airways are linked from anatomical, histological, and immunological perspectives with inflammation in one part of the airways influencing the other part, thus forming a united airway system.[336] New systemic treatment options make understanding of the relationship between upper and lower airways even more important.[337]

The mucosa of the upper and lower airways is similar, containing pseudostratified epithelium with ciliated columnar cells lining. Basal epithelial cells are also present, attached to the basement membrane (*lamina reticularis*), and have an epithelial stem cell function. In the submucosa there are vessels, mucus glands, fibroblasts and some inflammatory cells. The main difference in mucosal components is the absence of smooth muscles in the upper airways as compared to the lower airways, and the lack of extensive sub-epithelial capillaries, arterial systems and venous cavernous sinusoids in the lower airways as compared to the upper airways.

The characterization of phenotypes of rhinitis and asthma are very similar, with emphasis on allergy and eosinophilia, non-allergic phenotypes in both upper and lower airways, and the link between CRS, especially with nasal polyps, and late onset asthma.[319,338,339] Both AR and asthma may also be characterized by hyper-reactivity that is not correlated to the atopic state.[192,340] Also in endotyping, similarities can be pointed out with emphasis on type 2 versus non-type 2 immune responses. In allergic

diseases, the prominent endotype is type 2 (Th2 cells, type 2 B-cells, IL-4-producing natural killer [NK]/T cells, basophils, eosinophils, mast cells, ILC2, IL-4, IL-5, IL-13, IL-25, IL-31, IL-33).[319,341] In general, the type 2 profile in AR and asthma is associated with a good response to corticosteroid treatment. New targeted treatments that focus on (subgroup) type 2 elements, such as anti-IgE antibodies, anti-IL-5 (mepolizumab) and anti-IL-4/IL-13 (dupilumab) are currently used in asthma, but are not currently approved for use in the upper airways.[342] Similarities are not only found in the acquired immune response, but also in the role of innate immunity like epithelial barrier function[334] and innate lymphoid cells.[332] Epithelial barrier leakiness, particularly tight junctions that seal the upper and lower respiratory mucosal epithelial surface, has been shown in asthma, AR and CRS.[343,344]

Several mechanisms may explain the influence of sinonasal inflammation on the lower airways i.e. altered breathing pattern, pulmonary aspiration of nasal contents, the naso-bronchial reflex and the uptake of inflammatory mediators in the systemic circulation.[345] The nose acts as a filter and air conditioner, protecting the lower airways. Reduced filter and air-conditioning functions of the nose may lead to increased exposure of the lower airways to allergens. Mouth breathing is independently associated with asthma morbidity, indicating that air conditioning can be of major importance. The efficacy of the nasal filter depends on the size of the inhaled particles. Small molecules, such as molds and cat dander, are more associated with an increased risk for asthma, whereas larger molecules, such as tree and grass pollen, are primarily associated with upper airway symptoms. The role of preferential mouth breathing in the development of asthma is unclear.[346]

Although there is a relationship between postnasal drip and coughing, no direct association has been proven between overproduction of nasal secretions and bronchial hyper-reactivity. Moreover, after nasal application, deposits of radioactive-labeled allergen can be found in the digestive tract but not in the respiratory tract.[347] Stimulation of pharyngolaryngeal receptors is more likely to be responsible for a postnasal drip related cough.[348] Interestingly, cough is not induced in patients with rhinitis or healthy controls in simulated models of post nasal drip.[349]

There is not much evidence supporting the naso-bronchial reflex as an important contributor to the unified airway. Nasal allergen challenge can be blocked with a vasoconstrictor but not with lidocaine. Moreover, lower airway responses after allergen challenge are in general more delayed than would be expected following a nasal-bronchial reflex.[350]

Allergen provocation studies represent a good model to study nasal-bronchial cross talk in allergic airway disease. In patients with AR, segmental bronchial or nasal provocation can induce allergic inflammation in both the nasal and bronchial mucosa.[347-349] Presumably, absorption of inflammatory mediators (e.g. IL-5 and eotaxin) from sites of inflammation into the systemic circulation results in the release of eosinophils, basophils, and their progenitor cells from the bone marrow.[351] The systemic allergic response is further characterized by increased expression of adhesion molecules, such as vascular cell adhesion molecule 1 and E-selectin on nasal and bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue.[352]

Increases in CD34+ cells capable of eosinophil differentiation, as well as other circulatory mediators (IL-5, eotaxin, and cysteinyl leukotrienes), are associated with impaired lung function parameters and enhanced mucosal inflammation in asthmatic patients,[353] and react to local corticosteroids in AR.[354] Treatment with anti-IL-5 and other interleukins relevant in the eosinophilic

pathway has been shown to be effective in asthma, with some beneficial results in eosinophilic upper airway disease.[342]

In conclusion, these studies demonstrate that the same mechanisms behind AR may be important in airway inflammation throughout the respiratory tract, even in the absence of clinical asthma. Systemic factors, such as the number of circulatory eosinophils and atopic severity are indicative of more extensive airway disease.

IV. D. Cellular inflammatory infiltrates

A variety of cells are involved in the pathophysiology of AR. Due to the nature of the disease, with different mechanisms and endotypes, it is practically impossible to comprehensively describe each of these inflammatory cells in detail. This suggests a need for an extensive endotyping and characterization of the cellular infiltrate for each endotype.[355] In addition, many studies focusing on cell types in allergic diseases, including recently identified cells such as type 2 ILCs, Th17 and Th22 cells, have been mostly restricted to investigations of peripheral blood cells, not tissue biopsies. There is evidence from a limited number of studies that different cells are involved at different stages of inflammation, such as exacerbation, remission and extensive remodelling. Furthermore, different tissue sites such as sinus mucosa, polyp tissue or inferior turbinates show a variety of different infiltrating immune and inflammatory cells.

Nasal epithelial cells are at the interface of the human body and the environment, and often act as the first line of defense against external pathogens. Epithelial cells interfere with non-self allergens and regulate infiltrating cells in AR through the production of various co-stimulatory molecules, chemokines, cytokines and lipid mediators. These cytokines start to orchestrate a type 2 immune response characteristic of AR.[356] However, when allergens have additional protease activity and/or they are accompanied by microbial components such as endotoxins or inorganic particles, epithelial secretory responses can lead to mixed type 2 and type 17 immunity, or even type 1 responses.[357,358] In response to respiratory viruses, epithelial cells produce a wide range of mediators such as type I interferons, granulocyte macrophage colony-stimulating factor (GM-CSF), RANTES/C-C Motif Chemokine 5 (CCL5) and interferon gamma-induced protein 10/C-X-C Motif Chemokine 10 (IP-10/CXCL10).[359] These mediators orchestrate further downstream innate and adaptive antiviral cellular immune responses.

To activate allergen-specific CD4 T-cells, adequate co-stimulation is required. Dendritic cells are professional APCs that are directly related to AR, with increased numbers and concentrations of IgE in atopic disease.[360] They are in close contact with epithelial cells and ILCs and control T- and B-cell activation and differentiation.[356] Also, elimination of dendritic cells has been shown to suppress the development of AR.[360]

Both innate and effector mechanisms play essential roles during the development of allergic disease.[361] T-helper subset imbalance and production of typical Th2 cytokines[362] along with increased expression of GATA-3,[363] is generally seen in AR nasal mucosa. Furthermore, CD4+ memory T-cells and gamma/delta-T-cells are increased in PAR patients' mucosa.[364] Effector Th2 cells produce IL-4, IL-5, IL-9, and IL-13.[356,365] In addition, TSLP, IL-25, IL-31, and IL-33, contribute to the development and intensity of Th2 responses and inflammation. These cytokines have roles in production of sIgE, eosinophilia, mucus,

tissue migration of Th2 cells and eosinophils, regulation of tight junctions and epithelial barrier integrity.[343,356,366,367] T-regulatory (Treg) cell subsets have distinct phenotypes and include constitutive and inducible subsets of $CD4^+CD25^+$ Forkhead box P3 (FOXP3)+ Treg cells, and type 1 Treg cells.[368-370] Allergen tolerance and AIT are one of the most representative areas where Treg cells display their major role.[371-373] The production of IL-10 and transforming growth factor (TGF)-β from other cells is decisive for their immune regulatory functions. The ratio between effector and regulatory cell types determines whether an allergic response is triggered by an allergen or not.

Populations of lymphoid cells that lack rearranged antigen receptors and markers for myeloid and lymphoid lineages, such as T-, B- and NK-cells have been defined as ILCs. Type 1 ILC (ILC1) mainly produce interferon (IFN)-γ, ILC2 produce IL-5 and IL-13,[374] and ILC3 produce IL-17 and IL-22.[361] Type 2 ILCs are found in AR, where they closely interact with epithelial and other cells controlling the mucosal environment. Through the production of cytokines and induction of chemokines, a type 2 immune response is favored, supporting further development of an allergic tissue inflammation.[375]

Although it was believed that IgE-producing B-cells reside in lymphoid follicles of the Waldeyer ring[376] and antibodies are then transferred to the mucosa, newer evidence has identified B-cells and plasma cells capable of producing IgE in nasal tissue of AR patients.[377] The local production of allergen-specific antibodies is further supported by the detection of secondary lymphoid tissue and IgE formation to *Staphyloccoccus aureus* in CRSwNP.[378]

Within the nasal epithelium of allergic individuals increased numbers of major basic protein-positive and EG2+ (activated) eosinophils can be encountered during the pollen season. Similarly, mast cells are found within the epithelium and the submucosal layer; however, no increases are observed in cell counts of T-lymphocytes or their subsets, nor neutrophils or macrophages during seasonal allergen exposure.[379] Basophil numbers in the lamina propria of the nasal mucosa increase within one hour of allergen provocation.[380] Degranulation of both mast cells[381] and basophils occurs during the early and late phases of a type I reaction after allergen encounter and crosslinking of IgE molecules as well as upon stimulation by IL-33.[382]

In the late phase of the allergic reaction, the influx of inflammatory cells is facilitated by chemoattractants and upregulation of adhesion molecules.[383] This leads to further infiltration of the tissue by eosinophils, basophils and T-cells. Lastly, those inflammatory cells driving remodelling of the mucosa in AR, and upregulating factors like matrix metalloproteinases and angiogenic factors remain to be identified.[384]

IV. E. Cytokine network and soluble mediators

Cytokines are immunomodulatory proteins important in cellular signaling. Complex interactions of innate and adaptive immune cells, as well as structural cells and their cytokines, play crucial roles in regulating allergic airway inflammation. The inflammatory process underlying AR is coordinated by a network of cytokines.

Type 2 cytokines such as IL-4, IL-5, IL-6 and IL-13 are crucial in regulating the allergic inflammatory cascade characterized by an increased presence of eosinophils and mast cells and an upregulation of IgE production. Besides their role in the induction of IgE synthesis, type 2 cytokines

upregulate the production of other cytokines and chemokines from epithelial cells and fibroblasts,[283] which then leads to the influx of inflammatory cells including eosinophils and mast cells.[385,386] Scadding et al[387] demonstrated the immunological aspects of rhinitis with nasal allergen challenge. After nasal challenge with grass pollen in sensitive individuals, the levels of IL-4, IL-5 and IL-13 were elevated 2-3 hours post challenge and increased for up to 5 to 6 hours.[387] Similarly, levels of chemokines such as thymus and activation regulated chemokine (TARC, CCL17), macrophage derived chemokine (MDC, CCL22), eotaxin, RANTES, MCP-1 and macrophage inflammatory protein (MIP)-1α were elevated.[388-391] Increases in these type 2 cytokines and associated chemokines were strongly correlated to allergic clinical responses.

Although type 2 cytokines were originally referred to as Th 2 cytokines after their suspected cellular source, several other cells have been identified as significant sources including mast cells, epithelial cells, type 2 ILCs, and eosinophils. Airway mast cells are an important source of type 2 cytokines, proinflammatory cytokines, chemokines, and the IL-7-like cytokine TSLP.[283,392-394] IL-13 from mast cells plays a crucial role in mast cell-induced local IgE synthesis by B cells,[286,395] which in turn upregulate FcεRI expression on mast cells.[286] Further, several mast cell products heavily influence epithelial cells. TNF-α, a pro-inflammatory cytokine produced by mast cells, in concert with IL-4 and IL-13, enhances the production of TARC, TSLP and eotaxin from epithelial cells.[385] And chemokines such as tryptase and chymase can upregulate RANTES and GM-CSF production from epithelial cells.[385] Thus, there appears to be a crucial interplay between mast cells and epithelial cells in promoting and regulating the allergic inflammatory cascade.

In addition to the cytokines and chemokines listed above, nasal epithelial cells are an important source for IL-1, IL-6, IL-8, and TNF-α. Through these signals, epithelial cells play a crucial role in the migration and activation of eosinophils, basophils and Th2 cells.[396] In addition, epithelial cells release the cytokines IL-25, IL-33, and TSLP that orchestrate both the innate and adaptive Type 2 immune response. These same cytokines are also released by tissue damage, pathogen recognition and allergen exposure. They can regulate Th2 cell function either directly or via innate lymphoid cells, which in turn produce IL-5, IL-9, IL-13, TSLP, IL-25 and IL-33, which are all increased in the nasal mucosa of AR patients indicating a role of these cytokines in the pathophysiology of AR.[397-400] In fact, levels of IL-33 in nasal secretions have been shown to correlate with total nasal symptom scores.[400] Further, TSLP has been shown to activate dendritic cells, promote Th2 responses, and activate mast cells.[401]

Eosinophils are another cell type that appears to play a significant role in the pathophysiology of AR. They are a major source of the inflammatory cytokines macrophage migration inhibitory factor (MIF)[402] and nerve growth factor (NGF).[403] Eosinophils express 5-lipoxygenase, LTC4S, and $CysLT_1$ and $CysLT_2$ receptors, which play a role in the arachidonic acid pathway.[404] IL-5 has a key role modulating eosinophil maturation, differentiation, and survival.[405] Eosinophilic chemoattractants include eotaxin, MCP4, RANTES and cysteinyl leukotrienes among others.[406-408] As discussed previously, mast cells, and epithelial cells either directly produce or up-regulate these same chemoattractants.

Finally, Th17 cells are a unique subpopulation of CD4+ T cells. They produce IL-17A, IL-17F, IL-22, TNF-α, and IL-21.[409] They have been demonstrated in the nasal mucosa of AR patients and are therefore thought to play a role in allergic inflammation.[409,410] Further, IL-17A has been shown to be upregulated in SAR patients 5 hours after nasal allergen challenge.[411] Finally, increased numbers of $IL\text{-}17A^+$ cells and IL-

17A mRNA were demonstrated in the nasal mucosa of patients with dust mite allergy, indicating a possible role in AR.[412]

In summary, AR is a type 2-mediated disease, characterized by important regulatory cytokines like IL-4, IL-5 and IL-13. Newer type 2 cytokines have been identified in AR, including IL-17 family cytokines. Finally, Type 2 ILCs and epithelial cell derived cytokines like TSLP, IL-25 and IL-33 play a crucial role in the regulation of the allergic inflammatory cascade.

IV. F. Histologic and epithelial changes

Normal nasal mucosa comprises pseudostratified columnar ciliated epithelium with goblet cells over a basement membrane. The nasal submucosa contains stromal elements including fibroblasts, blood vessels, sero-mucinous glands, sensory nerves, and leukocytes. Leukocytes present in the nasal mucosa include CD4+ and CD8+ T lymphocytes, B lymphocytes, eosinophils, neutrophils, basophils, mast cells and macrophages. The combined functions of ciliated and secretory cells allow for naso-ciliary clearance, removing pathogens and allergens as a host defense mechanism. In addition to the physical barrier, nasal epithelium plays an important role in the innate and acquired immunologic defense against pathogens[359,413,414] by: (1) expressing pattern recognition receptors that recognize pathogen-associated molecular patterns; (2) secreting a vast arsenal of host defense molecules, such as antimicrobial enzymes, opsonins, permeabilizing proteins, collectins, and binding proteins; and (3) producing inflammatory cytokines in response to antigenic stimuli.

Allergy mediates epithelial change in the nasal mucosa. Nasal epithelium is thicker in patients with AR after allergen challenge,[415,416] but studies on epithelial thickness in AR without allergen challenge are conflicting.[415-417] While epithelial remodeling is a key feature of CRS (epithelial hyperplasia, goblet cell hyperplasia, squamous metaplasia[418-420] and asthma (epithelial desquamation, sub-epithelial fibrosis, smooth muscle hypertrophy), remodeling in AR is less marked. In general, limited studies have found no significant increase in basement membrane thickness, subepithelial fibrosis, goblet cell hyperplasia or blood vessel volume and surface density,[415,421,422] though increased vascular permeability was noted.[423] In contrast to epithelial remodeling, epithelial inflammatory response to allergens is a key feature of AR. Upon allergen exposure, there is significantly higher infiltration of inflammatory cells, and increased levels of cytokines (such as IL-4, IL-5, IL-13) in the nasal epithelium of allergic compared to non-allergic patients.[182] This inflammatory response translates into mucosal edema, autonomic neural stimulation and increased mucosal secretions, which manifest as the hallmark symptoms of nasal obstruction, pruritus, sneezing, rhinorrhea, and smell loss in severe cases.

The epithelial barrier is noted to have specific functions in allergy. Penetration of allergens through this barrier may lead to allergen sensitization and local and/or systemic inflammatory response. In the nasal mucosa, this barrier is comprised of mucus and epithelial cells, which are linked by apical junctional complexes (tight junctions and adherens junctions).[367] Mechanical or infective insults to the epithelium or defective epithelium leads to barrier breach and allergen penetration.[367,424-426] Loss of function mutations and polymorphisms in genes coding for epithelial barrier markers like filaggrin are associated with AR and eczema.[427,428] Some allergens can induce junctional dysfunction, leading to penetration of the epithelial barrier by allergens.[322,429] Proteolytic allergens directly disrupt the apical

junctional complex via proteolysis, leading to barrier dysfunction.[430] Detection of allergens by APCs, and the ensuing Th2 responses and cytokine release (such as IL 4, IL-13, IFN-γ) induces further "leakiness" of the apical junctional complex via various mechanisms, allowing increased levels of allergen penetration.[367] Evidence suggests that this barrier impairment may be reversed with corticosteroids. Fluticasone propionate has been found to increase expression of tight junction proteins zonula occludens 1 and occludin and a more intact nasal epithelial barrier.[322] Corticosteroids have not, however, been shown to cause thinning of nasal epithelium.[322,431]

Allergy is now considered both a systemic and local epithelial condition.[337] Evidence points to the epithelium being an active participant in the development and progress of allergy, rather than as a passive barrier.[432] Birch pollen has been found to rapidly bind to Bet v 1-binding proteins in sensitized nasal epithelium, and is transported through a lipid raft and caveolar-dependent process before binding to mast cells in the lamina propria.[433-435] Epithelial response to allergens differs from healthy individuals in that allergic patients do not mount as robust an epithelial defense response to allergens, leading to increased penetration of allergens.[432]

IV. G. Microbiome

The human microbiome comprises the complex community of microorganisms that resides in and interacts with the human body. An adult intestine is a haven to approximately 100 trillion microbes and it is thought that the microbiome accounts for roughly 90% of all the cells in the human body.[436,437] The microbiomes of individuals vary, likely due to the fact that the growth, development and composition of the microbiome are affected by intricate interactions between the environment, diet, and host-related factors.[437]

With the advent of culture-independent high throughput bacterial DNA sequencing techniques, a detailed description of the composition and variety of the microbiome can be described among organs and individuals.[438] The Human Microbiome Project began in 2007, and as a result, extensive data have emerged examining the associations of the microbiota of the respiratory tract, oral cavity, gut, skin and genitourinary tract to the development of disease processes including allergy and asthma.[437]

Increasing literature in animals and humans has implicated changes in the microbiome with the development of allergic disease.[439,440] Mechanistically, a disruption in gastrointestinal bacteria is thought to alter mucosal immunological tolerance.[441] Several authors have found associations of reduced gut microbial diversity with development of allergic disease in school-aged children.[442,443] For example, the development of allergic symptoms in children has been associated with overall lower microbial diversity, increased prevalence of *Bacteroides* and *Bifidobacertium adolescentis,* and lower counts of *Akkermansia muciniphilia, Faecalibacterium praunitizii,* and *Clostridium*.[444] In addition, Fujimura et al[445] recently noted that a lower abundance of *Bifidobacertium, Akkermansia*, and *Faecalibacterium* were associated with a higher risk of development of polysensitization by age 2 and physician-diagnosed asthma by age 4. The authors concluded that neonatal intestinal microbial dysbiosis may foster CD4+ T-cell dysfunction associated with childhood allergic disease.[445,446]

The most comprehensive collection of evidence evaluating a potential association between the microbiome and the development of allergic disease is from a recent systematic review by Melli et al.[444]

Studies included in this systematic review compared intestinal microbiota of allergic patients with healthy controls. A total of 21 studies were noted to report an association between the intestinal microbiota and allergic disease when stool collection was performed prior to the outcome assessments. Only four of the analyzed studies had specific outcomes related to AR or sensitization. Penders et al[447] found that the presence of *Clostridium difficile* at one month of age was associated with an increased risk for allergic sensitization (OR 1.54; 95% CI 1.09-2.31) until the age of 2 years. Adlerberth et al[448] noted an increased ratio of gram negative to gram positive bacteria at 1 year of age to be associated with IgE levels greater than 100 kU/L at 1.5 years of age. Bisgaard et al[449] found lower bacterial diversity was associated to higher risk of allergic sensitization (p=0.003) and AR (p=0.007). Johansson et al[450] reported lower frequency of colonization with *Lactobacilli* and *Bifidobacertium bifidum* in allergic children.[15] Ultimately, Melli et al[444] found that most of the studies linking the microbiome to the development of atopic disease are varied and difficult to interpret due to differing methodologies, samples sizes and culture techniques.

There are some thoughts that the composition and/or dysbiosis of the microbiota (viruses, fungi and/or bacteria) of other sites such as the nasopharynx, lungs and sinonasal cavities may also play a role in the development of allergic disorders. However, these studies are in their infancy and little can be concluded at this time.[451]

A thorough understanding of the role of the microbiome and how it influences allergic disease has not been fully elucidated. Although some data suggest associations between allergic disease and the microbiota, based on the current evidence it is difficult to distinguish between protective microorganisms and those that increase risk for allergic disease.[446] Future research should provide an enriched and diverse understanding of the human microbiome and the way it impacts AR.

V. Epidemiology of allergic rhinitis

V. A. Prevalence of allergic rhinitis in adults

A variety of population-based surveys have been used to estimate the prevalence of AR within the adult population. Prevalence estimates largely rely on self-reports of 'hay fever' or 'nasal allergies', or of nasal symptoms 'when you did not have a cold or the flu'. Questions on seasonality (to separate seasonal from perennial rhinitis) are sometimes asked, but there are few large-scale well-conducted population-based studies that have evaluated persistent (lasting more than 4 days/week for more than 4 consecutive weeks) versus intermittent symptoms. Because many surveys differ in terms of disease definitions, geography, and seasonality prevalence estimates drawn from surveys vary widely.

One of the earliest studies, conducted in Tecumseh, Michigan in 1959-1960 included a physician assessment and suggested that the prevalence of hay fever (diagnosed as 'upper respiratory symptoms believed to be allergic in origin and occurring predominantly in either spring, summer or autumn') was about 11% in those aged over 20 years.[452] About 20 years later, the National Health and Nutrition Examination Survey (NHANES) 1976-80 was conducted among a geographically representative sample of the US population. This survey gave broadly similar estimates for prevalence of AR, defined as 'physician diagnosis of hay fever or frequent nasal and/or eye symptoms that varied by both season and pollen during the last 12 months, not counting colds or the flu'.[453] A more recent report based on NHANES (2005-2006), presented population prevalence figures in which two-thirds were over the age of 20 years, and showed the lifetime prevalence of physician diagnosed hay fever was 11.3%, with 6.6% having symptoms in the last 12 months. However, reliance on physician diagnosis of AR is likely to considerably underestimate the actual prevalence of AR, since many patients self-diagnose and self-treat. Surveys involving patient self-reporting AR have shown that one-third of the population reported 'sneezing and/or nasal symptoms in the absence of cold or a flu', with about 24% reporting that this was seasonal in nature, and a further 10% reporting these symptoms occurred year-round (i.e. perennial).[454]

In the early 1990's, the European Community Respiratory Health Survey (ECRHS), a multicenter population-based study of adults age 20-44 years in 23 countries (mainly Western Europe, but also Australia and New Zealand), used a self-completed questionnaire to estimate the prevalence of 'hay fever or nasal allergies'. Prevalence varied between 10% and 40% across participating centers,[455] with even more participants (12% to 65%) reporting that they experienced a runny or stuffy nose or started to sneeze on exposure to sources of allergen.[456] If a positive SPT was included in the disease definition, the prevalence of AR fell by a variable amount (absolute fall in prevalence between 4% and 16% across all centers). In the Swiss Study of Air Pollution and Lung Disease in Adults (SAPALDIA), conducted around the same time as the ECRHS, the prevalence of self-reported 'nasal allergies including hay fever' in adults aged 18-60 years was 17.9%, and the prevalence of current symptoms ('hay fever this year or last year') was 14.2%.[457] Prevalence estimates were lower if a positive SPT was included (11.2% for current hay fever with at least one positive SPT and 9.1% for current hay fever with positive SPT to one of grass, birch or *Parietaria*). More recently, the Global Allergy and Asthma Network of Excellence (GA^2LEN) study suggested the prevalence of 'nasal allergies and hay fever' varied between 22% and 41% in adults age 18 to 75 years living in the 12 participating European nations.[458]

Population-based studies have shown increases in AR prevalence in the adult population in recent decades. For example, in Renfrew Paisley, UK, the prevalence of hay fever was higher in adults

and children in 1996 than in their mothers and fathers at an equivalent age in 1972.[459] Hay fever prevalence doubled between 1981 and 1990 in Busselton, Australia[460], increased in Italy from 1991 to 2010[461] and increased in eight of 11 cities in China surveyed in 2005 and again in 2011.[462] In Uppsala, Umea and Goteborg, in Sweden, 'hay fever and nasal allergies' increased from 21% to 31% between 1990 and 2008[463], although recent reports from Stockholm suggest there may be a levelling off in the increase in nasal allergies over more recent years.[464]

From these data, the lifetime prevalence of AR in the US can be estimated between 11% (physician-diagnosed) and approximately 33% (self-reported). In Europe, prevalence of AR in adults likely ranges between 10-41%, depending on the specific country.

V. B. Incidence and prevalence of allergic rhinitis in children

There are relatively few studies on the incidence of AR in children. There is evidence that AR may start as early as during the first year of life. In the Cincinnati Childhood Allergen and Air Pollution Study (CCAAPS), 9% of the 12-month-old children with a parental history of respiratory allergy fulfilled the criteria of AR.[465] In the PARIS birth cohort (Pollution and Asthma Risk: an Infant Study), 9.1% of the 18 month-old children had AR-like symptoms with a strong association with atopy and sensitization to inhalant allergens. Of these, 23.7% had rhinoconjunctivitis.[466] In a study of 29,662 children from the US that used health care records to follow participants, the incidence of physician diagnosed AR during the first year of life was 1%. From 1 to 5 years of age, the annual incidence was between 3.6 and 4.5%, with the highest incidence between 2 and 3 years of age.[467] This is broadly in line with estimates of a SAR incidence of 3-4% per year from 3 to 7 years of age reported in a birth cohort of 1,314 German children.[468]

In longitudinal studies, AR often occurs for the first time in childhood and increases in prevalence with increasing age.[467-471] Most children with symptoms of AR early in life have persistent symptoms for several years. [469-471] The International Study of Asthma and Allergies in Childhood (ISAAC) estimated the prevalence of allergic diseases in two different age groups, 6-7 years and 13-14 years, through a multicenter global survey. Two cross-sectional surveys were performed approximately 7 years apart (range 5-10 years). Overall, an increase in rhinoconjunctivitis prevalence was observed between the two surveys.[10] However, there were geographical differences in both baseline prevalence and in the increases observed; therefore, it is difficult to determine whether the observed differences represented a true increase in prevalence over time. The proportion of children with symptoms of rhinoconjunctivitis was higher in the older age group. Data from the second survey (ISAAC Phase Three 1999-2004) state that the worldwide prevalence of current rhinoconjunctivitis in the 6-7-year age group was 8.3% (range between countries 1.8-24.2%) and in the 13- to 14-year age group was 15.1% (range 4.5-45.1%).[472] In a more recent meta-analysis of all studies performed according to the ISAAC-protocol (1,430,329 children aged 0-18 years), the overall prevalence of AR was 12.66%.[473]

Rhinoconjunctivitis has been reported to be slightly more common among boys than girls in the 6-7 year age group, with the opposite tendency seen in the 13-14 year old age group.[474] However, gender differences were not seen in all countries in the survey. Other studies do show a greater prevalence of AR among boys of all ages. For example, in the Isle of Wight (UK) birth cohort of 1,456

children, the prevalence of rhinitis among boys as compared to girls was higher across all age groups, (4 years 4.7% vs. 2.1%, 10 years 14.9% vs. 11.7%, 18 years 31.0% vs. 24.0%).[469]

V. C. Geographic variation of allergic rhinitis

The prevalence of AR shows marked geographic variation. Many factors likely contribute to this disparity and not all are completely understood. The central difficulty in meaningfully comparing AR prevalence rates between locations is the difference in methods used to recruit participants to studies and differences in assessing the presence of disease. For example, Bauchau et al[9] diagnosed Belgian patients via serological IgE testing after a positive telephone screen and reported that Belgium had an AR prevalence of 28.5% (the highest of the European countries evaluated). In contrast, Bousquet et al[456] skin-tested a random sample of Belgian subjects and reported a positive rate in Belgium of 16.4% (one of the lowest of 15 countries examined).

There have been major international efforts to compare variations in the national prevalence of AR using standardized methods (i.e. ECRHS and ISAAC). These studies show marked geographic variation of 'hay fever or nasal allergies' (adults) or 'a problem with sneezing, or a runny, or a blocked nose when you DID NOT have a cold or the flu that was accompanied by itchy-watery eyes?' (children). A higher prevalence of these responses is seen in people living in 'English speaking' countries (e.g. UK, Australia, New Zealand), a lower prevalence in Eastern Europe than in Western Europe, and a diagnosis of AR is more frequently seen in countries with higher asthma rates and sensitization to seasonal allergens.[455,475] Because these studies have evaluated national rates based on only one or a few centers within each country, substantial intra-country variation may have been overlooked.

In understanding the effects of geographic location, differentiating between seasonal and perennial AR is an important consideration not examined in the ECRHS or ISAAC studies. Smaller studies over more limited geographic regions that examined PAR suggest increased sensitivity rates in urban settings and colder climates.[476-479] Several hypotheses have been put forward for these observed differences. Li et al[477] theorized that urban dwellers participate in more indoor activities compared to their rural counterparts, amplifying their exposure to HDM, and possibly leading to increased sensitization to these perennial allergens. Additionally, some reports suggest that exposure to urban pollutants may be associated with increased risk for developing AR in children.[476] Latitude may also play a role with regard to PAR. For example, the prevalence of persistent AR was found to be higher in both Northern Europe and Northern China compared to their southern counterparts.[9,477]

Latitude may also be an important determinant of SAR. Allergenic plant species may have a propensity for growing in certain geographic locations, and pollen concentrations of various species depend on the climate conditions of the area. Colder climates present at northern latitudes tend toward shorter growing seasons, and many allergenic species do not thrive in extreme northern climates. For instance, grass pollen, which is found across Europe, causes wide variations in atopic sensitizations across regions with different climates.[480] Additionally, this increased environmental exposure has been shown to affect development of AR and patient symptoms of atopic nasal diseases.[481,482]

Overall, improved knowledge of the prevalence and seasonal variations in AR based on geographic location is important in that it allows patients to anticipate and better manage their

symptoms through avoidance techniques and preemptive use of pharmacologic therapies.[480,482] Currently, prevalence data do not fully address the different phenotypes of AR and further study is needed to expand epidemiologic understanding of this disease.

VI. Risk factors for allergic rhinitis

VI. A. Genetics

AR is well-known to run in families, and one of the strongest risk factors is the presence of disease in first-degree family members.[483] Studies of twins support the genetic underpinnings of AR with a higher concordance rates for AR in monozygotic twins compared to dizygotic twins.[484,485] The estimated heritability of AR has been suggested to be as high as 70-80%. Like many complex diseases, no single gene or polymorphism accounts for the hereditary effect on AR. Instead, many genes and several variants, each with small effects, are believed to contribute to disease initiation, persistence and severity. In this section, the current literature on the genetics of AR is reviewed, including candidate gene studies and recent large-scale genome-wide association studies (GWASs). In addition, gene-environment interaction effects and epigenetics studies will be briefly covered.

Single nucleotide polymorphisms (SNPs) associated with AR

Genome-wide association studies. GWASs with an unbiased approach that include hundreds of thousands of common gene variants, or SNPs, have successfully identified important variants for complex diseases over the past decad. Five GWASs on AR (or hay fever) have been published as of September 2016, as summarized in **Table VI.A.** SNPs in leucine-rich repeat-containing protein 32 (*LRRC32*) have been strongly associated with AR in three of the GWASs[486-488], and with asthma,[487,489] eczema[488,490] and other allergy-related co-morbidities.[486,489,491] At the protein level, LRRC32 is known to regulate T-cell proliferation, cytokine secretion and TGF-β activation.[492] These associations suggest shared genetic mechanisms for AR and other allergy-related diseases, evidence further supported by the large-scale GWAS on self-reported cat, HDM and pollen allergies (as well as AR) which revealed 16 shared susceptibility loci with strong association ($p < 5 \times 10-8$; *TLR*-locus top hit).[487] In an accompanying GWAS on allergic sensitization, there was strong overlap between top hits for sensitization and self-reported allergies.[487,493] In the GWAS by Ferreira et al,[489] 11 variants were associated with the combined asthma phenotype and hay fever below the genome-wide significance level (*HLA-DQB1* top hit). TLRs play a crucial role in immune regulation and SNPs in different TLRs have been associated with AR in both GWASs (*TLR1, 6, 10*)[486,487] and candidate gene studies (*TLR8*), as discussed below.[494] In addition to shared genetic effects between different allergy-related diseases, a significant overlap between susceptibility loci for allergy and autoimmune diseases has been observed.[495]

Candidate gene studies. The candidate gene approach for selecting disease-relevant genes is based on previous associations reported from GWAS or biological features which could be relevant for disease risk. Studies on AR using this approach have found several well-replicated genes as summarized previously.[496-498] Notably, SNPs in genes involved in antigen presentation (for example *HLA-DQA1*), pathogen recognition (*TLR2,7,8*), IL signaling and pro-inflammation *(IL13, IL18* and *TSLP)* are considered important susceptibility variants for AR.[496-502] Recently, functional evidence in blood immune cells for genetic variants in brain-derived neurotrophic factor (*BDNF*), a secretory pro-inflammatory protein implicated in AR pathogenesis, was reported.[503] However, many of the candidate genes reported in the literature have not been well-replicated across studies and populations.[427,504] This could be due to inadequate statistical power related to small sample sizes, inconsistent phenotype definition, or lack of

true disease association. Additionally, rare variant studies focusing on candidate genes have not been particularly successful.[494] The candidate gene approach is particularly necessary for hypothesis-driven analyses and functional genetic analyses, for example in populations with specific environmental exposures or with mixed ethnic backgrounds.

Gene-environment interactions and epigenetic effects

Epigenetic mechanisms, defined as changes in phenotype or gene expression caused by mechanisms (e.g. methylation) other than changes in the underlying DNA sequence, have been proposed to constitute a link between genetic and environmental factors. Recent studies show that DNA methylation in children is very strongly influenced by well-known risk factors for allergic diseases such as maternal smoking during pregnancy[505] and air pollution exposure.[506] Currently, however, it is not known if these methylation changes are causally related to the development of AR and asthma, or if these "biomarkers" are solely markers of exposure. Several studies have convincingly linked methylation profiles to AR[507-509] and IgE-related outcomes,[510,511] but large-scale studies have yet to be completed.

In summary, a family history of AR remains a risk factor for disease development, and strong associations have been identified with genes involved in T-cell activation (e.g. *LRRC32*) and innate immunity (e.g. *TLRs*). Shared genetic mechanisms for AR and other allergy-related diseases have been very clearly identified in recent large-scale studies. There is, however, a need to functionally characterize variants in these candidate genes to understand mechanisms underlying the pathogenesis of AR. With increasing evidence for the role of epigenetics in AR, future research should also focus on investigating epigenetic mechanisms, thereby providing a functional explanation for the link between environmental exposures, genetic variants and disease development.

- Aggregate Grade of Evidence: C (Level 2a: 5 GWASs. Candidate gene studies not assessed regarding grade of evidence.)

Table VI.A. Key findings from genome-wide association studies (GWASs) on allergic rhinitis or hay fever

Author (year)	Study design	Sample size	Ethnicity	Top SNPs for AR	p-value	Nearby gene(s)	Reported association with other allergic diseases	Protein function	LOE
Bunyavanich et al[512] (2014)	Meta-analysis of seven cohorts	2,712 AR cases 2,921 controls	EA, L, AA	rs17133587	4.5E-09 (L)	*AKR1E2*	No	NAD(P)H-dependent oxido-reduction	2a
				rs6583203	1.4E-08 (L)	*DLG1*	No	Scaffolding protein involved in cell metabolism	
				rs7780001	2.0E-08 (all groups)	*FERD3L*	No	Transcription factor	
Hinds et al[487] (2013)	Private company data (23andMe)	46,646 total	>97% EA	rs1438673	3.7E-19	*WDR36*	Asthma,[487,513] eczema,[488] atopy[487]	Cellular processes and T-cell activation	2a
				rs2101521	6.0E-17	*TLR1-TLR6 - TLR10*	Asthma, eczema, atopy[487]	Pathogen recognition and activation of innate immunity	
				rs10189629	9.9E-15	*IL1RL2 - IL1RL1*	Asthma,[487,514] eczema,[487] atopy[487]	Pro-inflammatory effects, T-helper cell function	
Andiappan et al[515] (2011)	Nested case-control with replication	1,132 AR cases 997 controls	Chinese	rs811930	7.3E-05	*MRPL4*	No	Protein synthesis within the mitochondrion	2a
				rs505101	1.3E-04	*BCAP (PIK3AP1*)	Atopy[515]	Protein tyrosine kinase	
Ramasamy et al[488] (2011)	Meta-analysis of four cohorts	3,933 AR cases 8,965 controls	EA	rs2155219	3.8E-08	*LRRC32* or *C11orf30 SLCA25A46*	Co-morbidity: asthma-atopy,[489] asthma-eczema,[491] asthma-hay fever.[486] Eczema,[487,490]	LRRC32: T-cell regulation, TGF-β activity. C11orf30: regulation of viral immunity and interferon pathways	2a

							asthma, atopy[487]		
				rs17513503	7.4E-07	*TMEM232* or	No	Transmembrane protein	
				rs1044573	9.7E-07	*ENTPD6*	No	Catabolism of extracellular nucleotides	
Ferreira et al[486] (2010)	Meta-analysis of four cohorts/datasets	16,513 hay fever cases 17,256 controls	EA, L, AA	rs4833095	4E-12	*TLR1*	Asthma, eczema, atopy[487]	Pathogen recognition and activation of innate immunity	2a
				rs2155219	7E-10	*LRRC32* or *C11orf30*	Co-morbidity: asthma-atopy,[489] asthma-eczema,[491] asthma-hay fever,[486] Eczema,[487,490] asthma, atopy[487]	See above	
				rs10197862	2E-09	*IL1RL1*	Asthma,[487,514] eczema,[487] atopy[487]	Pro-inflammatory effects, T-helper cell function	

GWASs: genome-wide association studies; AR: allergic rhinitis; LOE: level of evidence; EA: European ancestry; L: Latino; AA: African American

VI. Risk factors for allergic rhinitis
VI. B. Inhalant allergens (*in utero* and early childhood exposure)

AR is characterized by a loss of immunological and clinical tolerance toward a specific allergen. This involves production of sIgE which initiates allergic inflammation following allergen exposure. Therefore, sIgE is a hallmark of allergy and its production defines sensitization. Sensitization is a complex phenomenon, regulated by genetic and environmental factors, requiring a primitive exposure to a specific allergen. If a subject is never exposed to an allergen, sensitization to that allergen cannot occur. On the other hand, it is fundamental to distinguish between sensitization and allergy. Allergy, which involves the development of symptoms after the sensitizing exposure, is different from mere sensitization. Without sensitization allergy cannot exist, but not vice versa. In this section, the *in utero* and early childhood exposure to inhalant allergens, including mites, pollens, animal dander, and fungal allergens, will be evaluated as risk factor the development of AR.

Mites. There are six studies on the topic of early mite exposure and the development of AR. **[Table VI.B-1.]** Most of the studies failed to demonstrate an association between early exposure to mites and the development of AR.[468,516-519] Marinho et al[520] reported that early exposure to HDM is not a protective factor for current AR, and Kim et al[521] proposed exposure to spider mites as a risk factor for AR. Interestingly, pets may be a relevant source of mites, as their fur is often settled by mites; this association may confound AR evaluation and treatment. Ultimately, the studies on early mite exposure and the development of AR are conflicting and additional research is needed.

- Aggregate Grade of Evidence: C (Level 2b: 5 studies; Level 3b: 1 study; *Table VI.B-1.*)

Pollens. There are only two studies that addressed the impact of early pollen exposure on AR. **[Table VI.B-2.]** Kihlström et al[519] reported no association to allergic rhinoconjunctivitis whereas Erbas et al[481] showed that pollen exposure during infancy is a risk factor for hay fever.

- Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 3b: 1 study; *Table VI.B-2.*)

Animal dander. Numerous studies have evaluated the association between early exposure to animal dander and subsequent development of AR, with conflicting results. **[Table VI.B-3.]** Studies are divided according to the findings: positive studies (reporting a protective effect on AR development[522-535]), negative studies, (showing that early exposure to pets represents a risk factor for AR[523,536-542]), and neutral studies (reporting that early exposure to animal dander is not associated with AR[468,517,518,520,524,528,530,532,536,538,539,543-554]). Additional factors should be considered: pet age, gender and species, number of household pets, home characteristics, atopic predisposition of the pet owners, and others. Considering these complex variables, debate regarding the influence of early pet exposure on developing allergic disease remains unresolved. Thus, evidence-based guidelines regarding having pets

at home cannot be established. *(See Section VI.G.2. Protective Factors – Childhood Exposure to Pets for additional information on this topic.)*

- Aggregate Grade of Evidence: C (Level 2b: 15 studies; Level 3b: 24 studies; *Table VI.B-3.*)

Fungal allergens. Several studies have explored the role of early exposure to fungal allergens as a predisposing factor for AR. **[Table VI.B-4.]** Most studies demonstrated evidence that early exposure to fungal allergens represents a risk factor for AR development.[527,538,551,553,555-560] However, three studies demonstrated that early exposure to fungal allergens is not associated with AR.[465,542,557] Home moisture level, which is closely and positively associated with the presence of fungal allergens in the home, may be a confounding factor in interpreting the evidence on fungal exposure and AR. Ambient humidity may an intrinsic risk factor, but high moisture is also associated with increased level of mites, as mites grow in presence of elevated moisture. Moisture can be easily assessed both by direct measurement with a hygrometer and indirectly by observing the presence of mold spots on the walls.

- Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 3b: 10 studies; *Table VI.B-4.*)

In summary, the clinical relevance of early inhalant allergen exposure to AR development is still debated. Despite several in-depth reviews and a growing body of literature,[561-563] no definitive and consensus may be drawn regarding risk-benefit of early inhalant allergen exposure, and further research is welcomed to address the unmet needs on this issue.

Table VI.B-1. Evidence for the effects of mite allergen exposure (*in utero* and early childhood exposure) on the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Type of exposure	Conclusion
Schoos et al[518]	2016	2b	Prospective birth cohort	399 children (7-13 years old) from COPSAC study	Der p 1 in dust sample at 1 year	No association with AR at 7 years (OR 0.9, CI 0.7-1.1).
					Der f 1 in dust sample at 1 year	No association with AR at 7 years (OR 0.9, CI 0.7-1.1).
Illi et al[517]	2014	2b	Prospective birth cohort	513 children (5 years old) from PAULA study	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).
Marinho et al[520]	2007	2b	Whole-population birth cohort	815 children (5 years old) from MAAS	Der p exposure at 0-5 years old (measured as allergen levels recovered from child's bed, child's bedroom floor, parental bed and lounge floor)	Protective factor for current rhinoconjunctivitis (OR 0.8, CI 0.7-0.98). This finding failed to reach significance in multivariate analysis.
Corver et al[516]	2006	2b	Prospective birth cohort	416 children (4 years old) from PIAMA study	Der p 1 and Der f 1 exposure on the children's mattresses	No association with rhinitis in 4th year (OR 0.9, CI 0.6-1.3).
Kulig et al[468]	2000	2b	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 SAR (OR not reported).
Kim et al[521]	2002	3b	Cross-sectional	16,624 children (7-18 years old)	History of spider mite exposure	Risk factor for rhinitis (OR 1.3, CI 1.2-1.5).

Odds ratios are unadjusted and reported with 95% confidence intervals.
LOE: level of evidence; COPSAC: Copenhagen Prospective Study on Asthma in Childhood; AR: allergic rhinitis; OR: odds ratio; CI: 95% confidence interval; PAULA: Perinatal Asthma and Environment Long-term Allergy; MAAS: Manchester Asthma and Allergy Study; PIAMA: Prevention and Incidence of Asthma and Mite Allergy; SAR: seasonal allergic rhinitis

Table VI.B-2. Evidence for the effects of pollen allergen exposure (*in utero* and early childhood exposure) on the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Type of exposure	Conclusion
Erbas et al[481]	2013	2b	Prospective birth cohort	620 children (6-7 years old) from MACS RCT (with at least one 1st degree family member with a history of eczema, asthma, hay fever, severe food allergy)	Pollen exposure* during infancy (at 3-6 months).	Risk factor for hay fever (OR 1.1, CI 1.01-1.3).
Kihlström et al[519]	2002	3b	Cross-sectional	583 children with atopic heredity (4-5 years old)	High-dose exposure to birch pollen at 0-3 months	No association to allergic rhinoconjunctivitis (OR 1.0, CI 0.6-1.8).
					High-dose exposure to birch pollen at 1 year	No association to allergic rhinoconjunctivitis (OR 1.3, CI 0.8-2.2)

*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).
Odds ratios are adjusted and reported with 95% confidence intervals in parentheses.
LOE: level of evidence; MACS: Melbourne Atopy Cohort Study; RCT: randomized controlled trial; OR: odds ratio; CI: 95% confidence interval

Table VI.B-3. Evidence for the effects of pet dander exposure (*in utero* and early childhood exposure) on the development of allergic rhinitis*

Study	Year	LOE	Study design	Study groups	Type of exposure	Conclusion
Early exposure to animal danders as a protective factor for AR (Level 2b studies listed. Level 3b studies referenced.[522,523,525-528,530,533,535])						
Lodge et al[534]	2012	2b	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, CI 0.5-1.02). Stronger protective effects if children of non-sensitized fathers (OR cats alone 0.3, CI 0.2-0.8); (OR cats or dogs 0.4, CI 0.2-0.8).
Alm et al[531]	2011	2b	Prospective birth cohort	4,465 children (4½ years old); 246 children with current AR	Exposure to cats at 1 year	Protective factor for AR (unadjusted OR 0.5, CI 0.4-0.8, not significant in multivariate analysis).
Lampi et al[532]	2011	2b	Prospective birth cohort	5,509 adults (31 years old)	Exposure to farm animals (cows, pigs, sheep, poultry, minks)	Borderline protective factor for AR ever (OR 0.9, CI 0.7-1.03).
					Exposure to cats or dogs at age less than 7 years old	Borderline protective factor for AR (OR cat 0.8, CI 0.7-0.96); (OR dog 0.9, CI 0.8-1.01).

Perzanowski et al[529]	2008	2b	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, CI 0.2-0.9).
Nafstad et al[524]	2001	2b	Birth cohort	2,531 children (4 years old)	Exposure to cats at birth	Borderline protective factor for AR (OR 0.5, CI 0.2-1.4).
					Exposure to dogs at birth	Borderline protective factor for AR to grass/pollen (OR 0.8, CI 0.4-1.6).
Early exposure to animal dander as a risk factor for AR (All studies Level 3b.[523,530,536-542])						
Early exposure to animal dander is not associated with AR (Level 2b studies listed. Level 3b studies referenced.[528,530,536,538,539,543-546,548,551,553,554])						
Schoos et al[518]	2016	2b	Prospective birth cohort	399 children (7-13 years old) from COPSAC study	Prenatal (at 3rd trimester of pregnancy) and perinatal (at 1 year) cat exposure	No association with AR at 7 years old (OR prenatal 0.4, CI 0.06-3.6); (OR perinatal) 0.9, CI 0.2-3.9).
					Prenatal (at 3rd trimester of pregnancy) and perinatal (at 1 year) dog exposure	No association with AR (OR prenatal, AR at 13 years old 0.9, CI 0.2-4.3); (OR perinatal, AR at 7 years old 0.9, CI 0.1-7.4).
Illi et al[517]	2014	2b	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)	No association with current AR (OR not reported as value, only in figure).
Lodrup-Carlsen et al[552]	2012	2b	Prospective birth cohort	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, CI 0.8-1.3); (OR dog only 0.8, CI 0.6-1.1); (OR cat and dog only 0.8, CI 0.4-1.4); (OR bird only 1.3, CI 0.9 -1.8); (OR rodent only 0.8, CI 0.5-1.5).
Kellberger et al[550]	2012	2b	Prospective population-based cohort	2,810 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.

Sandini et al[549]	2011	2b	Prospective birth cohort, RCT	1,223 children (5 years old) born to allergic families, who participated in a RCT	Dog/cat at home at 0-2 years old or 0-5 years old	No association with AR (OR 0.98, CI 0.5-1.8).
Lampi et al[532]	2011	2b	Prospective birth cohort	5,509 adults (31 years old)	Maternal work with farm animals (cows, pigs, sheep, poultry, minks) during pregnancy	No association with AR (OR 0.9, CI 0.7-1.2).
Marinho et al[520]	2007	2b	Whole-population birth cohort	815 children (5 years old) from MAAS study	Cat and dog 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 1.02, CI 0.9-1.1); (unadjusted OR dog 1.03, CI 0.9-1.2).
Chen et al[547]	2007	2b	Prospective birth cohort	2,166 children (4-6 years old) (hay fever: 66 /1,599) from LISA study	Cat allergen exposure at 3 mos (measured as Fel d 1 levels from children's or parents' mattress)	No association with doctor-diagnosed hay fever (OR parents' mattress 0.9, CI 0.5-1.5); (OR children's mattress 0.7, 0.4-1.1).
Nafstad et al[524]	2001	2b	Birth cohort	2,531 children (4 years old)	Cat keeping at birth	No association with AR (OR 0.5, CI 0.2-1.4).
					Dog keeping at birth	No association with AR to grass/pollen (OR 0.8, CI 0.4-1.6).
Kulig et al[468]	2000	2b	Prospective birth cohort	587 children (7 years old) from MAAS	Cat (Fel d 1) exposure at 0-18 months (measured as allergen levels obtained from carpet dust samples)	No association with SAR (OR not reported).
					Pets in household (at 18 months)	No association with SAR (OR not reported).

*Level 2b studies are listed in the table. Level 3b studies are referenced.

All odds ratio (OR) are adjusted unless differently specified and are reported with 95% confidence intervals in parentheses

LOE: level of evidence; AR: allergic rhinitis; OR: odds ratio; CI: confidence interval; COPSAC: Copenhagen Prospective Study on Asthma in Childhood; PAULA: Perinatal Asthma and Environment Long-term Allergy; RCT: randomized controlled trial; MAAS; Manchester Asthma and Allergy Study; LISA: Lifestyle-Immune-System-Allergy; SAR: seasonal allergic rhinitis

Table VI.B-4. Evidence for the effects of fungal allergens exposure (*in utero* and early childhood exposure) on the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Type of exposure	Conclusion
Early exposure to fungal allergens as a risk factor for AR						
Thacher et al[559]	2016	2b	Birth cohort	3,798 adolescents (16 years old) from BAMSE study; 785 with AR	Visible mold at 2 months	Risk factor for AR (OR 1.3, CI 1.04-1.6).
Stark et al[555]	2005	2b	Birth cohort	405 children of asthmatic/allergic parents from metropolitan Boston, Massachusetts (younger than 5 years old)	Exposure to high levels of dust-borne *Aspergillus* at 0-3 months	Risk factor for doctor-diagnosed AR at 0-5 years (HR: 3.3, CI 1.5-7.1).
					Exposure to high levels of dust-borne *Aureobasidium a*t 0-3 months	Risk factor for doctor-diagnosed AR at 0-5 years (HR: 3.0, CI 1.3-6.9).
					Exposure to high levels of dust-borne yeasts at 0-3 months	Risk factor for doctor-diagnosed AR at 0-5 years (HR 2.7, CI 1.3-5.7).
Deng et al[557]	2016	3b	Cross-sectional	2,598 children (3-6 years old) attending kindergarten	Prenatal (whole pregnancy) or postnatal (from birth to the current) exposure to indoor mold/dampness	Risk factors for rhinitis-like current symptoms: prenatal (OR 1.5, CI 1.2-1.9); postnatal (OR 2.1, CI 1.6-2.8).
Lin et al[558]	2016	3b	Cross-sectional	4,246 children (3-8 years old) from 18 day cares	Visible indoor mold (weekly/sometimes vs. never) at 0-2 years	Risk factor for new onset of rhinitis symptoms (OR 1.3, CI 1.01-1.6). Exposure was a significant risk factor for the remission of rhinitis (OR 0.6, CI 0.3-0.9).
Lam et al[553]	2014	3b	Cross-sectional	508 preschool children (4-6 years old)	Exposure to moisture/mold <1 year	Risk factor for rhinoconjunctivitis (OR 2.1, CI 1.2-3.8).
Kim et al[551]	2012	3b	Cross-sectional	4,554 schoolchildren (mean age 9.50 years old, SD 1.73)	Mold exposure in house during infancy	Risk factor for current AR (OR 1.8, CI 1.4-2.4).
Lombardi et al[538]	2010	3b	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, CI 1.2-1.6).
Ibargoyen-Roteta et al[527]	2007	3b	Cross-sectional	3,360 schoolchildren (5-8 years old)	Having mold on walls at 0-1 year	Risk factor for allergic rhinoconjunctivitis (OR 2.5, CI 1.5-4.0).

Kuyucu et al[556]	2006	3b	Cross-sectional	2,774 children (9-11 years old)	Dampness/mold at 1 year	Risk factor for AR (OR 1.7, CI 1.3-2.3).
Bornehag et al[560]	2005	3b	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, CI 1.4-5.4).
Early exposure to fungal allergens is not associated with AR						
Biagini et al[465]	2006	2b	Cross-sectional	585 infants (1 year) born to families with at least one parent with positive SPT	High mold exposure (mold in one room ($\geq$0.2 m^2 or a combined area of visible mold and water damage on the same surface $\geq$0.2 m^2) during early infancy (average 7.5 months)	No association with AR (OR 1.2, CI 0.6-2.5).
					Low mold exposure (mold in one room (<0.2 m^2 or a combined area of visible mold and water damage on the same surface <0.2 m^2) during early infancy (average 7.5	No association with AR (OR 3.2, CI 0.7-14.8).
Deng et al[557]	2016	3b	Cross-sectional	2,598 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, CI 0.4-1.1), postnasal (OR 1.0, CI 0.6-1.7).
Yang et al[542]	2014	3b	Cross-sectional	7,389 schoolchildren (mean age 13.9 years, SD 0.9)	Mold exposure during infancy	No association with AR (OR 0.99, CI 0.8-1.3).

1 Odds ratio are adjusted unless otherwise specified.
2 LOE: level of evidence; AR: allergic rhinitis; BAMSE: Barn/Child Allergy Milieu Stockholm Epidemiology; OR: odds ratio, CI: 95% confidence interval; HR: hazard
3 ratio; SD: standard deviation; SIDRIA-2: StudiItaliani sui Disturbi Respiratori del l'Infanzia el Ambiente; SPT: skin prick test
4

VI. C. Food allergens (*in utero* and early childhood exposure)

In some studies, early sensitization to food allergens has been linked to the development of AR in childhood.[468,564,565] A meta-analyses by Alduraywish et al demonstrated that food sensitization in the first 2 years of life was associated with an increased risk of AR during childhood (OR=3.0, 95% CI=2.1-4.2).[564] **[Table VI.C.]** The relationship between sensitization to food allergens and the subsequent development of AR during childhood has been investigated in both population-based and high-risk cohorts.[468,565-568] While there is a statistically significant correlation in the high-risk cohort[567], there are mixed results in the population-based studies.[566,568,569] These findings prompted prospective investigation of the effects of allergen avoidance *in utero* and during early childhood.

In a RCT evaluating the effects of *in utero* exposure to food antigens and the development of AR, 162 high-risk pregnant women (history of respiratory allergy to animal danders and/or pollens) were randomized one of two diets during the last 3 months of pregnancy: either very low ingestion of hen's egg and cow's milk, or a daily ingestion of one hen's egg and 1 [liter] of cow's milk. One hundred and sixty-three infants were followed prospectively up to 18 months of age, at which time the incidence of atopic disease, including AR, was evaluated in a blinded fashion. There was no significant difference in the incidence of AR between the two groups.[570] In another RCT, restricted diet during pregnancy (cow's milk- and egg-free diet from week 28 to delivery) was associated with a small but statistically significant lower mean gestational weight gain and did not protect the offspring from atopy.[571] The pooled results of two trials suggest that maternal food antigen avoidance may be associated with a higher risk of preterm birth and a possible adverse effect on mean birthweight without beneficial effects on AR development in the children.[570,571]

Studies have also evaluated the early introduction of foods compared to food avoidance with respect to the effects on development of allergic disease. In a prospective birth cohort study 2,073 children, delayed introduction of solids (past 4 or 6 months of age) was not associated with decreased odds for AR, asthma, or sensitization against food or inhalant allergens at 6 years of age. In fact, food sensitization occurred more frequently in children who were introduced to solids later.[572] In a prospective, RCT of food allergen avoidance in infancy, the incidence of subsequent allergic disease, including AR, was assessed. The intervention arm of the trial required mothers to avoid cow's milk, egg, and peanut during the last trimester of pregnancy and subsequent lactation, and required infants to avoid cow's milk until age 1 year (casein hydrolysate supplementation before age 1), egg until age 2 years, and peanut and fish until age 3 years. Compared to maternal-infant control pairs who followed standard feeding practices, infants in the food-avoidance arm showed a significant reduction in rates food allergy and milk sensitization before age 2 years. However, by the age of 7, the prevalence of food allergy was no longer different between the two groups. Furthermore, there was no difference in rates of AR, AD, asthma, and other atopic disease at age 7.[573]

Based on the presented meta-analysis, prospective randomized studies, and a large prospective birth cohort study, there is no data to support maternal diet as a contributing factor for the development of food allergy and AR; however, there is some evidence that the presence of food allergy during childhood (greater than 2-years-old) is a risk factor for AR.

- Aggregate Grade of Evidence: A (Level 1b: 3 studies; Level 2a: 1 study; Level 2b: 1 study; *Table VI.C.*)

Table VI.C. Evidence for the effects of food allergen exposure (*in utero* and early childhood exposure) on the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Zeiger et al[573]	1995	1b	RCT	1. infants whose mothers avoided cow's milk, egg, and peanut in the last trimester of pregnancy and lactation and who themselves avoided cow's milk until age 1 year (casein hydrolysate supplementation before age 1), egg until age 2 years, and peanut and fish until age 3 years 2. standard feeding practices	Food allergy, atopic dermatitis, AR, asthma, any atopic disease, lung function, food or aeroallergen sensitization, serum IgE level, presence of nasal eosinophils or basophilic cells at age 7.	No significant difference between treatment groups, though children with food allergy by 4-years had a higher 7-year prevalence of AR and asthma.
Lilja et al[570]	1989	1b	RCT	Women with respiratory allergy to animal danders and/or pollens in the last 3 months of pregnancy randomized to: 1. very low ingestion of egg and cows' milk 2. daily ingestion of egg and cows' milk.	Incidence of atopic diseases at 18 months of age	No significant difference in the distribution of atopic disease in relation to the maternal diet during late pregnancy.
Falth-Magnusson et al[571]	1987	1b	RCT	1. strictly cow's milk- and egg-free diet from week 28 to delivery 2. normal diet including cow's milk and egg	Skin prick, serum IgE, atopic manifestations (not AR)	Maternal elimination diet during late pregnancy does not protect the baby against atopy. Maternal elimination diet during late pregnancy is associated with low weight gain and preterm birth.
Aldurayw ish et al[564]	2016	2a	Meta-analysis		Asthma, AR, eczema or sensitization against food allergens	Food sensitization in the first 2 years of life can identify children at high risk of subsequent allergic disease, including AR.
Zutavern et al[572]	2008	2b	Population-based, prospective birth cohort study		Asthma, AR, eczema or sensitization against food or inhalant allergens	No evidence supporting a delayed introduction of solids beyond 4-6 months.

LOE: level of evidence; RCT: randomized controlled trial; AR: allergic rhinitis; IgE: immunoglobulin E;

VI. D. Pollution

The relationship between pollution and AR has received increasing attention over the past decade. Environmental air pollutants contain several compounds; however, most studies have primarily focused on particulate matter <10 microns (PM_{10}), particulate matter <2.5 microns ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3). These particles may potentiate atopy through multiple mechanisms, including injuring the nasal epithelium, altering the immune response, and increasing the allergenicity of certain antigens.[574,575] For example, pollution may damage the nasal mucosa and impair MCC, thereby facilitating the access of inhaled allergens to cells of the immune system.[576] Additionally, airborne particles, including diesel fuel exhaust, are also able to carry allergens, thus potentially increasing the spread of allergens or the duration of their exposure.[574] In nasal provocation studies of HDM-sensitive individuals, a combined nasal challenge with HDM allergens and diesel exhaust particles led to enhanced mast cell degranulation and increased severity of rhinitis symptoms compared to a challenge with HDM alone.[577]

Numerous studies have examined the effects of air pollutants on the development of AR in both pediatric and adult patients. **[Table VI.D.]** However, three prospective cohort studies (the highest level of evidence identified for this topic) found no significant correlation.[578-580] Codispoti et al[578] specifically looked at the relationship between exposure to diesel exhaust particles (DEP) at 1 year of age and the subsequent development of AR at 2, 3, and 4 years of age. While they found that DEP had a marginally positive association with aeroallergen sensitization at 2 and 3 years, and increased aeroallergen sensitization increased the risk of AR, they failed to identify a significant direct correlation between DEP and AR development. Additionally, Kim et al[579] evaluated exposure to NO_2, SO_2, CO, and PM_{10} in children and found no significant association with a new diagnosis of AR after 2 years. However, they did note a positive association between increased levels of O_3 and an AR diagnosis in industrial areas only; O_3 was also significantly associated with the development of new sensitizations to outdoor allergens, which may explain the mechanism for the related increase in AR prevalence. Finally, Gehring et al[580] pooled 4 prospective pediatric birth cohort studies with 14-16 year follow-up and found no indication that NO_2, $PM_{2.5}$, or PM_{10} levels influenced the development of rhinoconjunctivitis.

Several international case-control and cross-sectional studies have also evaluated the relationship between pollution and AR with varied results. Anderson et al[581] performed the largest cross-sectional study evaluating the effect of PM_{10} levels on the development of rhinoconjunctivitis in 322,529 children from 51 countries. There was no between-country association of rhinitis with modelled pollution levels, and within countries (24 countries had more than one study center) there were weakly positive associations between PM_{10} levels and rhinoconjunctivitis symptoms in 6-7 year olds and diagnosed hay fever in 13-14 year olds. Interestingly, they did show a positive association between high PM_{10} levels and the development of atopy.[581] Some pediatric studies have identified a positive correlation between increased exposure to various pollutants and an increased diagnosis of AR during childhood.[476,557,582-589] Liu et al[586] and Deng et al[557] even found that prenatal/gestational exposure to high concentrations of NO_2 were associated with a higher prevalence of AR diagnosis during childhood. However, almost all of these studies utilize nearby traffic density or home address geocodes to estimate local pollution exposure. In many countries, people living in more polluted areas with high levels of traffic may also be more likely to have other confounding features that influence their development of

AR (i.e. SES, exposure to different aeroallergens) and not all studies fully adjust for these potential confounders. Additionally, several of these studies were restricted to specific cities in Asia, in turn, limiting generalizability.

Overall, the relationship between pollution exposure and the development AR is currently unclear. More prospective pediatric and adult studies in diverse geographic locations are needed to better understand this complex relationship.

- Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 3b: 2 studies; Level 4: 9 studies; *Table VI.D.*)

Table VI.D. Evidence for the effects of pollution exposure on the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Codispoti et al[578]	2015	2b	Prospective cohort	DEP exposure at 1 year: 1. $\geq 66^{th}$ percentile 2. $<66^{th}$ percentile	Development of AR by age 4	High DEP exposure did not correlate with the development of AR.
Gehring et al[580]	2015	2b	Pooled prospective cohort	1. high exposure to NO_2, $PM_{2.5}$, PM_{10} 2. low exposure to air pollutants	Incidence and prevalence of rhinoconjunctivitis from age 4 to 14-16 years	No association between air pollution exposure and rhinoconjunctivitis incidence or prevalence at various ages.
Kim et al[579]	2011	2b	Prospective cohort	Concentrations of 5 air pollutants (NO_2, O_3, SO_2, CO, PM_{10}): 1. industrial area 2. metropolitan city	Development of AR in children over 2 years	Incidence of AR is not associated with air pollutants; however, there was a positive association between higher O_3 levels and AR in industrial areas.
Chiang et al[587]	2016	3b	Case-control study	Exposure to SO_2 over 11 years: 1. high exposure 2. low exposure	Diagnosis of AR in children	High exposure to SO_2 correlates with an increased diagnosis of AR.
Chung et al[588]	2016	3b	Case-control study	Exposure to 5 air pollutants (PM_{10}, NO_x, SO_2, CO, O_3): 1. high exposure 2. low exposure	Diagnosis of AR in preschool children	Pre-diagnosis levels of CO and NO_x were significantly related to AR diagnosis.
Singh et al[584]	2016	4	Cross-sectional	Frequent passage of trucks near home: 1. almost all day 2. less frequent	Diagnosis of AR in children ages 6-7 and 13-14	Frequent passage of trucks was correlated with the occurrence of AR in both age groups.
Wang et al[585]	2016	4	Cross-sectional	Exposure to 6 air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, O_3): 1. high exposure 2. low exposure	Diagnosis of AR in children	High levels of $PM_{2.5}$ correlate with an increased risk of AR.
Liu et al[586]	2016	4	Cross-sectional	Exposure to 3 air pollutants (PM_{10}, NO_2, SO_2): 1. high exposure 2. low exposure	Diagnosis of AR in children	High exposures to NO_2 during gestation, the first year of life, second year, and throughout life correlated with the development of AR.
Deng et al[557]	2016	4	Cross-sectional	Exposure to 3 air pollutants (PM_{10}, NO_2, SO_2): 1. high exposure 2. low exposure	Diagnosis of AR in kindergarten children	Prenatal exposure to high NO_2 correlated with AR; postnatal exposure to high PM_{10} correlated with AR.

Kim J et al[476]	2016	4	Cross-sectional	Exposure to 5 air pollutants (PM_{10}, NO_2, SO_2, CO, O_3): 1. high exposure 2. low exposure	Diagnosis of AR by the age of 6-7	Higher exposure to CO was associated with an increased lifetime prevalence of physician-diagnosed AR.
Kim HH et al[589]	2016	4	Cross-sectional	Exposure to 5 air pollutants (PM_{10}, NO_x, SO_2, BC, O_3): 1. high exposure 2. low exposure	AR treatment over the past 12 months in children	High exposure to BC, SO_2, and NO_2 were significantly associated with increased treatment of AR.
Jung et al[582]	2015	4	Cross-sectional	1. living less than 75 m from main road 2. living more than 75 m	Lifetime AR, past-year AR symptoms, diagnosed AR, and treated AR in children	Positive correlation between distance from main road and AR symptoms, diagnosis, and treatment.
Shirinde et al[583]	2015	4	Cross-sectional	1. trucks passing near residence almost all day 2. trucks passing less frequently	Diagnosis of AR in 13-14 year-old children	Diagnosis of AR is significantly associated with the frequency of trucks passing by the residence.
Anderson et al[581]	2010	4	Cross-sectional study	Exposure to PM_{10}: 1. high exposure 2. low exposure	Diagnosis of rhinoconjunctivitis at ages 6-7 and 13-14	Only significantly increased association between PM_{10} levels and rhinoconjunctivitis and atopy in 13-14 year olds in countries with more than one testing center.

LOE: level of evidence; DEP: diesel exhaust particles; AR: allergic rhinitis; NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter <2.5 microns; PM_{10}: particulate matter <10 microns; O_3: ozone; SO_2: sulfur dioxide; CO: carbon monoxide; NO_x: nitrogen oxides; BC: black carbon

VI. E. Tobacco smoke

AR has frequently been associated with both active and passive (secondhand) exposure to tobacco smoke. However, the pathophysiology behind this relationship is complex and, at times, contradictory. Studies have shown that tobacco smoke exposure can propagate the development of atopic diseases via several mechanisms including direct surface damage to nasal mucosa, altered epigenetic mechanisms through histone acetylation, expression of microRNA, and DNA methylation.[590,591] Alternatively, it has also been shown that nicotine may exert an immunosuppressive effect on allergic disease by suppressing eosinophil trafficking and Th2 cytokine/chemokine responses.[592]

Recently, two large meta-analyses were published which sought to better define the relationship between tobacco and AR. **[Table VI.E.]** Saulyte et al[593] identified a significant correlation between passive smoke exposure and the development of AR, but no significant relationship between active smoking or maternal prenatal passive smoke exposure and AR. However, they did find a significant correlation between active smoking and non-allergic/chronic rhinitis. Hur et al[594] also systematically evaluated the relationship between secondhand smoke and AR and that meta-analysis of studies in adults showed an association between passive smoke and AR, while a similar analysis of pediatric studies did not. This raises the possibility that the atopic effects of secondhand smoke in the nasal mucosa may take several years to manifest. In fact, Lin et al[595] found that allergic adults were more likely to have been exposed to secondhand smoke 20 years prior when compared to non-allergic adults.

Five prospective cohort studies examined the effect of tobacco on the development of AR, all of which failed to find a correlation between active or passive tobacco smoke and the development of AR.[596-600] Keil et al[596] found that while passive smoke was not significantly related to AR, it was strongly associated with allergic sensitization and asthma symptoms in children with a genetic predisposition (at least 1 or more atopic parents). Additionally, Wright et al[597] found that while there was no significant association between secondhand smoke exposure and AR, 63% of asthmatics born to heavy smokers developed rhinitis in the first 6 months, versus 43% of asthmatics whose mothers did not smoke. Finally, Bendtsen et al[598] found that actively smoking more than 15 cigarettes per day actually decreased a patient's risk of developing AR.

This inverse correlation has been identified in several other studies.[124,601-603] Eriksson et al[124] found that while smoking was associated with a high prevalence of chronic rhinitis in both men and women, it was correlated with a low prevalence of AR in men. Additionally, they found a significantly lower prevalence of sensitization to common airborne allergens in current and ex-smokers compared to nonsmokers. In contrast, the significant positive association between tobacco and the development of non-allergic/chronic rhinitis has been repeatedly identified.[124,128,604] Therefore, when discussing the effects of tobacco on rhinitis, differentiating between allergic and non-allergic/chronic is paramount.

Finally, tobacco does not appear to influence the efficacy of AR treatment. Katotomichaelakis et al[605] evaluated 163 patients (both smokers and non-smokers) receiving sublingual immunotherapy (SLIT) for AR and found that, regardless of tobacco status, total symptom scores and QOL questionnaires equally improved. Overall, while most studies evaluating AR and tobacco are case-control or cross-sectional in nature, multiple prospective cohort studies and two systematic reviews predominantly found no correlation between active or passive tobacco smoke and AR. Additionally, some studies

suggest that tobacco may have a protective effect against the development of AR. Further investigation is needed to identify if specific patient populations (e.g. asthmatics or those with atopic parents) or temporal variations (e.g. exposure for 20+ years) may alter our understanding of this relationship.

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 2b: 5 studies; Level 3a: 1 study; *Table VI.E.*)

Table VI.E. Evidence for the effect of active and passive tobacco smoke exposure on the development of allergic rhinitis

Study	Year	LOE	Study design	Active vs Passive Smoke Exposure	Study groups	Clinical endpoint	Conclusion
Saulyte et al[593]	2014	2a	SR of cohort, cross-sectional, and case-control studies	Both	1. active smoking 2. passive smoking 3. no active or passive smoking	Diagnosis of AR	No association between active smoking and maternal pre-natal passive smoking and AR. Significant association between all other passive smoking and AR.
Codispoti et al[599]	2010	2b	Prospective cohort study	Passive	1. environmental tobacco smoke exposure 2. no exposure	Diagnosis of AR by age 3	Environmental tobacco exposure has no effect on the development of AR by age 3.
Keil et al[596]	2009	2b	Prospective cohort study	Passive	Maternal smoking vs no smoke exposure with: 1. 2 allergic parents 2. 1 allergic parent 3. non-allergic parents	Diagnosis of AR over the first 10 years of life	There was no association between maternal smoking and the development of AR regardless of the allergic status of the parents.
Bendtsen et al[598]	2008	2b	Prospective cohort study	Active	1. current smoking 2. no current smoking	Self-reported SAR or PAR	Smoking more than 15 cigarettes/day was associated with a decreased risk of SAR.
Annesi-Maesano et al[600]	1997	2b	Prospective cohort study	Active	1. lifetime non-smokers 2. ex-smokers (>1 month) 3. current smokers	Chronic rhinitis, SAR, or perceived nasal hyper-responsiveness	No association between smoking and seasonal AR. Significant association between chronic rhinitis and current smoking.
Wright et al[597]	1994	2b	Prospective cohort study	Passive	1. maternal smoking 2. no smoking in the first year	Physician diagnosed AR at age 6	No significant association between maternal smoking and physician diagnosed AR
Hur et al[594]	2014	3a	SR of predominantly case-control studies	Passive	1. exposure to passive smoking 2. no exposure to passive smoking	Diagnosis of AR	Most studies did not show a relationship between passive smoke exposure and AR.

LOE: level of evidence; SR: systematic review; AR: allergic rhinitis; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis

VI. F. Socioeconomic factors

In 1829 John Bostock described 29 cases in the UK, including himself, of individuals who suffered from *catarrhus aestivus*, "summer cold" which he noted occurred in patients of middle to high socioeconomic status (SES).[606] During the 1870s, Blackley found no hay fever among farmers and people living in deprived areas of cities.[606] The positive association between hay fever and high social class was later reported in the British 1958 and 1970 cohorts,[607,608] as well as a Swedish survey of conscripts born from 1952 to 1977.[609] However, during the study period, this association seemed to weaken with an OR estimate for AR among subjects with low SES changing from 0.79 to 0.92.

In 2000, a paper was published from the German MAS (Multicentre Allergy Study) birth cohort including 1,314 children born in 1990.[610] In this study, it was found that the lifetime prevalence of hay fever was elevated in parents of high SES compared to low. However, in their children, the occurrence of hay fever was not elevated in families with high SES. Alternatively, in the Swedish birth cohort BAMSE (Swedish abbreviation for Children Allergy, Milieu, Stockholm, Epidemiology) with 4,089 children born between 1994-1996, it was noted that high SES actually resulted in a decreased risk of AR, along with decreases in asthma and food sensitization rates.[611] In a recent study from Denmark of 9,720 children born between 1994 and 2006, AR was associated with low educational level of the parents.[612] Interestingly, in the follow up of the German MAS birth cohort study, SES was not associated with AR at all by the age of 20 years.[613] Thus, among children born in the Western world before 1970 high SES was a risk factor, but among children born in the same regions after 1990 low SES, particularly early in life, seemed to be a risk factor.[614] **[Table VI.F.]**

More recently, two studies from Korea have reconfirmed the previously noted association between high SES and the development of AR. Ahn et al[478] found a positive association between higher family income and symptom-based AR diagnosis (but not allergy test based AR diagnosis). Lee et al[615] also found family affluence, or high SES, to be a significant risk factor for AR in Korean adolescents. However, additional recent studies from South America and Europe have shown varying results. In 2016, Penaranda et al[616] found high SES to be associated with AR in children/adolescents but not in adults, while Wronka et al[617] identified a significantly higher incidence of AR in adult female university students (19-25 years old) from families with high SES.

Overall, SES is likely a proxy for various exposures like number of siblings, viral infections, exposure to tobacco smoke, housing conditions and location, allergen exposures, dietary factors, and nutrition including breastfeeding and general diet. Some of those exposures are associated with the hygiene hypothesis, introduced by Strachan in the late 1980s.[618] However, It is worth noting that exposures relevant to the hygiene hypothesis were important predictors for the development of AR at an early age.[614]

Currently, there is conflicting evidence regarding the association between SES and AR. While most studies show an association between high SES and the diagnosis of AR, this is not a consistent outcome. This disparity may be explained by the additional factors evaluated in several of these studies which may confound the exact relationship between SES and AR. Additionally, there may be a temporal relationship between SES and AR considering different outcomes in children compared to adults. Additional investigation is needed to determine the true relationship between AR and SES.

- Aggregate Grade of Evidence: C (Level 2b: 4 studies; Level 4: 6 studies; *Table VI.F.*)

Table VI.F. Evidence for the association between allergic rhinitis and socioeconomic factors

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Grabenhenrich et al[613]	2015	2b	Prospective cohort	Parental SES: 1. rich 2. average 3. poor	Diagnosis of AR by age 20	No association between SES and diagnosis of AR.
Almqvist et al[611]	2005	2b	Prospective cohort	Parental SES: 1. blue-collar workers 2. low/intermediate white collar 3. one high level white collar 4. two high level white collar	Diagnosis of AR at 4 years old	Parents of higher SES had children with a lower risk of AR, asthma, and food allergens.
Bergmann et al[610]	2000	2b	Prospective cohort	Parental SES: 1. high 2. middle 3. low	Diagnosis of AR parents and in children 3-6 years old	Parental high SES correlated to high AR rates in parents; however, SES had no correlation with AR in children 3-6 years old.
Lewis & Britton[608]	1998	2b	Prospective cohort	Level of "social advantage": 1. most disadvantaged 2. disadvantaged 3. average 4. advantaged 5. most advantaged	Diagnosis of hay fever at ages 5, 10, and 16	Social advantage was significantly related to the diagnosis of AR with the "most advantaged" having the highest prevalence of AR.
Ahn et al[478]	2016	4	Cross-sectional survey	SES: 1. greater than average income 2. less than average income	1. symptom-based AR 2. allergy test-based AR	Significant association between higher SES and symptom-based AR; but no association between SES and allergy test-based AR.
Lee et al[615]	2016	4	Cross-sectional survey	Family Affluence Scale: 1. low 2. middle 3. high	Diagnosis of AR in adolescents	High Family Affluence Scale was associated with higher prevalence of AR.
Penaranda et al[616]	2016	4	Cross-sectional survey	SES: 1. low 2. middle 3. high	Diagnosis of AR in children and adults	Middle and high SES was associated with increased AR symptoms in children but not in adults.
Wronka et al[617]	2016	4	Cross-sectional survey	SES: 1. high 2. low	Diagnosis of AR in university students (ages 19-25)	Higher proportion of AR in students from high SES compared to low.

Hammer-Helmich et al[612]	2014	4	Cross-sectional survey	Parental SES	Diagnosis of AR in children 11-15 and 3-6 years old	No association between household income and diagnosis of AR.
Braback et al[609]	2005	4	Cross-sectional study	High vs low SES	Diagnosis of AR upon enrollment in military service	In the 1950s, low SES and AR were inversely related, but this association significantly decreased by 1970.

1 LOE: level of evidence; SES: socioeconomic status; AR: allergic rhinitis

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VI. G. Protective factors

VI. G. 1. Breastfeeding

Breastfeeding is associated with several beneficial effects on mother and child health and therefore has been recommended for all infants.[619] One potential benefit is the prevention of allergic disease.[620] Breast milk is an immunologically complex solution, containing multiple compounds that support infant growth and facilitate development of the infant immune response.[621,622] The association between breastfeeding and the prevention of allergic disease has been frequently studied and often debated.

Mimouni Bloch et al[623] performed a meta-analysis of prospective studies evaluating the effects of exclusive breastfeeding for the first 3 months of life on the development of AR. **[Table VI.G.1.]** Six prospective studies met the inclusion criteria. In their pooled analysis, they found a protective effect of exclusive breastfeeding for the first 3 months of life that approached statistical significance in the general population (OR 0.74; 95% CI 0.54-1.01). Interestingly, the protective effect was not seen in children with a family history of atopic disease (OR 0.87; 95% CI 0.48-1.58).

More recently, Lodge et al[624] performed a systematic review and meta-analysis in 2015. Their analysis evaluated the association between breastfeeding and AR and included 5 cohort studies[550,599,607,625,626] and 11 cross-sectional studies.[627-637] The number of participants varied between 361 and 13,889 for the cohorts, and 1,402 to 206,453 for the cross-sectional studies. Pooling of estimates from the various studies found a non-significant protective effect of breastfeeding on the development of AR (OR 0.92; 95% CI 0.84-1.01). The results were then stratified by incidence of AR in different age groups. After stratification by age, a reduced risk of AR in patients under 5 years of age was associated with breastfeeding (OR 0.79; 95% CI 0.63-0.98). However, there was no association after 5 years of age (OR 1.05; 95% CI 0.99-1.12). While the authors of this meta-analysis argued for the benefit of breastfeeding in the prevention of AR, they do acknowledge that the protective effect of breastfeeding seen in patients less than 5 years of age may have been confounded by known protective effects of breast milk against viral respiratory infections. The authors hypothesized that, given the difficulty of differentiating between AR and viral rhinitis in young children, a reduction in viral respiratory infections have been possibly interpreted as a reduction in rhinitis symptoms.[624]

- Aggregate Grade of Evidence: C (Level 3a: 2 studies; *Table VI.G.1.*)
- Benefit: Possible benefit from breastfeeding with reduction in AR, especially seen in young children.
- Harm: None. No studies have shown harm with breastfeeding for 6 months.
- Cost: Low.
- Benefits-Harm Assessment: Possible benefit with no harm.
- Value Judgments: There is evidence that breastfeeding may reduce the risk of AR with no perceived harm. Given the general benefits to the mother and child, breastfeeding for 4 months and possibly 6 months had been advocated.
- Policy Level: Option for breastfeeding for the specific purpose of AR prevention, based upon current evidence. In general, breastfeeding has been strongly recommended due to its multiple benefits.

- Intervention: Breastfeeding is generally encouraged for at least 4 months due to its multiple benefits. When specifically related to the prevention of AR, breastfeeding is an option.

Table VI.G.1. Evidence for the effects of breastfeeding on the development of allergic rhinitis*

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Mimouni Bloch et al[623]	2002	3a	SR	Prospective studies evaluating the effects of exclusive breastfeeding for the first 3 months on AR development	Development of AR	Protective effect close to statistical significance in the general population but not in children with a family history of atopic disease.
Lodge et al[624]	2015	3a	SR	Association between breastfeeding and AR	Development of AR	Non-significant protective effect overall. Protective benefit for children under 5, but not over 5.

*The systematic reviews presented above include all published studies to date.

LOE: level of evidence; SR: systematic review; AR: allergic rhinitis

VI. G. 2. Childhood exposure to pets

Among subjects sensitized to pet allergens, exposure tends to exacerbate symptoms. However, the association of pet-keeping in childhood with the subsequent development of AR is more controversial, and difficult to establish. *(See Section VI.B.3. Risk Factors for Allergic Rhinitis – Pets for additional information on this topic.)*

Prevalence of household pet ownership is used to estimate pet allergen exposure. However, pet owners are frequently contaminated with pet allergens, leading to generalized exposures via social contact. Therefore, a non-exposed reference population does not exist, limiting our ability to clearly understand the relationship between exposure to pet allergens and development of AR.

The timing of pet allergen exposure early in life may be an important factor for the maturing immune system. Therefore, self-reported perinatal and newborn exposures are frequently analyzed. Few studies have measured the concentration of the major cat allergen (Fel d 1) or the major dog allergen (Can f 1) in home dust. Rather, most studies merely report exposure to cats and/or dogs, or furred pets, and some to rodents and birds. In a systemic review of epidemiologic studies of allergy and asthma, only 10 of 96 included studies reported avoidance of pets.[638] Additionally, studies may often fail to account for confounding variables such as a family history of pet allergy which, in turn, may predispose likely atopic children to pet avoidance.

There is significant inconsistency with regards to pet ownership in childhood and the subsequent development of allergy. Demographic features related to pet-keeping, including race, urban vs. rural environment, family size, and SES may help account for some of the conflicting results. A meta-analysis of thirty-two studies reported a lower prevalence of AR among subjects with furred pets in cross-sectional studies, and less asthma among cat-exposed subjects.[639] An extensive systematic review of 62 studies found different associations depending on study design.[640] In most of the birth cohort studies, dog exposure in early childhood was protective for sensitization against aeroallergens.[640,641] On the contrary, cross-sectional studies reported inconsistent associations between cat or dog exposure and sensitization as well as the subsequent development of atopic diseases later in life.[562,640] **[Table VI.G.2.]**

The impact of pet avoidance on AR development is best evaluated via longitudinal birth cohort studies. A systematic review of nine studies conducted solely in urban environments evaluated perinatal pet exposure.[642] Six studies found that exposure to dogs, or cats/dogs protected against allergic disease. Two studies found increased risk of allergy only in highly atopic families. Furthermore, in a cohort of 620 children with family history of allergic diseases, exposure to cats or dogs was protective only in children with non-allergic fathers.[534]

In a pooled analysis of 11 European birth cohorts, any furred pet ownership during the first two years was associated with lower risk of sensitization to aeroallergens, but not with a decreased prevalence of AR later in childhood.[552] In a recent study which investigated urban vs rural differences, the risk of AR in adulthood was 20% lower in subjects exposed to pets at birth or during childhood. However, pet keeping did not explain the protective effect of living on farm with livestock compared to urban dwelling.[643]

Overall, pet allergens are ubiquitous. There is no evidence that pet avoidance in childhood prevents the development of AR or sensitization to aeroallergens later in life. Alternatively, early pet

exposure may induce immune tolerance and thus reduce the chance of development of allergic disease. This protective effect seems to be strongest in non-allergic families with dog exposure in early childhood.

- Aggregate Grade of Evidence: C (Level 2a: 6 studies; Level 2b: 2 studies; *Table VI.G.2.*)

Table VI.G.2. Evidence for the effect of early childhood pet exposure of the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Smallwood and Ownby[641]	2012	2a	SR	26 articles. Exposure to dogs 20 weeks from gestation to one year.	Association of allergic symptoms with exposure to dogs	Inconsistent association. Dog exposure at birth may be protective against allergic symptoms.
Dharmage et al[562]	2012	2a	SR	19 studies (2011-2012): 9 longitudinal, 8 cross-sectional, 2 case-control	Association of AR with exposure to cats	Inconsistent association. If exposure during the first year, less AR or sensitization, or no effect. Possible protective effect until adulthood.
Lodge et al[642]	2012	2a	SR	(2001-2008) 9 longitudinal studies 6498 subjects aged 0-11 years	Association of physician diagnosed hay fever with exposure to pets, or cats and dogs during perinatal period in urban environment	Dogs may reduce sensitization or allergic disease in families with low risk of allergy. No association with cats.
Lodrup-Carlsen et al[552]	2012	2a	Pooled analysis of individual data first year of recruitment	(1989-1997) 11 European birth cohorts, 11,489 participants aged 6-10 years	Association of sensitization to aeroallergens with ownership of cats only, dogs only, cats and dogs only, birds only or rodents only during 0-2 years of age	Dog and rodent exposure protective against sensitization to aeroallergens. No association with AR.
Chen et al[640]	2010	2a	SR of birth and non-birth cohort studies and cross-sectional studies	62 articles (2000-2009): Subjects 6-69 years old 1. 17 birth cohorts reported cat exposure or Fel d 1 in dust 2. 13 reported dog ownership or Can f 1 in dust 3. 26 cross-sectional studies reported cat or dog exposure	Association of AR with exposure to cats or dogs in cross-sectional studies	Inconsistent association. Dog exposure may be protective. Design of the study influences the association.
Takkouche et al[639]	2008	2a	Meta-analysis	32 studies (1985-2006); 5 studies (n=6818) reported rhinitis	Association of AR with exposure to furred pets	Inconsistent association. Possible protective effect of furred pets on rhinitis.
Christensen et al[643]	2016	2b	Population based cross-sectional study follow up	RHINE cohort (2010-2012): 13,376 subjects born in Northern Europe 1945-1973	Association of AR in adulthood with exposure to pets at birth, during childhood and to livestock farm in childhood	Exposure to pets in childhood decreases the risk of AR in adulthood independently of urban or rural upbringing.

Lodge et al[534]	2012	2b	Prospective birth cohort	MACS cohort 620 infants with family history of allergic disease	Association of hay fever after 7 years of age with exposure to cats and dogs at birth	In high risk cohort, pet exposure at birth is protective against hay fever at age 7 in children with non-sensitized fathers

LOE: level of evidence; SR: systematic review; AR: allergic rhinitis; RHINE: Respiratory Health in Northern Europe; MACS: Melbourne Atopy Cohort Study

VI. G. 3. Hygiene (aka. Biodiversity or Microflora) hypothesis

The inverse association of the number of siblings and the prevalence of hay fever was reported nearly three decades ago in British cohorts.[618] Strachan proposed the term "hygiene hypothesis" and speculated that exposure to frequent infections in large families could be the protective factor. The hygiene hypothesis has evolved towards a more contemporary "biodiversity hypothesis" that looks beyond the effect of infections and single protective microbes to the potential protective effect of the colonization of mucous membranes and the skin with diverse environmental microflora.[644] Recently, the term "Microbiota hypothesis" has been proposed. In addition, the term "microflora" should be substituted for the term "microbiota". Various related potential co-factors and their relationship to the development of AR are discussed this this section.

Number of siblings. The association between number of siblings and presence of allergic diseases has been studied extensively. In a meta-analysis of 53 studies, 48 studies demonstrated that higher number of siblings was associated with decreased atopy, an effect that was more evident for AR than for sensitization and asthma.[645] **[Table VI.G.3.]** A large study based on questionnaire data for children aged 6-7 years from 31 countries and 13-14 years from 52 countries confirmed that the inverse association between the number of older siblings and prevalence of hay fever was strongest in more affluent countries.[646]

Farming. Since the first publications in 1999-2000, there is a growing interest in the "farm effect" on allergy. In a meta-analysis of eight studies, the risk of sensitization, measured by sIgE or SPT in childhood or adulthood, was 40% lower (OR 0.60, 95% CI 0.52-0.70) among subjects who had lived on a farm during the first year of life.[647] In a recent US case-control study, farm exposure *in utero* and in early childhood protected against allergen sensitization but not asthma in adulthood.[648] The protective farm effect seems to be stronger when exposed to farm animals and stables.[522,649-655] The protective effect is greatest with highest exposure occurring early in life.[650]

Bacterial endotoxin. Exposure to bacterial endotoxin has been studied as a possible protective factor. Inverse association between exposure to endotoxin in infancy and childhood and the development of allergic sensitization has been shown in rural and urban environments, but the results have not been uniform between the studies.[656,657]

Probiotics. A meta-analysis of 29 randomized controlled studies showed no significant association of probiotics supplementation of pregnant or breastfeeding mothers or infants with sensitization or allergic rhinitis at age 12 to 36 months.[658] *(See Section IX.B.9. Management – Pharmacotherapy – Probiotics for additional information on this topic.)*

Microbial diversity. Changes in lifestyle, urbanization, diet and the use of antibiotics have changed the microbiota of the environment, human skin and mucosal membranes. Differences in the microbiota may explain the difference in atopic diseases between rural and urban areas, as well as Finland and the

Russian Karelia (a part of Russia geographically adjacent to Finland).[659-661] Households with dogs have rich, diverse house dust microbiota with abundance of *Firmicutes* and *Bacteroides* species.[662]

In the GABRIEL study the mattress dust of farm children and their controls was analyzed by quantitative DNA analysis. Especially high mattress levels of *Mycobacterium* sp.*, Bifidobacteriacae* sp. and *Clostridium* sp. were found among farm children, and that high level was inversely associated with atopy.[661]

Low diversity of gut microbiota in early infancy has been related to greater risk of asthma and sensitization in some longitudinal studies with different designs in childhood.[442,445,449,663] The dysbiosis of the microbiome driven by higher *Bacteriodes* and reduced *Clostridia* taxa in adulthood was associated with greater prevalence of seasonal and nut allergies in adulthood in the American Gut Project.[664]

Skin microbiota may also be associated with protection from atopy. Compared with healthy individuals, atopic individuals have shown to have lower environmental biodiversity at home and significantly lower generic diversity of gammaproteobacteria on their skin.[665] Skin *Acinetobacter* (gammaproteobacteria) species were associated with anti-inflammatory immune responses only in healthy subjects.[666]

In summary, hygiene is important to prevent infections worldwide. Urbanization first in affluent and later in developing countries has led to reduced microbial diversity in the environment. Large microbial diversity of the skin, airways and gut in childhood is important for the prevention of sensitization and of allergic disease in populations. More longitudinal studies are needed to show the association.

- Aggregate Grade of Evidence: B (Level 2a: 2 studies; Level 2b: 10 studies; Level 3a: 2 studies; Level 3b: 1 study; *Table VI.G.3.*).
- Studies included in the Aggregate Grade of Evidence are systematic reviews and meta-analyses for the various aspects of the hygiene hypothesis discussed above. Also included are recent studies, published after the noted systematic reviews and meta-analyses. If systematic reviews and meta-analyses are not available, individual studies are listed.

Table VI.G.3. Evidence for the hygiene hypothesis in the development of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Campbell et al[647]	2015	2a	SR	29 studies (1999-2014): 26 cross-sectional, 3 longitudinal. Meta-analysis: 8 studies.	Association of farm exposure with sensitization in childhood or adulthood	Protective effect of farm exposure in infancy on allergic disease in childhood and adulthood in majority of studies. Exposure during adulthood had no consistent relationship with sensitization.
Karmaus and Botezan[645]	2002	2a	Meta-analysis	53 studies (1986-2000). 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[648]	2016	2b	Nested case-control study	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.
Fujimura et al[445]	2016	2b	Longitudinal birth cohort study	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)	Reduced colonization of *Bifidobacteria, Lactobacillus, Faecalibacterium and Akkermansia* and *Malazzesia* during the neonatal period may influence the risk of multisensitization predictive for asthma.
Hua et al[664]	2016	2b	Cross-sectional study	1879 adult subjects	Association of seasonal allergy with fecal microbial biodiversity	Reduced fecal biodiversity and altered composition associated with more allergy, No association with asthma and eczema.
Valkonen et al[661]	2015	2b	Cross-sectional stratified population study	GABRIELA study: 224 children, 6-12 years	Association of sensitization with mattress bacterial diversity	Exposure to more diverse bacterial flora associated with less sensitization.
Arrieta et al[663]	2015	2b	Longitudinal nested case-	319 children followed from birth until 5 years of age	Association of sensitization and wheezing at 1 year with fecal	Reduced colonization of *Faecalibacterium, Lachnospira, Veillonella* and *Rothia* during the

			control study		microbiota at age 3 months and 1 year	first 3 months of life may increase the risk of atopic asthma.
Strachan et al[646]	2015	2b	Cross-sectional study	Children 6-7 years of age in 31 countries (n=210,200); 13-14 years of age 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 AR. Effect was significantly stronger in affluent countries.
Tischer et al[657]	2011	2b	Nested case-control study	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.
Ege et al[659]	2011	2b	Two cross-sectional studies	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.
Bisgaard et al[449]	2011	2b	Longitudinal study	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.
von Hertzen et al[660]	2007	2b	Cross-sectional study	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.
Cuello-Garcia et al[658]	2015	3a	Systematic review and meta-analysis	29 randomized controlled trials in infants	Association of AR with probiotic supplementation to pregnant mothers, breast-feeding women, or infants	No effect on allergies.
Simpson and Martinez[656]	2010	3a	Review	6 rural studies 10 urban studies (2000-2007)	Association of sensitization with exposure to endotoxin	Exposure to endotoxin protective in over 50% of studies. Endotoxin may be marker of other protective factors.
Abrahamsson et al[442]	2014	3b	Longitudinal case-control study	47 infants (n=20 IgE-associated eczema, n=27 healthy controls) followed until 7 years of age	Association of sensitization, asthma and AR with fecal diversity in infancy.	Low microbial diversity associated with asthma later in childhood. No association with sensitization or rhinitis.

LOE: level of evidence; SR: systematic review; AR: allergic rhinitis; GABRIELA: GABRIEL Advanced Survey; PARSIFAL: Prevention of Allergy-Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle; IgE: immunoglobulin E

VII. Disease burden

VII. A. Individual burden

VII. A. 1. Effect on quality of life

Two systematic reviews have evaluated the effect of AR on QOL, with both concluding that AR patients suffer from significantly decreased general and disease-specific QOL due to the impact of physical and mental health. Furthermore, both studies demonstrated that treatment of AR leads to improvement in QOL.[667,668] **[Table VII.A.1.]** While the impact of AR on QOL has been suggested in the literature for decades, only recently has the effect of AR on QOL been rigorously studied. This is in part due to the development of validated general and disease-specific QOL instruments, and their use in clinical investigations and trials. The most commonly used general QOL instruments in the AR literature appear to be the Short Form 12 and 36 (SF-12/36),[669,670] which measure generic physical and mental health-related QOL. The most commonly used AR disease-specific QOL tool is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), or one of its variations (i.e. mini-RQLQ, nocturnal RQLQ).[671] However, despite the availability of these instruments, many studies in the published literature rely upon non-validated methods to assess QOL, leading to difficulty comparing outcomes between some studies.

Several high-quality studies have evaluated the impact of AR on overall and disease-specific QOL. **[Table VII.A.1.]** Most level 1b evidence includes RCTs evaluating the effect of topical nasal corticosteroids[671-673], antihistamines[672,674-677], or AIT.[678,679] The general consensus of these studies is that AR has a significant negative impact on general and disease-specific QOL, and that the successful treatment of AR by any of the aforementioned therapies leads to the improvement of symptoms and QOL. One RCT that examined monotherapy versus polytherapy showed that the combination of mometasone with either levocetirizine or montelukast led to greater symptom and QOL improvement than mometasone alone, but there was no difference between the levocetirizine and montelukast groups.[672] Additionally, a RCT of acupuncture versus medical therapy showed that the improvement in QOL occurred in both groups, but the degree of improvement was larger in the acupuncture group.[680]

While the remaining evidence is of lower quality, it includes important and interesting findings in addition to the conclusions reached by the RCTs and systematic reviews. For example, extra-nasal symptoms, particularly ocular symptoms, have a significant impact on QOL and should not be ignored in the evaluation and management of AR.[681-684] Furthermore, the productivity, practical/activity, emotional, social, and memory function of patients appear to be significantly impacted by AR.[685-689]

No high-quality studies have explicitly attempted to establish variations of QOL in AR patients over time, and most have short follow-up periods or only a single follow-up. However, some observations regarding the natural variation in QOL in AR can be extracted from the placebo arms of level 1 studies. Two RCTs have studied the effect of levocetirizine over 6 months.[675,677] These RCTs show that over a 6-month period, both the placebo and treatment group experience clinically and statistically significantly improvements in generic and disease-specific QOL; however, the improvement is greater in the treatment arm. The AIT RCTs have longer follow-up periods (12 to 18 months) and show similar results, with placebo patients either staying at their baseline QOL impairment, or improving to a lesser degree than the treatment arms.[678,679] As expected in patients with SAR, QOL is better outside of peak season and worsens during allergen exposure.[690,691]

- Aggregate Grade of Evidence: B (Level 1b: 11 studies; Level 2a: 2 studies; Level 2b: 16 studies; Level 2c: 1 study; Level 3b: 3 studies; *Table VII.A.1.*)
- Benefit: Successful management of AR leads to improved overall and disease-specific QOL.
- Harm: Management strategies for AR are associated with variable levels of harm and are further specified in Section IX. Management.
- Cost: Management strategies for AR are associated with variable levels of cost and are further specified in Section IX. Management.
- Benefits-Harm Assessment: The benefits of treating patients with AR to improve QOL may outweigh risks of treatment.
- Value Judgments: Successful control of AR symptoms leads to important improvements in generic and disease specific QOL.
- Policy Level: Recommend treatment of AR to improve QOL.
- Intervention: AR patients may be offered various management strategies to improve general and disease-specific QOL.

Table VII.A.1. Effect of allergic rhinitis on general and disease-specific quality of life

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Bousquet et al[674]	2013	1b	RCT	AR (n=716): 1. desloratadine (n=360) 2. placebo (n=356)	Symptoms scores, sleep questionnaire, RQLQ, WPAIAS	Desloratadine improves symptoms, QOL, and functional impairment.
Tatar et al[672]	2013	1b	RCT	AR (n=56): 1. mometasone (n=14) 2. mometasone + levocetirizine (n=21) 3. mometasone + montelukast (n=21)	Mini-RQLQ	QOL significantly affected by AR. Combination of mometasone with levocetirizine or montelukast improves QOL more than mometasone alone.
Yamada et al[673]	2012	1b	RCT, double-blind, crossover	PAR (n=57): mometasone	TSS, QOL score, sleep quality, nasal nitric oxide	Nasal mometasone improves nasal symptoms, QOL, and sleep quality and decreases nitric oxide.
Hoiby et al[678]	2010	1b	RCT	AR (n=53): 1. SCIT (n=27) 2. placebo (n=26)	Symptom and medication scores	SCIT reduces symptom and medication scores compared to placebo.
Holmberg et al[676]	2009	1b	RCT, double-blind, crossover	AR (n=584): 1. desloratadine (n=293) 2. placebo (n=291)	RQLQ, symptom score	Desloratadine improves RQLQ and symptom score significantly compared to placebo.
Witt et al[692]	2009	1b	RCT	AR (n=981): 1. acupuncture (n=487) 2. control (n=494)	SF-36	Acupuncture improves QOL more than control at 3 months.
Brinkhaus et al[680]	2008	1b	RCT	AR (n=5,237): 1. randomized to acupuncture (n=487) 2. conventional medical care (n=494) 3. not randomized but received acupuncture (n=4,256)	RQLQ, SF-36	QOL significantly affected by AR. Acupuncture group improves more than conventional medical care.
Canonica et al[677]	2006	1b	RCT, double-blind	AR (n=551): 1. levocetirizine (n=278) 2. placebo (n=273)	RQLQ, SF-36	QOL significantly affected by AR. Levocetirizine improves QOL compared to placebo.
Colas et a[679]	2006	1b	RCT, double-blind	AR (n=60): 1. SCIT (n=41) 2. control (n=19)	RQLQ, symptoms score, medication score	QOL significantly affected by AR. SCIT improves RQLQ, symptom and medication scores.
Bachert et al[675]	2004	1b	RCT, double-blind	PAR (n=551): 1. levocetirizine (n=278) 2. placebo (n=273)	SF-36, RQLQ	Levocetirizine improves QOL and decreases disease-related costs.

Radcliffe et al[693]	2003	1b	RCT, double-blind	SAR (n=183): 1. enzyme potentiated desensitization (n=90) 2. placebo (n=93)	RQLQ, problem-free days	Enzyme potentiated desensitization does not improve QOL compared to placebo.
Gerth Van Wijk et al[694]	2000	1b	RCT	AR and nasal capsaicin (n=26)	VAS, RQL	Capsaicin does not sufficiently control rhinitis symptoms.
Juniper et al[671]	1991	1b	RCT, double-blind	AR questionnaire development (n=85); validation (n=60)	RQLQ	In addition to local symptoms, patients experience impaired QOL through systemic, sleep, emotional symptoms and practical/activity limitations. Beclomethasone use correlated to RQLQ.
Linneberg et al[667]	2016	2a	SR	AR	QOL	Patients with AR suffer from decreased QOL in terms of both physical and mental health.
Hahn-Pedersen et al[668]	2014	2a	SR	AR	QOL	AR patients have significantly worse general and disease-specific QOL with physical, practical and activity domains most affected. SCIT improves QOL and symptoms.
Filanowicz et al[695]	2016	2b	Observational cohort	SCIT (n=200): 1. allergic asthma (n=101) 2. AR (n=99)	RQLQ	QOL is significantly affected by AR. SCIT significantly improved QOL in asthma and AR.
Jaruvongvanich et al[684]	2016	2b	Observational cohort	AR (n=260)	SF-12, TSS	Extra-nasal symptoms in AR correlate with physical and mental health QOL domains.
Bousquet et al[681]	2013	2b	Observational cross-sectional	AR (n=990)	VAS, RQLQ, TSS	20% mid intermittent, 17% mild persistent, 15% mod-severe intermittent, 48% mod-severe persistent. Severity and duration of AR impaction QOL. Ocular symptoms impact RQLQ more than nasal obstruction. Sneezing/rhinorrhea do not impact RQLQ.
Demoly et al[696]	2013	2b	Observational cohort	AR (n=990)	VAS, RQLQ, TSS	20% mild intermittent, 17% mild persistent, 15% mod-severe intermittent, 48% mod-severe persistent. VAS can

						detect QOL variations with high sensitivity.
de la Hoz Caballer et al[697]	2012	2b	Observational cross-sectional	primary care patients (n=616)	SF-36, generic HRQOL, WPAI	AR impacts productivity to a greater magnitude than hypertension and DM type II, but not depression.
Meltzer et al[698]	2012	2b	Observational cross-sectional	nasal allergy (n=522); no nasal allergy (n=400)	Non-validated phone interview questions	AR patients rate overall health lower, have worse sleep function, and decreased productivity than those non-AR.
Ciprandi et al[699]	2010	2b	Observational cohort	AR undergoing SLIT(n=167)	RQLQ	QOL is significantly affected by AR. SLIT effective at improving QOL and symptoms
Stull et al[682]	2009	2b	Observational cross-sectional	AR (n=404)	Symptom scale, nocturnal RQLQ, WPAI, MOS-12 Sleep, PANAS-X	Nasal congestion is more strongly correlated to outcomes, but ocular symptoms can have significant impact of QOL.
Cadario et al[683]	2008	2b	RCT	AR treated with SLIT (n=40)	Non-validated QOL scale	QOL is significantly affected by AR. SLIT improves QOL and symptoms.
Petersen et al[700]	2008	2b	Observational cross-sectional	AR (n=248); AR and asthma (n=121)	RQLQ; 15D	AR patients have worsened QOL during allergen exposure. 15D generates more comprehensive view of impact on QOL than RQLQ.
Ciprandi et al[701]	2007	2b	Observational cohort	AR (n=123)	RQLQ	QOL is significantly affected by AR. >2 sensitivities, eosinophil count, and nasal flow related to QOL. Eye symptoms correlate most strongly to QOL.
Di Rienzo et al[702]	2006	2b	RCT, double-blind	AR (n=34): 1. SIT (n=19) 2. placebo (n=15)	RQLQ	QOL is significantly affected by AR. SLIT improved QOL compared to placebo.
Laforest et al[703]	2005	2b	Observational cohort	1. SAR (n=83) 2. asthma (n=52)	Mini-RQLQ, SF-12	QOL is significantly affected by SAR and asthma. Female gender, rural residence, and lower education levels associated with worse QOL in SAR.
Majani et al[691]	2001	2b	Observational cohort	SAR (n=33)	SF-36, SAT-P	QOL is significantly affected by AR during peak season.
Leynaert et al[689]	2000	2b	Observational cross-sectional	1. AR and asthma (n=76) 2. AR but not asthma (n=240) 3. neither AR or 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.
Cingi et al[704]	2013	2c	Outcomes research	PAR treated with desloratadine and montelukast (n=40)	acoustic rhinometry, RQLQ	Desloratadine + montelukast improves nasal obstruction and QOL
Bukstein et al[688]	2016	3b	Observational cohort	PAR treated with beclomethasone (n=527)	RCAT, treatment satisfaction, WPAI, PSQI, mini-RQLQ	Beclamethasone improves QOL, school-related activities, satisfaction, productivity, and sleep quality.
Song et al[685]	2015	3b	Observational cross-sectional	Middle school students, cross-sectional stratified random sampling (n=814)	Questionnaire	AR in 17.2%. AR impacts QOL, sleep, emotions, and memory.
Katelaris et al[687]	2013	3b	Observational cross-sectional	AR (n=303)	Questionnaire	AR impacts work/school performance, general QOL, and sleep quality.

LOE: level of evidence; RCT: randomized controlled trial; AR: allergic rhinitis; RQLQ: rhino-conjunctivitis quality of life questionnaire; WPAIAS: Work Productivity and Activity Allergy Specific questionnaire; QOL: quality of life; PAR: perennial allergic rhinitis; TSS: total symptom score; SCIT : subcutaneous immunotherapy; SF-36: short form 36; VAS: visual analogue scale; RQL: rhinitis quality of life; SR; systematic review; SF-12: short form 12; HRQOL: Health Related Quality of Life; WPAI: Work Productivity and Activity questionnaire; DM: diabetes mellitus; SLIT: sublingual immunotherapy; MOS-12 Sleep: Medical Outcomes Study 12-Item Sleep Scale; PANAS-X: Positive and Negative Affect Schedule-Expanded Form; 15D: Generic 15 Dimension Instrument for measuring health related quality of life; SAR: seasonal allergic rhinitis; SAT-P: satisfaction profile; RCAT: Rhinitis Control Assessment Test; PSQI: Pittsburgh Sleep Quality Index

VII. A. 2. Effect on sleep

Like generic and disease-specific QOL, validated tools exist for the assessment of sleep-related QOL in AR, but they are not always utilized in studies reported in the AR literature. Some studies evaluating generic and disease-specific QOL suggest that AR negatively impacts patients' sleep.[673,685,687] **[Table VI.A.1.]** Several studies have specifically investigated the relationship between AR and sleep in adults and children. **[Table VI.A.2-1. and Table VI.A.2-2.]** The general conclusion from the aggregate data is that, like overall and rhinitis-specific QOL, AR negatively impacts sleep QOL and the successful treatment of AR reduces sleep disturbance. The overall quality of the data is higher for adults than for children. For the adult population, there is level 1b evidence supporting the conclusion that AR negatively impacts sleep.[705-709] These data deal with subjective reporting of daytime sleepiness, sleep quality, and symptoms usually through validated tools, in the setting of testing the effect of nasal corticosteroids and/or montelukast. Results demonstrate that AR patients have improvements in sleep quality and daytime sleepiness, in addition to sinonasal symptoms and QOL after treatment with nasal corticosteroids[705,706,709,710] or a combination of corticosteroids and montelukast.[709] Additionally AR has been associated with worse sleep fragmentation[711,712] and snoring.[713,714] Treatment of AR has been also suggested to also improve continuous positive airway pressure (CPAP) compliance in patients with OSA.[715] The data on the effects of AR on polysomnogram (PSG) parameters in adults is mixed. Most studies that included PSG analysis found that AR iss associated with worsened PSG parameters;[712,714,716-719] however, two level 3b studies found either no difference or a modest change.[720,721]

Two studies looked at variations in sleep symptoms with changes in nasal inflammation over time. It seems that changes in nasal cytokine levels are associated with changes in PSG[719] and that AR patients have worse PSG parameters and sleep disturbance when their symptoms are present or during their peak allergen season.[718] In children, level 2 and 3 studies suggest that AR is associated with sleep disturbance in the form of increased risk of snoring, sleep disordered breathing, and OSA. Furthermore, AR has been suggested to be a risk factor for deterioration of OSA QOL after adenotonsillectomy.[722] *(See section X.K. Associated Conditions – Sleep Disturbance for additional information on this topic.)*

- Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 10 studies; Level 2c: 3 studies; Level 3a: 1 study; Level 3b: 21 studies; Level 4: 6 studies; *Tables VI.A.2-1. VI.A.2-2.*)
- Benefit: Successful management of AR leads to decreased sleep disturbance.
- Harm: Management strategies for AR are associated with variable levels of harm and are further specified in Section IX. Management.
- Cost: Management strategies for AR are associated with variable levels of cost and are further specified in Section IX. Management.
- Benefits-Harm Assessment: The benefits of treating patients with AR for symptoms of sleep disturbance may outweigh risks of treatment.
- Value Judgments: Successful control of AR symptoms leads to improvements in sleep.
- Policy Level: Recommend treatment of AR to decrease sleep disturbance.
- Intervention: AR patients may be offered various management strategies to improve sleep.

Table VI.A.2-1. Effect of allergic rhinitis on sleep in adults

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Shanqun et al[709]	2009	1b	RCT	AR and OSA (n=89): 1. montelukast + budesonide (n=44) 2. placebo (n=45)	ESS, RQLQ, TSS, CSAQLI, symptoms diary	Montelukast + budesonide improves AR and OSA QOL, sleep quality and daytime somnolence.
Mansfield and Posey[708]	2007	1b	RCT	1. fluticasone (n=16) 2. placebo (n=16)	TOVA, ESS, TSS	Fluticasone improves daytime sleepiness, cognitive performance, and nasal symptoms.
Gurevich et al[705]	2005	1b	RCT, crossover	PAR (n=26), nasal budesonide	ESS, sleep diary, questionnaire	Budesonide reduces nasal congestion, daytime somnolence/fatigue, and improve sleep quality in PAR.
Hughes et al[706]	2003	1b	RCT, crossover	PAR (n=22), nasal budesonide vs placebo	ESS, FOSQ, RQLQ, symptom diary	Budesonide improves daytime fatigue and sleep quality in PAR.
Craig et al[707]	1998	1b	RCT, crossover	AR (n=20), flunisolide vs placebo	Symptom and sleep diary	Nasal corticosteroids improve symptoms and subjective sleep compared to controls.
Parikh et al[715]	2014	2b	Observational cohort	OSA and rhinitis (n=43)	ESS, symptoms scores, CPAP compliance	Control of rhinitis (with varying regimens of steroid sprays, antihistamines, leukotrienes inhibitors, anticholinergics, etc.) important for OSA control. No difference: AR vs NAR.
Acar et al[716]	2013	2b	Observational cohort	OSA and AR (n=80)	ESS, PSG	Nasal corticosteroids improve sleep quality and AR symptoms. Addition of antihistamine did not have effect.
Lavigne et al[717]	2013	2b	Observational cross-sectional	1. OSA and AR (n=34) 2. OSA without rhinitis (n=21)	PSG, nasal biopsies	In AR, nasal corticosteroids reduce nasal inflammation and improve PSG parameters.
Udaka et al[723]	2007	2b	Observational cross-sectional	daytime workers (n=3,442)	Questionnaire, ESS, SF-36	Severity of nasal obstruction (non-validated questionnaire) correlates with worse ESS and lower QOL.
Mintz et al[724]	2004	2b	Individual cohort	AR (n=651)	Nocturnal RQLQ, PSQI	Treatment with triamcinolone improves nocturnal rhinitis QOL and sleep quality.
Camhi et al[713]	2000	2b	Case-control	n=437 from TESOAD with sleep problems/snoring	Questionnaire	AR risk factor for snoring.
Janson et al[725]	1996	2b	Observational cross-sectional	n=2,661 random population of the ECRHS	SPT, methacholine challenge, questionnaire	AR independently associated with difficulty initiating sleep and daytime sleepiness (OR 2.0).

Colas et al[726]	2012	2c	Population-based	AR (n=2,275)	TSS, RQLQ, PSQI	AR disease severity has strong relationship with sleep disturbance.
Leger et al[727]	2006	2c	Population-based	AR (n=591)	SDQ, ESS, symptom score	All dimensions of sleep impaired by AR, disease severity correlated with degree of sleep impairment.
Young et al[714]	1997	2c	Population-based	survey subjects (n=4,297); objective testing subjects (n=911)	Questionnaire, PSG	AR and nasal obstruction associated with snoring, daytime sleepiness, and SDB.
Gadi et al[728]	2017	3b	Observational 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 cohorts.
Bozkurt et al[721]	2017	3b	Case-control	1. PAR and OSA symptoms (n=150) 2. controls (n=95)	SPT, PSG	PAR did not affect PSG findings compared to controls.
Park et al[729]	2012	3b	Observational cross-sectional	1. OSA and AR (n=37) 2. 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[720]	2011	3b	Case-control	1. PAR (n=98) 2. controls (n=30)	PSG	PSG parameters showed modest changes in PAR patients.
Rimmer et al[711]	2009	3b	Observational cohort	1. PAR (n=10) 2. control (n=10)	Acitigraphy	AR has increased sleep fragmentation and reduced sleep quality.
Canova et al[730]	2004	3b	Case-control	1. OSA (n=72) 2. COPD controls (n=44)	Symptom score, spirometry, SPT	OSA more likely to be sensitized to perennial allergens (11% in OSA vs. 2.3% COPD).
Stuck et al[731]	2004	3b	Observational cohort	1. SAR (n=25) 2. controls (n=25)	ESS, SF-36, PSG	SAR leads to increased daytime sleepiness compared to controls.
Krouse et al[719]	2002	3b	Exploratory cohort	1. AR (n=4) 2. controls (n=4)	PSG, serum and nasal cytokines	Differing cytokine levels associated with variations in PSG.
Lavie et al[712]	1981	3b	Observational cohort	1. AR (n=14) 2. controls (n=7)	PSG	AR patients had 10-fold increase in micro-arousals compared to controls.
McNicholas et al[718]	1982	4	Case series	AR (n=7)	Nasal resistance, PSG	AR patients have worse OSA symptoms when symptoms are present and have high nasal resistance.

LOE: level of evidence; RCT: randomized controlled trial; AR: allergic rhinitis; OSA; obstructive sleep apnea; ESS: Epworth Sleepiness Scale; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; TSS: total symptom score; CSAQLI: Calgary Sleep Apnea Quality of Life Index; QOL: quality of life; TOVA: Test of Variables Attention; PAR: perennial allergic rhinitis; FOSQ: Functional Outcomes of Sleep Questionnaire; CPAP: continuous positive airway pressure; PSG: polysomnogram; NAR: non-allergic rhinitis; PSQI: Pittsburgh Sleep Quality Index; SF-36: Short Form 36; SDQ: Sleep Disorders Questionnaire; TESOAD: Tucson

Epidemiology Study of Obstructive Airway Disease; SDB: sleep disordered breathing; ECRHS: European Community Respiratory Health Survey; SPT: skin prick test; OR: odds ratio; COPD: chronic obstructive pulmonary disease; SAR: seasonal allergic rhinitis

Table VI.A.2-2. Effect of allergic rhinitis on sleep in children

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Koinis-Mitchell et al[732]	2015	2b	Individual cohort	non-white Latino and African American urban children (n=195)	Clinical evaluation and follow-up	Poor AR and asthma control related to high frequency of sleep problems and poor sleep hygiene.
Kim et al[722]	2015	2b	Individual cohort	SDB undergoing T&A (n=70)	OSA-18, SPT, questionnaire	AR may be risk factor for deterioration of OSA QOL after T&A.
Barone et al[733]	2009	2b	Case-control	1. children from sleep disorders clinic (n=149) 2. controls (n=139)	PSG	AR associated with OSA, OR 2.24.
Lin et al[734]	2013	3a	Systematic review	N/A	Association between AR and SDB	Most studies show association between AR and SDB in children, but all studies were low level of evidence.
Di Francesco et al[735]	2016	3b	Cross-sectional	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[736]	2015	3b	Case-control	1. AR and adenoid grade I-II (n=32) 2. AR and adenoid grade III-IV (n=27)	History	AR may influence development of nocturnal enuresis.
Poachanukoon et al[737]	2015	3b	Case-control	1. AR (n=65) 2. control (n=104)	Questionnaire	Higher incidence of sleep disturbance in AR.
Kwon et al[738]	2013	3b	Population-based	children with AR (n=85,002)	National survey data	Association between late sleep time and short sleep duration with AR.
Li et al[739]	2010	3b	Cross-sectional	children (n=6,349)	Questionnaire	Habitual snoring associated with AR (OR 2.9, CI 2.0-4.2).
Vichyanond et al[740]	2010	3b	Case-control	children with rhinitis (n=302)	History	Upper airway obstruction associated with NAR.
Sogut et al[741]	2009	3b	Cross-sectional	Turkish children (n=1,030)	Questionnaire	AR associated with habitual snoring (OR 3.7, CI 1-13).
Liukonnen et al[742]	2008	3b	Population-based	children in Helsinki (n=2100)	Questionnaire	AR more common in snorers.

Kalra et al[743]	2006	3b	Cross-sectional	children in CCAAPS (n=681)	Questionnaire	29% of patients with HS have positive SPT, significant association.
Ng et al[744]	2005	3b	Cross-sectional	school children (n=3,047)	Questionnaire	AR associated with witnessed apnea.
Sogut et al[745]	2005	3b	Cross-sectional	Turkish children (n=1,198)	Questionnaire	AR associated with habitual snoring (OR 4.23, CI 2.14-8.35).
Chng et al[746]	2004	3b	Cross-sectional	school children (n=11,114)	Questionnaire	Snoring in 34%, AR associated with snoring (OR 2.9, CI 2.06-4.08).
Anuntaseree et al[747]	2001	3b	Cross-sectional	randomly selected children (n=1,142)	PSG, questionnaire	Prevalence habitual snoring 8.5%, OSAS 0.69%. OR 5.27 in children with AR.
Bhattacharjee et al[748]	2010	4	Prognostic cohort	children undergoing AT for OSA (n=578)	PSG	AR identified in 39% of children with OSA undergoing AT.
Goldbart et al[749]	2005	4	Case series	SDB (n=24)	PSG, lateral neck x-ray	Montelukast treatment for 16 weeks decreased adenoid size and respiratory sleep disturbances.
Kidon et al[750]	2004	4	Case series	children with AR undergoing SPT (n=202)	History	17% of AR patients reported HS.
Mansfield et al[751]	2004	4	Case series	children with AR (n=14)	PSG, RQLQ	Treating AR decreases AHI.
McColley et al[752]	1997	4	Case series	children with HS (n=39)	PSG	Positive skin test associated with OSA.

AR: allergic rhinitis; LOE: level of evidence; SDB: sleep disordered breathing; T&A; tonsillectomy and adenoidectomy; OSA-18: 18-item quality-of-life survey for obstructive sleep apnea; SPT: skin prick test; QOL: quality of life; PSG: polysomnogram; OR: odds ratio; REM; rapid eye movement; OSA: obstructive sleep apnea; AHI: apnea-hypopnea index; CI: 95% confidence interval; NAR: non-allergic rhinitis; CCAAPS: Cincinnati Allery and Air Pollution Study; HS: habitual snoring; OSAS: obstructive sleep apnea syndrome; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

VII. B. Societal burden

As described in Section VII.A.1., AR may have significant negative effects on QOL with considerable consequences if left untreated. For many years, AR has been trivialized despite its prevalence, chronicity, and the burden it imposes on individuals and society.[101,681,753] The total burden for AR lies not only in the impairment of physical and social functioning, but also in the financial burden, which is greater when its role in comorbid conditions such as asthma and rhinosinusitis are taken into account.[754-756] In Europe, the total societal cost of AR and its comorbidities in 2002 was estimated at 355.06 Euros per patient per month.[755] The burden of AR is now being recognized by the European Academy of Allergy & Clinical Immunology (EAACI) and also at the European Union (EU) parliament level in order to feature the dramatic impact this condition has on the QOL of patients with AR.[757,758]

In terms of the overall economic burden of illness, AR ranks fifth among chronic conditions in the US.[759] Estimates of the annual direct cost of AR range from $2 billion to $5 billion, with more than half of the AR direct costs coming from prescription medications.[760-762] The direct costs attributed to AR include physician office visits, laboratory tests, medications, and AIT.[763] Compared with matched controls, patients with AR have an almost two-fold increase in medication costs and a 1.8-fold increase in visits to a healthcare provider.[756,764,765] Hidden direct costs include treatment of comorbid conditions that occur at an increased incidence in patients with AR.

Recently, the TOTALL (TOTal costs of ALLergic rhinitis in Sweden) study estimated the total cost of AR using a sample representing the entire Swedish working-age population. Data from this study suggested that patients with mild AR have less impact on the health economy, with costs averaging about 25% of the costs for those with moderate to severe disease.[667,766] Patients with moderate to severe AR reported visiting their primary care provider for their AR more frequently than those with mild AR (1.61 vs 1.19 times per year).[753]

The indirect costs of AR, such as absenteeism and presenteeism, are also significant and actually make up the majority of the cost burden of AR.[767,768] Impaired productivity and/or missed work occurred as a result of AR in 52% of patients.[753] In a survey of over 8,000 US employees at 47 employer locations, 55% reported AR symptoms for an average of 52.5 days per year. They reported missing 3.6 days of work per year because of AR and reported being unproductive 2.3 hours per workday when symptomatic. The mean total productivity losses (absenteeism and presenteeism) for AR were calculated at $593 per employee per year.[769] In another UK study, patients with moderate to severe AR reported 37.7 days a year when their productivity was affected by their AR symptoms; this is almost double that reported by patients in the same study with mild AR symptoms (21.0 days).[753]

Health impairments associated with AR are often not severe enough to cause absenteeism, but they do interfere with cognitive functioning, resulting in fatigue and an impaired ability to learn, concentrate, and make decisions.[770] In a study by Blanc et al,[771] more than one-third of AR patients reported reduced workplace performance.

In the US, AR results in 3.5 million lost workdays and 2 million lost school days annually.[772] On any given school day in the US, approximately 10,000 children are absent from school because of AR.[773] This absence from school may also affect parents' productivity or cause them to be absent from work themselves.

In a study by Hellgren et al,[774] the average productivity loss for all Swedish workers because of absenteeism, presenteeism, and caregiver absenteeism during a year was 5.1 days, of which 2.3 days were accounted for by absenteeism and 2.0 days by presenteeism. If only those with children aged 0-7 years in their household were included in the analyses, the average number of days for caregiver absenteeism was 3.6 days. The cost of caregiver absenteeism comprised 19% of the mean total costs per year in this study. The cost related to caregiver absenteeism was highest for women aged 30-44 years.

AR is the most common chronic disorder in the pediatric population. AR can affect sleep, result in daytime sleepiness, and impair cognition and memory, which may significantly affect the learning process and impact school performance. Even when present during school hours, children with AR exhibit decreased productivity. Comorbidities associated with AR, such as like rhinosinusitis, Eustachian tube dysfunction and associated conductive hearing loss may further contribute to learning dysfunction.[775,776]

AR poses a substantial burden to individuals and society. It can reduce productivity and QOL in affected patients, and contribute to comorbid conditions. This results in a significant impact to the overall health system.[773]

VIII. Evaluation and diagnosis

In an individual patient, the clinical suspicion for a diagnosis of AR is highlighted by the clinical history and often supported by the physical examination. The diagnosis is confirmed by objective testing, which may be performed by various means. This section reviews the existing evidence behind various aspects of evaluation and diagnosis of the AR patient.

VIII. A. Clinical examination

History. Clinical history is an essential part of the evaluation of patients with a suspected diagnosis of AR.[7,26,218,761,777] History taking includes the type of symptoms experienced, timing and duration of symptoms, frequency of symptoms, any environmental exposures eliciting symptoms at home/work/school, and medications or other measures that relieve or exacerbate symptoms.[7,26,218,761,777,778] In addition, past medical history including comorbid conditions such as asthma or obstructive sleep apnea, family history of atopic disorders, social history (i.e. pets, work exposures, home environment), and current medications should be obtained.[7,26,218,761,777,778] Information regarding patient response to self-treatment with over-the-counter medications for AR is also helpful.

Nasal congestion or obstruction, nasal pruritis, clear rhinorrhea, and sneezing are classic symptoms of AR.[7,26,218,761,777,778] Patients may complain of associated symptoms of ocular pruritis, erythema, and/or tearing, oral cavity or pharyngeal pruritis, and wheezing or cough (reactive airway disease and/or asthma).[7,26,778] Additional associated symptoms may include hyposmia or anosmia, snoring or sleep-disordered breathing, aural congestion or pruritis, cough, sore throat, and wheezing.[778,779] Commonly, patients with suspected AR will present with multiple complaints, with 96% presenting with two or more symptoms.[778] Patients with PAR tend to report more congestive symptoms (sinus pressure, nasal blockage/congestion, and snoring) than patients with SAR and are more likely to report the presence of sore throat, cough, sneezing, rhinorrhea, and postnasal drip.[778] Rhinorrhea, sneezing, sniffing, hyposmia/anosmia, nasal obstruction, and itchy nose rank highest for diagnostic utility among symptoms of AR.[779]

Several guidelines suggest the diagnosis of AR be made when patients present with a history consistent with an allergic cause and one or more of the above listed symptoms, despite the lack of high-level evidence to support such a recommendation.[7,26,218,761,777,780] **[Table VIII.A.]** However, the lack of higher level evidence is not surprising as a clinical history and physical examination is essential to any medical diagnosis and randomized studies would require participants to receive an intervention without a clinical history. Using a physical examination alone to diagnose AR has been shown to have poor predictive value.[781] The reliability and predictive value of the patient history alone for AR exceeds that of the physical exam alone.[781] In clinical practice, the diagnosis of AR is often made by history alone.[780]

Physical examination. Physical examination is part of the evaluation of patients with suspected AR.[7,26,218,761,777] This includes an assessment of the multiple organ systems of the head and neck, such as the integumentary system; external auditory canal, tympanic membrane, and middle ear; nasal cavities; orbits and periorbital tissues; oral cavity and pharynx; larynx via indirect laryngoscopy; and cervical

tissues.[26,218,761,777] It may include auscultation of the lungs, given comorbid conditions of asthma, or complaints of wheezing or coughing with exposure.[7]

It is not uncommon for physical examination of patients with AR complaints to be completely normal, particularly in patients with intermittent exposure.[779] However, physical signs suggestive of AR may include mouth-breathing, nasal itching or a transverse supratip nasal crease, throat clearing, periorbital edema, or "allergic shiners" (dark discoloration of the lower lids and periorbital area).[26,777] Examination of the ear may reveal retraction of the tympanic membrane or transudative fluid.[26,218,777] Examination of the nose may reveal inferior turbinate hypertrophy, congested/edematous nasal mucosa, purplish or bluish nasal mucosa, and clear rhinorrhea. [26,218,761,777] Examination of the eyes may reveal conjunctival erythema and/or chemosis.[26,777]

Physical examination alone is poorly predictive and more variable when compared to history taking in the diagnosis of AR, with the average sensitivity, specificity, positive predictive value, and negative predictive values of the patient history higher than those of the physical examination.[781] Most guidelines recommend a physical examination as part of the diagnosis of AR, despite a lack of high-level evidence. Without a physical examination, other potential causes of symptoms such as CRS, could not be fully evaluated or eliminated. A patient history combined with a physical examination improves diagnostic accuracy.[781]

- Aggregate Grade of Evidence: D (Level 3b: 1 study; Level 4: 3 studies; Level 5: 4 guidelines; *Table VIII.A.*)
- Benefit: Improve accuracy of diagnosis, avoid unnecessary referrals, testing, or treatment. Possible improved diagnosis of AR with physical examination findings, evaluation/exclusion of alternative diagnoses.
- Harm: Possible patient discomfort from routine examination, not inclusive of endoscopy. Potential misdiagnosis, inappropriate treatment.
- Cost: Minimal.
- Benefits-Harm Assessment: Preponderance of benefit over harm, potential misdiagnosis and inappropriate treatment if physical exam used in isolation.
- Value Judgments: Making a presumptive diagnosis of AR on history (ideally combined with physical examination) is reasonable and would not delay treatment initiation. Confirmation with diagnostic testing is required for progression to AIT, or desirable with inadequate response to initial treatment.
- Policy Level: Recommendation.
- Intervention: History taking is essential in the diagnosis of AR. Physical examination is recommended in the diagnosis of AR, and when combined with patient history, it increases diagnostic accuracy and excludes alternative causes.

Table VIII.A.1. Evidence for the role of history taking and physical examination in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Raza et al[781]	2011	3b	Cross-sectional	Adults with AR	History, physical examination, SPT	Physical examination alone yields unreliable and inconsistent results in diagnosing AR.
Costa et al[780]	2011	4	Cohort study	Adults with AR	Physician interview and structured questionnaire	Many patients diagnosed on history alone without confirmatory testing.
Shatz[778]	2007	4	Survey	1. adults and children >12 years with AR 2. physicians of group 1	Self-completed patient questionnaire, physician patient record form	Persistent AR patients reported more symptoms than intermittent AR patients.
Ng et al[779]	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 in diagnostic utility. Physical examination performed to eliminate other potential causes of symptoms.
Seidman et al[761]	2015	5	Guideline		Recommendations on diagnosis and treatment of AR	Clinical diagnosis of AR made with a history and physical examination consistent with AR.
Wallace et al[26]	2008	5	Guideline		Recommendations on the diagnosis and treatment of rhinitis	Thorough allergic history remains the best diagnostic tool available. All organ systems potentially affected by AR should be examined. Typical allergic exam findings are supportive but not specific.
Small et al[777]	2007	5	Guideline		Recommendations on diagnosis and treatment of rhinitis	History of allergic symptoms is essential in the diagnosis of AR. Physical exam aids in supporting the diagnosis of AR.
Bousquet et al[7]	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. Lung exam is recommended in asthmatic patients with symptoms of AR.

LOE: level of evidence; AR: allergic rhinitis; SPT: skin prick test; sIgE: antigen-specific immunoglobulin E

VIII. B. Nasal endoscopy

Diagnostic nasal endoscopy is an option for the evaluation of patients with suspected AR. Several uncontrolled observational studies evaluated the association of endoscopic findings with symptomatic rhinitis, with inconsistent results. **[Table VIII.B.]** Ameli et al[782] evaluated children with suspected AR, reporting that endoscopic findings of inferior or middle turbinate septal contact was predictive for AR, while pale turbinates were not. Conversely, Eren et al[783] evaluated a population of adult patients with rhinitis, concluding that findings of nasal endoscopy do not provide a reliable diagnosis of AR. Among adults and children with AR that is confirmed by allergy testing, no significant correlation was found between nasal endoscopy and specific nasal symptoms.[784]

Central compartment atopic disease (CCAD) represents the recently described association between atopic states and centrally-located inflammation involving the middle/superior turbinates or superior nasal septum.[785-787] In a recently published parallel case series (LOE=4), Brunner et al[788] evaluated patients with CRSwNP versus isolated polypoid change of the middle turbinate. Significant findings include a higher prevalence of AR in patients with middle turbinate polypoid change (83% vs 34%, $p < .001$), further supporting CCAD as a unique atopic condition.

Although the association of endoscopic findings with AR has been shown to be inconsistent, nasal endoscopy may aid in the identification or exclusion of other possible causes of symptoms, such as nasal polyposis or CRS.

- Aggregate Grade of Evidence: D (Level 3b: 2 studies; Level 4: 3 studies; *Table VIII.B.*)*
- Benefit: Possible improved diagnosis with visualization of turbinate contact or isolated central compartment edema.
- Harm: Possible patient discomfort.
- Cost: Moderate equipment and processing costs, as well as procedural charges.
- Benefits-Harm Assessment: Equal.
- Value Judgments: None.
- Policy Level: Option.
- Intervention: Nasal endoscopy may increase diagnostic sensitivity among children and adults with AR and may aid in ruling out other causes for nasal symptoms.

*Due to recent publication and in accordance with ICAR methodology, DelGaudio et al[787] and Brunner et al[788] are excluded from the Aggregate Grade of Evidence.

Table VIII.B. Evidence for the role of nasal endoscopy in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hamizan et al[786]	2016	3b	Cross-sectional	Adults with rhinitis and nasal obstruction	Nasal endoscopy, allergy testing	MT edema is a useful nasal endoscopic feature to predict presence of inhalant allergy.
White et al[785]	2014	3b	Cross-sectional	Adults with isolated MT polypoid edema	Nasal endoscopy, allergy testing	Isolated MT polypoid edema is associated with positive allergy testing.
Eren et al[783]	2013	4	Case series	Adults with rhinitis	Nasal endoscopy, AR diagnosis	Nasal endoscopic findings do not provide reliable diagnosis of AR.
Ameli et al[782]	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[784]	1999	4	Case series	Adults and children with PAR	Nasal endoscopy, nasal symptoms	No significant correlation between individual symptoms and endoscopic findings.

LOE: level of evidence; MT: middle turbinate; AR: allergic rhinitis; PAR: perennial allergic rhinitis

VIII. C. Radiology

Routine radiographic imaging is not recommended for the diagnosis of AR, although may be considered to rule in/out other conditions (i.e. rhinosinusitis). Some recent studies have established the association between central compartment mucosal disease and aeroallergen sensitivity.[787,788] However, concerns regarding unnecessary exposure to ionizing radiation, with the risk for future cancer development, preclude recommendations for routine use.[789,790]

- Aggregate Grade of Evidence: Not applicable.*
- Benefit: None appreciated.
- Harm: Unnecessary radiation exposure with concern for tumor development.
- Cost: High equipment and processing costs.
- Benefits-Harm Assessment: Preponderance of harm over benefit.
- Value Judgments: Long-term risks of unnecessary ionizing radiation exposure outweigh potential benefit.
- Policy Level: Recommend against.
- Intervention: Routine imaging is not recommended in the evaluation of suspected AR, but may be considered to rule in/out other sinonasal conditions.

*Due to recent publication and in accordance with ICAR methodology, DelGaudio et al[787] and Brunner et al[788] are excluded from the Aggregate Grade of Evidence.

VIII. D. Use of validated survey instruments

Validated clinical outcome surveys and questionnaires may be used as precise clinical assessment instruments to evaluate patients with suspected AR. Clinicians often use SPT, sIgE serology, and other laboratory tests to confirm or refute the diagnosis, but these tests are only useful in the context of an effective clinical history.[791] Validated clinical assessment tools offer a more structured way to expose important historical elements. Furthermore, in regions where resources are scarce, SPT and laboratory testing may not be as readily available. Advancing technologies such as multiplex allergen screening, component serology, and automated SPT imaging devices may be expensive and unattainable by some clinicians.[792-795] In these settings, validated surveys offer a rapid and simple point-of-care tool to formally evaluate allergic disease.

Patient reported outcome measures (PROMs) can assess a number of different aspects of how AR affects patients.[796] These include symptom severity surveys, such as the Total Nasal Symptom Score (TNSS) and health-related QOL questionnaires, such as the RQLQ. Additional surveys measure aspects such as medication usage (Daily Medication Score), disease prediction (Respiratory Allergy Prediction) and disease control (Rhinitis Control Test). Each of these surveys examines slightly different, although related aspects of clinical outcomes. Several of these instruments have been used extensively in many large clinical trials to determine the effectiveness of drugs and biologics for treating AR.[797-802] SPT and nasal challenge may be used to cross-validate these clinical survey tools but ultimately, how a patient reports their own symptoms could very well be the best predictor of disease control.

Validated clinical surveys for AR often include questions about congestion, rhinorrhea and/or sneezing and may either be instantaneous or reflective over a period of days or weeks. The TNSS is typically administered as an instantaneous daily survey comprised of only four questions about runny nose, nasal itching, sneezing, and congestion. Some studies have used the TNSS as a reflective score calculated as the average of both the 12-hour nighttime and 12-hour daytime average (rTNSS). The TNSS score can be combined with questions about rescue medication use to yield the Daily Combined Score (DCS) and the Total Combined Rhinitis Score (TCRS). Both have been used in many therapeutic intervention studies.[803] The RQLQ is a more comprehensive survey that asks the patient to reflect upon the past week and includes global QOL questions. While this test can suffer somewhat from potential recall bias, it can be administered on site and avoids the possibility that self-administered daily scores could be missed periodically when the patient is home. The Control of Allergic Rhinitis and Asthma Test (CARAT10) evaluates rhinoconjunctivitis and asthma symptoms over the past four weeks giving a broader evaluation of seasonal symptom control.[804] The Respiratory Allergy Prediction (RAP) test is a nine-question survey incorporating upper and lower respiratory queries as well as a question about medication use. If conjunctivitis is to be assessed simultaneously with rhinitis symptoms, then the Rhinitis Total Symptom Score (RTSS) can be combined with Rescue Medication Score (RMS) to yield the combined score (CS).[805] **Table VIII.D-1.** lists several validated clinical survey tools.[696,804,806-813]

The choice of which validated survey to use depends on which aspect of clinical outcomes is being studied. For example, if the goal is for a primary care physician to determine the need for referral and further testing, then the RAP test may be used because it has been scrutinized in this setting.[814] The mini-RQLQ and DCS have been used extensively in clinical trials to evaluate the effectiveness of drugs and immunotherapies,[797-801] and therefore may be helpful in selecting the right medication for a given population. It is important to note that some tools use a higher score to indicate severe disease whereas other tools use a higher score to indicate better control of symptoms. For example, a high score on the RCAT, ARCT and CARAT10 indicate good control of allergic symptoms.

Unfortunately, not all studies use consistent terminology and interpretation of the scoring systems.[801] Inconsistent use of questionnaires can weaken the conclusions drawn in certain therapeutic intervention studies. However, a well-executed and validated survey can be essential in research settings and help clinicians screen patients for AR and further render specific diagnostic decisions.

Overall, validated clinical survey instruments may be used as a tool to assist with the diagnosis of AR and determine the success of various therapies. This conclusion is based on review of more than 30 studies of which 9 of these reports range from level 1a to 2b (overall Grade A evidence). **[Table VIII.D-2.]** An example approach, using specific validated survey instruments is as follows: The TNSS may be used for daily symptom monitoring to determine the effectiveness of therapies and control of AR. The TNSS should be combined with a daily medication score to account for the effects of pharmaceuticals on symptomatology. Assessment of both conjunctivitis and rhinitis symptoms as well as medication use can be performed with the Combined Score (RTSS + RMS) or the Rhinoconjunctivitis Allergy Control Score (RC-ACS). The RQLQ or mini-RQLQ can be used as an additional measure to incorporate disease impact on QOL and can be administered in person by the clinician. For quick assessments or to follow a patient's therapeutic success, a simple visual analogue scale (VAS) or global assessment is acceptable. The RAP test can be used as quick and easy tool for primary care physicians to

determine the need to refer to an allergist for further testing. Many validated options are available for AR and should be tailored to the patient and clinical setting.

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 4 studies; Level 2b: 4 studies; *TableVIII.D-2.*) Note: multiple additional studies reviewed, but Grade A evidence reached with these 10 studies, so an extensive listing of all studies employing validated survey instruments is not provided here.
- Benefit: Validated surveys offer a simple point-of-care option for screening and tracking symptoms, QOL and control of allergic disease.
- Harm: Minimal to none.
- Costs: No financial burden to patients. Some fees associated with validated tests used for clinical research.
- Benefits-Harm Assessment: Preponderance of benefit over harm. Low risk of misdiagnoses leading to unnecessary additional testing. Likewise, there is a low risk that false negative responses may lead to delay in testing and further management.
- Value Judgments: Level 1 evidence to use validated surveys as a screening tool and primary or secondary outcome measure.
- Policy Level: Strong recommendation.
- Intervention: Validated surveys may be used to screen for AR, follow treatment outcomes and as a primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathological scenarios and should be tailored to the patient and clinical setting.

Table III.D-1 Validated surveys used to diagnose AR or evaluate disease severity and treatment

Survey	Disease Targeted	Number of questions	Symptom questions	Medication questions	Scoring range	Comments and indications
TNSS Total Nasal Symptom Score	AR	4	Yes	No	0-12	Simple daily symptom score to evaluate AR severity and control used in clinical trials
DMS Daily Medication Score	AR, AC, asthma	Varies	No	Yes	0-36*	Varies depending on medication scoring
DCS Daily Combined Score	AR, AC, asthma	Varies	Yes	Yes	0-48*	Combined symptom and medication score for clinical trials
TCRS Total Combined Rhinitis Score	AR	Varies	Yes	Yes	0-24*	The sum of the combined symptoms medication scores
Mini-RQLQ Mini-Rhinoconjunctivitis Quality of Life Questionnaire	Rhinoconjunctivitis	14	Yes	No	0-84	Shortened version of RQLQ often used in clinical trials
RQLQ Rhinoconjunctivitis Quality of Life Questionnaire	Rhinoconjunctivitis	28	Yes	No	0-168	Reflective assessment of previous week's symptoms often used in clinical trials
VAS Visual Analogue Scale	Rhinitis	1 or more	Yes	No	0-10 cm	Tool may be used to evaluate multiple symptomatologies
RCAT Rhinitis Control Assessment Test	AR, NAR	6	Yes	No	6-30**	Self-assessment of rhinitis symptom control
ARCT Allergic Rhinitis Control Test	AR	5	Yes	Yes	5-25**	Self-assessment of ongoing AR symptoms control
CARAT10 Control of Allergic Rhinitis and Asthma Test	AR, NAR, asthma	10	Yes	Yes	0-30**	Used to compare groups in clinical trials
ACS Allergy Control Score	Rhinitis, AC, asthma	10 + meds	Yes	Yes	0-60	Combined tool used for clinical trials and daily clinical practice
RC-ACS Rhinoconjunctivitis Allergy Control Score	Rhinitis, AC	7 + meds	Yes	Yes	0-42	Similar to ACS but without asthma related questions
RAP Respiratory Allergy Prediction	AR, asthma	9 + meds	Yes	Yes	0-9	Used to determine the need for referral and additional testing
SFAR Symptom Score For Allergic Rhinitis	AR	8	Yes	No	0-16	Weighted score used to detect prevalence of AR
RMS Rescue Medication Score	Rhinoconjunctivitis	meds	No	Yes	0-3	Evaluates medication use only
RTSS	Rhinoconjunctivitis	6	Yes	No	0-18	Evaluates symptoms only

Rhinoconjunctivitis Total Symptom Score						
CS Combined Score	Rhinoconjunctivitis	6 + meds	Yes	Yes	0-3	Combined scores of RTSS/6 + RMS/2
Global Assessment Global Assessment of Severity of Allergy	Total nasal and non-nasal symptoms	1	Yes	No	1-7	Single question about rhinitis severity

* Maximum score may vary depending on specific number of symptom related questions and specific medication score included.
** Higher score equates to better control of disease. A score of 0 denotes zero control of symptoms.
AR: allergic rhinitis; AC: allergic conjunctivitis; NAR: non-allergic rhinitis; meds: medications

Table III.D-2 Evidence for the role of validated survey instruments in the evaluation, diagnosis, and follow-up of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical end-point	Conclusion
Di Bona et al[815]	2015	1a	Systematic review	ARC	Meta-analysis of grass SLIT efficacy	Combined symptom and medication score showed efficacy of grass SLIT.
Calderon et al[801]	2014	1a	Systematic review	AR	Comparison of scoring systems	TNSS and combined medication scores should be used in clinical trials.
Demoly et al[803]	2016	1b	DBRPCT	AR	Efficacy of HDM SLIT tablet	TCRS confirmed efficacy of SLIT.
Zieglmayer et al[798]	2016	1b	RCT	AR	Efficacy of B-cell vaccine	TNSS score used to determine efficacy in large study.
Klimek et al[805]	2015	1b	RCT	ARC	Effectiveness of recombinant birch SCIT	Combined score and VAS revealed no difference between recombinant and standard birch SCIT.
Mosbech et al[799]	2015	1b	RCT	AR	Efficacy of HDM SLIT for AR	RQLQ used effectively in this evaluation.
Devillier et al[802]	2016	2b	Cohort	AR	Evaluation of AR by VAS, RTSS and RQLQ	Comparison of various outcome measures validates their utility.
Galimberti et al[814]	2015	2b	Cohort	AR, AC, asthma	Evaluation of RAP test	RAP test is valid for screening allergic disease
Devillier et al[813]	2014	2b	Cohort	ARC	Minimal clinically important difference of RTSS	RTSS vs RQLQ showed minimal clinically important difference of 1.
Hafner et al[806]	2012	2b	Cohort	ARC	Evaluation of RC-ACS test in 81 subjects	RC-ACS is a valid test for evaluating ARC without asthma.

LOE: level of evidence; ARC: allergic rhinoconjunctivitis; SLIT: sublingual immunotherapy; AR: allergic rhinitis; TNSS: Total Nasal Symptom Score; DBRPCT: double-blind randomized placebo controlled trial; HDM: house dust mite; TCRS: Total Combined Rhinitis Score; RCT: randomized controlled trial; SCIT: subsutaneous immunotherapy; VAS: visual analog scale; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RTSS: Rhinoconjunctivitis Total Symptom Score; AC: allergic conjunctivitis; RAP: Respiratory Allergy Prediction; RC-ACS: Rhinoconjunctivitis Allergy Control Score

VIII. E. 1. Skin prick testing (SPT)

SPT can be used, along with the history and physical examination, to confirm the diagnosis of AR and differentiate from non-allergic types of rhinitis. The confirmation of an IgE-mediated process guides avoidance measures and appropriate pharmacologic therapy. Skin testing is crucial to directing AIT, and therefore, should be utilized in eligible patients when AIT is being considered. According to the ARIA guidelines, patients should be considered for AIT when they have failed a 2- to 4-week trial of moderate-dose INCS combined with antihistamines.[101]

When an antigen is applied to the skin of a sensitized patient, the antigen cross-links IgE antibodies on the surface of cutaneous mast cells resulting in degranulation and release of mediators (including histamine) which leads to the formation of a wheal and flare reaction within 15-20 minutes.[816,817] Given the limited depth of penetration, SPT is safe with very rare reports of anaphylaxis and no reported fatalities.[818] SPT can be performed in any age group and is of particular value in pediatric populations given the speed at which multiple antigens can be applied and the limited discomfort experienced during testing.

Skin testing is not appropriate in all patients. Contraindications to SPT include uncontrolled or severe asthma, severe or unstable cardiovascular disease, concurrent beta-blocker therapy, and pregnancy. Certain medications and skin conditions may interfere with skin testing. These are covered in detail in section VIII.E.4. Issues that affect the performance or interpretation of skin tests – VIII.E.4.a. Medications and VIII.E.4.b. Skin conditions, respectively.

Aside from an excellent safety profile, SPT has a reported sensitivity and specificity around 80%.[818-820] It is reported to be more sensitive than serum testing with the added benefit of lower cost.[818,821,822] Despite studies aimed at comparing SPT, intradermal testing and serum testing, conclusive evidence marking one form of testing as superior to the others is lacking.[761]

The number and choice of antigens used in testing varies considerably between clinical practices. A panel of antigens representing an appropriate geographical profile of allergens that a patient would routinely be exposed to is recommended. Positive (histamine) and negative (glycerin or saline) controls should always be included. Variability in quality and potency between commercially available allergen extracts has been demonstrated.[823,824] Therefore, whenever possible, standardized allergens should be used.[820]

SPT is performed with lancets, which come in a variety of forms. Generally, lancets are designed to limit skin penetration depth to 1 mm. However, varying amounts of pressure applied to the delivery device can alter the depth of skin penetration, which ultimately influences the skin reaction to an antigen.[825] Prick testing devices can come as single lancet devices or multiple lancet devices. Multiple lancet devices have the advantage of being able to rapidly apply multiple antigens to the skin at one time with a more consistent amount of pressure.[826,827] Wheal size, sensitivity, and reproducibility all differ from one device to another;[826-828] therefore, any healthcare provider performing SPT must thoroughly familiarize themselves with his/her testing device. Typically, the lancet is dipped into a well containing an antigen and then applied to the skin.

The volar surfaces of the forearms and the back are the most common testing sites for SPT. Choice of site is directed by the age/size of the patient. Tests should be applied 2 cm or greater apart as placing them closer to one another can cause cross-contamination.[829] After 15-20 minutes, the results

are read by measuring the size of the wheal by its greatest diameter. A wheal 3 mm or larger than the negative control is considered positive.

There is a large body of evidence detailing the use of SPT in clinical practice. **[Table VIII.E.1.]** Based upon several prospective studies and systematic reviews, SPT has been demonstrated to be a safe method of allergy testing. It is not inferior to serum or intradermal testing and is less expensive than serum testing. It does carry a risk of systemic reaction, so caution should always be exercised. It is also associated with some discomfort during testing; however, the discomfort is generally less than that experienced during intradermal testing. Reviewing the available literature, a preponderance of benefit over harm for SPT exists. Therefore, the use of SPT is recommended in situations where the diagnosis of AR needs to be supported or a patient with presumed AR has failed appropriate empiric medical therapy.

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 3b: 7 studies; *Table VIII.E.1.*)
- Benefit: Supports diagnosis and directs pharmacological therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance, directs AIT.
- Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, and anaphylaxis, inaccurate test results, misinterpreted test results.
- Cost: Low.
- 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: SPT is recommended for evaluation of allergen sensitivities in appropriately selected patients. Regular use of the same SPT device 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 VIII.E.1. Evidence for the role of skin prick testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Nevis et al[830]	2016	1a	Systematic review and meta-analysis	Not applicable	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.
Krouse et al[831]	2004	3b	Prospective case-control	1. Alternaria SPT positive 2. Alternaria intradermal #2 dilution positive 3. Alternaria negative	Acoustic rhinometry of minimal cross sectional area of nasal cavity	Analysis of nasal provocation test results among groups showed a sensitivity of 42% and specificity of 44% for SPT using Alternaria antigen.
Krouse et al[832]	2004	3b	Prospective case-control	1. Timothy grass SPT positive 2. Timothy grass intradermal #2 dilution positive 3. Timothy grass negative	Acoustic rhinometry of minimal cross sectional area of nasal cavity	Analysis of nasal provocation test results among groups showed a sensitivity of 87% and specificity of 86% with multi-test application of timothy grass antigen
Gungor et al[833]	2004	3b	Prospective case-control	1. nasal provocation test positive 2. nasal provocation test negative	Sensitivity and specificity of SPT versus SET for diagnosing AR	SPT 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.
Zarei et al[834]	2004	3b	Prospective case-control	1. nasal provocation test positive 2. nasal provocation test negative	Wheal size that best identifies clinical allergy to cat based on nasal provocation testing	On SPT with cat antigen, a wheal size of $\geq$3 mm had a sensitivity of 100% and specificity of 74.1%. This improved with increasing size of wheal.
Pumhirun et al[835]	2000	3b	Prospective case-control	Perennial rhinitis patients	Compared sensitivity and specificity of intradermal testing to SPT and specific IgE assay for *D. pteronyssinus* and *D. farinae*	SPT for *D. pteronyssinus* and *D. farinae* were 90.4% and 86.4% sensitive and 99.5% and 93.1%, specific respectively. This compared to sensitivity of 96.3% and 88.9% and specificity of 96.2% and 88.9% of specific IgE assay.
Wood et al[793]	1999	3b	Prospective case-control	Patients with cat allergy determined by history and a cat-exposure model	Compared the predictive values of SPT, intradermal testing and RASTs in the diagnosis of cat allergy	SPT and RAST values exhibited excellent efficiency in diagnosis of cat allergy. Intradermal testing added little to the diagnostic evaluation. Sensitivity and specificity of SPT were 79 and 91%, respectively.
Tschoop et al[822]	1999	3b	Prospective case-control	A randomly selected sample of 8329 Swiss adults	Compared the sensitivity, specificity,	Sensitivity of fluoroenzyme immunoassay was significantly higher than SPT and IgE. However,

					PPV and NPV of SPT, IgE levels and fluoroenzyme immunoassay in diagnosing AR	SPT was more specific and had a better PPV. SPT was the most efficient test to diagnose AR.
Seidman et al[761]	2015	5	Guideline	Not applicable	Not applicable	Clinicians should perform and interpret or refer for specific IgE (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.
Heinzerling et al[836]	2013	5	Review	Not applicable	Not applicable	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.
Bernstein et al[818]	2008	5	Practice parameter	Not applicable	Not applicable	Sensitivity of SPT ranges from 85-87% while specificity is 79-86%. Many studies have verified the sensitivity and specificity of SPT.

LOE: level of evidence; SPT: skin prick test/testing; AR: allergic rhinitis; SET: skin endpoint titration; PPV: positive predictive value; NPV: negative predictive value; IgE: immunoglobulin E; RAST: radioallergosorbent test

VIII. E. 2. Skin intradermal testing

The placement of allergenic proteins in the intradermal space is often used for diagnosing AR. Intradermal testing has also been described in the evaluation of sensitivities to other substances, including local anesthetic agents, neuromuscular blocking agents, antibiotics and contrast media.[837-840] While previous protocols have described the use of intradermal testing for suspected food or chemical allergies, this type of diagnostic testing is currently not recommended in routine practice.[841,842] Intradermal testing may be used as a primary testing modality, or as a secondary test following SPT. Intradermal testing has also been used, primarily by otolaryngic allergists, as a method to help determine the starting point for specific AIT and as a vial safety test prior to an injection from a new treatment vial, though the level of evidence supporting these uses is low.[843,844]

Intradermal testing may be performed as a single injection. A short bevel needle is used to inject a diluted allergenic extract solution into the superficial dermis. Approximately 0.02 mL is used, or enough to produce a well-defined wheal which is 4 mm in diameter.[845] The wheal will expand to 5 mm by hydrostatic forces, and the reaction is observed for 10 minutes. The positive control for intradermal testing is histamine and the negative controls are typically phenolated saline and a glycerin solution which equals the concentration of glycerin in the test solution. If the diameter of the resulting wheal is at least 7 mm, and at least 2 mm wider than the glycerin control, this is considered a positive test.[846] While this is a very reproducible test, it is more technically demanding than SPT, is difficult to perform in young children and carries a higher risk of adverse reactions.[847] Severe adverse events related to intradermal testing are rare. Over a 42-year period, from 1945 to 1987, only 5 fatalities were attributed to intradermal testing without prior prick/puncture testing.[848]

Intradermal testing may also be performed using multiple dilutions of the same allergen to more precisely quantify the level of sensitivity to that allergen and suggest a starting point for immunotherapy.[849] A series of dilutions of concentrated allergenic extract (typically supplied as a 1:20 weight/volume solution) can be prepared in either a 1:5 or 1:10 ratio. Intradermal dilutional testing (IDT, previously referred to as skin endpoint titration, or SET) begins with the intradermal placement of a dilute allergen, along with appropriate controls, followed by the placement of progressively more concentrated dilutions of that allergen. The dilution producing the first positive test, as defined above, followed by progressively larger wheals is called the “endpoint”. To establish progression, a confirmatory wheal, produced by the next higher concentration, must be at least 2 mm wider than the suspected endpoint. IDT endpoint correlates with SPT wheal.[844,850,851] While IDT endpoints have been shown to correlate with biologically relevant measures, such as basophil histamine release, a clear correlation with other measures, such as *in vitro* sIgE levels, has not yet been established.[852,853] Currently, no studies have demonstrated a clear benefit of quantitative intradermal testing over single intradermal testing with regard to the diagnosis of clinical allergy or the outcome of specific immunotherapy. **[Table VIII.E.2.]**

As a stand-alone diagnostic test for AR, estimates for sensitivity for intradermal testing range between 60% (95% CI 31-83%) and 79% (63-90%), while estimates for specificity range between 68% (95% CI 49-82%) and 69% (52-86%).[793,833] This is lower than the pooled estimates of sensitivity (85-88%) and specificity (77%) for SPT, calculated from recent meta-analyses.[830,854] Factors affecting the predictive

value of intradermal testing include the comparator used and the concentration of allergen used with the intradermal test.[855]

It has been suggested that intradermal testing could potentially increase the sensitivity of SPT by injecting allergenic proteins into deeper tissue layers beneath the keratinized epidermis.[847] However, the literature has not supported a clear benefit of intradermal testing for this purpose. Using intradermal testing in addition to SPT to predict a positive response from nasal challenge with timothy grass only increased the sensitivity from 87-93%.[832] In a similar study, Krouse and colleagues determined that adding intradermal testing to SPT as a method to predict positive nasal challenge to *Alternaria* increased the sensitivity from 42-58%.[831] These studies suggest marginal increase in sensitivity that may vary based upon the allergen being tested.

Nelson and colleagues studied 28 individuals with a history of SAR.[856] One group had negative SPT to timothy and Bermuda grass, but positive intradermal testing for timothy grass, while the other group had negative SPT and negative intradermal testing for timothy and Bermuda grass. In both groups, 11% of individuals had a positive nasal challenge with timothy grass. Likewise, when 39 individuals with clinical cat allergy and negative SPT underwent a cat challenge, there was no difference in the development of upper respiratory symptoms between those who had positive or negative intradermal testing (24% vs. 31%, p=0.35).[793] Reddy, et al[857] evaluated allergy test results in 34 patients with perennial rhinitis. Patients with only intradermal positive skin tests (SPT negative) did not have a positive RAST nor a positive leukocyte histamine release. In contrast, SPT positivity was associated with positive RAST test and leukocyte histamine release assay.[857] Schwindt, et al[858] studied 97 subjects with allergic rhinoconjunctivitis symptoms. Prick testing was followed by intradermal testing if prick was negative. If patients were prick negative and intradermal positive, a nasal challenge was performed against 5 different allergens. If SPT with the multi-test II device was negative, only 17% of subjects had a positive intradermal test that corresponded with clinical history. None of these positive ID tests corresponded with a positive nasal challenge.[858] Taken together, these studies suggest that intradermal testing does not improve the diagnosis of allergy in subjects with negative SPT.

Nevis and colleagues conducted a systematic review of four studies to determine the sensitivity and specificity of intradermal testing when used as a confirmatory test following negative SPT.[830] Sensitivity ranged from 27% (95% CI 10-57%) to 50% (sample sizes were too small to calculate CI), while specificity ranged from 69% (95% CI 51-83%) to 100% (95% CI 83-100%). From a retrospective study by Larrabee and Reisacher, when the clinician was guided by high clinical suspicion, the incidence of positive intradermal testing following negative SPT was 36.9% for indoor allergens (*D. pteronyssinus*, *D. farinae*, cat, dog and cockroach), 12.7% for outdoor allergens (ragweed, red birch, timothy grass, white oak and red maple) and 9.2% for molds (*Aspergillus*, *Candida*, *Penicillium*, *Alternaria* and *Cladosporium*).[859] However, no correlation between positive intradermal testing and nasal challenge testing was performed in this study. Escudero et al[860] found that in rhinitis patients, SPT, intradermal and conjunctival challenge were more sensitive than serum sIgE. All testing methods had the same specificity.

In summary, current evidence supports the use of intradermal testing for the diagnosis of AR due to airborne allergens as a stand-alone test, although this form of testing demonstrates no clear superiority over SPT when comparing sensitivity and specificity. There were no studies identified which directly compared single dilution intradermal testing with IDT in terms of sensitivity, specificity or

patient outcomes. There appears to be a small gain in sensitivity when intradermal testing is used as a confirmatory test following negative SPT; however, positive intradermal test results in this setting could represent false positive test results. It is also more likely that an intradermal test following a negative SPT will be positive when indoor allergens are being tested and least likely to be positive when testing for mold sensitivity. It is unknown whether the type of allergen has an impact on the sensitivity and specificity, as most studies examined used only one allergen, but intradermal testing seemed to be least sensitive and specific when mold was being tested. Other limitations of the studies identified for this review include low sample population sizes (the largest included 120 participants), variable study design and the lack of randomized, controlled trials.

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 2b: 11 studies; Level 3b: 4 studies; Level 4: 1 study; *Table VIII.E.2.*).
- Benefit: Generally well tolerated, easy to perform and a favorable level of sensitivity and specificity when used as a stand-alone diagnostic test.
- Harm: Very low risk of severe adverse reactions.
- Cost: Low.
- Benefits-Harm Assessment: Benefit over harm when used as a stand-alone diagnostic test. Balance of benefit and harm when used to confirm the results of SPT, as a quantitative diagnostic test or as a vial safety test.
- Value Judgments: It is important to determine the presence of IgE-mediated sensitivity for individuals with suspected AR. If SPT is negative, there is limited clinical benefit to performing intradermal testing for confirmation.
- 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. The evidence for quantitative IDT is sparse and prevents a recommendation for this specific testing technique.
- Intervention: Intradermal testing may be used to determine specific airborne allergen sensitization for individuals suspected of having AR.

Table VIII.E.2. Evidence for the role of intradermal skin testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Nevis et al[830]	2016	1a	Systematic review	AR patients who underwent skin testing (n=430)	Sensitivity and specificity of skin testing methods	ID testing had higher sensitivity and specificity when used as a stand-alone test than when used to confirm SPT.
Larrabee et al[859]	2015	2b	Cohort	AR patients who underwent ID testing based on high suspicion after negative SPT (n=87)	Result of ID test	21% were ID positive, more likely for indoor allergens.
Gungor et al[833]	2004	2b	Cohort	Patients with SAR and ragweed sensitivity (n=62)	Nasal provocation testing, rhinomanometry	Sensitivity and specificity of ID testing was comparable to SPT
Krouse et al[832]	2004	2b	Cohort	SAR (n=37) 1. positive SPT 2. negative SPT, positive ID test 3. negative SPT, negative ID test	Nasal provocation with timothy grass, rhinomanometry	ID testing after SPT increased the sensitivity from 87% to 93%.
Krouse et al[831]	2004	2b	Cohort	AR (n=44) 1. positive SPT 2. negative SPT, positive ID test 3. negative SPT, negative ID test	Nasal allergen provocation score for Alternaria, visual analog scale, rhinomanometry	ID testing after SPT increased the sensitivity from 42% to 58%.
Wood et al[793]	1999	2b	Cohort	Patients with a history of symptoms with cat exposure (n=120)	Cat exposure challenge, symptom scores, FEV1	ID scores added little value beyond SPT and RAST values.
Nelson et al[856]	1996	2b	Cohort	(n=70) 1. SAR, negative SPT, positive ID test 2. SAR, positive SPT 3. SAR, positive SPT, positive ID test 4. no rhinitis	Nasal challenge with timothy grass	Positive ID along with negative SPT did not indicate the presence of clinically significant sensitivity.
Niemeijer et al[846]	1993	2b	Cohort	Allergy patients (n=41)	Simultaneous SPT, ID testing with varying concentrations	Coefficient of variation of ID test histamine wheal size is 6% within patients and 12%

					of Phleum and D. pteronyssinus, as well as pRAST on all subjects.	between patients. Optimum concentration of tested allergens was 10-100 BU/mL, a 7.5 mm ID wheal is ideal cutoff value for positive result (0.83X the size of average histamine wheal).
Niemeijer et al[855]	1993	2b	Cohort	Suspected allergy patients (n=497)	Simultaneous ID, pRAST, and clinical history compared. Standardized grass pollen, tree pollen, cat, dust mite tested.	Ideal cutoff for positive ID test is wheal diameter 0.7 times the size of histamine control. ID has 83% predictive value vs RAST and 77% predictive value vs clinical history.
Escudero et al[860]	1993	2b	Cohort	Rhinitis patients (n=66), 31 with Alternaria allergy	SPT, ID, challenge tests and *in vitro* sIgE. Clinical history and nasal/bronchial challenge considered gold standard.	For rhinitis patients, SPT, ID, and conjunctival challenge were more sensitive than serum sIgE. All testing methods had similar specificity.
Perera et al[853]	1975	2b	Cohort	Patients referred for allergy diagnostic testing (n=54)	Positive clinical histories compared to RAST results and IDT results	High degrees of skin reactivity (positive ID tests at high allergen concentrations) correspond with a higher rate of positive clinical history and positive RAST results.
Reddy et al[857]	1978	2b	Cohort	Patients with perennial rhinitis (n=34), negative SPT for 60 allergens but with at least one positive ID test	RAST, nasal provocation and leukocyte histamine release compared to ID positivity, SPT negativity	Patients with only ID positive skin tests (SPT negative) did not have a positive RAST nor a positive leukocyte histamine release. In contrast, SPT positivity was associated with positive RAST test and leukocyte histamine release assay. When SPT are negative for perennial rhinitis patients, positive ID tests are not likely to indicate the presence of IgE-mediated allergy.
Peltier & Ryan[844]	2007	3b	Cohort	Volunteers underwent simultaneous SPT and IDT for 5 common allergens (n=134)	SPT wheal size compared to IDT endpoint	IDT endpoint directly correlates with SPT wheal size for all antigens tested, especially for Bermuda, dust mite, and ragweed.
Peltier & Ryan[850]	2006	3b	Cohort	Volunteers tested simultaneously for mold allergens with SPT and IDT (n=86)	SPT wheal size compared to IDT endpoints	In subjects with clinical symptoms of allergy there was a direct statistically significant correlation between SPT wheal size and IDT endpoint. ID tests identified 10% more positive results compared to SPT alone.

Purohit et al[852]	2005	3b	Cohort	Patients with birch pollen allergy (n=18)	Correlations among IDT endpoint, serum sIgE, and provocation thresholds for basophil histamine release.	IDT endpoint correlated directly with basophil histamine release in response to allergen exposure. IDT endpoint did not correlate with rBet v 1 serum sIgE level.
Schwindt et al[858]	2005	3b	Cohort	Patients with allergy (n=97)	Using clinical history as gold standard, prick, ID and challenge test results compared	If SPT with multi-test II device was negative, 17% of subjects had a positive ID test that corresponded with clinical history. None of these positive ID tests corresponded with a positive nasal challenge. When multi-test II results are negative, positive ID tests are unlikely to identify clinically relevant aeroallergen sensitivity.
Simons et al[851]	2004	4	Retrospective cohort	Allergy clinic patients (n=34)	Patients tested for aeroallergen sensitivity with both IDT and SPT.	A significantly greater number of patient tested positive with IDT compared to SPT. SPT wheal size and IDT endpoint correlated for several allergens. IDT may be more sensitive than SPT.

1 LOE: level of evidence; AR: allergic rhinitis; ID: intradermal; SPT: skin prick test; SAR: seasonal allergic rhinitis; FEV1: forced expiratory volume in 1 second;
2 RAST: radioallergosorbent test; pRAST: Phadebas radioallergosorbent test; sIgE: antigen-specific immunoglobulin E; IDT: intradermal dilutional titration;
3
4

VIII. E. 3. Blended skin testing techniques

Blended allergy skin testing involves the combined use of SPT and intradermal testing to establish an 'end-point' for a specific antigen.[844,847,850] The protocol, initially described by Krouse and Krouse, and referred to as 'modified quantitative testing' (MQT), serves as an example of a blended technique.[861] MQT involves an algorithm where a SPT is used initially to apply an antigen. Depending upon the SPT result, an intradermal test may or may not be applied.[844,847,850,861] With these results, the algorithm is used to determine an endpoint for each antigen tested.[844,847,850,861] The endpoint signifies the skin reactivity to the applied antigen on a graded scale and is considered to be a safe starting dose for the application of AIT.[861] There is a small amount of literature on blended techniques, but AIT based upon the MQT results has been shown to be successful, with immune system alterations in line with other skin testing techniques.[861] **[Table VIII.E.3.]**

The advantages of blended techniques, such as MQT, are that they provide the practitioner with both qualitative data (the patient demonstrates sensitivity) and quantitative data (endpoint; safe starting dose for AIT) for specific antigen sensitivities in less time than IDT.[844,847,850] Disadvantages include the additional risk and time involved in placing intradermal tests. In comparison to IDT and *in vitro* testing methods, MQT has been shown to be more cost-effective when the prevalence of AR in a population is 20% or higher.[862] While blended skin testing techniques may be considered in the evaluation of AR, especially to determine the starting point for AIT, the evidence to support this technique is not strong.

- Aggregate Grade of Evidence: D (Level 3b: 1 study; Level 4: 4 studies; *Table VIII.E.3.*)
- Benefit: Ability to establish an endpoint in less time than IDT.
- Harm: The additional risks, including systemic or anaphylactic reactions, of intradermal tests; additional time and discomfort.
- Cost: Similar to intradermal testing.
- Benefits-Harm Assessment: Benefit outweighs harm.
- Value Judgments: AIT can be initiated from SPT results alone; however, endpoint-based AIT may decrease time to reaching therapeutic dose.
- Policy Level: Option.
- Intervention: MQT is a skin testing technique that may be used to determine a starting point for AIT.

Table VIII.E.3. Evidence for the role of blended skin testing techniques in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lewis et al[862]	2008	3b	Systematic review with cost effectiveness analysis		Comparison of sIgE, intradermal tests, and MQT from a payer perspective	MQT most cost-effective when population prevalence of AR is 20% or higher.
Fornadley[847]	2014	4	Systematic review		Review of skin testing techniques	MQT is a valid form of skin testing.
Peltier and Ryan[844]	2007	4	Case series	Adults with AR (n=134)	1. Intradermal tests for 5 antigens 2. SPT and subsequent IDT following MQT protocol for 5 antigens	MQT is a safe alternative to classic IDT for determining AIT starting doses.
Peltier and Ryan[850]	2006	4	Case series	Adults with AR (n=86)	1. Intradermal tests for 6 mold antigens 2. MQT for 6 mold antigens	MQT-based testing is a safe method for determining starting AIT doses for fungal allergens.
Krouse and Krouse[861]	2006	4	Case series	Adults with AR (n=9)	1. MQT 2. IgE and IgG4 levels for 3 antigens 3. SNOT-20, AOS, RSDI	MQT-based AIT demonstrates immune system changes and QOL improvement.

LOE: level of evidence; sIgE: antigen-specific immunoglobulin E; IDT: MQT: modified quantitative testing; AR: allergic rhinitis; SPT: skin prick testing; AIT: allergen immunotherapy; IgG4: immunoglobulin G4; SNOT-20: Sinonasal Outcome Test 20-question; AOS: Allergy Outcome Survey; RSDI: Rhinosinusitis Disability Index; QOL: quality of life

VIII. E. 4. Issues that affect the performance or interpretation of skin tests

VIII. E. 4. a. Medications

The wheal and flare reaction seen in allergy skin testing depends upon the physiologic actions of histamine released from mast cells upon degranulation. Thus, any medications that inhibit mast cell degranulation or that function as histamine H1 receptor antagonists have the potential to suppress appropriate skin test responses. The suppressive effects of H1 antihistamines on allergen and histamine induced wheal and flare responses vary greatly,[863,864] and the duration of this suppression depends upon the skin tissue concentration and half-life of these agents.[865,866] In fact, skin test suppression can be used as a biological assay for the onset and duration of action of antihistamines.[865] Agents such as astemizole (now removed from the market due to QT prolongation) have the potential to suppress skin test reactions for a period of weeks after cessation.[867] However, most antihistamines only suppress skin test responses for a period of 2-7 days after cessation.[867,868] Topically administered antihistamines have the potential to suppress skin wheal and flare responses. One randomized placebo-controlled study showed that 14 days of azelastine nasal spray treatment reduced the histamine induced wheal and flare response, and this suppression disappeared by 48 hours after cessation.[869] **[Table VIII.E.4.a-1]**

Randomized, placebo-controlled trials have demonstrated that H2 receptor antagonists such as ranitidine can reduce skin whealing responses,[870,871] and one study showed an additive effect of H1 and H2 antihistamines on skin wheal suppression.[872] Some antidepressants have the potential to suppress skin wheal and flare responses, in particular the tricyclic antidepressants that have antihistaminic properties (such as doxepin).[873] However, newer classes of antidepressants such as selective serotonin reuptake inhibitors (SSRI) do not appear to affect allergy skin test responses.[874]

Recombinant humanized anti-IgE monoclonal antibody (mAb), omalizumab, interferes with IgE mediated mast cell degranulation reactions in the allergy skin test response. A randomized placebo-controlled trial demonstrated a significant reduction in allergen-induced skin whealing after 4 months of treatment.[874] Omalizumab appears to suppress skin test reactivity in tandem with dramatic reductions in serum free IgE, and allergy skin test responses return to normal within 8 weeks of discontinuation.[875]

Leukotriene receptor antagonists (LTRAs) do not appear to interfere with allergy skin test results. Hill and Krouse[876] as well as Simons et al[866] found no effect of montelukast on intradermal skin test results in allergic subjects. Cuhadaroglu et al[877] found no change in skin prick test results in allergic subjects before and treatment with zafirlukast.

In general, the highest level evidence shows that systemic steroid treatment has no effect on SPT and intradermal test results,[878,879] though some less rigorous retrospective studies suggest that systemic steroid treatment could affect skin whealing responses.[880,881] Topical steroid treatment has been demonstrated to suppress the wheal and flare reaction in treated skin areas, creating the possibility of false negative test results.[882-885] No studies were identified that examined the effect of intranasal or inhaled steroids on skin test results.

The effects of many classes of medications on allergy skin test responses remain inadequately studied. Benzodiazepines have been implicated as possibly suppressing skin test responses.[886,887] The calcineurin inhibitor tacrolimus was shown to inhibit skin prick test whealing,[885] whereas a study of a similar drug, pimecrolimus, did not show any effect on skin whealing responses.[888] The pharmacologic effects of herbal preparations are generally unstudied, and it is unclear which of these agents could

interfere with allergy skin test responses. More et al[889] performed a double-blind placebo-controlled, single dose crossover study in 15 healthy volunteers, examining the histamine induced skin test response. None of the 23 herbal supplements tested caused suppression of the histamine induced wheal response.

There are many classes of medications for which the actual impact on allergy skin testing are unknown. To mitigate against the risk of false negative skin test results induced by medications, all allergy testing should be performed after application of appropriate positive controls (usually histamine) to ensure that the histamine induced skin test reaction is intact at the time of testing. See **Table VIII.E.4.a-1.** for a comprehensive review, with Aggregate Grades of Evidence in **Table VIII.E.4.a-2.**

Table VIII.E.4.a-1 Evidence for the effect of medication on allergy skin test reactivity

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusion
Kupczyk et al[871]	2007	1b	DBPCT, crossover	Atopic subjects (n=21). SPT with histamine, codeine, allergen, negative control after 5 days of ranitidine, loratadine, or placebo	Wheal, flare measured in mm. Pruritis measured with 10-point scale	Relative to placebo, ranitidine reduced histamine wheal (41%), flare (16%); allergen wheal (23%), and flare (22%). Loratadine reduced histamine wheal (51%) and flare (33%); allergen wheal (40%)and flare (44%) respectively. Ranitidine and loratadine both reduced pruritis scored by almost 30%.
Spergel et al[888]	2004	1b	RDBT, within subject comparison	Atopic dermatitis and AR or asthma (n=12 adults). Vehicle or pimecrolimus on each arm.	Allergen skin prick test wheal and flare, before and after topical 1% pimecrolimus cream	1% pimecrolimus cream does not significantly impact allergy skin test results.
Hill & Krouse[876]	2003	1b	RDBPCT	Atopic subjects (n=23)	Intradermal whealing response after loratadine, montelukast or placebo treatment	Loratadine, but not montelukast, reduced the intradermal wheal diameter after allergen injection.
More et al[889]	2003	1b	RDBPCT	Healthy volunteers (n=15). Single blinded dose of placebo, fexofenadine, 23 other herbal preparations. Minimum 72 hr washout period between doses.	Histamine 1mg/mL wheal at baseline and 4 hours after single dose of herbal preparation.	Fexofenadine significantly reduced SPT wheal size compared to placebo. None of the 23 herbal preparations tested showed a statistically significant effect on wheal size compared to placebo.
Noga et al[890]	2003	1b	RDBPCT	Moderate-severe asthmatics (n=35) treated with placebo or omalizumab.	Skin prick tests for allergen before and 16 weeks after treatment	Omalizumab caused significant reduction in SPT wheal size compared to placebo.
Pearlman et al[869]	2003	1b	RPCT	SAR patients (n=78)	Inhibition of histamine induced wheal after single dose or 2 weeks of azelastine nasal spray	2 weeks of azelastine inhibited wheal and flare in some patients. Histamine skin test responses returned to baseline at 48 hours after cessation.
Simons & Simons[865]	1997	1b	RDBPCT, crossover	Adult males (n=20)	SPT wheal and flare response after single day dosing of PO fexofenadine and loratadine	Fexofenadine and loratadine both inhibited SPT wheal and flare response for 24 hrs.

Miller & Nelson[870]	1989	1b	RDBT	Healthy subjects (n=23)	Histamine and compound 48/80 induced skin prick wheal and flare after placebo or raniditine 150mg x7 doses	Ranitidine reduced the histamine induced wheal and flare by 22%. No significant reduction in compound 48/80 induced wheal and flare.
Pipkorn et al[891]	1989	1b	RDBPCT	AR patients (n=10)	Allergen SPT wheal and flare before and after 2 to 4 weeks of twice daily clobetasol cream applied to forearm skin test sites	Clobetasol treated skin had significantly reduced wheal and flare response to allergen. Histamine induced wheal was reduced at 4 weeks by topical steroid.
Andersson & Pipkorn[883]	1987	1b	DBPCT	AR patients (n=17)	Effect of topical clobetosol (BID application for 1 week) on histamine and allergen SPT response.	Topical clobetosol significantly suppresses allergen induced wheal and flare response.
Slott & Zweiman[879]	1974	1b	DBPCT, crossover	Atopic patients (n=15)	Intradermal wheal size differences for histamine, allergen, and compound 48/80 after 7 days of methylprednisolone 24 mg per day	No effect of 7 days methylprednisolone on intradermal wheal size.
Cook et al[868]	1973	1b	Double blind randomized controlled study	AR patients (n=18 adults)	Intradermal wheal size suppression after 3 day course of chlorpheniramine, tripelennamine, promethazine, hydroxyzine and diphenhydramine	All antihistamines suppressed wheal size to varying degrees. Hydroxyzine suppressed responses for 4 days after cessation vs. 2 days for diphenhydramine.
Isik et al[874]	2011	2b	Cohort	Patients on SSRIs for depression (n=24)	Histamine and allergen induced prick test wheal responses before and after starting SSRI treatment.	SSRIs fluoxetine, sertraline, and escitalopram did not significantly affect skin prick whealing responses.
Corren et al[875]	2008	2b	Cohort	PAR patients (n=40)	Dust mite allergen skin test reactivity (titrated prick tests) before during and after omalizumab therapy.	Omalizumab (anti-IgE) therapy significantly reduces allergy skin test reactivity.
Gradman & Wolthers[885]	2008	2b	Randomized crossover cohort	Atopic eczema patients (n=12 children)	SPT for 10 allergens before and after active treatment with topical mometasone or topical tacrolimus. Skin test sites were presumably treated daily for a total of 2 weeks.	Topical mometasone and tacrolimus significantly reduced SPT wheal diameter. Topical mometasone also reduced histamine induced wheal, while tacrolimus did not.
Narasimha et al[882]	2005	2b	Cohort	26 subjects	Effect of topical clobetasol application on histamine induced wheal response.	Topical clobetasol inhibited skin prick whealing response to histamine at the site of topical steroid application in a dose and duration dependent manner.

Cuhadaroglu et al[877]	2001	2b	Cohort	1. asthma/AR patients (n=9) 2. controls (n=8)	SPT to histamine and allergens before and after zafirlukast 20 mg BID for at least 5 days.	Zafirlukast did not suppress histamine or allergen induced wheal and flare response.
Des Roches et al[878]	1996	2b	Cohort	1. steroid dependent asthma patients (n=33) 2. asthma and/or AR (n=66)	Codeine and dust mite induced SPT response with or without exposure to long term systemic steroids.	Systemic steroid therapy does not alter SPT reactivity to codeine or allergen.
Almind et al[867]	1988	2b	Cohort	Healthy individuals (n=23)	Effect on histamine SPT wheal size after 2-day treatment with dexchlorfeniramine, cyproheptadine, astemizole, loratidine, terfenadine. Duration of SPT wheal suppression after cessation.	All antihistamines suppressed SPT wheal response to histamine. Duration of suppression exceeded 72 hours for all agents tested.
Rao et al[873]	1988	2b	Cohort	Healthy subjects (n=33)	Histamine prick tests for 1 week after single dose of desipramine or doxepin.	Desipramine inhibits wheal response for 2 days; doxepin inhibits wheal response for 4 days.
Long et al[863]	1985	2b	Cohort	18 subjects. 10 had positive SPT to grass or ragweed allergens.	Effect of 6 different antihistamines on SPT wheal and flare reaction to histamine or morphine or relevant aeroallergen. Effect of hydroxyzyine and chlorpheniramine on skin test responses to other antihistamine classes.	Antihistamines varied in their ability to suppress SPT wheal response. Administration of hydroxyzine for 3 weeks leads to reduced skin test suppression for the antihistamines tested, suggesting induction to tolerance to antihistamine effects.
Phillips et al[864]	1983	2b	Cohort	Atopic subjects (n=10)	Inhibition of allergen and histamine induced wheals by local intradermal antihistamine and cromoglycate injection.	Antihistamines ketotifen, clemastine, and chlorpheniramine significantly inhibit skin whealing responses. Sodium cromoglycate had no effect.
Harvey & Schocket[872]	1980	2b	Cohort	Healthy subjects (n=10)	Titrated intradermal histamine wheal before and after. treatment with hydroxyzine, cimetidine or both.	Hydroxyzine inhibited cutaneous wheal response to histamine. Cimetidine did not. However, the 2 together produced significantly reduced whealing compared to either alone.
Geng et al[881]	2015	3b	Case-control	1. cases with negative histamine control tests despite avoidance of antihistaminic medications (n=52)	OR that multiple clinical variables including medication use predict negative histamine control test.	ICU stay, systemic steroid use, H2 blockers and older age associated with negative histamine control test.

				2. controls (n=125)		
Shah et al[886]	2010	4	Retrospective cohort	Histamine SPT responses in patients with variable exposure to a variety of medications	SPT wheal area and SPT positivity as function of medication exposure and time since last dose.	H1 antagonists impaired whealing responses within 3 days of discontinuation; tricyclic antidepressants, benzodiazepines, mirtazapine, quetiapine had wheal suppression; other SSRIs and SNRIs as well as H2 antagonistis were not independently associated with wheal suppression.
Olson et al[880]	1990	4	Retrospective cohort	1. atopic patients with chronic systemic steroid treatment (n=25) 2. atopic patients without systemic steroid use (n=25)	Intradermal skin test reactivity to codeine and histamine.	Chronic systemic steroid use reduces codeine induced wheal response but not histamine induced wheal response.
Duenas-Laita et al[887]	2009	4	Cohort	Drug abusers taking alprazolam 2 mg TID (n=42)	Histamine (10mg/mL) SPT.	All subjects taking alprazolam had negative histamine SPT.

LOE: level of evidence; DBPCT: double-blind placebo controlled trial; RDBT: randomized double blind trial; RDBPCT: randomized double-blind placebo controlled trial; SPT: skin prick test; RPCT: randomized placebo controlled trial; SAR: seasonal allergic rhinitis; PO: per os (by mouth); AR: allergic rhinitis; BID: twice a day; SSRI: selective serotonin reuptake inhibitor; PAR: perennial allergic rhinitis; IgE: immunoglobulin E; ICU: intensive care unit; SNRI: selective norepinephrine reuptake inhibitor

Table VIII.E.4.a-2 Aggregate grades of evidence: medications that affect allergy skin testing

H1 antihistamines	Aggregate Grade of Evidence: A (Level 1b: 2 studies, Level 2b: 3 studies) • *Should be discontinued 2-7 days prior to testing.*
H2 antihistamines	Aggregate Grade of Evidence: B (Level 1b: 2 studies) • *Ranitidine suppresses skin whealing response, may result in false negatives.*
Topical antihistamines (nasal, ocular)	Aggregate Grade of Evidence: Unable to determine from one Level 1b study. • *Should be discontinued 2 days prior to testing.*
Anti-IgE (omalizumab)	Aggregate Grade of Evidence: A (Level 1b: 2 studies) • *Results in negative allergy skin test results.*
Leukotriene receptor antagonists	Aggregate Grade of Evidence: A (Level 1b: 2 studies, Level 2b: 1 study) • *May be continued during testing.*
Tricyclic antidepressants	Aggregate Grade of Evidence: Unable to determine from one Level 2b study. • *Agents with antihistaminic properties suppress allergy skin test responses.*
Topical (cutaneous) corticosteroids	Aggregate Grade of Evidence: A (Level 1b: 2 studies, Level 2b: one study) • *Skin tests should not be placed at sites of chronic topical steroid treatment.*
Systemic corticosteroids	Aggregate Grade of Evidence: C (No effect – Level 1b: 1 study, Level 2b: 1 study; Suppression – Level 3b: 1 study, Level 4: 1 study) • *Systemic corticosteroid treatment does not significantly impair skin test responses.*
Selective serotonin reuptake inhibitors (SSRIs)	Aggregate Grade of Evidence: B (Level 2b: 1 study, Level 4: 1 study) • *Does not suppress allergy skin test response.*
Benzodiazepines	Aggregate Grade of Evidence: C (Level 4: 1 study, Level 5: 1 case report) • *May suppress skin test responses.*
Topical calcineurin inhibitors (i.e. tacrolimus, picrolimus)	Aggregate Grade of Evidence: D (Level 1b: 1 study, Level 2b: 1 study – results conflicting) • *Conflicting results regarding skin test suppression.*

VIII. E. 4. b. Skin conditions

The usefulness of allergy skin testing depends upon the ability to detect a Type I hypersensitivity reaction after allergen introduction into the skin. Abnormal skin (e.g. dermatitis) may not respond appropriately to histamine, glycerin, or allergen. Additionally, the physical trauma of prick/puncture or intradermal testing may induce a local inflammatory response. The wheal and flare reaction also may be difficult to detect due to pre-existing skin changes. Further, skin color may inhibit the ability to visualize the flare reaction, especially in darker skinned individuals.

Common sense dictates that allergy skin testing should not be performed at sites of active dermatitis, but clinical studies to investigate this phenomenon are lacking. Individuals with dermatographism may have exaggerated responses to allergy skin testing, requiring close attention to the results of negative control tests. In some cases, it may be preferable to perform *in vitro* specific IgE testing in patient with skin disease or dermatographism, but this is not based on data or outcomes from controlled studies.

Due to the lack of published studies on this topic, an Aggregate Grade of Evidence and evidence based recommendation cannot be provided.

VIII. F. *In vitro* testing

VIII. F. 1. Serum total IgE (tIgE)

The literature addressing the role of serum tIgE in the evaluation and diagnosis of allergic disease offers conflicting outcomes and divergent opinions. Positive studies, demonstrating a relevant role of measuring tIgE in the evaluation and diagnosis of AR, are listed in **Table VIII.F.1-1**. Negative studies that report a limited role of measuring tIgE are listed in **Table VIII.F.1-2**. When taken together, however, this body of literature provides some information that can inform decisions related to the utility of tIgE in directing patient care decisions.

Perhaps the strongest statement that can be made on behalf of tIgE is its ability to generally identify patients or populations with atopic or allergic disease. For example, Ando and Shima[892] reported that tIgE is higher in children with AR than in peers with NAR. Marinho et al[893] found a borderline association between tIgE and current rhinitis. In a retrospective study, Kalpaklioglu et al[894] reported that tIgE is higher in AR than in NAR. Jung et al[895] conducted a prospective study that showed a tIgE cut-off of 98.7 IU/mL as a strong predictor of AR. Salo et al[454] performed a cross-sectional study reporting significant associations between tIgE levels and current hay fever in different age classes. Demirjian et al[896] demonstrated that a tIgE level over 140 IU/mL is suggestive of an atopic cause for patients with clinical symptoms of AR. Hatcher et al[897] showed that an elevated tIgE in the presence of a negative inhalant-specific IgE screen may suggest the presence of unidentified inhalant allergen sensitization or chronic respiratory inflammatory disease other than AR. Karli et al[898] reported that tIgE is helpful in confirming the diagnosis but it cannot be recommended for routine use due to its high cost and the time to perform the test. Chung et al[899] reported that tIgE (cut-off value 150 IU/mL) is a reliable biomarker for AR diagnosis. Jacobs et al[900] reported a favorable role of measuring tIgE in diagnosing AR, mainly if levels are higher than 100 IU/mL. Li et al[901] observed that tIgE is higher in AR than in NAR in a retrospective study. Finally, in a 2-year follow-up study, Park et al[902] showed that in subjects without allergic

sensitization at the initial examination, tIgE greater than 17.7 IU/mL was associated with the risk for allergic sensitization, whereas in patients with allergic symptoms but negative SPT results at the initial examination, tIgE greater than 17.4 IU/mL was associated with newly developed allergic sensitization.

In contrast, there are 4 studies with negative results in the setting of tIgE and AR/allergy. Satwani et al[903] reported no association between tIgE level and AR diagnosis. Tu et al[904] demonstrated an insufficient diagnostic accuracy of tIgE levels to detect allergic diseases regardless of which cutoff value is being used; tIgE was linked more to atopy than directly to symptoms. In the same follow-up study noted above, Park et al[902] reported that in subjects without allergic sensitization at the initial examination, tIgE less than 17.7 IU/mL was not associated with newly developed allergic nasal symptoms. Finally, Tay et al[905] conducted a retrospective analysis in patients with high tIgE levels (>1000 IU/mL) and concluded that the elevated IgE level in AR is of limited clinical/diagnostic value.

Another opportunity offered by tIgE assessment is the ratio between allergen-specific and tIgE. It has been reported that this ratio might be useful in the prediction of AIT effectiveness,[906-908] as recently outlined by the EAACI Position Paper.[909]

In summary, tIgE is frequently increased in AR, but the clinical utility is modest in common practice. In fact, the literature is a divergent set of studies that fails to find a consistent role or value for tIgE in the management of AR patients.

- Aggregate Grade of Evidence: C (Level 2b: 5 studies; Level 3b: 10 studies; *Tables VIII.F.1-1. and VIII.F.1-2.*)
- Benefit: Possibility to suspect allergy in a wide screening.
- Harm: Low level does not exclude allergy.
- Cost: Modest cost of test.
- Benefits-Harm Assessment: Slight preponderance of benefit over harm. In addition, the ratio tIgE/sIgE may be useful.
- Value Judgments: The evidence does not support a routine use.
- Policy Level: Option
- Intervention: Total IgE assessment is an option to assess atopic status.

Table VIII.F.1-1 Evidence supporting the use of total IgE in allergic rhinitis or allergy diagnosis

Study	Year	LOE	Study design	Study groups	Endpoint	Conclusion
Park et al[902]	2016	2b	Prospective cohort	313 school children, 2-year follow-up study	Initial examination: no allergic sensitization, serum tIgE >17.7 IU/mL	Associated with the risk for allergic sensitization (sensitivity: 46.3%; specificity: 85.3%; OR: 4.8).
					Initial examination: allergic symptoms but negative SPT, serum tIgE >17.4	Associated with newly developed allergic sensitization (sensitivity: 69.9%; specificity: 100.0%).
Demirjian et al[896]	2012	2b	Prospective cohort	Patients referred to allergy clinic. Total patients (n=358,184 with rhinitis), mean age 57 years.	serum tIgE (IU/mL), continuous variable	tIgE levels >140 IU/mL is suggestive of an atopic etiology for patients with rhinitis.
Jung et al[895]	2011	2b	Prospective cohort	Patients with AR symptoms (n=442), median age 33 years.	Serum tIgE >98.7 IU/mL	tIgE cut-off: 98.7 IU/mL is a strong predictor of AR. (OR 6.93, CI 4.19-9.62, p<0.001), (AUC: 0.79 [0.74-0.83]), PPV: 71.3%, NPV: 73.7%.
Marinho et al[893]	2007	2b	Whole-population birth cohort	478 children from MAAS	Serum tIgE (kU/L), continuous variable	Borderline association with current rhinitis (UnAdjOR* 1.2, CI 1.02-1.3), not significant at multivariate analysis. Association with current rhinoconjunctivitis (UnAdjOR* 1.3, CI 1.1-1.5), not significant at multivariate analysis.
Li et al[901]	2016	3b	Retrospective case series	Patients from otolaryngology clinic. Total patients (N=610 adults, 349 with AR), median age 27.0 years.	Serum tIgE (IU/mL), continuous variable	Serum tIgE were higher in AR (166.0 [58.4-422.5] IU/mL) than in NAR pts (68.8 [24.5-141.0]) IU/mL. p<0.001
Chung et al[899]	2014	3b	Retrospective case series	Patients from otolaryngology clinic. Total patients (n=1073 children and adults, 753 with rhinitis), mean age 36.9 years.	Serum tIgE level >150 IU/mL	Serum tIgE levels (cutoff value: 150 IU/mL) has good PPV (89.6%), and NPV (10%) in the *in vitro* diagnosis of AR (AUC: 0.88).

Jacobs et al[900]	2014	3b	Cross-sectional	547 children (6-14 years) from randomly selected households; 265 with skin test positive AR.	Log serum tIgE (kU/L)	serum tIgE level are significantly associated with increased odds of skin test positive AR in children with asthma (OR 2.3, CI 1.5-3.5) but not with those without asthma (OR 1.6, CI 0.9-2.8). AR can be diagnosed if serum tIgE=>100 kU/L both in asthmatics (AUC: 0.77 [0.72-0.82], PPV: 85.1%, NPV: 68%) and in non-asthmatics (AUC: 0.84 [0.79-0.89], PPV: 77.8%, NPV: 90.9%).
Hatcher et al[897]	2013	3b	Retrospective case series, followed by a prospective study	1. 30 pts (>=6 years) with a negative allergy screen and serum tIgE >116 kU/L 2. 26 control pts with negative allergy screen and stIgE<2.95 kU/L (Chronic sinusitis in 76.9% of study group and 19.2% of control group [p<0.0001].)	Serum tIgE (kU/mL), continuous variable	Elevated serum tIgE in the presence of a negative inhalant-specific IgE screen may suggest the presence of unidentified inhalant allergen sensitization or chronic respiratory inflammatory disease other than AR. Mean serum tIgE of the study group was 363.3 kU/L vs. control group 2.2 kU/L, p<0.0001.
Karli et al[898]	2013	3b	Retrospective case series	Patients from otolaryngology clinic with at least 2 complaints of nasal itching, nasal obstruction, rhinorrhea, and sneezing, and/or presumed AR (n=295), mean age 33.9 years.	Serum tIgE (U/mL), continuous variable	tIgE <20 U/mL in 23.7%, tIgE 20-100 U/mL in 38.3%, tIgE>100 U/mL 33.8%. tIgE is a factor in confirming the diagnosis, but routine use is not recommended due to high cost and testing time.
Salo et al[454]	2011	3b	Cross-sectional	7,398 subjects (>6 years) from NHANES 2005-2006.	Serum tIgE (kU/L), continuous variable	Association with current HF (OR 1.9, CI 1.4-2.4).
				Children (6-17 years)	Serum tIgE >40.8 kU/L (median).	Association with current HF (OR 2.1, CI 1.4-3.1).
					Serum tIgE (kU/L), continuous variable	Association with current HF (OR 2.2, CI 1.1-4.4).
				Adults (>18 years)	Serum tIgE (kU/L), continuous variable	Association with current HF (OR 1.9, CI 1.4-2.6).
				Male	Serum tIgE (kU/L), continuous variable	Association with current HF (OR 2.1, 1.6-2.8).

				Female	Serum tIgE (kU/L), continuous variable	Association with current HF (OR 1.7, 1.2-2.3).
Kalpaklioglu et al[894]	2009	3b	Retropective case series	Consecutive and unselected pts from a tertiary care clinic. (n=323,205 with AR), mean age 31.7 years.	Serum tIgE (IU/mL), continuous variable	Serum tIgE higher in AR (261) than in NAR (126), p<0.01.
Ando & Shima[892]	2007	3b	Cross-sectional	School children (n=98 with AR), 9-10 years old	Serum tIgE levels (IU/mL) expressed as geometric means, continuous variable	Serum tIgE higher in AR (230.4, CI 157.6-337.0) than in NAR (96.5, CI 76.9-121.1), p<0.001

* The OR indicates an increase in the risk of current rhinitis/chronic RC per log unit increase of IgE levels.
All reported odds ratio (OR) are adjusted unless differently specified and are reported with 95% confidence intervals in parentheses.
IgE: Immunoglobulin E; LOE: level of evidence; tIgE: total immunoglobulin E; OR: odds ratio; CI: 95% confidence interval; AUC: area under the curve; SPT: skin prick test; AR: allergic rhinitis; PPV: positive predictive value; NPV: negative predictive value; MAAS: Manchester Asthma and Allergy Study; UnAdj: unadjusted odds ratio; NAR: non-allergic rhinitis; NHANES: The National Health and Nutrition Examination Survey; HF: hay fever

Table VIII.F.1-2 Evidence indicating a limited role for the use of total IgE in allergic rhinitis or allergy diagnosis

Study	Year	LOE	Study design	Study groups	Endpoint	Conclusion
Park et al[902]	2016	2b	Prospective cohort	313 schoolchildren, 2-year follow-up study	Initial examination: no allergic sensitization, serum tIgE <17.7 IU/mL	No association with newly developed allergic nasal symptoms.
Tu et al[904]	2013	2b	Population-based cohort	1,321 children (5-18 yrs) from PATCH study	Serum tIgE (kU/L)	AUC of serum tIgE for diagnosing rhinitis: 0.70.
					Serum tIgE >77.7 kU/L	Sensitivity: 74.7%, specificity: 56.6%, PPV: 41.9%, NPV: 84.2%
					Serum tIgE >164.3 kU/L	Sensitivity: 57.0%, specificity: 71.3%, PPV: 45.5%, NPV: 79.8%
					Serum tIgE >100 kU/L	Sensitivity: 68.1%, specificity: 62.5%, PPV: 43.2%, NPV: 82.4%
						Insufficient diagnostic accuracy of serum tIgE levels to detect allergic diseases regardless of cutoff value used. Serum tIgE is linked more to atopy than directly to symptoms.

Tay et al[905]	2016	3b	Retrospective case series	352 pts with serum tIgE >1000 IU/mL attributable to atopic eczema, allergic broncho-pulmonary aspergillosis, helminthic infection and rare primary immunodeficiencies. (n=84 with AR).	serum tIgE (IU/mL)	The elevated IgE level in AR is of limited diagnostic utility.
Satwani et al[903]	2009	3b	Cross-sectional	258 pts (6 months-12 years) from a Pediatric Medicine Unit; (n=172 with AR).	Elevated serum tIgE	No association of tIgE and AR (UnAdjOR 1.3, CI 0.8-2.2).

IgE: Immunoglobulin E; LOE: level of evidence; tIgE: total immunoglobulin E; PATCH: Prediction of Allergies in Taiwanese Children; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; AR: allergic rhinitis; UnAdj: unadjusted odds ratio; CI: 95% confidence interval

VIII. F. 2. Serum antigen-specific IgE (sIgE)

sIgE testing became commercially available in 1967 with an assay reliant on radioactive anti-IgE for labeling IgE in serum.[910,911] This radioactive technique, known as RAST, has largely been replaced with other technologies using enzymatically-driven reactions to produce a chemiluminescent, colorimetric, or fluorimetric reaction quantified or "read" by an autoanalyzer.[910,912] The process is as follows: allergens are bound to a substrate (typically in the form of a solid or liquid phase) to which a patient's serum is added. sIgE in the patient's serum then binds to the allergen on the substrate. Excess serum is washed off and with it, any unbound IgE. Non-human anti-IgE antibodies tagged by a marker are subsequently added and bind any corresponding sIgE that is immobilized. Excess anti-IgE antibodies are then washed off and the autoanalyzer reads the intensity of the radioactive, chemiluminescent, colorimetric or fluorimetric reaction. The intensity of the reaction is proportional to the amount of sIgE in the serum and a report is generated. All tests approved by the US FDA are calibrated against a World Health Organization (WHO) tIgE standard serum.[913] Different units are reported depending on the assay system used, but many vendors offer conversion factors.

Serum sIgE testing offers several benefits. The safety profile of serum sIgE testing is the best of all available allergy tests as the risk for anaphylaxis is non-existent. Furthermore, the use of skin testing is limited by the presence of certain medical conditions. In patients where skin testing is contraindicated or potentially impacted by medications or skin conditions, sIgE testing offers a safe and effective option for determining the presence of sensitization as a biomarker of IgE-mediated hypersensitivities and confirming specific allergen triggers.

There are some important similarities and differences between skin testing and sIgE testing that warrant discussion. First, studies have indicated that while patients are accepting of both *in vitro* and *in vivo* allergy testing, skin testing may be preferred because it allows for immediate feedback and visible results.[914] Second, neither skin or sIgE testing can definitively predict the severity of a patient's sensitivity to an aeroallergen. Third, cross-reacting allergens and poly-sensitizations can confound both skin and *in vitro* testing, leading to false positive results.[915] In contrast to skin testing, sIgE tests use more extensively quality-controlled allergens and defined human serum controls. Whereas skin testing depends upon the clinician administering and interpreting the test, sIgE tests have coefficients of variation less than 15% in the College of American Pathologists diagnostic allergy proficiency survey, which is performed 3 times per year by all Clinical Laboratory Improvement Act of 1988 licensed Clinical Immunology Laboratories. However, several reports have demonstrated poor agreement in results from testing the same sera by different commercially available assay systems.[916,917] As with skin testing, sIgE results should be interpreted within the context of the patient's clinical history.

One application of sIgE technology is multi-allergen screens consisting of 10-15 allergens. In scenarios where a clinician wishes to either rule in or out allergy as a driving factor behind symptoms without subjecting patients to the time and cost of a full testing battery, sIgE screens are an option. Generally, either a negative or positive result is given. Screens testing for 10-12 allergens (i.e. molds, regional pollens, cat and mite) are positive in up to 95% of patients who would have tested positive on a larger battery.[912,918] Therefore, they are effective in identifying allergic patients. Conversely, if the test is negative, there is evidence that this reliably supports an absence of allergy.[910] A second application lies in the fact that levels of sIgE may correlate with severity of AR symptoms.[919-923] Given that patients with

more severe symptoms have been shown to respond better to AIT than those with milder symptoms, sIgE may help in the selection of candidates for AIT and possibly predict the response.[919,924] Third, in polysensitized patients, it can be difficult to determine the most relevant allergen on SPT. In these situations, sIgE levels can help discriminate the most relevant allergen and guide AIT.[920]

Studies have shown that sIgE testing has a sensitivity between 67-96% and specificity of between 80-100%.[793,822,835,925,926] Further, it has been demonstrated that sIgE shows excellent correlations with both NPT and SPT in the diagnosis of AR.[793,822,835,857,911] There is good evidence to show that sIgE is, in many ways, equivalent to SPT.[218,818,925] The decision to perform sIgE must be based upon a thorough history and physical examination to confirm the presence of allergy and guide therapy when necessary. It is important to note that while sIgE levels are a biomarker of allergic sensitization, this test alone cannot provide a definitive diagnosis of allergy due to the high rate of clinically irrelevant (false positive) tests without an indicative clinical history. Based on the reviewed literature, sIgE testing is an acceptable alternative to skin testing and is safe to use in patients who are not candidates for skin testing. **[Table VIII.F.2]**

- Aggregate Grade of Evidence: B (Level 3b: 7 studies; *Table VIII.F.2.*)
- Benefit: Confirms sensitization in support of an AR diagnosis and directs appropriate therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance measures, directs AIT.
- Harm: Adverse events from testing including discomfort from blood draw, inaccurate test results, false positive test results, misinterpreted test results.
- Cost: Moderate cost of testing.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Patients can benefit from identification of their specific sensitivities. Further, in some patients who cannot undergo skin testing, sIgE testing is a safe and effective alternative.
- Policy Level: Recommendation.
- Intervention: Serum sIgE testing may be used in the evaluation of AR. Using standardized allergens and rigorous proficiency testing on the part of laboratories may improve accuracy.

Table VIII.F.2. Evidence for the use of serum sIgE testing in the diagnosis of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Chinoy et al[927]	2005	3b	Prospective cohort	Patients with AR and/or bronchial asthma (n=118)	Compare skin test reactivity with serum sIgE antibodies	For 4 indoor allergens, skin test was more sensitive than RAST. Skin test and RAST scores showed weak to moderate correlation.
Pumhirun et al[835]	2000	3b	Prospective cohort	Perennial rhinitis patients	Compared sensitivity and specificity of SPT to sIgE assay for D. pteronyssinus and D. farinae	sIgE for D. pteronyssinus and D. farinae had sensitivity of 96.3% and 88.9% and specificity of 96.2% and 88.9%, respectively. This compared to sensitivity of 90.4% and 86.4% and specificity of 99.5% and 93.1% for SPT.
Tschoop et al[822]	1998	3b	Prospective cohort	Randomly selected sample of 8329 Swiss adults	Compared the sensitivity, specificity, PPV and NPV of SPT, tIgE, and fluoroenzyme immunoassay in diagnosing AR	Sensitivity of fluoroenzyme immunoassay was significantly higher than SPT and IgE. SPT was more specific and had a better PPV. SPT was the most efficient test to diagnose AR.
Wood et al[793]	1999	3b	Prospective cohort	Patients with cat allergy determined by history and a cat-exposure model	Compared the predictive values of SPT, IDT and RASTs in the diagnosis of cat allergy	SPT and RAST values exhibited excellent efficiency in diagnosis of cat allergy. IDT added little to the diagnostic evaluation. Overall sensitivity and specificity of RAST was 69% and 100%, respectively.
Ownby & Bailey[925]	1986	3b	Prospective cohort	Children age 4-19 years	Diagnostic levels by MAST and RAST were compared to skin test reactions for ragweed, grass, house dust and mite	MAST had a sensitivity of 59%, specificity of 97%, efficiency of 72%, compared with 67%, 97%, and 78%, respectively for RAST. Neither MAST or RAST as sensitive as skin test.
Ferguson & Murray[926]	1986	3b	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 and specificity was 71-74% and 88-90%, respectively. SPT sensitivity and specificity 68-76% and 83-86%, respectively.
Reddy et al[857]	1978	3b	Prospective cohort	1. 34 patients with history of PR but negative SPT 2. 19 patients with history PR and positive SPT 3. Healthy controls	To determine the clinical relevance of positive intracutaneous test when epicutaneous test is negative	Good agreement between SPT, RAST and NPT. Poor agreement between positive IDT at 1:1,000 concentration and SPT, RAST and NP tests.
Wide et al[911]	1967	3b	Prospective cohort	31 allergic patients	AcR of minimal CSA of nasal cavity	Good correlation between provocation tests and *in vitro* tests for allergy.

Seidman et al[761]	2015	5	Guideline	Not applicable	Not applicable	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.
Bernstein et al[818]	2008	5	Review-practice parameter	Not applicable	Not applicable	Sensitivity of sIgE ranges from 50-90% with an average of 70-75%. sIgE may be used along with history and physical for diagnosis of allergy and may be preferable in certain conditions.

LOE: level of evidence; AR: allergic rhinitis, ST: RAST: radioallergosorbent test, IDT: intradermal testing, SPT: skin prick testing, PPV: positive predictive value, NPV: negative predictive value, MAST: multiple allergosorbent test, NP: nasal provocation, AcR: acoustic rhinometry, CSA: cross-sectional area

VIII. F. 3. Correlation between skin and *in vitro* testing

Allergen skin testing has been used to diagnose allergic disease since first introduced by Blackley 140 years ago.[791,928] The discovery of IgE in 1969 allowed for the development of *in vitro* serological tests which have become increasingly utilized.[929] However, skin testing and sIgE serology portend unique biological functions. Therefore, the two tests are not fully interchangeable.

Modern SPT of aeroallergens can be up to 25% more sensitive than sIgE serology depending on the patient population and the methodologies employed.[793,930-934] In the United States, SPT also generally costs about half as much as sIgE serology ($6.82 versus $12.50 per allergen tested).[935] Other factors to consider include access to laboratory technology, comorbid disease and the age of the patient. *In vitro* testing avoids the need to withhold medications that affect skin testing and allows for testing in subjects with dermatographism or other widespread skin disorders. SPT measurements are directly observable within 20 minutes, which is typically much faster than laboratory reports are obtained. Both sIgE serology and SPT are considered very safe techniques; however, SPT does carry a very small risk of anaphylaxis. Nonetheless, there have only been two recorded deaths from skin testing ever reported in the literature and one involved over 90 scratch tests to foods.[936]

The sensitivity and specificity of SPT depends on the allergen tested, quality of reagents, the specific methodologies employed, technician expertise, and patient demographics.[928,937-942] For example, SPT wheal size and sensitivity depend on the specific device selection and the choice of control reagents used for testing.[928,938] Nonetheless, a recent meta-analysis indicates that SPT remains an accurate test, which when combined with a detailed clinical history, helps confirm the diagnosis of AR.[830] **[Table VIII.F.3-1]**

The performance and reliability of serum sIgE testing likewise depends on several factors including the choice of reagents, modernization of equipment, and patient demographics.[932] The cutoff value for a positive test affects both the sensitivity and specificity.[943] In a Korean population, SPT was found to be superior to ImmunoCAP for measuring dust mite sensitivity if the patient was less than 30 years of age.[792] For the group older than age 50, ImmunoCAP was more sensitive.[792] Intradermal or epicutaneous testing demonstrates higher sensitivity but lower specificity than SPT for several allergens.[793,856,931,932,944] Based on this, intradermal tests should be selected judiciously. There is evidence to suggest that a positive intradermal reaction to grass pollen in the setting of negative prick testing may not be clinically relevant.[793,856]

In recent years, microarray allergy testing systems such as ImmunoCAP ISAC have been introduced in an effort to offer a comprehensive *in vitro* allergen test panel[794] The precision and utility of microarray testing needs more rigorous scrutiny so that consensus guidelines can be more firmly established.[794,945] The cost of a single ImmonoCAP ISAC test which includes 112 components from 51 allergens is approximately $500-$600 in the US[794,945]

Various studies have compared sIgE serology to allergen SPT.[793,943,946,947] Both techniques are sensitive and are generally well correlated; however, interpretation of the results depends upon the gold standard reference used to define allergic status. Environmental chambers, nasal challenge, and validated questionnaires are typically used to determine the diagnostic accuracy of allergen testing. **Table VIII.F.3-2** summarizes several comparative studies between skin testing for aeroallergens, specific IgE serology, and other *in vitro* tests.

It is important to understand that selection and interpretation of allergen testing is not based on sensitivity and specificity alone. The intended physiological mechanism to be interrogated also needs to be considered. SPT and intradermal testing both measure end-organ pathological mechanisms associated with sIgE bound to the surface of mast cells. In contrast, serum sIgE testing and microarray approaches measure circulating IgE that may or may not represent downstream allergic inflammatory responses. Both intradermal testing and SPT rely heavily on technician skill for interpretation of the wheal and flare reaction.[856,928,937] In the case of subjects with dermatographism (or other inflammatory skin conditions in the testing area), hairy arms, or darkly pigmented skin color, the interpretation of the SPT can prove to be difficult.[942] Specialized imaging systems have been developed to measure the wheal reaction in an automated fashion in both light and dark skinned individuals, but additional validation is required. Until these automated systems become more widespread, *in vitro* testing affords the benefits of temporal and multi-center reproducibility.

The average pooled sensitivity of SPT is 85% which is often slightly higher than that of serum sIgE testing;[830] however, this is not universally true depending on the allergen tested and the characteristics of the patient. Based on accuracy, convenience, cost, and promptness of results, SPT is often chosen as the first line diagnostic instrument to detect sensitivity to aeroallergens. Intradermal testing can be used as a second line test to exclude reactivity if the clinical suspicion is very high. In cases where dermatographism is present and/or patients are unable to wean off medications that affect skin testing, sIgE testing may be a better choice. More studies are required to determine the role of small volume blood testing through emerging microarray technology such as the ImmunoCAP ISAC.

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 1b: 7 studies; Level 1c: 1 study; Level 2a: 1 study; Level 2b: 6 studies; Level 3a: 2 studies; Level 5: 1 study; *Table VIII.F.3-1.*)

Table VIII.F.3-1 Evidence for various allergy testing techniques

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Nevis et al[830]	2016	1a	Systematic review	AR	SPT accuracy	Various factors determine SPT accuracy.
de Vos et al[931]	2013	1b	Validating cohort	AR and asthma	Concordance of SPT and serology	SPT and serology are discordant.
Sharma et al[932]	2008	1b	Validating cohort	Mouse allergy	RAST vs. SPT vs. intradermal test	Sensitivity and specificity differ across tests.
Carr et al[939]	2005	1b	Prospective controlled trial	AR	Evaluation of 8 devices for skin testing	Consensus guidelines on skin testing.
Wood et al[793]	1999	1b	Validating cohort	Cat allergy	RAST vs. SPT vs. intradermal test	Sensitivity and specificity differ across tests.
Nelson et al[937]	1998	1b	Validating cohort	All subjects	Wheal and flare of various devices.	Results of SPT depend on device, technique and control reagents chosen.
Nelson et al[856]	1996	1b	Validating cohort	AR to grass	Intradermal test vs. challenge	Positive intradermal test may not be relevant if SPT negative.

Adinoff et al[948]	1990	1b	Validating cohort	AR	SPT results	SPT is accurate for various aeroallergens.
Jung et al[792]	2010	1c	All or none case series	HDM allergies	ImmunoCAP versus SPT	Sensitivity and specificity depend on patient demographics.
Gendo & Larson[930]	2014	2a	Systematic review	AR	Utility of allergy testing	History and pre-test probability determine allergy testing utility.
Haxel et al[947]	2016	2b	Retrospective cohort	AR	Nasal challenge vs. SPT vs. RAST	Nasal challenge should be performed to confirm eligibility for HDM AIT.
Tantilipikorn et al[949]	2015	2b	Individual cohort	AR	Intradermal test vs. serum sIgE	Intradermal testing has higher sensitivity and lower specificity than sIgE for HDM.
Tversky et al[928]	2015	2b	Individual cohort	All subjects	Wheal and flare of various devices	Results of SPT depend on device, technique and control reagents chosen.
Choi et al[943]	2005	2b	Retrospective cohort	HDM allergy	RAST vs. SPT	IgE cutoff level determine sensitivity and specificity.
McCann & Ownby[942]	2002	2b	Individual cohort	AR	SPT measurements	SPT results are not reproducible across centers.
Pastorello et al[946]	1995	2b	Exploratory case-control	AR	ImmunoCAP vs. SPT	Specific IgE accuracy depend on cutoff values.
Westwood et al[794]	2016	3a	SR	AR	Microarray results	Utility and cost of microarray testing needs further validation.
Mucci et al[791]	2011	3a	SR	AR	Review of AR	Review of AR diagnosis and treatment.

LOE: level of evidence; AR: allergic rhinitis; SPT: skin prick test; RAST: radioallergosorbet test; HDM: house dust mite; AIT: allergen immunotherapy; sIgE: allergen-specific IgE; IgE: immunoglobulin E

Table VIII.F.3-2 Comparative studies of allergy testing techniques

Test	Allergen	Sensitivity	Specificity	Gold standard
Skin prick test	HDM	66.3-90.5%	47.6-95.2%	bronchoprovocation[943], survey[946], nasal challenge[943,947]
	Grass	61.6-76%	61-85.7%	survey[856,946]
	Cat	90%	90-92.7%	survey[948], cat room[793]
	Mouse	67%	94%	nasal challenge[932]
Skin intradermal test	HDM	N/A	85%	nasal challenge[949]
	Grass	78.6%	75%	nasal challenge[856]
	Cat	60%	39.5-46.2%	cat room[793]
	Mouse	100%	65%	nasal challenge[932]
sIgE (ImmunoCap)	HDM	61.6-76.3%	47.6-72.8%	bronchoprovocation[943], survey[946], nasal challenge[943,947,949]
	Grass	69-75.5%	76.5%	survey[946]
	Cat	48%	100%	cat room[793]
	Mouse	74-92.2%	91%	nasal challenge[932]

HDM: house dust mite; sIgE: allergen-specific IgE

VIII. F. 4. Nasal specific IgE

AR is classically diagnosed by clinical history and with objective testing for confirmation, usually SPT or *in vitro* testing with serum sIgE.[301] In addition to positive systemic sIgE, AR patients have been shown to have sIgE in the nasal mucosa with evidence that class switching and antibody production occurs locally.[309-312,377,950,951] However, some patients have negative SPT or serum sIgE despite a clinical history suggestive of AR and meeting ARIA clinical criteria.[101,300] These patients are usually given the diagnoses of idiopathic rhinitis, vasomotor rhinitis, or NAR.[300] However, it has been demonstrated that many of these patients may have local allergic phenomena or LAR, a type of rhinitis characterized by the presence of a localized allergic response in the nasal tissues, with local production of sIgE and positive response to NPT without evidence of positive SPT or serum sIgE elevation.[107] LAR may affect more than 45% of patients otherwise categorized as NAR,[296,302,952] and up to 25% of patients referred to allergy clinics with suspected AR.[291] Like traditional AR patients, LAR can be classified as perennial or seasonal, and similar findings in the nasal mucosa have been reported in both of these populations.[300,301,953] It has even been suggested that some patients with occupational rhinitis may suffer from LAR.[107] Recent studies suggested a low rate of conversion of LAR to systemic AR.[296,302] The first 5 years of a long-term follow-up study performed in a cohort of 194 patients with LAR and 130 healthy controls found that patients with LAR of recent onset (less than 18 months from the diagnosis) had a similar conversion to systemic AR when compared to controls.[296] A small retrospective study performed in 19 patients with a long clinical history of LAR (greater than 7 years from the diagnosis) and negative SPT to a wide panel of allergens had a similar rate of development of systemic AR[302] compared with epidemiologic data of prevalence of atopy in healthy population from that geographic area.[954] Upcoming data from the 10-year follow-up study should help to clarify the rate of a long-term conversion to systemic AR in patients with LAR. In fact, LAR can present later in life, and in elderly patients with rhinitis the incidence of LAR has been reportedly been as high as 21%.[304]

The diagnosis of LAR is confirmed by positive response to NPT, and evidence of sIgE in the nasal secretions. A variety of allergens have been tested in this fashion including dust mites, grasses, pollens, and molds.[300,301,306,307,955] The production of nasal mast cells, eosinophils, and sIgE rapidly increases after allergen-specific stimulation in the nasal mucosa.[288,294,307] Different methods have been reported regarding how to best identify nasal sIgE including nasal lavage, cellulose disks, mucosal biopsy, and brushing. **[Table VIII.F.4.]** While there is no gold standard, most of these techniques appear to yield similar results in identifying nasal sIgE in LAR patients. Additionally, normative data for nasal sIgE levels and their clinical correlations have yet to be established and agreed upon, but work has begun in this area.[956]

When evaluating a rhinitis patient, in the setting of negative systemic testing, the differentiation of LAR from NAR can provide important information for management. While both typically respond to pharmacologic treatment, identification of offending allergens in LAR may permit allergen avoidance and immunotherapy.[107] AIT is the treatment of choice for patients with AR who have failed allergen avoidance and medical therapy. Patients who are classified as NAR, would not typically be candidates for AIT. However, as previously noted, roughly 50% of patients with negative systemic testing have been shown to have LAR. In this LAR population, early studies suggest that AIT can decrease symptoms and medication usage, and improve QOL.[288,957]

- Aggregate Grade of Evidence: C (Level 2b: 13 studies; Level 3b: 3 studies; Level 4: 8 studies; *Table VIII.F.4.*).
- Benefit: Identifying patients with LAR allows for the opportunity to treat a subset of patients who may respond to avoidance or AIT. Identification of nasal sIgE allows for diagnosis and AIT.
- Harm: Measurement of nasal sIgE is minimally invasive, and no adverse effects have been reported.
- Cost: Associated costs consist of the direct costs of testing, and indirect cost of increased time and effort for performing nasal sIgE diagnostic test.
- Benefits-Harm Assessment: The benefits of identifying patients with an allergic component to their rhinitis may outweigh any associated risks.
- Value Judgments: In patients with rhinitic symptoms and negative systemic testing, identifying nasal sIgE may assist with appropriate treatment. Standards for abnormal levels of nasal sIgE have not been established nor correlated with clinical outcomes.
- Policy Level: Option.
- Intervention: Nasal sIgE levels is an option in patients with suspected or known LAR to aid in diagnosis or guide allergen-specific therapy.

Table VIII.F.4. Evidence for nasal sIgE testing

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kim et al[958]	2016	2b	Cross-sectional	Collection technique: cotton ball. 1. NPT positive (n=39) 2. NPT negative (n=21)	NPT, nasal sIgE	Nasal sIgE detected in all patients, no difference between NPT groups. No comparison pre- and post-NPT was performed.
Lee et al[959]	2016	2b	Cross-sectional	Collection technique: nasal lavage. 1. NAR, children (n=12) 2. AR, children (n=15) 3. NAR, adults (n=9) 4. 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[304]	2015	2b	Cross-sectional	Collection technique: nasal lavage. Elderly patients, (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[960]	2014	2b	Cross-sectional	Collection technique: suction of nasal secretions (n=46 participants, 33 sensitized to allergen)	Nasal sIgE	93% had nasal sIgE, higher levels in sensitized subjects, correlation between nasal and serum sIgE.
Fuiano et al[955]	2011	2b	Cross-sectional	Collection technique: cellulose membrane. 1. perennial AR, children (n=20) 2. perennial NAR, children (n=36)	NPT, nasal sIgE	Nasal sIgE to *Alternaria* detected in 69% of positive NPT.
López et al[306]	2010	2b	Cross-sectional	Collection technique: nasal lavage. 1. LAR (n=40) 2. control (n=50)	Nasal tIgE, sIgE, tryptase, eosinophil cationic protein, symptoms	LAR: Nasal sIgE to *D. pteronyssinus* detected in 25% immediately and at 24 hours, increase mast cells/eosinophils. Controls: Negative NPT, nasal sIgE and other markers.
Powe et al[950]	2010	2b	Cross-sectional	Collection technique: cotton ball, immunohistochemistry. 1. AR (n=90) 2. NARES (n=90) 3. control n=90)	Nasal Ig free light chains	Free light chains increased in AR and NAR nasal mucosa, suggesting role in hypersensitivity.
Rondon et al[307]	2009	2b	Cross-sectional	Collection technique: nasal lavage. 1. LAR (n=30) 2. control (n=30)	Nasal sIgE, sIgE, tryptase, eosinophil cationic protein	30% with nasal sIgE. LAR have local production of sIgE, mast cell/eosinophil activation.
Rondon et al[300]	2008	2b	Cross-sectional	Collection technique: nasal lavage. 1. seasonal NAR (n=32) 2. AR to pollen (n=35)	NPT, nasal sIgE	Nasal sIgE to grass pollen detected in 35% NAR patients with positive NPT, and with similar sIgE profile as AR.

				3. AR to HDM (n=30) 4. control (n=50)		
Rondon et al[301]	2007	2b	Cross-sectional	Collection technique: nasal lavage. 1. NAR (n=50) 2. AR to HDM (n=30) 3. control (n=30)	NPT, nasal sIgE	Nasal sIgE to HDM detected in 22% of NAR patients with positive NPT.
Powe et al[284]	2003	2b	Cross-sectional	Collection technique: mucosal biopsy. 1. NAR (n=10) 2. AR (n=11) 3. control (n=12)	Nasal sIgE	Nasal sIgE to grass detected in 30% NAR. No nasal sIgE to HDM was detected.
KleinJan et al[377]	2000	2b	Cross-sectional	Collection technique: mucosal biopsy. 1. SAR (n=12) 2. PAR (n=16) 3. 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[951]	1997	2b	Cross-sectional	Collection technique: mucosal biopsy. 1. SAR (n=11) 2. PAR (n=10) 3. control (n=10)	Nasal sIgE to grass and HDM	sIgE to grass and HDM found in SAR and PAR subjects, respectively.
Takhar et al[312]	2005	3b	Cross-sectional, nonconsecutive	Collection technique: mucosal biopsy. 1. AR (n=12) 2. control (n=4)	Nasal mRNA and gene transcripts	Allergen stimulates local class switching to IgE in the nasal mucosa.
Durham et al[310]	1997	3b	Cross-sectional, nonconsecutive	Collection technique: mucosal biopsy. 1. AR (n=21) 2. control (n=10)	NPT, nasal IgE heavy chain	Local IgE synthesis and cytokine regulation occur is the nasal mucosa of AR patients.
Huggins & Brostoff[303]	1975	3b	Cross-sectional, nonconsecutive	Collection technique: filter paper. 1. NAR (n=14) 2. AR (n=6) 3. 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.
Ota et al[961]	2016	4	Descriptive	Collection technique: mucosal biopsy. AR (n=11)	Nasal and serum sIgE	Detection of sIgE in inferior turbinate mucosa and serum.
Zicari et al[292]	2016	4	Descriptive	Collection technique: nasal lavage. NAR, children (n=20)	NPT, nasal sIgE	66% had positive NPT. Nasal sIgE present in 8-42%.
Becker et al[962]	2015	4	Descriptive	Collection technique: cotton ball. NARES (n=19)	Nasal sIgE	No detectable nasal sIgE in any of the patients

Reisacher[9] 63	2013	4	Descriptive	Collection technique: mucosal brush. NAR (n=20)	Nasal sIgE	Nasal sIgE detected in 100% of patients. Varied from 0% *Alternaria* to 90% cockroach. No association to QOL.
Reisacher[9] 64	2012	4	Descriptive	Collection technique: mucosal brush. AR (n=18)	Nasal sIgE, SPT	Nasal sIgE in 75% of subjects, association between brush testing and SPT.
Coker et al[309]	2003	4	Descriptive	Collection technique: mucosal biopsy. AR (n=6)	Nasal IgE heavy chain	Somatic hypermutation, clonal expansion, and class switching occurs within the nasal mucosa of AR patients.
Sensi et al[965]	1994	4	Descriptive	Collection technique: nasal lavage. Children with asthma and rhinitis (n=18)	Nasal and serum sIgE measured after allergen avoidance	Nasal sIgE may be more sensitive than serum sIgE.
Platts-Mills[311]	1979	4	Descriptive	Collection technique: nasal lavage. AR (n=50)	Nasal IgG, IgA, and IgE	Antibody response in AR patients is local in the nasal mucosa.

sIgE: allergen-specific immunoglobulin E; LOE: level of evidence; NPT: nasal [allergen] provocation test; NAR: non-allergic rhinitis; AR: allergic rhinitis; HDM: house dust mite; LAR: local allergic rhinitis; tIgE: total immunoglobulin E; NARES: non-allergic rhinitis with eosinophilia syndrome; Ig: immunoglobulin; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; SPT: skin prick test; IgG: immunoglobulin G; IgA: immunoglobulin A

VIII. F. 5. Basophil activation test (BAT)

BAT is an *ex vivo* peripheral blood test that has been shown to be useful in the diagnosis of allergy to food and drugs, along with other hypersensitivity syndromes, when first line tests (SPT and serum sIgE) are discordant with clinical history or do not exist, and for monitoring of AIT.[966] Within the field of AR, there are small scale trials evaluating the utility and reliability of BAT in testing for the diagnosis of specific allergens related to AR symptoms and monitoring therapy. **[Table VIII.F.5.]**

BAT methodology was found to be heterogeneous between trials. Most data pertaining to its accuracy used the tetraspanin CD63 (Lysosome-Associated Membrane Glycoprotein 3; LAMP 3) as an activation marker.[967-971] CD203c (ecto-nucleotide pyrophosphatase/phosphodiesterase 3) is less frequently used.[968,972] In one trial, it held potential as a sensitive and specific method of testing for AR as compared to CD63.[968]

The diagnosis of AR is a clinical decision guided by skin or serological tests; *ex-vivo* basophil testing is rarely required. However, BAT has been shown to be comparable with traditional allergen testing methods.[967,970,973,974] BAT has been shown to be useful in defining the allergen responsible for LAR in patients who have had false negative results with first line tests and a high suspicion for clinically-relevant allergy.[308,318]

Basophil reactivity (% CD63+ cells determined at one allergen concentration) does not reflect the effect of allergen immunotherapy. There is good evidence to suggest that basophil sensitivity (EC50 for allergen concentration, named CD-sens if it is inverted and multiplied by 100) is a marker for treatment effect of allergen immunotherapy[969-971,975-977] and anti-IgE treatment.[975]

In summary, BAT may be a useful *ex vivo* test when diagnosis of AR is in doubt or the allergen responsible for clinical symptoms is unknown. Basophil sensitivity is also useful for measuring response to AIT. When the methodology of BAT is more clearly standardized, it may become a more useful second line test in AR diagnosis, as using an *ex vivo* test is beneficial in terms of time taken to undergo testing and symptoms evoked during testing. Most studies included small samples sizes with less than 100 patients. There is an opportunity for a meta-analysis of these studies or a larger scale trial to confirm the findings of the works included in this review.

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 2 studies; Level 3b: 8 studies; Level 4: 3 studies; *Table VIII.F.5.*)
- Benefit: *Ex vivo* test, patient discomfort minimal, less time consuming than nasal provocation and skin prick testing for patient, reliable correlation between clinical symptoms and basophil sensitivity when measuring response to therapy, no risk of anaphylaxis compared to provocation testing.
- Harm: None known.
- Cost: Requires proximity of laboratory trained in basophil testing. Cost of testing.
- Benefits-Harm Assessment: Balance of benefit over harm.
- Value Judgments: Basophil sensitivity may be a useful marker for following response to immunotherapy. Differences in BAT methodology for diagnosis of AR and rare need for laboratory tests to diagnose AR make it likely to be implemented for diagnosis in tertiary care centers only.

- Policy Level: Option.
- Intervention: BAT is an option for AR diagnosis when first-line tests are inconclusive or for measuring response to AIT. Many small-scale studies have been completed. There is scope for meta-analysis and for larger trials to be completed.

Table VIII.F.5. Evidence for the use of basophil activation testing in allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Schmid et al[971]	2014	1b	Open RCT	SAR to grass pollen (n=24) 1. SCIT 2. open control	Clinical measures of allergy, basophil sensitivity, basophil reactivity.	Basophil sensitivity changes correspond to clinical changes in allergy symptoms in patients on SCIT. Basophil reactivity did not change.
Van Overtvelt et al[978]	2011	1b	RCT	SAR to grass pollen (n=89) 1. SLIT tablet 2. placebo	BAT using CD203c at 2 and 4 months of treatment.	BAT using CD203c did not correlate with patient response.
Zidarn et al[977]	2015	2b	Cohort	Moderate-severe SAR to grass pollen 1. SCIT (n=30) 2. no treatment (n=20)	BAT using CD63 as marker for basophil response. Evaluated after 1st pollen season, after 2nd pollen season, and 1-2 years after finishing 3-5 years of SCIT.	BAT significantly decreased with SCIT; remains decreased 1-2 years after 3-5 years of SCIT treatment. BAT is an objective measure of response to AIT and is a stable marker of allergen response over a long period.
Zidarn et al[976]	2012	2b	Cohort	1. positive skin test and sIgE to timothy grass pollen (n=26) 2. positive NPT (n=13) 3. negative NPT (n=13) 4. non-sensitized healthy controls (n=10)	CD-sens, CD63 responsiveness. Tested before and after pollen season. 10-fold higher in symptomatic than asymptomatic subjects. Tested before then after pollination season.	CD-sens 10-fold higher in symptomatic patients. Significant difference between CD63 responsiveness in those with positive NPT vs negative NPT. CD-sens a good predictor of allergic rhinitis symptoms in those sensitized to timothy grass pollen.
Lesniak et al[974]	2016	3b	Case-control	Allergy patients (n=30) diagnosed by clinical symptoms, SPT, or serum IgE. 1. Birch positive, HDM negative (n=15) 2. Birch negative, HDM positive (n=15)	BAT, basophil reactivity	Sensitivity for basophil reactivity 83-100%; specificity 78-89%; PPV 75-87%; and NPV 89-100%. BAT may replace NPT when NPT is contraindicated. Small numbers of patients used needs to be validated in larger study.
Ando et al[979]	2015	3b	Case-control	1. SAR patients (n=18) 2. controls (n=11)	CD203c expression on basophils when stimulated with Japanese cedar pollen.	CD203c expression has diurnal variation and should be considered when using CD203c as a marker. This was also shown in basophils derived from marrow of mice-models.

Campo et al[308]	2015	3b	Case-control	1. AR patients (n=12) 2. LAR patients (n=12) 3. controls (n=12) controls Tested to olive tree pollen.	NPT, serum sIgE, BAT	NPT positive in all AR and 10/12 LAR. Serum sIgE positive in AR, negative in LAR. BAT positive in AR and in 8/12 LAR. NPT remains the gold standard, but if unable to be done BAT should be considered.
Gomez et al[318]	2013	3b	Case-control	1. LAR patients (n=16) 2. AR patients (n=14) 3. NAR patients (n=10) 4. controls (n=14) Tested to *Dermatophagoides pteronyssinus.*	BAT, nasal sIgE, NPT	AR: BAT sensitivity 85%, specificity 93%. LAR: BAT sensitivity 50%, specificity 93%. BAT diagnosed at least 50% of cases of LAR to *D. pteronyssinus* and was more sensitive than detection of nasal sIgE and less time-consuming than NPTs.
Ozdemir et al[972]	2011	3b	Case-control	1. SAR to grass pollen (n=31) 2. healthy non-atopic controls (n=9)	Discrimination of pollen allergic individuals from controls using CD203c expression as marker of allergy; cutoff values of 14%. Performed during off-season.	BAT CD203c can be used to test for grass allergens if conventional measures not available.
Nopp et al[969]	2009	3b	Case-control	1. patients sensitized to timothy grass (n=14) 2. patients sensitized to birch (n=19) Treated with conventional or ultra-rush AIT.	CD-sens	CD-sens decreases during early phases of treatment. No change in basophil reactivity. CD-sens good objective measure to use to assess response to AIT.
Ocmant et al[968]	2007	3b	Case-control	1. cat allergic patients (n=20) 2. controls (n=19)	Tested both CD63 and CD203c expression using prescribed protocol.	100% sensitivity for both CD63 and CD203c in cat allergic patients. CD203 is as reliable as CD63 for diagnosis of patients with IgE-mediated allergy to cat.
Sanz et al[967]	2001	3b	Case-control	1. AR or asthma patients sensitized to HDM (n=53) 2. AR or asthma patients sensitized to grass (n=51) 3. atopic, non-allergic patients (n=24)	Skin tests, BAT, histamine release tests, leukotriene production	Significant correlation between skin tests and BAT ($r=0.72$, $p<0.001$). Positive and significant correlation between BAT and histamine release tests ($r=0.80$, $p<0.001$); allergen-specific LTC4, LTD4, LTE4 production

				4. healthy controls (n=38)		(r=0.7, p<0.001); and the occurrence of serum sIgE (r=0.71, p<0.001). BAT is a highly reliable technique in the diagnosis of allergy to inhalant allergens. BAT sensitivity=93.3%, specificity=98.4%, when using a cut-off point of 15% activated basophils as positive result.
Lesniak et al[973]	2015	4	Case series	12 patients with AR sensitized to birch or mites.	Blood sample tested 1, 4, 24 hours after sampling compared to SPT, sIgE, and NPT	No differences in ROC characteristics between tests. BAT can be a useful approach to determine the clinically relevant allergen in sensitized patients.
Nopp et al[970]	2013	4	Case series	SAR to grass pollen (n=26)	CD-sens, nPIF	Positive nPIF and positive CD-sens in 92%. Positive nasal symptom scores and positive CD-sens scores in 85%. Subjects tested twice: CD-sens 100% reproducible vs 78% for nasal symptom scores and 94% for nPIF. CD-sens results reproducible and correlate well with other allergen testing methods. Has potential for diagnosis & follow up after treatment.
Nopp et al[975]	2006	4	Case series	1. SAR to Timothy grass (n=27) by clinical history, positive SPT and sIgE 2. patients receiving anti-IgE for 4 years (n=7)	CD-sens, SPT, NPT, IgE antibody concentration	CD-sens correlates significantly with SPT, NPT, and IgE antibody concentration. CD-max (reactivity) did not correlate with any sensitization measures. CD-max varies substantially between patients and does not correlate to treatment or other allergy testing measures. Using CD-sens as a quantitative measure of response to therapy or to complement other testing methods is more reliable.

1 LOE: level of evidence; RCT: randomized controlled trial; SAR: seasonal allergic rhinitis; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy;
2 BAT: basophil activation test; AIT: allergen immunotherapy; sIgE: specific immunoglobulin E; NPT: nasal provocation test; HDM: house dust mite; PPV: positive

predictive value; NPV: negative predictive value; AR: allergic rhinitis; LAR: local allergic rhinitis; LTC4, LTD4, LTE4: leukotriene C4, D4, E4; ROC: receiver operating characteristics; nPIF: nasal peak inspiratory flow; IgE: immunoglobulin E

VIII. F. 6. Component resolved diagnosis (CRD)

Molecular diagnosis (MD) or CRD is used in allergy to define the allergen sensitization of a patient at the individual protein level by measuring sIgE to purified natural or recombinant allergens, allowing identification of the potential disease-eliciting molecules. Overall, MD can potentially improve diagnostic accuracy (specificity), distinguish cross-reactivity phenomena from true co-sensitization, resolve low-risk markers from high-risk markers of disease activity, and may improve the indication and selection of suitable allergens for AIT when compared to diagnosis based on SPT and/or sIgE determination with raw commercial extracts.[980-984] Indeed, changes in immunotherapy prescription aided by MD have been demonstrated to be cost-effective in some scenarios.[985] Certain patterns of sensitization to grass or olive pollen allergens may also identify patients with higher risk of adverse reaction during immunotherapy.[986,987] Nevertheless, all *in vitro* test results should be evaluated alongside the clinical history, since allergen sensitization does not necessarily imply clinical responsiveness.

IgE to purified or recombinant allergens is usually measured by using a fluorescence enzyme immunoassay in singleplex platforms. However, a multiplex platform with 112 allergens is also available (ISAC, Thermo Fisher Scientific, Uppsala, Sweden). Results of singleplex and multiplex platforms are not interchangeable. When comparing the single- and multiplex assays, concordance of results vary between allergens tested, and the sensitivity of multiplex platform is lower than that of singleplex, particularly when sIgE levels are low.[983] Otherwise singleplex platforms are quantitative assays and multiplex are semi-quantitative.

Specific antigens. In the case of mite sensitivity, markers of specific sensitization include Der p 1 and Der p 2 for *Dermatophagoides pteronyssinus and Dermatophagoides farinae*,[988] Lep d 2 for *Lepidoglyphus destructor* (storage mite, with limited cross-reactivity with other HDMs)[989] and Blo t 5 for *Blomia tropicalis* (non-Pyroglyphidae mite).[990] Der p 10, a tropomyosin from *Dermatophagoides pteronyssinus*, has been shown to be a good maker of clinical sensitivity to crustaceans but not a marker of sensitization to mites.[991,992]

Can f 1, Can f 2 and Can f 5 are specific allergen components indicating specific sensitization to dog.[993] Interestingly, Can f 5, a prostatic kallikrein produced only by male dogs is responsible for monosensitivity in up to 25-38% of dog allergic patients.[994,995] In these cases, patients can tolerate exposure to female dogs. Fel d 1 is the major allergen component in cat allergy, indicating specific sensitization.[996] Other cat allergens have some cross-reactivity with allergens from other sources, e.g., Fel d 2 is likely to cross-react with other mammal albumins, such as dog Can f 3, horse Ecu c 3, pig Sus s PSA and cow Bos d 6[997] and Fel d 4 is shown to cross-react with major allergens from horse Equ c 1, dog or cow.[998] Therefore CRD for cat allergy provides more information about cross-reactivity and specifity of the diagnosis. Equ c 1, is the major allergen of horse dander and has some cross-reactivity with mouse Mus m 1 and cat Fel d 4.[999] Equ c 3 is a serum albumin showing cross-reactivity with other mammals' serum albumins mentioned above. In summary, CRD in patients with allergy to dog, cat, and horse are not only predictive markers of allergy, but may also help clinicians to predict clinical symptoms and their severity, since some patterns of sensitization are related to more severe rhinitis and asthma.[994,995]

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.[1000] Alt a 1 is a major allergen that is recognized in approximately 80-100% of Alternaria-allergic patients.[1001] Markers of sensitization to several pollen are summarized in **Table VIII.F.6.** 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.[987,1002] IgE antibodies to Phl p 1 and/or Phl p 5 can be used as specific markers of sensitization to grass pollen and Phl p 4 as a marker of sensitization to non-pooideae grasses. However, Phl p 6 is contained only in pooideae grasses. Allergens from groups 1, 2, 5 and 6 are only expressed in grasses but not in other plants, so they detect a genuine sensitization to grasses.[981]

In summary, CRD in patients with AR can help to better define the sensitization to inhalant allergens, especially in those who are polysensitized, have unclear symptoms and/or sensitization patterns, or who do not respond to treatment. On the contrary, monosensitized patients with a clear case history and symptom profile may not benefit from CRD compared to traditional diagnostic tests. Nevertheless, CRD remains a third-level approach, not to be used as a screening method in current practice. One of the most useful aspects of CRD is that it can help clinicians to better select patients and allergens for prescribing AIT,[1003] and in some cases, predict the risk of adverse reactions. The pattern of sensitization to allergens may predict the severity of the disease and could potentially predict the efficacy of AIT, provided these immunotherapy products contain a sufficient amount of allergen. As there are multiple individual allergens available for CRD and several different uses for CRD, extensive evidence grading is not undertaken in this document.

Table VIII.F.6. Pollen allergens

Pollen	Specific components	Cross-reactivity components
Ragweed	Amb a 1 (peptate lyase)	
Mugwort	Art v 1 (defensin) Art v 3 (lipid transfer protein)	Art v 3 (lipid transfer protein)
Parietaria, wall pellitory	Par j 2 (lipid transfer protein)	Par j 2 (lipid transfer protein)
Russian thistle or saltwort	Sal k 1 (pectinesterase)	
Goosefoot	Che a 1 (trypsin inhibitor)	
Timothy	Phl p 1 (expansin) Phl p 4 (berberine bridge enzymes) Phl p 5 (ribonuclease) Phl p 6 (pooideae grass only)	Phl p 4 (berberine) Phl p 7 (polcalcin) Phl p 11 (trypsin inhibibitor) Phl p 12 (profilin)
Bermuda grass	Cyn d 1 (expansin)	Cyn d 1 and Phl p 1
Alder	Aln g 1 (ribonuclease)	Aln g 1 (PR 10)
Birch	Bet v 1 (PR-10)	Bet v 1 (PR10) Bet v 2 (profilin) Bet v 4 (polcalcin)
Olive	Ole e 1 (trypsin Inhibitors) Ole e 7 (lipid transfer protein) Ole e 9 (glucanase)	
Japanese cedar	Cry j 1 (pectate lyases)	
Cypress	Cup a 1 (pectate lyases)	

Plane tree	Pla a 1 (invertase inhibitor) Pla a 2 (polygalacturonases)	Pla a 3 (lipid transfer protein)

VIII. G. Sensitization vs. clinical allergy

Sensitization vs. allergy. Although IgE-mediated sensitization has been consistently shown to be an important risk factor for rhinitis,[520,1004] the strength of this association is not consistent.[1005,1006] In epidemiology and clinical practice, patients are typically diagnosed as being "sensitized" based on a positive SPT (usually ≥3mm wheal diameter), or a positive specific serum IgE (usually >0.35 kU_A/L).[1007,1008] However, both of these tests can be positive in the absence of any symptoms, and neither positive SPT nor IgE can confirm the expression of rhinitis symptoms upon allergen exposure.[1009,1010] Thus, a clear distinction has to be made between "sensitization" (which usually refers to positive allergy tests, irrespective of any symptoms), and clinical allergic disease such as AR, which denotes the presence of sensitization *and* related clinical symptoms.

"Positive" allergy test vs. sIgE titer or SPT wheal size. Quantification of atopic sensitization by using the level of sIgE antibodies or the size of SPT wheals increases the specificity of allergy tests in relation to the presence and severity of rhinitis.[893,1004] This has changed the way we interpret the results of allergy tests, with a move from dichotomization (labelling patients as being sensitized based on a "positive" test using arbitrary criteria), to quantification of blood or skin tests using sIgE titer and SPT wheal size.[893,1010-1012]

Whole allergen extract vs. individual allergenic molecules. Homologous proteins present in the whole allergen extracts from different allergen sources may be cross-reactive (e.g. profilins and PR-10 proteins in various plants, or tropomyosin present in mites, various insects and shrimp). Thus, a positive test to the whole allergen extract may reflect sensitization to a cross-reactive component.[1013] Measuring sensitization to individual allergen molecules in a CRD may more be informative than standard tests using whole allergen extracts.[470,1014-1016] Current multiplex CRD platforms allow the testing for component-specific IgE to more than 100 allergenic molecules in a single assay, and in a small volume of serum.[1013,1015] The patterns of component-specific IgE responses to multiple allergenic proteins have a reasonable discrimination ability for rhinoconjuinctivitis,[1017] and distinct patterns of IgE responses to different protein families are associated with different clinical symptoms. For example, sensitization to proteins of plant origin strongly predicts AR, and sensitization to animal lipocalins is predictive of asthma.[1018,1019] The risk of allergic disease increases with the increasing number of sensitizations to individual allergenic proteins, and IgE polysensitization to several house dust mite molecules strongly predicts rhinitis.[1019,1020] It is important to emphasize that the age of onset of sensitization is crucially important, and that development of AR may be predicted by the unique molecular nature of IgE responses to individual allergen components.[1019]

Disaggregating atopic sensitization. It is becoming increasingly clear that "atopic sensitization" is not a single phenotype, but an umbrella term for several different atopic vulnerabilities which differ in their association with rhinitis and asthma.[1021,1022] Different subtypes of atopy are characterized by a unique pattern of the responses to different allergens and the timing of onset of allergen-specific sensitization.[1023] Translation of these findings into clinical practice requires the development of biomarkers which can differentiate between different subtypes of sensitization, and can be measured at the time of clinical evaluation.

Beyond IgE. Recent data suggest that amongst individuals sensitized to grass pollen, the decreasing ratio of grass allergen-specific IgG/IgE antibodies is associated with increasing risk of symptomatic SAR,[1024] suggesting that the IgG/IgE ratio may help distinguish between "benign" sensitization (sensitization with no symptoms) and "pathologic" sensitization.[1024] However, the measurement of allergen-specific IgG cannot as yet be recommended in a routine clinical practice.[1009,1010]

VIII. H. 1. Allergen challenge chambers (ACC)

Environmental exposure chambers (EEC) have been used for decades for controlled exposure of subjects to a well-defined atmosphere of a variety of substances such as allergens, particulate and gaseous air pollutants, chemicals, or climate conditions. The generation of valid exposure conditions with high temporal and spatial stability is technically demanding, and there are a limited the number of EECs worldwide. Besides the opportunity to use EECs for well-designed mechanistic studies on the effect of environmental pollutants on human health, allergen challenge in the chamber setting with induction of symptoms in patients with allergic disease is an intriguing way for efficacy testing of new drugs. Therefore, several chamber facilities were installed in recent years with the focus on allergen exposure resulting in currently 15 ACC facilities around the globe.[1025]

ACC studies have contributed to our understanding of the pathophysiology of allergic diseases. For example, it has been demonstrated that controlled allergen exposure exacerbates atopic dermatitis.[1026] Also, the impact of exposure with pollen allergen fragments on AR symptoms has been shown.[1027] Furthermore, the importance of the integrity of the epithelial barrier for induction of local and systemic inflammatory responses has been investigated in patients with allergic rhinoconjunctivitis using the ACC setting.[1028]

The use of ACCs in clinical trials for efficacy testing of investigational new drugs, and their acceptance by regulatory authorities is peremptorily dependent on the technical and clinical validation of ACCs. Many ACCs have been intensively validated regarding specificity and dose-dependency of symptom induction as well as technical aspects such as temporal stability and spatial homogeneity of the allergen exposure.[1029-1037] Also, repeatability of outcome measures in the ACC has been systematically investigated and found to have excellent repeatability as measured by TNSS.[1038] With the given level of technical and clinical validation, ACCs have been intensively used in clinical drug development to study pharmacological properties of new drugs during phase II trials, such as dose-finding,[1039-1041] onset of action,[1042-1046] and duration of action.[1047-1049] In this respect, numerous

randomized, placebo-controlled clinical trials have been conducted using parallel-group or cross-over designs in order to test the efficacy of drugs with immediate therapeutic activity, such as antihistamines,[1050-1053] or with prophylactic therapeutic potential, such as topical steroids,[1054-1056] novel anti-inflammatory compounds,[1057-1060] or probiotics.[1061] Major advantages in the ACC setting compared to field studies are better signal-to-noise ratios, a safeguarded minimum level of symptomatology in the ACC, and repeatability of symptoms allowing intra-individual comparisons.

With availability of a variety of validated allergen atmospheres in challenge chambers,[1029,1030,1034,1035] efficacy testing for dose-finding of AIT has also been performed in RCTs.[1062-1066] While regulatory authorities accept the use of ACC in phase II of drug development,[1067,1068] they have been reluctant to approve them in pivotal phase III studies because the clinical validation is still imperfect. Differences between natural exposure in field studies and ACC studies exist for example with regards to exposure time (continuous versus intermittent), exposure atmosphere complexity (natural mix versus artificial purity), or selection of study population (all-comers versus allergen challenge responders). Therefore, evaluation of efficacy during natural exposure in phase III field studies is still mandatory. However, recent joint activities of EAACI with experts from academia, chamber owners, and regulators have defined the most relevant unmet needs and prerequisites for clinical validation to further develop the use and regulatory acceptance of ACC in pivotal phase III studies.

In summary, numerous well-designed RCTs using technically validated ACCs for efficacy testing of investigational new drugs with detailed analysis of dose-response, onset of action, and duration of action provide evidence for the use of ACCs in phase II of clinical drug development.

VIII. H. 2. Local allergen challenge tests

Challenging the target organs of respiratory allergy (i.e. nose, bronchi, eye) with a suspected allergen is aimed at demonstrating the actual clinical reactivity when the results of the initial allergy tests (skin tests, *in vitro* measurement of sIgE) are inconclusive. The NPT is designed for AR, while conjunctival provocation test (CPT) may be used in patients with rhinoconjunctivitis or allergic rhinitis alone.[1069,1070]

Nasal challenge. The aim of nasal challenge is to reproduce the response of the upper airway upon nasal exposure to allergens.[1071,1072] However, currently the only technique fulfilling this aim is the EEC as described in the previous section, while the allergen amounts administered during a NPT usually exceed natural exposure levels, sometimes to a large extent. The allergen for NPT can be administered by various devices, including syringes, nose droppers, micropipettes, nasal sprays, or impregnated disks, none of them being free from limitations or pitfalls.[1071] The result of a NPT can be assessed by several measures, including symptom scores (especially the TNSS), rhinomanometry, acoustic rhinometry, optical rhinometry, peak nasal inspiratory flow, inflammatory markers in nasal lavage fluid, and nasal NO concentration.[1072] Contraindications to NPT are acute bacterial or viral rhinosinusitis, exacerbation of AR, history of anaphylaxis to allergens, severe general diseases, and pregnancy.[1073] Recent studies evaluating the sensitivity and specificity of the different techniques using specific allergens are available. **[Table VIII.H.2.]** It is apparent from the contrasting findings that a standardized technique for NPT is not yet

available. In fact, in the coming years, the use of NPT in the diagnosis of AR is likely to decrease, due to the diagnostic ability of emerging tools such as CRD[1074] and the BAT[1075], that are able to identify the causative allergen in patients with dubious results from initial analysis.

Despite its limitations, a pivotal role for NPT is currently acknowledged in diagnosis of occupational rhinitis and LAR. According to the position paper of EAACI, occupational rhinitis "can only be established by objective demonstration of the causal relationship between rhinitis and the work environment through NPT with the suspected agent(s) in the laboratory, which is considered the gold standard for diagnosis".[84] The best time to perform a NPT is in the morning to limit the effects of common daily-life stimuli. Baseline evaluation of symptoms and nasal function should be done after adaptation to room temperature. A control test must be performed to ensure that the nasal response is specific to the tested agent.[1076] A positive control test suggests rhinitis induced by irritants or nonspecific hyper-responsiveness.

In regard to LAR, the absence of sIgE in serum and in the skin requires that IgE are found locally or that they are revealed by a positive NPT.[1077] Despite the introduction of techniques to detect IgE in the nose in the 1970s,[1078] the ability to measure locally-present IgE in the clinic setting is not currently available. This makes NPT of critical importance, though contrasting observations have been reported. NPT with mites, pollens and *Alternaria* was positive in 100% of 22 adults with previously diagnosed LAR,[1079] but in a case-controlled, prospective study on 28 children with a diagnosis of NAR, tested with mites and grass pollen, NPT was positive in only 25% of subjects.[293]

Conjunctival challenge. While several different techniques exist for NPT, CPT is generally performed by instilling 20-30 µL of an allergen solution into the inferior external quadrant of the ocular conjunctiva, using diluent in the contralateral eye as a control.[1069] Also, the positive response to CPT is simple to evaluate, because it consists of an immediate reaction (from 5 to 20 minutes from the instillation) with ocular itching, tearing, redness and possibly conjunctival edema. In 1984, a study of 20 children with seasonal rhinoconjunctivitis tested 3 times with CPT reported good reproducibility.[1080] In 2001, a diagnostic sensitivity and specificity of 90% and 100%, respectively, was reported in mite allergic patients.[1081] A very recent systematic review was performed and the results were published in the EAACI guidelines for daily practice of CPT, with grade B evidence for the capacity to individuate the allergen trigger.[1082] The conclusion highlighted that allergists should be more familiar with CPT due to its simplicity. However, the scales to assess the symptoms need to be validated, the standardization of allergen extracts must be improved and the indication to perform CPT in patients with forms of conjunctivitis other than allergic remains uncertain.

- Aggregate Grade of Evidence for Nasal Provocation Testing: C (Level 2b: 4 studies). Of note, this evidence grade is based on the studies listed in Table VIII.H.2. However, due to the variation in NPT technique and outcome measures, a reliable evidence grade for NPT is difficult to determine.

Table VIII.H.2. Recent studies evaluating the sensitivity and specificity of nasal provocation testing

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Agarwal et al[1083]	2013	2b	Open controlled	1. allergic to molds (n=11) 2. controls (n=11)	Results of NPT by optical rhinometry	No significant difference between allergic and control subjects.
Jang & Kim[1084]	2015	2b	Open controlled	House dust mite allergy 1. strongly positive SPT (n=99) 2. weakly positive SPT (n=53) 3. negative SPT (n=110)	Sensitivity and specificity of NPT by acoustic rhinometry, TNSS	TNSS ≥6.5 had 90.6% sensitivity and 77.4% specificity, acoustic rhinometry had 73.4% sensitivity and 58.1% specificity for diagnosis of AR
de Blay et al[1085]	2015	2b	Open controlled	1. HDM allergy patients (n=49) 2. controls (n=39)	Sensitivity and specificity of a rapid NPT by clinical symptoms and rhinomanometry, safety also evaluated	Rapid NPT had a sensitivity of 83.7% and a specificity of 100%. No adverse reactions.
Krzych-Fałta et al[1086]	2016	2b	Open controlled	1. allergic (n=30) 2. controls (n=30)	Sensitivity and specificity of NPT by optical rhinometry, TNSS	TNSS had a 93.3% sensitivity and a 77.4% specificity, optical rhinometry had a 100% sensitivity and specificity for diagnosis of AR.

LOE: level of evidence; NPT: nasal provocation test; SPT: skin prick test; TNSS: Total Nasal Symptom Score;

VIII. I. Nasal cytology and histology

Nasal cytology (NC) is a simple diagnostic procedure that evaluates the health of the nasal mucosa by recognizing and counting cell types and their morphology.[1087] NC requires three steps. The first is sampling the surface cells in the nasal mucosa with an appropriate device via anterior rhinoscopy. The most commonly used collection device is the Rhino-probe (Arlington Scientific, Springville, UT, USA).[1088] The second step is staining by the May-Grunwald-Giemsa method, which allows for identification of all inflammatory cells present in the nasal mucosa (i.e. neutrophils, eosinophils, lymphocytes and mast cells) as well as normal mucosal cells (ciliated and mucinous), and even bacteria or fungi. The third step is examination through an optical microscope able to magnify up to 1,000X. For the analysis, at least 50 microscopic fields must be read to be sure to detect all the cells in the sample.[1087] NC may detect viruses, fungi and bacteria (including biofilms) in the nose, allowing for the diagnosis of infectious rhinitis.[1089] Specific cytological patterns on NC can help in discriminating among various forms of rhinitis, including AR, NAR, idiopathic rhinitis, and overlapping forms. AR is commonly diagnosed by the combination of clinical history and results of *in vivo* and/or *in vitro* tests for sIgE antibodies.[1090] When assessed by NC, the predominant cell type is the eosinophil, followed by mast cells and basophils.[1091-1094] In a logistic regression model, elevated nasal eosinophil counts on NC has an OR of 1.14 (95% CI 1.10-1.18) to identify AR.[1092] It has been described that NC in poly-allergic patients shows a more intense inflammatory infiltrate than in mono-allergic patients.[1093] NC has also demonstrated seasonal changes of inflammatory cells in the nose, probably mirroring the variations in allergen exposure, in patients with mite-induced rhinitis.[1095]

Negative allergy testing in patients with persistent rhinitis usually suggest a diagnosis of NAR.[1096] The first variant of NAR, known as NARES, was described after the identification of a subset of patients with perennial rhinitis, negative skin tests and marked eosinophilia in nasal secretions.[174] In more recent years, other variants have been defined, including NAR with mast cells (NARMA), with neutrophils (NARNE), and with eosinophils and mast cells (NARESMA).[1097] Idiopathic rhinitis is also characterized by high levels of eosinophils and mast cells in some patients.[1098] Overlapping forms may occur.[1099]

NC is one method of diagnosing NAR and has been used to differentiate between variants in experiments.[1100] However, few studies investigating the diagnostic performance of NC in diagnosing AR or NAR are available. **[Table VIII.I-1]**

- Aggregate Grade of Evidence: C (Level 3b: 3 studies; Level 4: 1 study; *Table VIII.I-1.*)

Nasal histology as assessed by biopsies of the nasal cavity was the only technique to study tissues and cells in patients with AR for many decades. In the 1990s, biopsy based investigations allowed researchers to define the role of the different inflammatory cells in AR.[379] The original technique begins by spraying a local anesthetic and topical vasoconstrictor into the nasal passages. After anesthesia has taken effect, a piece of tissue is removed from the middle turbinate using small punch biopsy forceps. After immediately placing the tissue in buffered formalin, each specimen can then be stained with various reagents to detect different tissue components and cells.[1101] Reagents used include Giemsa, hematoxylin/eosin, periodic acid-Schiff, Masson trichrome, azure A and chloroacetate esterase.[299,415,1101]

After staining, the slides are examined by an optical double-headed light microscope, using a grid reticule divided into 100 squares to quantitate cells and tissue per square millimeter.

The introduction of NC made it possible to obtain the similar information as histology, but without the associated discomfort and potential risk for bleeding. Further, NC allows for sequential sampling where histology does not. In addition, when Lim et al[415] compared nasal histology with cytology in patients with perennial and seasonal rhinitis compared to controls, the results suggested that nasal secretions and the nasal mucosa represent two distinct cellular compartments. Specifically, following allergen challenge an influx of inflammatory cells was detected by cytology, while the epithelial layer assessed by histology was unchanged from baseline.[415] In 2005, Howarth et al[1102] stated that, compared to simple techniques such as NC or nasal lavage, nasal biopsy requires expertise both in tissue sampling and in biopsy processing, thus being applicable only in specialist centers. This issue, as well as the previously reported drawbacks, makes nasal histology a technique of interest in the research on pathophysiology of AR but hardly feasible for routine clinical practice. **Table VIII.I-2.** shows the available studies on AR pathophysiology as evaluated by nasal histology.

- Aggregate Grade of Evidence: B (Level 1b: 8 studies; Level 3b: 3 studies; *Table VIII.I-2.*)

Table VIII.I-1 Studies assessing the diagnostic performance of nasal cytology

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Gelardi et al[1093]	2015	3b	Case-control	AR patients (n=83): 1. mono-allergic (n=35) 2. poly-allergic (n=48)	Comparison of NC cell counts	Higher number of eosinophils (p=0.005) and mast cells (p=0.001) in poly-allergy.
Di Lorenzo et al[1092]	2011	3b	Cohort	1. AR (n=1107) 2. NAR (n=404)	NC eosinophil count	High eosinophil count had an odds ratio of 1.14 (95% CI 1.10-1.18) to identify AR.
Gelardi et al[1094]	2011	3b	Case-control	AR patients (n=62): 1. mild (n=30) 2. moderate-severe (n=32)	Association of cell counts with ARIA stage of disease	In moderate-severe AR there was a significantly higher number of eosinophils (p=0.01), mast cells (p=0.001), neutrophils (p=0.046) and lymphocytes (p=0.001).
Gelardi[1099]	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	In patients with NARES, NARMA and NARESMA there was a significantly higher rate of sneezing (p<0.01).

LOE: level of evidence; AR: allergic rhinitis; NC: nasal cytology; NAR: non-allergic rhinitis; ARIA: Allergic Rhinitis and its Impact on Asthma; NARES: non-allergic rhinitis with eosinophilia syndrome; NARESMA: non-allergic rhinitis with eosinophils and mast cells; NARMA: non-allergic rhinitis with mast cells

Table VIII.I-2 Studies investigating allergic rhinitis pathophysiology by nasal histology from biopsies

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Sivam et al[1103]	2010	1b	DBRPCT	SAR (n=17): 1. mometasone (n=10) 2. placebo (n=7)	Measurement of olfactory function and histological analysis of the olfactory region	Mometasone use associated with reduced olfactory eosinophilic inflammation and improved AR symptoms
Uller et al[1104]	2010	1b	DBRPCT	SAR to grass or birch (n=21): 1. budesonide (n=10) 2. placebo (n=11)	Mucosal eosinophilia, apoptotic eosinophils, and expression of CCL5 and CCL11 (eotaxin)	Inhibition of CCL5-dependent recruitment of cells to diseased tissue, reduced cell proliferation and general cell apoptosis, but not increased eosinophil apoptosis, are involved in early phase steroid-induced resolution of AR.
Yang et al[1105]	2010	1b	DBRPCT	PAR to dust mite or animal epithelia (n=100): 1. Chinese herbal Xin-yi-san (n=62) 2. placebo (n=38)	To determine the effectiveness of Xin-yi-san in the treatment of AR and investigation of its molecular mechanism of anti-allergic activity.	Xin-yi-san exerts diverse immunomodulatory effects, including suppression of serum IgE levels and increased production of IL-10, sICAM-1, and IL-8 compared to placebo group.
Asai et al[1106]	2008	1b	RPCT	SAR to ragweed (n=19): 1. AIT (n=12)	To determine the *in vivo* effect of short-course AIT on CD4+CD25+	AIT increases CD4+ CD25+ regulatory T-cell infiltration in the nasal mucosa

				2. placebo (n=7)	regulatory T-cells in the nasal mucosa of ragweed-sensitive subjects.	following allergen challenge after seasonal ragweed-pollen
Rak et al[1107]	2005	1b	DBRPCT (double dummy)	SAR to birch (n=41): 1. AIT 2. budesonide	Measurement of the number of CD1a+, IgE+ and FcεRI+ cells during birch pollen season	Treatment with budesonide, but not AIT, decreased the number of CD1a+, IgE+ and FcεRI+ cells
Plewako et al[1108]	2002	1b	SBRPCT	SAR to grass (n=30): 1. omalizumab (n=19) 2. placebo (n=11)	Comparison of anti-CD4, CD8, anti-eosinophil peroxidase, anti-human neutrophil lipocalin, and antibodies against IgE and FcεRI.	The number of eosinophil peroxidase-positive staining cells significantly increased in the placebo-treated pts but not in the actively treated patients.
Pullerits et al[1109]	2001	1b	RPCT	SAR to grass pollen (n=21): 1. beclomethasone (n=16) 2. placebo (n=5)	Comparison of IL-16 expression during the pollen season in actively vs. placebo treated patients.	Local upregulation of IL-16 expression contributes to the inflammation observed in seasonal AR.
Wilson et al[1110]	2001	1b	RPCT	SAR to grass pollen (n=37): 1. AIT (n=20) 2. placebo (n=17)	Relationship between symptomatic improvement after AIT and eosinophil numbers and IL-5 expression in the nasal mucosa during the pollen season	Improvement in symptoms after grass pollen AIT may result from inhibition of IL-5-dependent tissue eosinophilia during the pollen season.
Kujundzić et al[1111]	2013	3b	Case-control	AR (n=90) : 1. mometasone (n=30) 2. control (n=30) 3. untreated (n=30)	Compare by histochemical staining with anti-CD31 and VEGF-C the vascularization of the nasal mucosa of non-allergic, non-treated allergic and allergic patients treated with mometasone.	Significantly lower values of CD31 and VEGF-C expression were observed in non-allergic compared with non-treated allergic and patients treated with mometasone
Radulovic et al[1112]	2008	3b	Case-control	SAR to grass pollen (n=22): 1. AIT (n=13) 2. control (n=9)	Effect of AIT on the numbers of Foxp3(+) CD4(+) and Foxp3(+) CD25(+) T-cells in and out of season and expression of IL-10 in nasal mucosa.	The presence of local Foxp3(+)CD25(+) cells in the nasal mucosa, their increase after AIT and their association with suppression of seasonal allergic inflammation support a role for T-reg cells in the induction of allergen-specific tolerance
Till et al[1113]	2001	3b	Case-control	SAR to grass pollen (n=46): 1. fluticasone (n=23) 2. control (n=23)	Effect of allergen exposure on nasal antigen-presenting cell and epithelial CD1a+ Langerhans	Recruitment of CD1a+ Langerhans cells to the nasal mucosa during seasonal allergen exposure may contribute to local T-cell responses

					cells, CD68+ macrophages and CD20+ B-cells	

LOE: level of evidence; DBRPCT: double-blind randomized placebo-controlled trial; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; IgE: immunoglobulin E; IL: interleukin; ICAM: intercellular adhesion molecule; RPCT: randomized placebo-controlled trial; AIT: allergen immunotherapy; SBRPCT: single-blind randomized placebo-controlled trial; AR: allergic rhinitis; VEGF: vascular endothelial growth factor; T-reg: T-regulatory cell

IX. Management

IX. A. Allergen avoidance

Allergen avoidance and environmental controls (EC) are frequently discussed as part of the treatment strategy for AR, along with pharmacologic management and AIT. AR patients are keen to learn about avoidance measures and EC, especially those who wish to avoid medications or cannot commit to an AIT regimen. Considering this, it is important to examine the evidence supporting allergen avoidance and EC measures for the allergic patient.

IX. A. 1. House dust mite

Techniques to reduce environmental HDM exposure have been investigated for the treatment of AR. HDMs represent one of the most common triggers of AR,[1114] and EC measures have been advocated as a management strategy, with evaluation of both physical barriers and chemical treatments.[1114-1118] Various physical techniques (e.g. heating, ventilation, freezing, barrier methods, air filtration, vacuuming and ionizers) have been evaluated for the treatment of AR, with variable findings. While several studies have demonstrated decreased concentrations of environmental HDM antigens,[1119-1124] an associated reduction in clinical symptoms has not been reliably demonstrated. **[Table IX.A.1.]** Despite reductions in HDM antigen concentration, Ghazala et al[1120] and Terreehorst et al[1124] both found no clinical benefits of HDM impermeable bedding as an isolated intervention. Similar findings were reported by Antonicelli et al[1125] following a trial of high efficiency particulate air (HEPA) filtration.

Chemical techniques include the use of acaricides in household cleaners to reduce HDM concentration. Geller-Bernstein et al[1119] evaluated an acaricide spray in the bedrooms of patients with HDM sensitization, demonstrating improved mean symptom scores versus control patients without acaricide. Similar findings were reported by Kniest et al.[1121] No serious adverse effects were reported from any of the evaluated interventions, and no study evaluated cost-effectiveness as an outcome measure. A 2010 Cochrane review examined the effectiveness of environmental measures for HDM including impermeable covers, HEPA filters, acaracides, or combination treatments.[1126] This systematic review found acaricides to be the most effective as a single measure or in combination with other measures to decrease HDM levels and improve AR symptoms.

- Aggregate Grade of Evidence: B (Level 1a; 1 study; Level 1b: 3 studies; Level 2a: 1 study; Level 2b 7 studies; *Table IX.A.1.*)
- Benefit: Reduced concentration of environmental HDM antigens with potential improvement in symptom scores and QOL.
- Harm: None.
- Cost: Low to moderate, however cost-effectiveness was not evaluated.
- Benefits-Harm Assessment: Benefit outweighs harm.
- Value Judgments: The use of acaricides and/or bedroom-based control programs in reducing HDM concentration is promising, but further, high-quality studies are needed to evaluate clinical outcomes.

- Policy Level: Option.
- Intervention: Concomitant use of acaricides and EC measures, such as personalized air filtration techniques, are options for the treatment of AR.

Table IX.A.1. Evidence of the effectiveness of house dust mite avoidance and environmental controls in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Sheikh et al[1126]	2010	1a	SR	RCTs examining the effectiveness of environmental measures for HDM	Symptoms	Acaricides are the most effective as a single measure or in combination with other measures to decreased HDM and improve symptoms.
Ghazala et al[1120]	2004	1b	Randomized cross-over study	1. adults with atopy and use of impermeable encasings 2. adults with atopy without use of impermeable encasings	Allergen content (Der p 1, Der f 1, mite group 2), subjective clinical complaints	Impermeable encasings significantly reduce allergen concentration, without difference in subjective symptom scores.
Terreehorst et al[1124]	2003	1b	Double-blind RCT	1. children with atopy and HDM impermeable bedding 2. children with atopy without HDM impermeable bedding	Rhinitis-specific visual analogue scale, daily symptom score, nasal allergen provocation, Der p1 and Der f1 concentration	Impermeable encasings significantly reduce allergen concentration, without difference in symptoms or nasal provocation testing.
Nurmatov et al[1114]	2012	2a	SR of RCTs	1. use of HDM impermeable bedding (n=4) 2. acaricides (n=2) 3. HEPA filtration (n=2) 4. acaricides and HDM impermeable bedding in isolation and combination (n=1)	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.
Stillerman et al[1127]	2010	2b	RDBPCT, crossover	1. adults with atopy and PAF 2. same adults with atopy, without PAF	Reported nasal symptoms, QOL scores using the nocturnal RQLQ	PAF is associated with improved nasal symptom and quality of life scores.
Brehler and Kneist[1128]	2006	2b	RDBPCT, parallel-group	1. children with atopy and HDM impermeable bedding 2. children with atopy without HDM impermeable bedding	Allergy symptom scores, use of anti-allergic medication	HDM impermeable bedding is associated with significant reduction in symptom scores without change in anti-allergic drug utilization.
Moon and Choi[1122]	1999	2b	Open RCT	1. adults and children with atopy and multi-modality environmental control 2. adults and children with atopy and verbal advice on allergen avoidance	Change in HDM load, daily rhinitis symptom scores	Multi-modality environmental control is associated with reductions in mean dust mite concentration and nasal symptom scores.
Geller-Bernstein et al[1119]	1995	2b	Double-blind RCT	1. children with atopy, bedroom sprayed with acaricide	Daily rhinitis and asthma symptom scores, medication use, twice weekly PEF	Acaricide is associated with decreased mean symptom scores.

				2. children with atopy without acaricide		
Kniest et al[1121]	1992	2b	Double-blind matched pair controlled trial	1. adults and children with atopy and intensive home cleaning plus acaricide 2. adults and children with atopy and intensive home cleaning alone	Daily symptoms and medication scores, physician assessment, tIgE, sIgE, serum and nasal eosinophils, guanine exposure	Arcaricide associated with improvement in all outcome measures except for mite-specific IgE.
Antonicelli et al[1125]	1991	2b	Randomized cross-over study	1. adults and children with atopy and HEPA filtration 2. 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[1123]	1990	2b	Double-blind cross-over RCT	1. adults with atopy and HEPA filtration 2. adults with atopy and placebo filtration	Particulate counts in bedroom air, symptom and medication scores, patients' subjective response to treatment	HEPA filtration is associated with improved particulate counts and symptom/medication scores.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; HDM: house dust mite; HEPA: high efficiency particulate air; QOL: quality of life; RDBPCT: randomized double-blind-placebo-controlled trial; PAF: personal air filtration; RQLQ; Rhinoconjunctivitis Quality of Life Questionnaire; PEF: peak expiratory flow; tIgE: total immunoglobulin E; sIgE: antigen specific immunoglobulin E; IgE: immunoglobulin E

IX. A. 2. Cockroach

Cockroach infestation and allergen concentrations are often high in multi-occupant dwellings in densely populated inner city areas; although elevated levels of cockroach allergen are also found in homes in warmer, rural regions.[1129-1131] Interventions are targeted at eliminating infestations and abating cockroach allergen in homes. A systematic review by Le Cann and colleagues,[1132] identified three key strategies for home environmental interventions: (1) education-based methods that included instruction on house cleaning measures and sealing cracks and crevices in areas where infestation occurs (i.e. kitchens); (2) physical methods using insecticides or bait traps; and (3) combination therapy containing both educational-based interventions and physical methods. **[Table IX.A.2.]**

Most studies included one or more interventions aimed at reducing cockroach counts and allergen (Bla g 1 and Bla g 2) levels,[1133-1140] however a few focused on eliminating multiple allergens (e.g. house dust mite, cockroach, rodent, cat, dog).[1141,1142] The most effective treatment for eliminating infestation and reducing allergen load was professional pest control.[1135] Sever et al[1133] found placement of insecticide bait traps to be more effective in reducing cockroach populations with a concomitant reduction in cockroach allergen compared to homes that received applications of insecticide formulations to baseboards, cracks, and crevices monitored over a 12-month period.

When cost was considered, the price of bait traps along with labor and monitoring costs were found to be less expensive than multiple commercial applications of insecticide sprays to baseboards and cracks.[1133] As the expense of integrated home management consisting of professional cleaning, education, and pest control is not economically sustainable, investigations are focused on assessing the efficacy of single interventions, such as extermination alone, to assess possible cost benefits.[1135,1143] In addition, family adherence to home-based interventions was generally poor resulting in elevated cockroach concentrations over time.[1138]

Although there are a substantial number of RCTs that evaluated the efficacy of specific environmental control measures to eliminate the number of cockroaches and reduce cockroach allergen level, respiratory health outcomes were rarely measured. Even though cockroach count and Bla g1 and Bla g2 allergen levels were reduced in many studies with home interventions, the level of cockroach allergen following treatment remained higher than acceptable median levels associated with clinical benefits in sensitized individuals.[1134,1137-1140] Although cockroach count could be significantly reduced in single-family homes using bait traps, re-infestation and high allergen levels remained an ongoing problem in multi-family buildings.[1140] Thus it is difficult to dramatically reduce cockroach allergen levels in the home unless a significant reduction in cockroach counts is maintained over time.[1133] Most studies did not include clinical endpoints, however those that did evaluate clinical outcomes focused on asthma symptoms, hospitalizations or emergency room visits, and medication usage.[1141,1142] No studies included any assessment of symptoms associated with AR or its treatment.

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 1b: 8 studies; Level 2b: 1 study; Level 3b: 1 study; *Table IX.A.2.*)
- Benefit: Reduction in cockroach count, but allergen levels (Bla g 1 & Bla g 2) often above acceptable levels for clinical benefits. No studies included clinical endpoints related to AR.
- Harm: None reported.

- Cost: Moderate. Multiple treatments applications required as well as a multi-interventional approach.
- Benefits-Harm Assessment: Balance of benefit and harms, given lack of clear clinical benefit.
- Value Judgments: Control of cockroach populations especially in densely populated, multi-family dwellings is important to controlling allergen levels.
- Policy Level: Option.
- Intervention: Combination of physical measures (such as insecticide bait traps, house cleaning) and educational-based methods are options in the management of AR related to cockroach exposure.

Table IX.A.2. Evidence of the effectiveness of cockroach avoidance and environmental controls on the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Le Cann et al[1132]	2016	1a	SR of RCTs	Home group interventions in 3 categories: 1. education-based methods 2. physical methods 3. combination of both Interventions included multiple-allergen control measures.	Allergic and respiratory symptoms (e.g. cough, daytime symptoms, wheeze, night time symptoms); lung function; medication use; urgent care use for respiratory symptoms	Overall studies supported effectiveness of home interventions in decreasing respiratory symptoms and urgent care use.
Sever et al[1133]	2007	1b	3-arm RCT; follow up for 12 months	1. insecticide baits and CR monitoring 2. pest control by randomly assigned commercial company 3. control	No direct clinical endpoints. CR trap counts and CR allergen levels (Bla g 1 & Bla g 2)	Significant reduction in CR counts in both treatment groups vs. control. Insecticide bait traps more effective in reducing CR infestation than sprays. Elimination of CR populations leads to reduction in CR allergen and exposure.
Eggleston et al[1141]	2005	1b	RCT	1. home-based education, CR and rodent extermination, mattress and pillow encasings, HEPA filters 2. control	Primary outcome: Bla g 1 CR allergen level. Secondary outcome: asthma symptoms.	CR allergen reduced by 51% at 6 mos. in treatment group but not sustained at 1 year; only modest effect on morbidity.
McConnell et al[1134]	2005	1b	RCT	1. education-based intervention (sealing cracks and crevices; cleaning with bleach solutions; insecticide bait traps) 2. comparison group	No direct clinical endpoints; CR count and CR allergen level	Achieved 60% reduction in CR count in intervention group. Greatest reduction in allergen level in homes with heavier CR infestation but levels still higher than median level associated with severe symptoms.
Morgan et al[1142]	2004	1b	RCT with blocked randomization	1. education-based intervention (environmental remediation for multiple allergens); Professional pest control provided for CR-sensitized children. 2. control	Asthma symptoms, use of health care services	Intervention group: Reduced levels of CR allergen in bedroom were strongly correlated with decreased asthma-related morbidity.
Arbes et al[1135]	2004	1b	RCT with cross-over of control group	1. intervention: education; insecticide bait placement; professional cleaning	No direct clinical endpoints, Bla g 1 & Bla g 2 CR allergen level	CR allergen levels reduced in 6 months with professional cleaning and insecticide bait traps; but lower CR allergen levels maintained at month 12 with bait traps alone.

				2. control: no intervention for months 0-6; insecticide bait placement at months 6 and 9		
McConnell et al[1136]	2003	1b	RCT	1. professional cleaning & insecticide bait traps 2. professional cleaning & bait traps with no insecticide 3. no cleaning or bait traps	No direct clinical endpoints, CR count and Bla g 2 CR allergen level	Decreased CR count and allergen concentration in insecticide bait treatment was low. Homes with high initial CR counts had larger reductions in Bla g 2 CR allergen concentration. Professional cleaning may help in homes with higher CR.
Wood et al[1137]	2001	1b	RCT	1. professional cleaning with sodium hypochlorite and insecticide bait traps 2. control without cleaning, extermination	No direct clinical endpoints, CR count and Bla g 1 CR allergen level	Professional extermination reduced CR numbers and 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.
Gergen et al[1138]	1999	1b	RCT: Phase II of a multi-city study	1. education-based intervention for parents: asthma triggers, environmental controls; pest control; house cleaning. 2. control	No direct clinical endpoints, Bla g 1 CR allergen level	CR allergen levels decreased within 6 months but returned or exceeded baseline levels by 12 months. Compliance with cleaning protocol was poor.
Eggleston et al[1139]	1999	3b	Prospective case-control	Professional cleaning followed by pest control treatments	No direct clinical endpoints, CR counts and Bla g 1 CR allergen level	CR numbers eliminated in most inner-city homes with professionally applied insecticides. CR allergen levels decreased by 78-93% over 8 months; mean allergen concentrations still above threshold of asthma morbidity.
Williams et al[1140]	1999	2b	Single-blind, non-random, stratified, placebo-controlled study	1. bait traps with insecticide 2. identical appearing placebo bait traps	No direct clinical endpoints, CR counts and CR allergen levels Bla g 1 & Bla g 2	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 CR allergen. No significant difference: active vs placebo.

1 LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; CR: cockroach; HEPA: high efficiency particulate air

IX. A. 3. Pets

Pet avoidance and EC represent options for the treatment of AR. Pet removal is a commonly cited strategy without high-quality outcomes evaluation.[1118,1144,1145] Sánchez et al[1146] evaluated compliance rates among sensitized patients (n=288), finding 4% of patients with direct exposure to home animals complied with removal recommendations. **[Table IX.A.3.]** EC has therefore been evaluated to decrease antigen exposure, with mixed results. Björnsdottir et al[1147] evaluated outcomes of multi-modality EC among 40 patients with diagnosed cat (Fel d 1) sensitization, finding significant improvements in nasal airflow and clinical symptoms. However, despite reductions in environmental antigens, single-modality EC has not been associated with improved symptoms. Wood et al[1148] 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. Several lower-quality studies have evaluated the duration of antigen reduction following pet washing, finding that cat and dog washing must be completed at least twice weekly to maintain significant reductions in environmental antigens.[1149,1150] Furthermore, pet removal may only result in decreased allergen levels after several months[1151] and Can f 1 levels in homes with "hypoallergenic" animals are generally similar to homes with non-hypoallergenic species.[1152]

An additional study has identified benefits of pet avoidance in the secondary prevention of asthma among previously sensitized individuals.[1153] Similarly, current asthma treatment guidelines recommend pet removal from a sensitized individual's home.[1154]

- Aggregate Grade of Evidence: B (Level 1b: 1 study; Level 2b: 2 studies; *Table IX.A.3.*)
- Benefit: Decreased environmental antigen exposure with possible reduction in nasal symptoms and secondary prevention of asthma.
- Harm: Emotional distress caused by removal of household pets. Financial and time costs of potentially ineffective intervention.
- Cost: Low to moderate.
- Benefits-Harm Assessment: Equivocal.
- Value Judgments: While several studies have demonstrated an association between EC and reductions in environmental antigens, only a single, multi-modality RCT has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity. The secondary prevention and treatment of asthma in sensitized individuals must also be considered.
- Policy Level: Option.
- Intervention: Pet avoidance and EC strategies, particularly multi-modality EC among patients with diagnosed Fel d 1 sensitivity, are an option for the treatment of AR related to pets.

Table IX.A.3. Evidence of the effectiveness of pet avoidance and environmental controls

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wood et al[1148]	1998	1b	RCT	Cat-sensitive adults: 1. HEPA filter 2. placebo	Cat allergen levels (airborne and settled dust), symptom scores, medication scores, spirometry	HEPA filters are associated with reduced airborne but not settled dust, cat allergen levels without effect on disease activity.
Sánchez et al[1146]	2015	2b	Cohort Study	Patients with diagnosed allergy	Sensitization to household animals, compliance with avoidance recommendations and EC	Avoidance recommendations may be impractical with high rates of sensitization, indirect exposure, and low rates of compliance.
Björnsdottir et al[1147]	2003	2b*	RCT	Cat-allergic patients: 1. EC 2. unchanged environment	Environmental (settled dust) Fel d 1 levels, nasal inspiratory flow, nasal symptoms	Multi-modality EC is associated with decreased allergen concentration and significant improvements in nasal inspiratory flow and patient symptoms.

LOE: level of evidence; RCT: randomized controlled trial; HEPA: high-efficiency particulate air**;** EC: environmental control;

*Follow-up <80% prevents 1b

IX. A. 4. Other (pollen, occupational)

For patients with pollen allergy, avoidance measures aim to minimize allergen exposure during the respective pollen season.[101] However, pollination is a global natural phenomenon which periodically occurs, making it nearly impossible for patients to thoroughly avoid exposure. There are some practical methods to minimize patients' exposure via EC measures. However, there is a paucity of clinical trials evaluating the clinical efficacy of therapeutic strategies. Most of the recommended strategies are based on expert consensus and clinical experience.[1155]

One potential EC strategy is limiting residential exposure during periods of high pollination (i.e. vacationing in geographical regions with a reduced intensity of local pollen concentration).[1156] Patients can get further information about the current pollen count in their respective region through internet sources (i.e. the European Aeroallergen Network [EAN] database (https://ean.polleninfo.eu/); Foundation German Pollen Information Service, (www.pollenstiftung.de); American Academy of Allergy Asthma and Immunology [AAAAI] (www.aaaai.org/global/nab-pollen-counts)). This information may be used, for example, in avoidance of extensive outdoor exercise during peak pollen levels or timing of preventive medication.[1157,1158] Although expert opinion endorses these strategies, there is no evidence to support their clinical efficacy.

In addition, patients may open their home windows when the pollen counts are low or keep windows closed and use air conditioning during times of high pollination. Special dust and pollen filters may be used in cars to reduce the pollen concentration within the car. Furthermore, pollen allergic patients may be educated on removal of clothing and washing their hair before entering their bedrooms during pollen season as pollen grains stick to both hair and clothing. Again, expert opinion endorses these strategies, but there is no evidence to support their clinical efficacy.[1159,1160]

Another EC strategy utilizes physical barriers to minimize mucosal exposure to airborne allergens. In a prospective trial, 70 patients with SAR caused by grass pollen were randomized to receive wrap-around eyeglasses in addition to standard medical care (first study group) or just standard medical care (second study group) during three consecutive grass pollen seasons.[1161] Interestingly, the authors found a significant improvement in ocular and nasal symptoms as well as RQLQ in the group provided with wraparound eyeglasses compared to the controls. Another approach is an active nasal filter by means of a membrane removing particles from the inhaled air.[1162] In a prospective, single-center, randomized double-blind, placebo-controlled crossover study performed in an ACC, 24 adult patients with grass-pollen induced SAR were randomly assigned to either a group that received this nasal filtering membrane or to a group that did not.[1162] Under repeated exposure in the ACC, patients with the membrane filter significantly improved in some of their nasal symptoms. However, the primary endpoint measuring maximum TNSS in this trial was not significant; thus, meaningful conclusions are difficult to draw from this study.[1162] The small sample size was a notable limitation. A real-world single-center double-blind crossover trial of 65 patients by the same researchers, however, did find significant reductions in daily TNSS and maximum TNSS with nasal filters used in-season compared to placebo.[1163] **[Table IX.A.4.]**

Avoidance of exposure to occupational inhalant allergens is feasible, in principal, in occupational allergic patients.[112] Several modalities of reducing workers' exposure to OA such as 'engineering controls' and 'administrative controls' have been described in the literature.[1164] The former includes

substitution of a hazardous chemical with a nonhazardous or less-hazardous alternative, isolation of the hazardous chemical or efficient ventilation to reduce workers' exposure. The latter includes workers' education and personal protective equipment. A prospective controlled trial of 20 patients with confirmed diagnosis of occupational allergy demonstrated that cessation of the exposure of the causal allergen in the workplace led to a significant improvement of patients' nasal symptom scores as well as disease specific QOL.[1165]

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 1 study; *Table IX.A.4.*)
- Benefit: Decreased allergen exposure with possible reduction in symptoms and need for allergy medication, along with improved QOL.
- Harm: Financial and time costs of potentially ineffective intervention.
- Cost: Low, but dependent on the EC strategy (i.e. for occupational allergy ventilation measures and other 'engineering controls' may be high)
- Benefits-Harm Assessment: Equivocal.
- Value Judgments: A limited number of studies show clinical effects of investigated EC measures. General EC recommendations are mainly based on expert opinions rather than evidence.
- Policy Level: Option.
- Intervention: Pollen and occupational allergen avoidance by EC strategies are an option for the treatment of AR; however, clinical efficacy has not been definitively demonstrated. More RCTs with larger samples are warranted to prospectively evaluate clinical efficacy.

Table IX.A.4. Evidence of the effectiveness of pollen and occupational allergen avoidance and environmental controls

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Comert et al[1161]	2016	1b	RCT	SAR to grass pollen (n=70): 1. wrap-around eyeglasses plus standard medical care 2. standard medical care alone	Nasal and conjunctival symptom scores, rescue medication use, RQLQ	Significant improvement of ocular/nasal symptoms and RQLQ in wrap-around eyeglass group
Kenney et al[1163]	2015	1b	Randomized double-blind, placebo-controlled crossover	Adults with SAR to grass pollen (n=65): 1. nasal membrane filter 2. placebo filter	In-season exposure: TNSS, individual symptoms	Daily sum TNSS and maximal TNSS were significant. Individual symptoms (sneezing, watery eyes, rhinorrhea) were also significantly decreased compared to placebo.
Kenney et al[1162]	2014	1b	Randomized double-blind, placebo-controlled crossover	Adults with SAR to grass pollen (n=24): 1. nasal membrane filter 2. placebo filter	Following ACC exposure: nasal symptom scores, conjunctival symptom scores, throat irritation, intranasal volume, oral FeNO	Primary endpoint, TNSS, was not significant. Some secondary endpoints were positive. In the absence of natural allergen exposure, the conclusions of this trial are limited.
Castano et al[1165]	2013	2b	Cohort, prospective, open trial	Occupational allergy (n=20)	Nasal symptoms, disease-specific QOL, nasal patency, nasal inflammation, olfactory function	EC in occupational allergy patients results in improved QOL, rhinitis associated symptoms, and general well-being.

LOE: level of evidence; RCT: randomized controlled trial; SAR: seasonal allergic rhinitis; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; ACC: allergen challenge chamber; FeNO: fraction of exhaled nitric oxide; QOL: quality of life

IX. Management

IX. B. Pharmacotherapy

Whether selected by patients themselves or prescribed by medical personnel, medications are the primary modality for control of allergic symptoms. There are numerous options for oral or systemic use, topical intranasal application, and alternative therapies that can be considered. It is, therefore, imperative to understand the data supporting the efficacy and appropriate use of these pharmacotherapy options.

IX. B. 1. Antihistamines

IX. B. 1. a. Oral H_1 antihistamines

Histamine is a major mediator associated with the symptomatology of AR. Oral H_1 antihistamines block the action of histamine by binding the histamine H_1 receptor, thereby inhibiting the pro-inflammatory effects of histamine. Antihistamines are typically categorized by generation, such as first or second-generation agents. The older first-generation agents (i.e. diphenhydramine, chlorpheniramine, brompheniramine) were lipophilic and readily crossed the blood-brain barrier. This caused unwanted side effects such as sedation, drowsiness, fatigue and impaired concentration and memory as well as anti-muscarinic effects. First-generation antihistamines are also inhibitors of the CYP2D6 hepatic enzymes. They may, therefore, alter the metabolism of other medicines dependent upon CYP2D6 metabolism, such as tricyclic antidepressants, some antipsychotics, β-blockers, anti-arrhythmics, and tramadol. Because of these significant side effects, in previously published guidelines and other papers, first-generation antihistamines have not been recommended for the treatment of AR.[218,1166,1167] The newer-generation agents (i.e. loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine) were developed to minimize the adverse effects of earlier drugs. They are highly selective for the H_1 receptor, lipophobic and have limited penetration across the blood-brain barrier.

Newer-generation antihistamines, except for cetirizine, levocetirizine, bilastine and fexofenadine, are metabolized by the hepatic cytochrome P450 CYP3A4 system. Practitioners should be cognizant that the concurrent use of other medicines (e.g. macrolides, antifungals or calcium-channel blockers) that inhibit CYP3A4 can result in accumulation of drug concentrations and increase the risk for side effects and toxicity. Furthermore, adverse cardiac effects (torsades de pointes, arrhythmia and prolongation of the QT interval) were reported with astemizole and terfenadine, leading to their ultimate withdrawal from the market.[1168,1169] RCTs have established the long-term safety and efficacy of the newer-generation H_1 antihistamines cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine. **[Table IX.B.1.a-1.]**

Because oral antihistamines have been in use since the early 1940s, there have been many RCTs establishing oral antihistamines as an appropriate pharmacotherapy for AR.[218] As such, this section will not list every published study but summarize the highest-grade evidence that has been published. Guidelines on AR have been published, including those by the AAO-HNS[761] and the ARIA group.[1167] The AAO-HNS concluded, based upon RCTs and a preponderance of benefit over harm, a “strong recommendation” for the use of newer-generation oral H_1 antihistamines for patients with AR.[218] Similar consensus came from ARIA where a “strong recommendation” was given for oral H_1 antihistamines for

AR.[1167] Furthermore, ARIA and EAACI have published a set of recommendations that outline the pharmacological criteria that should be met by medications commonly used in the treatment of AR.[1170] The main thrust of the ARIA/EAACI criteria was to assess the efficacy, safety and pharmacology of newer-generation oral H_1 antihistamines using level 1a studies. Using these criteria, a favorable risk-benefit ratio was determined for using newer-generation oral H_1 antihistamines over first-generation oral antihistamines.[1170] The evidence was further strengthened with several meta-analyses of the current data, where accurate and robust effect estimations can be derived from a large population.[1171] **[Table IX.B.1.a-1.]**

The choice of a specific oral H_1 antihistamine is often based upon the dosing, onset, drug interactions and potential cost. **[Table IX.B.1.a-2.]** Systematic reviews evaluating multiple oral H_1 antihistamines note benefits of certain drugs that may be important in deciding which drug to recommend or prescribe. Direct costs of newer-generation antihistamines are similar given the availability of many of these drugs as over the counter medications. In contrast, the cost of prescription only formulations (levocetirizine and desloratadine) is much higher. Indirect costs would be expected to be similar amongst the newer-generation oral antihistamines given similar side-effect profiles.

- Aggregate Grade of Evidence: A (Level 1a: 21 studies; *Table IX.B.1.a-1.*). There is a preponderance of high-grade investigations that have examined oral H_1 antihistamines. Only level 1a studies are summarized in the table.
- Benefit: Reduced nasal itching, sneezing, rhinorrhea, and nasal obstruction.
- Harm: Mild drowsiness, fatigue, headache, nausea and dry mouth.
- Cost: Direct costs low (average $2 per daily dose). Indirect costs for newer generation agents lower than first generation agents.[1172,1173]
- Benefits-Harm Assessment: Benefits outweigh harm for use of newer-generation oral H_1 antihistamines.
- Value Judgments: Due to the central nervous system side effects of the first-generation oral H_1 antihistamines, their use is not recommended for typical AR.
- Policy Level: Strong recommendation for use of newer-generation oral antihistamines to treat AR.
- Intervention: Prescribing newer-generation oral H_1 antihistamines for patients with AR should be considered early in treatment.

Table IX.B.1.a-1. Evidence for the role of oral H_1 antihistamines in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ridolo et al[1174]	2015	1a	SR	bilastine cetirizine desloratadine	Subjective and objective measures, TNSS, RQLQ	Bilastine at therapeutic dose has similar efficacy to other second-generation oral antihistamines. Demonstrated improvement in TNSS and RQLQ with good safety profile.
Mullol et al[1175]	2015	1a	SR	rupatadine	Allergy symptoms, ARIA criteria, AE	Rupatadine is recommended for use in adults and children for intermittent/persistent AR and SAR/PAR.
Scadding[1176]	2015	1a	Review of consensus statements: ARIA, EAACI, Royal College of Paediatrics and Child Health	oral antihistamines	---	Second-generation, non-sedating, antihistamines are recommended for mild to moderate AR and in combination for severe AR. Sedating antihistamines should not be used.
Compalati and Canonica[1171]	2013	1a	SR	rupatadine	Allergy symptoms, AE	Favorable risk-benefit ratio for rupatadine in treating AR
Mösges et al[1177]	2013	1a	SR and meta-analysis	desloratadine ebastine fexofenadine levocetirizine	TSS and TNSS	Second-generation levocetirizine significantly improved symptom scores especially in severe AR cases.
Compalati et al[1178]	2011	1a	SR and meta-analysis	fexofenadine	TSS, individual symptoms (sneezing, rhinorrhea, itching congestion), AE	Fexofenadine has good efficacy with improvement in outcome measures. No significant AE compared to placebo.
Ferrer[1179]	2011	1a	SR	levocetirizine desloratadine fexofenadine	TSS, PNIF, decongestion test, QOL, pruritus, ESS, wheal and flare, AE	Oral newer-generation antihistamines are well tolerated in adults and children. Efficacy and improvement in QOL and nasal obstruction. Benefits outweigh harm. Very low risk of sedation. No QT prolongation found.
Mösges et al[1180]	2011	1a	SR and meta-analysis	levocetirizine loratadine	TSS, DNS, DES, in patients with persistent and SAR/PAR	Improvement in TSS, Total 5 Symptoms Score, daytime nasal symptoms, and QOL
Brozek et al[1167]	2010	1a	SR with consensus statement	oral antihistamines	Evidence was graded and recommendation given.	Strong recommendation to use second-generation oral antihistamines that do not cause sedation and do not interact with CYP450 enzyme.

Katiyar and Prakash[1181]	2009	1a	SR	rupatadine ebastine cetirizine loratadine desloratadine	ARIA criteria evaluated for: intermittent/persistent, SAR/PAR. TSS, DTSSm, DSSm, QT changes	Rupatadine is a non-sedative, efficacious, and safe oral H_1 antihistamine for intermittent/persistent, SAR/PAR.
Bachert[1182]	2009	1a	SR	desloratadine fexofenadine levocetirizine cetirizine loratadine terfenadine	TSS, PNIF, TSSC (with nasal obstruction), nasal congestion & obstruction	Oral anti-histamines have good efficacy for improving both subjective and objective measures, effective in relieving nasal congestion associated with AR compared to placebo.
Bachert and van Cauwenberge[1183]	2007	1a	SR	desloratadine	TSS, TNSS, TNNSS, PNIF, for intermittent/persistent SAR/PAR	Desloratadine is well tolerated and efficacious for intermittent and persistent AR with reductions in congestion, TSS, TNSS, TNNSS with improved QOL.
Canonica et al[1184]	2007	1a	SR and meta-analysis	desloratadine	TSS, TNSS, nasal airflow	Reduction in TSS, TNSS, and improved nasal airflow.
Patou et al[1185]	2006	1a	SR and meta-analysis	levocetirizine	Nasal obstruction	Improved nasal obstruction under artificial and natural allergen exposure
Schenkel[1186]	2006	1a	SR	desloratadine	Morning symptoms, TSS, TNSS, TNNSS	Desloratadine improves TSS and improved QOL in patients with SAR/PAR. 24-hour action makes it effective in controlling morning symptoms.
Hore et al[1187]	2005	1a	SR of RDBCT	H_1 antihistamine vs placebo	Nasal obstruction	Oral H_1 antihistamines improve nasal obstruction by 22% over placebo.
Passalacqua and Canonica[1188]	2005	1a	SR	levocetirizine desloratadine	Nasal symptoms, wheal-flare response, QOL, TSS	Improved QOL and TSS for SAR/PAR. Levocetirizine has a faster onset.
Bousquet et al[1170]	2004	1a	SR with consensus statement	desloratadine	ARIA/EAACI criteria efficacy, safety, pharmacology	Desloratadine is recommended for treating patients with AR.
Greisner[1189]	2004	1a	SR	cetirizine desloratadine fexofenadine loratadine	Onset of action	Inconsistent results. Onset of action is dependent on how it is defined and measured.

Limon and Kockler[1190]	2003	1a	SR	desloratadine	TSS, TNSS, TNNSS, nasal congestion, nasal airflow, TASS for SAR/PAR	Desloratadine is a safe and efficacious for patients with SAR/PAR. Improved TSS, TNSS and TNNSS, TASS, nasal congestion. Nasal congestion was excluded in the PAR group.
Bojkowski et al[1191]	1989	1a	SR	acrivastine (40 studies reviewed)	rhinoconjunctivitis symptoms, nasal congestion, adverse events, drowsiness, CNS depression for SAR/PAR	Newer-generation oral H1 antihistamine acrivastine has excellent efficacy for patients with SAR/PAR. Improved nasal congestion. Small increase in drowsiness over terfenadine. No CNS depression found.

H_1: histamine receptor H_1; LOE: level of evidence; SR: systematic review; AE: adverse effects; TNSS: Total Nasal Symptom Score; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; ARIA: Allergic Rhinitis and its Impact of Asthma; AR: allergic rhinitis; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; EAACI: European Academy of Allergy and Clinical Immunology; TSS: Total Symptom Score; PNIF: peak nasal inspiratory flow; QT: measure of time between the onset of ventricular depolarization and completion of ventricular repolarization; ESS: Epworth Sleepiness Scale; QOL: quality of life; DNS: Daytime Nasal Symptoms; DES: Daytime Eye Symptoms; DTSSm: mean Total Daily Symptom Score; DSSm: mean Daily Symptom Score; TSSC: Total Symptom Severity Complex; TNNSS: Total Non-Nasal Symptom Score; RDBCT: randomized double-blind controlled trial; TASS: Total Asthma Symptom Score; CNS: central nervous system

Table IX.B.1.a-2. List of commonly used second-generation antihistamines

Antihistamine	**Onset (h)**	**Duration (h)**	**Drug interactions**	**Elimination (h)**	**Dosage**	
Medication					**Adults**	**Children**
cetirizine	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	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
bilastine	2 h	24 h	Unlikely	14.5 h	20 mg QD	6-11 y: 10 mg QD
fexofenadine	1-3 h	>24 h	Unlikely	11-15 h	60 mg BID or 180 mg QD	2-11 y: 30 mg BID
levocetirizine	0.7 h	>24 h	Unlikely	7 h	5 mg QD	2-5 y: 1.25 mg QD 6-11 y: 2.5 mg QD ≥ 12 y: 2.5-5 mg QD
Loratadine (Claritin®)	2 h	>24 h	Unlikely	7.8 h	10 mg QD or 5 mg BID	2-5y; 5 mg QD ≥ 6 y; 10 mg QD

mg: milligram (mg); BID: twice a day; QD: once a day; h: hour; y: year; N/A: not applicable

IX. B. 1. b. Oral H_2 antihistamines

The role of the H_2 receptor in mediating histamine-related nasal symptoms in AR is controversial. Few small studies have investigated the impact of H_2 receptor antagonism, with varied results. **[Table IX.B.1.b.]** Further, no data exists comparing H_2 receptor antagonism efficacy to common modern first line therapy such as nasal topical corticosteroids. Finally, the clinical significance of the changes associated with H_2 antihistamines has not been clearly defined. Despite these caveats, some studies support the addition of an H_2 antihistamine for patients with recalcitrant nasal airway obstruction while on oral H_1 antihistamines. There are drug-drug interactions that can occur with H_2 antihistamines through decreased gastric acidity and inhibition of P450.[1192] However, due to the low cost of these medications, clinical situations may arise that would justify their use.

All but one of the RCTs investigating the efficacy of H_2 antihistamines are within the context of pre-treatment of a subject prior to a nasal allergen challenge. Wood-Baker et al[1193] compared oral cetirizine to oral ranitidine. Objective measures of nasal airway resistance showed greater improvement with ranitidine, yet cetirizine decreased objective measures of nasal secretion more than ranitidine. Taylor-Clark et al[1194] found similar improvement in nasal airway resistance between cetirizine and ranitidine, but a significant improvement with the use of combination therapy. Combination therapy was also shown to improve nasal airflow when cimetidine was added to cetirizine.[1195] Two studies did not find improvement in nasal airflow with the addition of an H_2 antihistamine.[1196,1197] The clinical significance of these objective findings is unclear, and the studies that employed PROMs did not demonstrate subjective improvement in nasal obstruction.

Four studies investigated the impact of H_2 antagonism on symptoms, however these studies did not utilize standardized outcome measures as they pre-dated the development of such tools. Subjects were asked to report some combination of congestion, blockage, itching, drainage, sneezing, eye symptoms and asthma with a categorical severity measure. Three of the four studies examined symptoms after nasal allergen challenge, and none demonstrated efficacy of H_2 antihistamines, either alone or in conjunction with an H_1 antihistamine in diminishing allergic symptoms.[1195-1198] One study of 23 subjects[1198] did investigate the impact of cimetidine in conjunction with chlorpheniramine in a real-world setting. Subjects with known late-summer AR were randomized during this season to receive alternating two-week courses of either chlorpheniramine plus placebo, or chlorpheniramine plus cimetidine, and symptom scores were recorded twice daily along with adjuvant medical therapies (specifically, oral corticosteroids). Patients receiving both H_1 and H_2 antihistamines reported decreased medication usage (28 corticosteroid days vs 44 corticosteroid days, $p<0.02$) and decreased symptoms scores during one of the eight weeks when weed pollen counts were high. A caveat of this study is its utilization of a first-generation antihistamine which is no longer recommended as a first-line treatment of AR.

The data existing on the use of H_2 antihistamines in AR are limited in scope and quality. The objective findings of improved nasal airway resistance suggest that the H_2 histamine receptor does modulate nasal tissue response to histamine.[1193-1195] However, the clinical significance of this mechanism is not clear, particularly in the context of modern treatment algorithms.[1195-1198] The relatively manageable side effect profile and costs of H_2 antihistamines, does offer patients with otherwise recalcitrant AR symptoms an additional treatment option.

- Aggregate Grade of Evidence: B (Level 1b: 6 studies; *Table IX.B.1.b.*).
- Benefit: Decreased objective nasal resistance, and improved symptom control in one study when used in combination with H_1 antagonists.
- Harm: Drug-drug interaction (P450 inhibition, inhibited gastric secretion and absorption),
- Cost: Increased cost associated with H_2 antagonist.
- Benefits-Harm Assessment: Unclear benefit and possible harm.
- Value Judgments: No studies evaluating efficacy of H_2 antihistamines in context of topical nasal corticosteroids.
- Policy Level: No recommendation. The data available does not adequately address the question as to the benefit of H_2 antihistamines in clinical AR as part of modern treatment protocols.
- Intervention: Addition of an oral H_2 antagonist to an oral H_1 antagonist may improve symptom control in AR; however, the evidence to support this is not strong.

Table IX.B.1.b. Evidence for the role of oral H_2 antihistamines in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Taylor-Clark et al[1194]	2005	1b	RCT	Histamine challenge with premedication: 1. PO cetirizine 2. PO ranitidine 3. PO cetirizine + ranitidine 4. placebo	Nasal airway resistance	Cetirizine alone and ranitidine alone improve nasal resistance. Cetirizine plus ranitidine improves nasal resistance more than either alone.
Juliusson and Bende[1196]	1996	1b	RCT	Allergy challenge with premedication: 1. PO terfenadine 2. PO cimetidine 3. PO terfenadine + cimetidine 4. placebo	Laser Doppler flowmeter, allergic symptoms	No difference in symptoms or flowmetry with cimetidine. No additive effect of cimetidine with terfenadine.
Wang D et al[1195]	1996	1b	RCT	Allergy challenge with premedication: 1. PO cetirizine 2. PO cetirizine + cimetidine	Symptoms (itching, sneezing, rhinorrhea, congestion), sneeze count, nasal airway resistance	Combination of cetirizine + cimetidine showed improved nasal airway resistance and nasal airflow over cetirizine alone.
Wood-Baker et al[1193]	1996	1b	RCT	Allergy challenge with premedication: 1. PO cetirizine 2. PO ranitidine	Nasal lavage fluid protein concentration, nasal airway resistance	Ranitidine improved nasal resistance more than cetirizine. Cetirizine decreased total protein and albumin more than ranitidine.
Carpenter et al[1198]	1983	1b	RCT	During allergy season medicated with: 1. PO chlorpheniramine 2. PO chlorpheniramine + cimetidine	Symptoms (rhinorrhea, sneezing, nasal congestion, nasal pruritus, eye discomfort), medication usage beyond study therapy	Reduced symptoms and medication scores in cimetidine plus chlopheniramine group.
Brooks et al[1197]	1982	1b	RCT	Allergy challenge with premedication: 1. PO cimetidine 2. placebo	Subjective symptoms (congestion, itch, drainage, sneeze), nasal resistance, nasal secretion weight	No difference in subjective scores. Increased secretion and sneeze count, no difference in nasal resistance.

H2: histamine receptor H2; LOE: level of evidence; RCT: randomized controlled trial; PO: per os (medication taken orally)

IX. B. 1. c. Intranasal antihistamines

The use of intranasal antihistamine spray for AR has been well studied. Two agents are currently available in North America for intranasal use as a topical spray, azelastine hydrochloride and olopatadine hydrochloride. A systematic review of the English-language literature was performed for clinical trials of azelastine or olopatadine for the treatment of AR. A total of 44 papers were identified that reported results of RCTs of intranasal antihistamine monotherapy against either placebo or active control.[1046,1199-1241] **[Table IX.B.1.c.]** Of these, 11 studies included comparison of different doses of intranasal antihistamine[1204,1205,1207,1211,1212,1216,1218,1219,1231,1235,1237] and 29 studies utilized inactive placebo.[1201,1202,1204,1205,1207-1209,1211-1214,1216,1218-1222,1224,1225,1227-1231,1233,1235,1237-1239] Overall, there were 38 studies of azelastine[1046,1199-1201,1203,1205,1207-1213,1215,1217,1220-1241] and 10 studies of olopatadine[1202,1204,1206,1208,1210,1211,1214,1216,1218,1219] as monotherapy.

Outcome measures were predominantly patient-reported symptom scores or QOL assessments. The most common outcome measure was the TNSS (23 studies), which records the severity of runny nose, sneezing, itching and congestion. Other outcome measures included the RQLQ (7 studies), the Total Ocular Symptom Score (TOSS, 5 studies), the Caregiver Treatment Satisfaction Questionnaire (2 studies), the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (1 study), the Short Form-36 (1 study), the Epworth Sleepiness Scale (ESS, 1 study), the Rhinitis Severity Score (1 study) and a Subjective Global Assessment (1 study). Multiple studies, particularly those published prior to 2002, used a variety of non-validated symptom scoring systems ranging from 5 to 13 items each (19 studies). Objective measures included nasal lavage (3 studies), response to methacholine challenge (2 studies), nasal flow rate (2 studies) and rhinomanometry (1 study).

Study duration ranged from 2 days to 8 weeks, with the most frequent duration being 14 days of treatment. The number of subjects in each study ranged from 20 to 1188. Intranasal antihistamine was compared to placebo in 29 studies,[1201,1202,1204,1205,1207-1209,1211-1214,1216,1218-1222,1224,1225,1227-1231,1233,1235,1237-1239] with primary outcomes showing superiority to placebo in all studies. Intranasal antihistamine was trialed against an active treatment comparator of a different medication class in in 24 studies.[1046,1199,1203,1206,1213-1215,1217,1220,1221,1224,1226,1227,1229,1231-1236,1238-1241] Although not reported in all studies, the intranasal antihistamine spray consistently had a more rapid onset of action, occurring as early as 15 minutes after administration. Azelastine and olopatadine were directly compared in 3 studies, with no significant difference in symptom relief between agents.[1208,1210,1211] In 2 additional studies, azelastine was compared with an experimental formulation of intranasal levocabastine, with either comparable or superior results for azelastine.[1200,1223]

Intranasal antihistamine was compared to INCS in 12 studies, with the primary outcome favoring antihistamine in 2 studies,[1213,1214] corticosteroid in 3 studies,[1224,1227,1229] and showing equivalency in 7 studies.[1199,1203,1206,1233,1238,1239,1241] In 2 of the studies showing equivalency, antihistamine was superior for ocular symptoms.[1203,1239] The 3 studies showing superiority of corticosteroids were all conducted prior to 2000 and used heterogeneous non-validated symptom scores as primary outcomes. Intranasal antihistamine was compared to oral antihistamine monotherapy in 8 studies, with the primary outcome favoring intranasal antihistamine in 3 studies[1215,1217,1232] and showing equivalency in 5 studies.[1221,1234-1236,1240] One study included a treatment arm with oral chlorpheniramine as a positive control without intent to compare efficacy with azelastine.[1231] One study comparing azelastine spray with oral loratadine

plus intranasal beclomethasone found that azelastine monotherapy was at least as effective as combination therapy.[1226] Two studies comparing intranasal azelastine plus oral antihistamine to intranasal azelastine monotherapy showed no additional benefit for combination therapy.[1220,1221]

The minimum age of subjects in the included studies was generally 12 years or older. Children aged 6-12 years old were included in 3 studies, which in aggregate showed superiority of intranasal antihistamine to placebo in improving symptoms and QOL.[1202,1204,1228]

Serious adverse effects were not reported in any study. Intranasal antihistamine was generally well tolerated, with the most commonly reported adverse effect of an unpleasant taste. One study that compared the commercially available form of azelastine with a reformulated vehicle found no difference in taste aversion.[1205] One study directly comparing olopatadine with azelastine reported better sensory attributes for olopatadine.[1210] Other reported adverse effects included somnolence, headache, epistaxis and nasal discomfort, all occurring in less than 10% of cases in any study.

- Aggregate Grade of Evidence: A (Level 1b: 43 studies; Level 2b: 1 study; *Table IX.B.1.c.*). Due to the large number of studies with high level of evidence, studies of lower evidence levels are not considered here.
- Benefit: Intranasal antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than INCS, and show consistent reduction in symptoms and improvement in QOL in RCTs compared to placebo.
- Harm: Concerns for patient tolerance, especially due to taste. Intranasal antihistamines are less effective for congestion than INCS.
- Costs: Low-to-moderate financial burden; available as prescription only.
- 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.
- Value Judgments: Extensive level 1 evidence comparing intranasal antihistamine monotherapy to active and placebo controls demonstrates overall effectiveness and safety.
- Policy Level: Recommendation.
- Intervention: Intranasal antihistamines may be used as first- or second-line therapy in the treatment of AR.

Table IX.B.1.c. Evidence for the role of topical intranasal antihistamines as monotherapy in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Carr et al[1199]	2012	1b	DBRCT (post-hoc analysis)	1. azelastine 0.28 mg BID 2. fluticasone propionate 0.1 mg spray BID	rTNSS, rTOSS, RQLQ	Fluticasone superior to azelastine for improving rhinorrhea; comparable symptom and QOL improvement.
Han et al[1200]	2011	1b	DBRCT	1. azelastine 0.1% (dose not given) 2. levocabastine hydrochloride 0.05% spray (dose not given)	rTNSS	Comparable symptom improvement.
Howland et al[1201]	2011	1b	DBRCT	1. azelastine 0.82 mg BID 2. placebo	rTNSS, rTOSS, RQLQ	Azelastine superior to placebo for nasal and eye symptoms and QOL.
Meltzer et al[1202]	2011	1b	DBRCT	1. olopatadine 1.33 mg BID 2. placebo	rTNSS, rTOSS, PRQLQ, CGTSQ-AR	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers.
Berger et al[1204]	2009	1b	DBRCT	1. olopatadine 1.33 mg BID 2. olopatadine 2.66 mg BID 3. placebo	TNSS, TOSS, PRQLQ, CGTSQ, SGA	Olopatadine superior to placebo in reducing symptoms in children, improving QOL, and satisfying caregivers.
Bernstein et al[1205]	2009	1b	DBRCT	1. azelastine 0.28 mg BID 2. reformulated azelastine 0.28 mg BID 3. azelastine 0.56 mg BID 4. reformulated azelastine 0.56 mg BID 5. placebo 2 sprays	TNSS	Both azelastine spray formulations superior to placebo; dose-response effect between dosages; no difference in bitter taste between formulations.
Kaliner et al[1206]	2009	1b	DBRCT	1. olopatadine 2.66 mg BID 2. fluticasone 0.2 mg spray daily	rTNSS, rTOSS	Both treatments improve symptoms; faster onset for olopatadine.
Shah et al[1207]	2009	1b	DBRCT	1. azelastine 0.82 mg BID 2. azelastine 0.56 mg BID 3. placebo	TNSS	Both azelastine doses superior to placebo; greater improvement with higher dose.
Shah et al[1208]	2009	1b	DBRCT	1. olopatadine 2.66 mg BID 2. azelastine 0.56 mg BID 3. placebo	TNSS	Both treatments superior to placebo; no difference between treatments; less bitter taste with olopatadine.
van Bavel et al[1209]	2009	1b	DBRCT	1. azelastine 0.82 mg daily 2. placebo	TNSS	Azelastine superior to placebo.
Meltzer et al[1210]	2008	1b	DBRCT	1. olopatadine 2.66 mg BID 2. azelastine 0.56 mg BID	Sensory perception	Olopatadine favored for taste, aftertaste and likelihood of use.

Pipkorn et al[1211]	2008	1b	DBRCT	1. olopatadine 0.1%, (dose not given) 2. olopatadine 0.2% (dose not given) 3. azelastine 0.1% (dose not given) 4. 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[1212]	2007	1b	DBRCT	1. azelastine 0.28 mg daily 2. azelastine 0.28 mg BID 3. placebo	TNSS	Azelastine both doses superior to placebo.
Patel et al[1213]	2007	1b	DBRCT	1. azelastine 0.56 mg daily 2. mometasone furoate 0.2 mg spay QD 3. placebo	TNSS	Azelastine superior to mometasone and placebo.
Patel et al[1214]	2007	1b	DBRCT	1. olopatadine 2.66 mg daily 2. mometasone furoate 0.2 mg spray QD 3. placebo	TNSS, patient satisfaction	Olopatadine superior to placebo and mometasone in reducing symptoms; faster onset for olopatatine.
Berger et al[1215]	2006	1b	DBRCT	1. azelastine 0.56 mg BID 2. cetirizine 10 mg tablet daily	TNSS, RQLQ	Azelastine superior for sneezing and nasal congestion; azelastine superior for QOL.
Hampel et al[1216]	2006	1b	DBRCT	1. olopatadine 2.66 mg BID 2. olopatadine 1.77 mg BID 3. placebo	Total Symptom Score, RQLQ	Olopatadine (both doses) superior to placebo in majority of domains for QOL improvement.
Horak et al[1046]	2006	1b	DBRCT	1. azelastine 0.4 mg daily 2. desloratadine 5 mg tablet daily 3. placebo spray	TNSS	Azelastine superior to desloratadine and placebo.
Corren et al[1217]	2005	1b	DBRCT	1. azelastine 0.56 mg BID 2. cetirizine 10 mg tablet daily	TNSS, RQLQ	Azelastine superior cetirizine for symptoms and QOL.
Meltzer et al[1218]	2005	1b	DBRCT	1. olopatadine 2.66 mg BID 2. olopatadine 1.77 mg BID 3. placebo	TNSS, RQLQ	Olopatadine (both doses) superior to placebo for symptoms and QOL improvement.
Ratner et al[1219]	2005	1b	DBRCT	1. olopatadine 2.66 mg BID 2. olopatadine 1.77 mg BID 3. placebo	TNSS	Olopatadine (both doses) superior to placebo.
LaForce et al[1220]	2004	1b	DBRCT	1. azelastine 0.56 mg BID 2. azelastine 0.56 mg BID + fexofenadine 60 mg tablet BID 3. placebo spray + placebo tablet	TNSS	Azelastine superior to placebo; no additional benefit of adding oral fexofenadine to azelastine monotherapy.
Berger and White[1221]	2003	1b	DBRCT	1. azelastine 0.56 mg BID 2. azelastine 0.56 mg BID + loratadine 10 mg tablet	TNSS	All treatments superior to placebo; azelastine at least as effective as desloratadine; no additional benefit of

				3. desloratadine 5 mg tablet + placebo spray 4. placebo spray + placebo tablet		adding oral loradatine to azelastine monotherapy.
Saengpanich et al[1222]	2002	1b	DBRCT	1. azelastine 0.28 mg BID 2. placebo	TNSS, nasal lavage, methacholine challenge	Azelastine superior to placebo for symptoms; no effect on nasal eosinophils or cytokines; azelastine inhibits methacholine response.
Falser et al[1223]	2001	1b	DBRCT	1. azelastine 0.56 mg BID 2. levocabastine 0.2 mg spray BID	10-item symptom score, global assessment	Azelastine superior to levocabastine.
Berlin et al[1224]	2000	1b	DBRCT	1. azelastine 0.56 mg BID 2. flunisolide 0.116 mg spray BID 3. placebo	9-item symptom score	Flunisolide superior to azeslastine; both treatments superior to placebo.
Golden et al[1225]	2000	1b	DBRCT	1. azelastine 0.56 mg BID 2. placebo	RSS, ESS	Azelastine superior to placebo for improving rhinorrhea and sleep quality.
Berger et al[1226]	1999	1b	DBRCT	1. azelastine 0.56 mg BID 2. loratadine 10 mg tablet daily + beclomethasone dipropionate 0.168 mg spray BID	5-item symptom score, global evaluation	Azelastine at least as effective as combination therapy with loratadine plus beclomethasone spray.
Stern et al[1227]	1998	1b	DBRCT	1. azelastine 0.28 mg BID 2. budesonide 0.256 mg spray daily 3. placebo	3-item symptom score	Budesonide superior to azelastine; both treatments superior to placebo.
Herman et al[1228]	1997	1b	DBRCT	1. azelastine 0.28 mg BID 2. placebo	TNSS	Azelastine superior to placebo for children.
Newson-Smith et al[1229]	1997	1b	DBRCT	1. azelastine 0.56 mg BID 2. beclomethasone 0.2 mg spray BID 3. placebo	6-item symptom score	Beclomethasone superior to azelastine for long-term symptom improvement; both treatments superior to placebo; azelastine more rapid onset.
Weiler and Meltzer[1230]	1997	1b	DBRCT	1. azelastine 0.56 mg spray BID + azelastine 0.5 mg tablet BID 2. placebo spray + azelastine 0.5 mg tablet BID	13-item symptom score	Azelastine spray showed limited benefit over placebo in patients already treated with systemic azelastine.
LaForce et al[1231]	1996	1b	DBRCT	1. azelastine 0.56 mg daily 2. azelastine 0.56 mg BID 3. chlorpheniramine 12 mg tablet BID	8-item symptom score	Azelastine superior to placebo at both doses; no comparison with chlorpheniramine.

				4. placebo		
Charpin et al[1232]	1995	1b	DBRCT	1. azelastine 0.28 mg BID 2. cetirizine 10mg tablet daily	8-item symptom score	Azelastine superior for nasal stuffiness and rhinorrhea; no difference in other symptoms.
Pelucchi et al[1233]	1995	1b	DBRCT	1. azelastine 0.28 mg BID 2. beclomethasone dipropionate 0.1 mg spray BID 3. placebo	8-item symptom score, nasal lavage, methacholine challenge	Azelastine superior to placebo and comparable to beclomethasone for symptom improvement; neither treatment prevented bronchial responsiveness; no effect of azelastine on eosinophils.
Gastpar et al[1234]	1994	1b	DBRCT	1. azelastine 0.28 mg daily 2. terfenadine 60 mg tablet daily	13-item symptom score	Comparable symptom improvement.
Meltzer et al[1235]	1994	1b	DBRCT	1. azelastine 0.28 mg daily 2. azelastine 0.28 mg BID 3. chlorpheniramine 12 mg tablet BID 4. placebo	11-item symptom score	Azelastine comparable to chlorpheniramine and superior to placebo at both doses.
Passali and Piragine[1236]	1994	1b	DBRCT	1. azelastine 0.28 mg BID 2. cetirizine 10 mg tablet daily	13-item symptom score	Azelastine at least as effective as cetirizine.
Ratner et al[1237]	1994	1b	DBRCT	1. azelastine 0.28 mg daily 2. azelastine 0.28 mg BID 3. placebo	8-item symptom score	Azelastine twice-daily superior to placebo.
Davies et al[1238]	1993	1b	DBRCT	1. azelastine 0.28 mg BID 2. beclomethasone dipropionate 0.1 mg spray BID 3. placebo	TNSS, rhinomanometry	Azelastine superior to beclomethasone and placebo for symptoms; no change in airway resistance with either treatment.
Dorow et al[1239]	1993	1b	DBRCT	1. azelastine 0.28 mg BID 2. budesonide 0.10 mg spray BID 3. placebo	13-item symptom score	Azelastine comparable to budesonide for nasal symptoms and superior for ocular symptoms; both treatments superior to placebo.
Gambardella[1240]	1993	1b	DBRCT	1. azelastine 0.28 mg BID 2. loratadine 10 mg tablet daily	12-item symptom score, global assessment	Azelastine at least as effective as loratadine.
Gastpar et al[1241]	1993	1b	DBRCT	1. azelastine 0.28 mg BID 2. budesonide 0.10 mg spray BID	10-item symptom score, nasal flow rate	Azelastine at least as effective as budesonide for symptoms; flow rate improved in both treatment groups.

Kalpaklioglu and Kavut[1203]	2010	2b	Single-blind RCT	1. azelastine 0.56 mg BID 2. triamcinolone acetonide 0.22 mg spray daily	TNSS, nPIFR, ESS, SF-36, mini-RQLQ	Comparable improvement in nasal symptoms, nPIFR, ESS and QOL; azelastine superior for ocular symptoms.

AR: allergic rhinitis; LOE: level of evidence; DBRCT: double-blind randomized controlled trial; RCT: randomized controlled trial; BID: twice a day; rTNSS: reflective Total Nasal Symptom Score; rTOSS: reflective Total Ocular Symptom Score; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; QOL: quality of life; CGTSQ-AR: Caregiver Treatment Satisfaction Questionnaire for Allergic Rhinitis; TNSS: Total Nasal Symptom Score; TOSS: Total Ocular Symptom Score; PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; CGTSQ: Caregiver Treatment Satisfaction Questionnaire; SGA: Subjective Global Assessment; RSS: Rhinitis Severity Score; ESS: Epworth Sleepiness Scale; RCT: randomized controlled trial; nPIFR: nasal peak inspiratory flow rate; SF-36, 36-Item Short Form

IX. B. 2. Corticosteroids

IX. B. 2. a. Oral corticosteroids

The anti-inflammatory effect of oral corticosteroids in AR is well known and has been demonstrated experimentally using the nasal challenge model and clinically in the context of seasonal disease. Compared to placebo, premedication with oral prednisone for 2 days prior to an allergen challenge showed a reduction in sneezes, and levels of histamine and mediators of vascular permeability in nasal lavages during the late phase response.[884] **[Table IX.B.2.a.]** Further, active treatment resulted in a reduction in the priming response to consecutive allergen challenge.[884] Prednisone has also been shown to reduce the influx of eosinophils and levels of the eosinophil mediators (major basic protein and eosinophil derived neurotoxin) into nasal secretions during the late phase response compared to placebo.[1242,1243] Non-placebo-controlled studies have demonstrated efficacy of oral corticosteroids for SAR. Schwartz et al[1244] demonstrated that 15 days of cortisone 25 mg four times daily during the ragweed season resulted in significant relief of symptoms in 21/25 patients. Similarly, 100 mg of cortisone daily for 4 day courses during the pollen season showed rhinitis symptom relief in 42/51 patients, with 20 patients relapsing within 7 days after cessation of therapy.[1245] Oral hydrocortisone 40-80 mg daily has also been shown to reduce symptoms of ragweed allergies.[1246] Brooks et al[1247] performed a placebo controlled study comparing the efficacy of methylprednisolone 6, 12, or 24 mg PO daily for 5 days to placebo in controlling nasal symptoms during the ragweed season. Whereas the 6 mg and 12 mg doses led to a significant reduction in some of the symptoms compared to placebo (congestion, postnasal drainage, and eye symptoms), the 24 mg dose resulted in a significant reduction of all symptoms (congestion, runny nose, sneezing, itching, postnasal drainage and eye symptoms).

Because of the recognized systemic adverse events associated with oral corticosteroids,[101] their use has been largely replaced by the intranasal preparations. In a double-blind placebo-controlled trial, the effect of intranasal flunisolide and its oral dose bioequivalent (an oral dose that would lead to similar systemic levels) were compared in ragweed induced SAR.[1248] The intranasal preparation was shown to be efficacious in reducing rhinitis symptoms while the oral dosing was not. This suggested that INCS achieve their benefit primarily by their local activity as opposed to systemic bioavailability. In a head-to-head comparison of the efficacy of intranasal vs systemic steroids, Karaki et al[1249] performed an open-label, parallel, randomized trial during the cedar pollen season in Japan. Patients received loratadine 10 mg daily alone, loratadine with intranasal mometasone furoate (200 mcg once daily), or loratadine with oral betamethasone 0.25 mg twice daily for 1 week. The groups receiving some form of steroid in addition to loratadine had significantly lower symptoms of sneezing, rhinorrhea, and nasal obstruction compared to loratadine alone, with no significant difference between the intranasal and oral preparations. The oral steroid was more effective than the INCS in controlling allergic eye symptoms.

The above data suggest that oral corticosteroids are effective for the treatment of AR. However, given the significant systemic adverse effects related to using oral corticosteroids for prolonged periods of time these agents are not recommended for the routine treatment of AR.

- Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 4: 3 studies; *Table IX.B.2.a.*).

- Benefit: Oral corticosteroids can attenuate symptoms of AR.
- Harm: Oral corticosteroids have known undesirable adverse effects. These include effects on the hypothalamic-pituitary axis, growth and musculoskeletal system, gastrointestinal system, hypertension, glycemic control, mental/emotional state, and others.
- Cost: Low.
- Benefits-Harm Assessment: The risks of using oral corticosteroids outweigh the benefits when compared to similar symptom improvement with the use of INCS.
- Value Judgments: In the presence of effective symptom control using INCS, the risk of adverse effects from using oral corticosteroids for AR appears to outweigh the potential benefits.
- Policy Level: Recommendation against the routine use of oral corticosteroids for AR.
- Intervention: Although not recommended for routine use in AR, certain clinical scenarios warrant the use of short courses of systemic corticosteroids after a discussion of the risks and benefits with the patient. This may include patients with significant nasal obstruction that would preclude penetration of intranasal agents (INCS or antihistamines). In these cases, a short course of systemic oral corticosteroids could improve congestion and facilitate access and efficacy of the topical agents.

Table IX.B.2.a. Evidence for the role of oral corticosteroids in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Brooks et al[1247]	1993	1b	Placebo-controlled, parallel group study	SAR during season (n=31): MP 6, 12, 24 mg QD x 5 days	Symptom scores	All doses more effective than placebo in reducing symptoms with the highest dose most effective.
Bascom et al[1243]	1989	1b	Placebo controlled, crossover, nasal challenge study	SAR out of season (n=13): prednisone 60 mg PO daily for 2 days	Number of eosinophils and levels of MBP and EDN in nasal lavages	Prednisone reduced the number of eosinophils and the levels of its mediators after allergen challenge.
Bascom et al[1242]	1988	1b	Placebo controlled, cross over, nasal challenge study	SAR out of season (n=10): prednisone 60 mg PO daily for 2 days	Number of neutrophils, eosinophils, and mononuclear cells in nasal lavages	Prednisone reduced the influx of eosinophils into nasal secretions after allergen challenge.
Pipkorn et al[884]	1987	1b	Placebo controlled, cross over, nasal challenge study	SAR out of season (n=13): prednisone 60 mg PO daily for 2 days	Sneezes, levels of histamine, TAME-esterase, kinins, PGD2, LTC4/D4, and albumin in nasal lavages	Prednisone inhibited the late phase response to nasal allergen challenge.
Kwaselow et al[1248]	1985	1b	Multicenter, randomized, double-blind, placebo-controlled study	SAR during season (n=99): 1. oral flunisolide 500 mcg BID x 4 weeks 2. intranasal flunisolide 50 mcg per nostril BID x 4 weeks	Symptom scores	Intranasal preparation only one to show efficacy in reducing rhinitis symptoms.
Karaki et al[1249]	2013	2b	Open label, parallel, randomized trial	SAR during season (n=72): 1. loratadine 10 mg daily 2. loratadine with intranasal MF (200 mcg QD) 2. loratadine with PO betamethasone 0.25 mg BID	Symptom scores	The groups on steroids had lower symptoms compared to loratadine alone, with no significant difference between them.
Schwartz[1246]	1954	4	Observational case series	SAR during season (n=10): hydrocortisone 40-80 mg daily	Symptom relief	7/10 patients reported symptom relief
Schiller and Lowell[1245]	1953	4	Observational case series	SAR during season (n=51): cortisone 100 mg daily x 4 days	Symptom relief	42/51 patients reported symptom relief
Schwartz et al[1244]	1952	4	Observational case series	SAR during season (n=25): cortisone 100 mg daily x 15 days	Symptom relief	21/25 patients reported symptom relief

LOE: level of evidence; SAR: seasonal allergic rhinitis; MP: methylprednisolone; PO: per os (medication taken orally); MBP: major basic protein; EDN: eosinophil derived neurotoxin; TAME: N-a-p-tosyl-L-arginine methyl ester; PGD2: prostaglandin D2; LTC4/D4: Leukotriene C4/D4; BID: twice daily; MF: mometasone furoate

IX. B. 2. Corticosteroids

IX. B. 2. b. Injectable corticosteroids

Corticosteroids have been injected intramuscularly or into the turbinates for management of AR. The evidence evaluating deep intramuscular injections will be reviewed first. Overall, several early studies[1250-1254] demonstrated clinical effectiveness in improving allergic symptoms; however, the safety outcomes demonstrated the risk of undesired systemic corticosteroid adverse effects. More recent evidence[1255] confirms the increased risk of endogenous cortisol suppression along with other corticosteroid-related adverse effects such as osteoporosis and hyperglycemia. **[Table IX.B.2.b.]**

Kronholm[1250] demonstrated that a single injection of either betamethasone dipropionate/betamethasone phosphate or methylprednisolone acetate given at the onset of the hay fever season led to a significant reduction of both nasal and ocular symptoms during the five weeks of the study, with the betamethasone combination being more effective. Ohlander et al[1251] compared three long acting corticosteroid injections given at the beginning of the season, and showed that all treatments led to significant reductions in nasal and ocular symptoms during the season with no difference between groups. However, all preparations also suppressed endogenous cortisol, in some cases for more than 14 days after injection, and two out of the three injections resulted in increases in blood sugar levels.

When compared to other agents, injected corticosteroids demonstrated similar effectiveness outcomes. Specifically, there were similar clinical outcomes when comparing preseasonal steroid injections to both daily oral prednisolone[1252] and daily intranasal beclomethasone dipropionate spray.[1253] An adrenal corticotropic hormone (ACTH) test performed at 3 weeks showed significant suppression of adrenal function in the oral steroid treatment group and no evidence of suppression in the corticosteroid injection or topical intranasal corticosteroid groups.[1252] This was probably related to the short duration of adrenal suppression expected after a single injection of corticosteroids compared to continuous administration.

When evaluating the timing of injectable corticosteroid therapy, Borum et al[1254] compared the effects of a single depot injection of methylprednisolone given either at the beginning of the allergy season or later when pollen counts peaked. Compared to placebo, intramuscular methylprednisolone was efficacious against nasal congestion with less pronounced effects against rhinorrhea and sneezing. The authors argue that depot injectable steroids may be considered after other safer medical therapy fails and may provide an effective alternative treatment even if provided late in the allergy season.

Injectable corticorticosteroid preparations may have significant side effects which include adrenal suppression and growth retardation.[1256] In a large retrospective study of Danish National Registries, the relative risk and incidence of both osteoporosis and diabetes were higher in allergic individuals receiving at least one depot corticosteroid injection during the allergy season compared to those receiving immunotherapy.[1255]

Several early reports detailed significant improvement in symptoms of AR in a large proportion of patients who received intraturbinate injections of cortisone,[1257] hydrocortisone acetate[1258] or prednisolone.[1259] Similar, non-controlled, studies showed improvement in AR symptoms after intraturbinate injections.[1260,1261] A more recent randomized, placebo-controlled single-blind trial by Yang et al[1262] compared the efficacy of intraturbinate injections of either onabotulinum toxin A,

triamcinolone, or isotonic saline in patients with PAR. Both onabotulinum toxin A and triamcinolone therapy showed better control of nasal symptoms than placebo with onabotulinum toxin A efficacy lasting longest.

Orbital complications have been reported with intraturbinate but not intramuscular injections. Based on a large clinical experience, Mabry cites an estimated incidence of visual loss after intraturbinate injections to be 0.006%.[1263] Other complications have included transient visual loss and diplopia,[1264] blurred vision and temporary blindness,[1265] temporary distorted vision, decreased visual acuity and paresis of the medial rectus.[1265] Martin reported the rapid onset of ocular pain, blurred vision, and decreased visual acuity after an intraturbinate injection of triamcinolone acetonide.[1266] Choroidal and retinal arterial embolization were confirmed as the cause and they resolved completely within 24 hours. The mechanism of embolization is likely related to retrograde flow from the anterior tip of the inferior turbinate to the ophthalmic artery, followed by anterograde flow with the particles lodging in the end arteries of the choroid and retinal vessels. Larger particle size steroids (e.g. methylprednisolone) are thought to present higher risk than lower sized particles (e.g. triamcinolone).

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 3 studies, Level 4: 7 studies; *Table IX.B.2.b.*).
- Benefit: Injectable corticosteroids improve symptoms of AR in clinical studies.
- Harm: Injectable corticosteroids have known adverse effects on the hypothalamic-pituitary axis, growth suppression, osteoporosis, hyperglycemia and other systemic adverse effects. Intraturbinate corticosteroids have a small, but potentially serious, risk of ocular side effects including decline or loss of vision.
- Cost: Low.
- Benefits-Harm Assessment: In routine management of AR, the risk of serious adverse effects outweighs the demonstrated clinical benefit.
- Value Judgments: Injectable corticosteroids are effective for the treatment of AR. However, given the risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of effective alternatives (i.e. topical INCS therapy), injectable corticosteroids are not recommended for the routine treatment of AR.
- Policy Level: Recommendation against.
- Intervention: None.

Table IX.B.2.b. Evidence for the role of corticosteroid injections in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Yang et al[1262]	2008	1b	Randomized, placebo-controlled single-blind trial	Patients with PAR received intraturbinal injections (n=39): 1. onabotulinum toxin A (25 units in each turbinate) 2. triamcinolone (20 mg, 1 cc in each turbinate) 3. isotonic saline (1cc in each turbinate)	Symptoms of rhinorrhea, nasal obstruction, sneezing and itching at 1, 4, 8, 12, 16 and 20 weeks after injections	Botox controlled nasal symptoms for the longest time after injection. Steroid injection was better than placebo but the duration of action was shorter than Botox.
Laursen et al[1253]	1988	1b	Double blind, double dummy, placebo controlled, study	SAR during season (n=30): 1. intranasal beclomethasone dipropionate (400 mcg daily) for 4 weeks 2. IM injection of 2 ml betamethasone dipropionate/betamethasone disodium phosphate at start of season	Rhinoconjunctivitis symptom scores	IM injection significantly more effective than placebo or intranasal preparation.
Borum et al[1254]	1987	1b	Double-blind, placebo controlled, parallel study during 2 consecutive pollen seasons	SAR during 2 consecutive allergy seasons (n=24): 1. IM injection of 80 mg methylprednisolone given either at the beginning of the season or at peak pollen count 2. placebo	Number of sneezes and nose blowing during the day. Symptom scores of sneezing, rhinorrhea, nasal blockage, eye itching recorded at the end of the day.	IM injection was efficacious against nasal congestion with less pronounced effects against rhinorrhea and sneezing in active vs placebo treatment irrespective of timing of administration.
Laursen et al[1252]	1987	2b	Randomized, double-blind comparative	SAR during season (n=37): 1. oral prednisolone 7.5 mg PO daily x 3 weeks 2. single IM injection of 2 ml betamethasone dipropionate/betamethasone disodium phosphate at start of season	Nasal peak flow and symptom scores. ACTH test performed at 3 weeks.	IM and oral steroid resulted in a significant reduction of nasal/ocular symptoms during season. Significant suppression of adrenal function with oral steroid treatment only.
Ohlander et al[1251]	1980	2b	Prospective, randomized, parallel group	SAR during season (n=60). Received 1 of 3 long-acting IM injections:	Scores of rhinorrhea, congestion and ocular	All treatments led to significant reductions in nose and eye symptoms during season; no

				1. betamethasone dipropionate (5 mg) 2. betamethasone disodium phosphate (3 mg)/acetate (3 mg) 3. methylprednisolone acetate (40 mg)	symptoms at 1, 2, and 4 weeks after injection. Cortisol and glucose blood levels in 38 subjects.	difference between groups. All preparations suppressed endogenous cortisol; 2 out of 3 injections caused increases in blood sugar levels.
Kronholm[1250]	1979	2b	Prospective, parallel, randomized, open label	SAR during season. IM injection at season onset (n=42): 1. 2 ml betamethasone dipropionate/betamethasone phosphate (5 and 2 mg/ml) 2. 2 ml methylprednisolone acetate (40 mg/ml)	Weekly nasal and ocular symptoms for 5 weeks	Both preparations led to a significant reduction of nose and eye symptoms; betamethasone combination was more effective.
Aasbjerg et al[1255]	2013	4	Retrospective study of Danish National Registries between 1995-2011	Patients receiving IM steroid injections in April-July or immunotherapy against grass or birch pollen. (n=47,382)	Incidence and relative risk of osteoporosis, diabetes, tendon rupture and respiratory tract infection	Relative risk and incidence of osteoporosis and diabetes were higher in individuals receiving at least one depot corticosteroid injection vs those receiving immunotherapy.

LOE: level of evidence; PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; IM: intramuscular; PO: per os (medication taken orally); ACTH: adrenal corticotropic hormone

IX. B. 2. c. Intranasal corticosteroids (INCS)

INCS are effective for the treatment of AR. Their potent anti-inflammatory properties directly affect the pathophysiologic mechanisms of nasal inflammation in AR. In both nasal allergen challenge models and seasonal disease, treatment with INCS results in significant reduction in mediator and cytokine release along with a significant inhibition in the recruitment of basophils, eosinophils, neutrophils, and mononuclear cells to the nasal mucosa and secretions.[187,389,1267,1268] INCS also reduce the antigen-induced hyper-responsiveness of the nasal mucosa to subsequent challenge by antigen[187] and histamine.[1269,1270]

Multiple placebo-controlled clinical trials in adults and children have demonstrated the effectiveness of INCS in the reduction of nasal symptoms in AR, including sneezing, itching, rhinorrhea, and congestion.[1271,1272] With the reduction of nasal symptoms, INCS significantly improve the QOL[1272-1274] and sleep[673,706,707,1275,1276] of these patients. No significant differences in efficacy between available agents have been demonstrated in studied populations;[1273] therefore, sensory attributes may be an important factor in patient preference and adherence to therapy.[1277] These sensory attributes include aftertaste, nose runout, throat rundown, and smell. Addressing some of these concerns are two intranasal non-aqueous preparations with hydrofluoroalkane (HFA) aerosols recently approved for the treatment of AR in the US. These include beclomethasone dipropionate and ciclesonide, both approved and effective for SAR and PAR in adults and children 12 years and older.[688,1278-1281] Onset of action for INCS starts at time points ranging from 3-5 hours to 60 hours after first dosing.[1282-1285] Although the recommended continuous daily use of INCS is superior to other dosing strategies,[1286,1287] studies have demonstrated the efficacy of as-needed use of intranasal fluticasone propionate compared to placebo.[1288,1289] **[Table IX.B.2.c-1.]**

Along with improved nasal symptoms, INCS have beneficial effects on allergic eye symptoms including itching, tearing, redness, and puffiness.[1290-1292] This is secondary to a reduction in the naso-ocular reflex, which contributes to these eye symptoms.[1293] Most INCS lead to improved ocular symptoms, but the evidence suggests that the effects are not equal among INCS preparations.[1294] Some studies have suggested that INCS improve asthma control measures in patients suffering from both AR and asthma.[1295,1296] **[Table IX.B.2.c-2.]**

In comparative studies, INCS have shown superior efficacy to H_1 antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference in the relief of ocular symptoms.[1297-1299] INCS are more effective than LTRAs.[1299,1300] **[Table IX.B.2.c-3.]**

The most common side effects of INCS are a result of local irritation and include dryness, burning, stinging, blood tinged secretions, and epistaxis. The incidence of epistaxis with different preparations ranges from 4% to 8% over short treatment periods (2-12 weeks) with no differences between placebo and active therapy.[1301,1302] In studies carried over one year, epistaxis is as high as 20%.[1303,1304] Septal perforations are rare complications of INCS.[51] A systematic review of published articles looking at biopsy studies in patients with AR or CRS using INCS identified 34 studies. Of those, 21 studies included patients with AR, mixed rhinitis and NAR, and 13 involved patients with CRS with/without polyposis.[1305] None of the studies that included atrophy of the nasal mucosa as an outcome measure reported any atrophy with INCS. A meta-analysis of a subgroup of the studies showed no significant chance of developing atrophy while taking INCS, and no difference between active and

control groups in basement membrane characteristics. The review also found a significant reduction in the odds ratio for the development of squamous metaplasia in patients using INCS, suggesting a favorable effect. Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis have assessed morning cortisol concentrations, cosyntropin stimulation, 24-hr serum cortisol and 24-hr urinary free cortisol excretion. They show no adverse effects.[1304,1306-1317] Although there has been a report of an association between the use of INCS and the development of posterior subcapsular cataracts,[1318] a systematic review of controlled trials did not demonstrate a clinically relevant impact of INCS on either ocular pressure, glaucoma, lens opacity, or cataract formation.[1319] The effect of INCS on growth in children has been investigated in controlled studies using both knemometry in short-term studies (2-4 weeks) and stadiometry in long-term (12 months) studies. A meta-analysis of 8 randomized controlled trials with appropriate controls showed that, compared to children using placebo, mean growth was significantly lower among children using INCS in trials using knemometry (n=4) and that there was no significant growth difference in studies using stadiometry (n=4).[1320] The data suggests that INCS might have deleterious effects on short-term growth in children, but the heterogeneity in the stadiometry studies makes the effects on long-term growth suppression unclear. **[Table IX.B.2.c-4.]**

INCS are first line therapy for the treatment of AR due to their superior efficacy in controlling nasal congestion and other symptoms of this inflammatory condition. Subjects with known SAR should start prophylactic treatment with INCS several days before the pollen season with an evaluation of the patient's response in 2 weeks. In addition to making changes to the treatment regimen according to the patient's response, a nasal exam evaluates for signs of local irritation due to the drug or mechanical trauma from the applicator itself. Aiming the spray away from the nasal septum may also redcue irritation in this area. Children receiving INCS should be on the lowest effective dose to avoid negative growth effects.

- Aggregate Grade of Evidence: A (Level 1a: 15 studies; Level 1b: 33 studies; Level 2a: 3 studies; Level 2b: 1 study; Level 5: 1 study; *Tables IX.B.2.c. 1-4*).
- Benefit: INCS are effective in reducing nasal and ocular symptoms of AR. They have superior efficacy compared to oral antihistamines and LTRAs.
- Harm: Intranasal corticosteroids have known undesirable local adverse effects such as epistaxis with some increased frequency compared to placebo in prolonged administration studies. There are no apparent negative effects on the hypothalamic-pituitary axis. There might be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression.
- Cost: Low.
- Benefits-Harm Assessment: The benefits of using INCS outweigh the risks when used to treat SAR and PAR.
- Value Judgments: None.
- Policy Level: Strong Recommendation for the use of INCS to treat AR.
- Intervention: The well-proven efficacy of INCS, as well as their superiority over other agents, make them first line therapy in the treatment of AR.

Table IX.B.2.c-1. Evidence for the clinical efficacy of intranasal corticosteroids in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Rachelefsky and Farrar[1274]	2013	1a	SR	SAR (n=2290) and PAR (n=800). Sixteen controlled clinical trials ≥2 weeks in duration. Children aged 2-18 years.	Measures that assessed impairment and/or risk of comorbid conditions.	Intranasal steroids improved risk outcomes associated with asthma and OSA.
Rodrigo and Neffen[1272]	2011	1a	SR with meta-analysis	16 trials (n=5348). SAR:7 studies; PAR: 9 studies. Adults and adolescents ≥12 years: 13 studies; children: 3 studies. FFNS vs placebo.	Primary outcomes: rTOSS, iTOSS, rTNSS and iTNSS. Secondary outcomes: QOL, and adverse effects.	FFNS significantly improved rTOSS, iTOSS, rTNSS, and iTNSS scores compared with placebo in patients with SAR and PAR. There were greater improvements in QOL with a favorable safety profile.
Penagos et al[1271]	2008	1a	Meta-analysis of RDBPCTs	16 trials (n=2998). MFNS vs placebo.	TNSS, individual nasal symptoms, and TNNSS.	MFNS was associated with a significant reduction in TNSS and TNNSS. Significant effect was seen for nasal stuffiness/ congestion, rhinorrhea, sneezing and nasal itching.
Yamada et al[673]	2012	1b	Randomized, placebo-controlled, double-blind, crossover study	PAR (n=57). MFNS vs placebo for 14 days.	Nasal symptom scores, QOL and sleep quality, ESS.	MFNS significantly improved nasal symptoms, QOL, and sleep quality. Significant reduction of the ESS observed in the MFNS group with high sleep disturbance.
Meltzer et al[1276]	2010	1b	Double-blind, parallel group, placebo-controlled study	Adults with PAR, moderate rhinitis and disturbed sleep (n=30). MFNS 200 mcg vs placebo, 4-week trial.	Primary endpoint: AHI. Secondary measures: TNSS, nighttime symptom score, daytime PNIF, nighttime flow limitation index, RQLQ, ESS, WPAI-AS	AHI was not statistically significantly different between groups. MFNS significantly improved morning and evening TNSS, nasal obstruction/ blockage/congestion, daily peak nasal inspiratory flow, ESS, QOL score, and 2 of 5 WPAI–AS domains.
Kaiser et al[1284]	2007	1b	Double-blind, parallel-group, randomized, placebo-controlled study	Adults and adolescents with SAR (n=299). FFNS 110 mcg vs placebo.	Nasal and ocular symptoms on 4-point scale. rTNSS, iTNSS, rTOSS, iTOSS	FFNS significantly improved daily rTNSS, morning pre-dose iTNSS, daily rTOSS, and patient-rated overall response to therapy. Onset of therapeutic effect occurred at 8 hours after initial administration.

Craig et al[1275]	2003	1b	Double-blind, placebo-controlled study	PAR (n=32). Fluticasone NS vs placebo.	Questionnaires, QOL instruments, daily diary, ESS, and polysomnography.	Fluticasone improved subjective sleep vs placebo. There was no difference in the AHI in treated subjects.
Dykewicz et al[1289]	2003	1b	RDBPCT	Adults and adolescents ≥12 year (n=241), SAR to fall allergen. FPNS 200 mcg PRN vs placebo for 4 weeks.	Mean change from baseline in TNSS.	Patients treated with FPNS PRN had a significantly greater reduction from baseline in TNSS. Individual symptoms were also significantly improved by active therapy.
Hughes et al[706]	2003	1b	Double-blind, placebo-con-trolled, crossover study	PAR (n=22). Budesonide 128 mcg/day or placebo for 8 weeks.	ESS, Functional Outcomes of Sleep Questionnaire, RQLQ. Daily diary of nasal symptoms, sleep problems, and daytime fatigue.	Budesonide significantly improved daytime fatigue, somnolence, and quality of sleep vs placebo.
Fokkens et al[1283]	2002	1b	RDBPCT, parallel-group, multicenter	PAR (n=202, age 6-16 years). BANS 128 mcg daily vs. placebo.	Daily nPIF, nasal symptom scores, and overall evaluation of treatment efficacy. Subset (n=76) QOL by validated questionnaires.	BANS significantly more effective than placebo for nPIF, combined and individual nasal symptom scores, and the overall evaluation of treatment efficacy. Onset of action within the first 12-hour time interval for combined nasal symptoms and within 48 hours for nPIF.
Day et al[1282]	2000	1b	RDBPCT, parallel-group	SAR, ragweed-sensitivity (n=217), symptoms for at least 1 year. Challenge via chamber. BANS 64 mcg vs BANS 256 mcg vs placebo.	Combined nasal score, individual nasal symptoms, overall evaluation of treatment efficacy, nPIF.	7-12 hours: BANS better than placebo in reducing combined nasal and blocked nose symptoms. nPIF: onset of action (3 hours) was shortest for BANS 256 mcg. Treatment efficacy was higher for those receiving BANS compared with placebo starting at 5 hours. All treatments well tolerated, no specific adverse events occurred.
Jen et al[1288]	2000	1b	RDBPCT, parallel-group.	Adults, SAR, ragweed sensitivity (n=52). FPNS PRN vs placebo for 4 weeks.	Nasal symptom score, QOL, eosinophil count and eosinophilic cationic protein in nasal lavage.	Nasal symptom score lower with FPNS vs placebo. QOL significantly improved with FPNS. Eosinophil count significantly lower in with FPNS.

Craig et al[707]	1998	1b	Double-blind, placebo-controlled study	PAR (n=20). Topical INCS vs placebo	Daily symptom diary of nasal symptoms, sleep, and daytime sleepiness.	Nasal congestion and subjective sleep improved significantly in the INCS treated subjects but not in the placebo group.
Day and Carrillo[1285]	1998	1b	RDBPCT, multicenter, parallel-group.	Adults, PAR (n=273). BANS and FNSP nasal sprays. Baseline: 8-14 days. 6 weeks: Active treatment.	Mean combined nasal symptoms scores (nasal blockage, runny nose, and sneezing).	BANS significantly decreased nasal symptoms vs FPNS. Both treatments significantly decreased nasal symptoms vs placebo. Time to achieve statistically significant improvement: BANS 36 hours, FPNS 60 hours. Adverse events were mild and transient.
Juniper et al[1286]	1990	1b	Randomized, double-blind, parallel-group	Adults, SAR, ragweed sensitivity (n=60). 1. 200 mcg aqueous beclomethasone diproprionate NS, twice daily, 1 week before until 1 week after the ragweed-pollen season (regular) 2. 100 mcg of the spray, taken PRN, up to 400 mcg daily	Sneezing, stuffy nose, and rhinorrhea, measured by a daily diary. QOL questionnaires and rescue medication use (terfenadine).	Nasal symptoms, QOL, and use of rescue medications were significantly better controlled in the regular-treated group as compared to the PRN group.
Herman[1273]	2007	2a	Review of randomized, controlled, comparison trials	SAR and PAR. 14 studies reviewed. BANS, MFNS, FPNS, or TANS.	Different endpoints for different studies	All four INCSs administered once daily were effective and well tolerated in the treatment of AR in adult patients, with similar efficacy and adverse event profiles. Based on sensory attributes, patients preferred BANS and TANS vs MFNS and FPNS.
Juniper et al[1287]	1993	2b	Randomized, non-blinded, parallel group comparison	Adults, SAR, ragweed sensitivity (n=60). Beclomethasone dipropionate NS regular use (400 mcg daily) vs PRN use.	Daily symptoms and medication use, QOL, and patient satisfaction with symptom control.	27% of PRN patients reported unsatisfactory control, worse QOL and increased medication use. Patients who achieved satisfactory control in the prn group had similar symptom and quality of life scores to the regular group.

LOE: level of evidence; SR: systematic review; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; OSA: obstructive sleep apnea; FFNS: fluticasone furoate nasal spray; rTOSS: reflective Total Ocular Symptom Score; iTOSS: instantaneous Total Ocular Symptom Score; rTNSS: reflective Total Nasal Symptom Score; iTNSS: instantaneous Total Nasal Symptom Score; QOL: quality of life; RDBPCT: randomized double blind placebo controlled trial; MFNS: mometasone

furoate nasal spray; TNSS: Total Nasal Symptom Score; TOSS: Total Nasal Symptom Score; ESS: Epworth Sleepiness Scale; AHI: apnea-hypopnea index; nPIF: nasal peak inspiratory flow; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; WPAI-AS: Work Productivity and Activities Impairment–Allergy Specific questionnaire; NS: nasal spray; FPNS: fluticasone propionate nasal spray; PRN: as needed; BANS: budesonide aqueous nasal spray; INCS: intranasal corticosteroid; TANS: triamcinolone aqueous nasal

Table IX.B.2.c-2. Effect of intranasal corticosteroids on comorbidities: ocular symptoms and asthma

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lohia et al[1296]	2013	1a	SR and meta-analysis	Asthma and AR. 18 studies (n=2162). Efficacy of INCS on asthma outcomes.	Asthma outcomes: pulmonary function, bronchial reactivity, asthma symptom scores, asthma-specific QOL, and rescue medication use.	Use of INCS resulted in significant improvements in FEV1, bronchial challenge, asthma symptom scores, and rescue medication use vs placebo. INCS improved morning and evening PEF. Addition of INCS spray to orally inhaled corticosteroids did not result in additional improvement.
DeWester et al[1290]	2003	1a	Retrospective analysis of multicenter, RDBPCTs	7 studies. Efficacy of FPNS 200 mcg daily for nasal and ocular symptoms in patients with SAR.	Mean change from baseline in the clinician-rated TOSS (itching, tearing, redness, and puffiness) at 7 and 14 days of therapy.	FPNS group had significantly greater mean changes from baseline in the TOSS and in all 4 individual symptom scores vs placebo at days 7 and 14.
Taramarcaz and Gibson[1295]	2003	1a	Meta-analysis of RCTs	Asthma and AR. 14 studies (n=477). INCS vs placebo/routine asthma treatment.	Asthma outcomes: symptom scores, FEV1, PEF, and methacholine airway responsiveness.	No statistically significant benefit of INCS in asthma.
Bielory et al[1291]	2011	1a	Meta-analysis of placebo- controlled RCTs	10 studies (n=3132). SAR: 6 studies. PAR: 4 studies. MFNS 200 mcg daily.	Severity of reflective ocular symptoms (itching/burning, redness, and tearing/watering) on a 4-point scale over 12 hours.	Overall treatment effect was significant for all three individual ocular symptoms in SAR and PAR studies.
Ratner et al[1292]	2015	1b	Randomized, double-blind, parallel, multicenter study	SAR (n= 614). FPNS 200 mcg daily vs placebo x 14 days.	Mean change from baseline in patient-rated rTOSS	FPNS was significantly more efficacious in reducing the ocular symptoms of AR vs placebo.

Baroody et al[1293]	2009	1b	Double-blind, placebo-controlled, crossover trial	SAR out of season (n=20). FFNS 110 mcg daily vs placebo x 1 week. Nasal antigen challenge.	Nasal and ocular symptoms after allergen challenge.	Pretreatment with FFNS significantly reduced eye symptoms after nasal allergen challenge.

LOE: level of evidence; SR: systematic review; INCS: intranasal corticosteroid; AR: allergic rhinitis; QOL: quality of life; FEV1: forced expiratory volume in 1 second; PEF: peak expiratory flow; RDBPCT: randomized double blind placebo controlled trial; FPNS: fluticasone propionate nasal spray; SAR: seasonal allergic rhinitis; TOSS: Total Ocular Symptom Score; RCT: randomized controlled trial; PAR: perennial allergic rhinitis; MFNS: mometasone furoate nasal spray; rTOSS: reflective Total Ocular Symptom Score

Table IX.B.2.c-3. Comparison of intranasal corticosteroids to other agents for the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Benninger et al[1299]	2010	1a	SR of RCTs of at least 2-week duration, and studying US-approved INCS indication/dose.	SAR: 38 studies (n=11,980 adults, 946 children). PAR: 12 studies (n=3,800 adults, 366 children).	Median percentage changes from baseline for TNSS.	INCS produce the greatest improvements in nasal symptoms in SAR. INCS effective for PAR, but data quality variable; oral antihistamines may be equally effective for some patients.
Wilson et al[1300]	2004	1a	SR and meta-analysis of RCTs of the effectiveness of LTRAs	SAR: 11 studies. 8 evaluating LTRAs (alone or plus other treatments) vs placebo or other treatments (n=3924). 3 evaluating LTRAs plus antihistamine (n=80).	Composite daily rhinitis symptom scores and rhinitis-specific quality of life.	LTRAs are modestly better than placebo, as effective as antihistamines, but less effective than INCS in improving symptoms and QOL in patients with SAR.
Yanez and Rodrigo[1298]	2002	1a	SR of RCTs	AR: 9 studies (n=648). INCS vs topical antihistamines.	Total nasal symptoms, sneezing, rhinorrhea, itching, and nasal blockage.	INCS produced greater relief of nasal symptoms vs topical antihistamines. No difference between the 2 treatments for ocular symptoms.
Weiner et al[1297]	1998	1a	Meta-analysis of RCTs	AR: 16 studies (n=2267). INCS vs oral antihistamines.	Nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, nasal discomfort, total nasal symptoms, nasal resistance, and eye symptoms and global ratings	INCS produced greater relief of nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, and total nasal symptoms vs oral antihistamines. No difference between the 2 treatments for nasal

						discomfort, nasal resistance, or eye symptoms.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; INCS: intranasal corticosteroid; US: United States; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; TNSS: Total Nasal Symptom Score; LTRA: leukotriene receptor antagonist; QOL: quality of life; AR: allergic rhinitis;

Table IX.B.2.c-4. Studies evaluating adverse effects of intranasal corticosteroids

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ahmadi et al[1319]	2015	1a	SR	19 studies of INCS reporting original ocular endpoints (10 RCTs, 1 case-control, 8 case series) included.	IOP, lens opacity, glaucoma or cataract incidence.	None of the 10 RCTs reporting IOP demonstrated changes vs control. None of the 6 RCTs reporting cataract or lens opacity demonstrated changes vs control.
Mener et al[1320]	2015	1a	SR with meta-analysis	8 RCTs (n=755) investigating INCS for AR in children 3-12 years.	Interval change in growth. Knemometry (n=342 participants, duration 2-4 weeks). Stadiometry (n=413 participants, duration 12 months).	Knemometry studies: Mean growth lower among children using INCS. Stadiometry studies: No significant growth difference in INCS vs placebo. Limitations: Difficulty in predicting longer-term or catch-up growth.
Verkerk et al[1305]	2015	1a	SR	34 studies (11 RCTs, 5 cohorts, 20 case series) included. INCS use with or without control group.	Histopathology of nasal mucosa. Mucosal atrophy reported in 17 studies.	The concept of nasal mucosal atrophy is poorly defined. No histological evidence for deleterious effects from INCS use on human nasal mucosa.
Hampel et al[1317]	2015	1b	RDBPCT	PAR, children 6-11 years. BDP 800 mcg daily (n=67) vs placebo (n=32) for 6 weeks.	Change in 24-hour serum cortisol from baseline.	Serum cortisol values remained stable in both groups. Concentration-time profiles similar for the placebo and BDP groups at baseline and week 6.
Meltzer et al[1302]	2009	1b	Subanalysis of 3 RDBPCTs, focusing on the 6-11 age group	SAR: 2-week US study. PAR: 12-week global study. HPA axis safety: 6-week US study. FF 55 mcg vs FF 110 mcg vs placebo daily (n=948).	Different endpoints which included: adverse event monitoring, nasal examinations, ophthalmic examinations, 24-hour urinary cortisol excretions and serum cortisol concentrations.	Epistaxis 4% in both active and placebo groups. No differences between groups for IOP, and no posterior subcapsular cataracts. No difference in HPA measures between groups.

Ratner et al[1304]	2009	1b	Multicenter, randomized, controlled trial	PAR, children 6-11 years (n=255). MFNS 100 mcg vs BDP 168 mcg daily for 12 months.	Symptom control and safety.	There was appropriate symptom control in both groups. Adverse events were mild. Incidence of epistaxis was 12.7% with MFNS and 9.4% for BDP.
Tripathy et al[1316]	2009	1b	Double-blind, randomized parallel-group study	PAR, children 2-11 years (n=112). FF 110 mcg vs placebo daily for 6 weeks.	24-hour serum and urinary cortisol. FF plasma measurements.	FF was non-inferior to placebo with respect to 24-hour serum cortisol. Urinary cortisol excretion over 24 hour at baseline and end of treatment similar between treatment groups.
Weinstein et al[1315]	2009	1b	RDBPCT, multicenter, parallel-group	PAR, children 2-5 years (n=474). TAA 110 mcg vs placebo daily for 4 weeks.	Adverse events, morning serum cortisol levels and growth as measured using office stadiometry.	Adverse event rates comparable between groups. No significant change from baseline in serum cortisol levels after cosyntropin infusion. Distribution by stature-for-age percentile remained stable.
Maspero et al[1301]	2008	1b	Double-blind, placebo-controlled study.	PAR, children 2-11 years (n=558). FF 110 mcg vs FF 55 mcg vs placebo daily for 12 weeks.	Nasal symptom scores for efficacy. Nasal and ophthalmic examinations, and HPA assessments for safety.	Epistaxis 6% in all groups. There were no significant ophthalmic or HPA related side effects in the treated subjects. The lower dose of FF reduced nasal symptoms.
Patel et al[1314]	2008	1b	RDBPCT, parallel-group	PAR, 12-65 years (n=112). FF 110 mcg daily for 6 weeks vs prednisone 10 mg daily for last 7 days of study vs placebo.	Change in 24-hour serum cortisol and 24-hour urinary free cortisol, total 24-hour urinary free cortisol, 6-beta hydroxycortisol excretion, and plasma concentration of FF.	Ratio from baseline in serum cortisol weighted mean: FF noninferior to placebo, prednisone significantly reduced the ratio. 24-hour urinary cortisol excretion was similar in the FF and placebo groups. Plasma levels of FF were undetectable after 6 weeks of treatment.
Chervinsky et al[1313]	2007	1b	RDBPCT	PAR patients $\geq$12 years (n=663). Ciclesonide 200 mcg vs placebo daily for up to 52 weeks.	Adverse events, exam findings, 24-hour urinary free cortisol, morning plasma cortisol, IOP, lens opacification.	No clinically relevant differences observed between the ciclesonide and placebo groups.
Kim et al[1312]	2007	1b	Two separate phase 3, double-blind, parallel-group,	PAR, children 2-5 years. Safety, tolerability, and efficacy of intranasal	Cortisol levels were measured at the beginning and end of each study. The systemic exposure of ciclesonide and its active	Changes in plasma or urine cortisol levels showed no difference in active vs placebo group. Serum concentrations were below the lower limit of

			placebo-controlled trials.	ciclesonide 200 mcg once daily. First study: 6 weeks. Second study: 12 weeks.	metabolite measured at treatment end in the 6-week study.	quantification, suggesting that systemic exposure to ciclesonide was low.
Rosenblut et al[1303]	2007	1b	RDBPCT, parallel-group	PAR (n=806). FF 110 mcg vs placebo daily for 12 months.	Adverse events, 24-h urinary cortisol excretion, nasal and ophthalmic examinations, electrocardiograms and clinical laboratory tests	Incidence of adverse events similar to placebo, except epistaxis (active 20%, placebo 8%). No clinically meaningful differences in ophthalmic parameters or urine cortisol excretion.
Galant et al[1311]	2003	1b	RDBPCT	AR, children 2-3 years (n=65). FP 200 mcg vs placebo daily for 6 weeks.	12-hour urinary-free cortisol concentration at baseline and after 6 weeks of treatment.	FP group equivalent to placebo group in mean change from baseline of 12-hour urinary-free cortisol at treatment end.

LOE: level of evidence; SR: systematic review; INCS: intranasal corticosteroid; RCT: randomized controlled trial; IOP: intraocular pressure; AR: allergic rhinitis; RDBPCT: randomized double bloing placebo controlled trial; BDP; beclomethasone dipropionate; PAR: perennial allergic rhinitis; FF: fluticasone furoate; SAR: seasonal allergic rhinitis; HPA; hypothalamic pituitary axis; US: United States; MFNS: mometasone furoate nasal spray; TAA: triamcinolone acetonide; FP: fluticasone propionate

IX. B. 3. a. Oral decongestants

Oral decongestants, such as pseudoephedrine, act on adrenergic receptors and lead to vasoconstriction, which can relieve nasal congestion in patients with AR. With extended-release oral decongestants nasal decongestion can last up to 24 hours. Oral decongestants are available for use alone or in combination with oral antihistamines. *(See Section IX.B.10.a. Combination Therapy – Oral Antihistamine and Oral Decongestant for additional information on this topic.)*

Availability of pseudoephedrine in the US has been limited to behind-the-counter at pharmacies since 2006 due to stricter control over the distribution and sale of substances that can be used to manufacture methamphetamine. In a study by Mucha et al,[1321] pseudoephedrine resulted in significant improvement in all symptoms in adults with ragweed-induced AR. **[Table IX.B.3.a.]** Phenylephrine has been marketed as an over-the-counter (OTC) medication as a substitute for pseudoephedrine for nasal decongestion. However, a RCT by Horak et al[1322] found that while pseudoephedrine was significantly more effective at reducing nasal congestion than both placebo and phenylephrine, there was no significant difference between phenylephrine and placebo. In addition, Meltzer et al[1323] performed a randomized, open-label, dose-range trial in 539 patients with SAR and found phenylephrine to be no more effective than placebo in reducing symptomatic nasal congestion.

Known side effects of this class of medications include insomnia, nervousness, anxiety, tremors, palpitations, and increased blood pressure. Two systematic reviews by Salerno et al[1324,1325] looked at the effect of oral decongestants on blood pressure. The first study showed that phenylpropanolamine significantly increased systolic blood pressure (SBP) by 5.5 mmHg (95%CI: 3.1-8.0) and diastolic blood pressure (DBP) by 4.1 (95% CI 2.2-6.0) with no effect on heart rate as compared to placebo.[1324] The second study found that pseudoephedrine also caused a small but significant increase in SBP by 0.99 mmHg (95% CI 0.08-1.9) and HR by 2.83 beats/min (95% CI 2.0-3.6) with no effect on DBP.[1325] Additionally, higher doses and immediate-release preparations of pseudoephedrine were associated with greater BP elevations.[1325] Further, in a study by Kernan et al,[1326] phenylpropanolamine use in women was an independent risk factor for hemorrhagic stroke. Phenylpropanolamine is no longer available on the market. Given these cardiovascular side effects, oral decongestants should be used with caution in patients who are already at risk for hypertension and its sequelae (e.g. coronary artery disease, cerebral vascular disease, hyperthyroidism, arrhythmias). Blood pressure should be closely monitored for any changes when using oral decongestants in this population.

Oral decongestants are known to be effective in children older than 6 years of age. However, care should be taken in the younger population (less than 2 years of age) as this population is more prone to toxicity, and safe dosing recommendations have not yet been established for this age group.[1327] In infants and young children, oral decongestants may have central nervous system (CNS) stimulatory effects with known cases of psychosis, ataxia, and hallucinations with ingestion.[1328,1329] Evaluation of risk and benefits should be considered in patients less than 6 years old.

- Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 1b: 3 studies; Level 3b: 2 studies; Level 4: 2 studies; *Table IX.B.3.a.*).
- Benefit: Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.

- Harm: Side effects include insomnia, loss of appetite, irritability, palpitations, and increased blood pressure. Risk of toxicity in young children.
- Cost: Low.
- Benefits-Harm Assessment: Balance of benefit and harm for pseudoephedrine. Harm likely outweighs benefit for phenylephrine.
- Value Judgments: Consideration of patient's other comorbidities and age should be considered before usage.
- Policy Level: Option for pseudoephedrine. Recommendation against for phenylephrine.
- Intervention: Pseudoephedrine as an oral decongestant can be effective in reducing symptom of nasal congestion in patients with AR; used for short term symptom relief. Side effects, comorbidities, and age of patient should be considered before use.

Table IX.B.3.a. Evidence for the role of oral decongestants in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Salerno et al[1324]	2005	1a	SR	1. pheynylpropanolamine 2. placebo	SBP, DBP, HR	Phenylpropanolamine caused increase in SBP.
Salerno et al[1325]	2005	1a	SR	1. pseudoephedrine 2. placebo	SBP, DBP, HR	Pseudoephedrine caused increase in SBP and HR.
Meltzer et al[1323]	2015	1b	RCT	1. phenylephrine 10mg (n=109) 2. phenylephrine 20mg (n=108) 3. phenylephrine 30mg (n=107) 4. phenylephrine 40mg (n=112) 5. placebo (n=103)	Daily reflective nasal congestion score	Phenylephrine is not better than placebo at relieving nasal congestion.
Horak et al[1322]	2009	1b	RCT	1. pseudoephedrine 2. phenylephrine 3. placebo	Subjective evaluation of nasal congestion	Pseudoephedrine resulted in improvement in nasal congestion. Phenylephrine did not improve nasal congestion.
Mucha et al[1321]	2006	1b	RCT	1. pseudoephedrine 2. montelukast	Nasal symptoms, nPIF, QOL	Significant improvement from baseline in all symptoms of AR, nPIF, and QOL with both pseudoephedrine and montelukast.
Vernacchio et al[1327]	2008	3b	Non-consecutive cohort		Pseudoephedrine use in pediatric population	Children less than 2 years of age are at the highest risk for toxicity with pseudoephedrine. Safe dosing recommendations are lacking for this age group.
Kernan et al[1326]	2000	3b	Case-control	1. history of subarachnoid or intracerebral hemorrhage 2. control	Association between the use of phenylpropanolamine and the risk of a hemorrhagic stroke.	Phenylpropanolamine is an independent risk factor for hemorrhagic stroke in women.
Roberge et al[1328]	1999	4	Case report			2-year-old developed psychosis and ataxia after being overmedicated with pseudoephedrine/dextromethorphan cough preparation.
Sauder et al[1329]	1998	4	Case report			3-year-old with visual hallucinations caused by inappropriately high doses of pseudoephedrine.

LOE: level of evidence; SR: systematic review; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RCT: randomized controlled trial; nPIF: nasal peak inspiratory flow; QOL: quality of life; AR: allergic rhinitis;

IX. B. 3. Decongestants

IX. B. 3. b. Intranasal decongestants

Topical decongestants, such as xylometazoline and oxymetazoline, are alpha-adrenergic stimulators delivered directly to nasal mucosal tissue that result in vasoconstriction and reduction of mucosal thickness. In an 18-day study, Barnes et al. found that nasal xylometazoline was a stronger decongestant than nasal corticosteroids.[1330] **[Table IX.B.3.b.]** Topical decongestants relieve the symptom of nasal congestion, however they have no effect on other symptoms of AR, such as sneezing, rhinorrhea, or nasal itching.

RM [rhinitis medicamentosa], a condition thought to result from prolonged usage of topical decongestants, involves an increase in symptomatic nasal congestion, thereby precluding a recommendation for chronic use of this medication. Studies to identify the duration of topical decongestant use that leads to rhinitis medicamentosa have shown variable results. Some studies show prolonged use up to 8 weeks does not produce any symptoms of rebound nasal congestion,[83,1331] while others note development of RM within 3 days of use.[72]

Known adverse effects of topical decongestants include nasal burning, stinging, dryness, epistaxis, and mucosal ulceration. While topical decongestants are effective at reducing nasal congestion, short term use of the medication, 3 days or less, is recommended to avoid the potential for rebound nasal congestion and effects on mucociliary activity. *(See section III.C.2. Differential Diagnosis – Rhinitis Medicamentosa for additional information on this topic.)*

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 1 study; *Table IX.B.3.b.*).
- Benefit: Reduction of nasal congestion with topical decongestants.
- Harm: Side effects include nasal burning, stinging, dryness, and mucosal ulceration. Potential for rebound congestion when used long term.
- Cost: Low.
- Benefits-Harm Assessment: Harm likely outweighs benefit if used more than 3 days.
- Value Judgments: Topical decongestants can be helpful for short-term relief of nasal congestion.
- Policy Level: Option.
- Intervention: Topical decongestants can provide effective short-term nasal decongestion in patients with AR, but recommend against chronic use due to risk for RM.

Table IX.B.3.a. Evidence for the role of topical intranasal decongestants in the management of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Barnes et al[1330]	2005	1b	RCT	(n=36) 1. nasal xylometazoline 2. nasal mometasone furoate	nPIF, nasal forced inspiratory volume in 1 second, nasal blockage score	Xylometazoline was a stronger nasal decongestant than mometasone fuorate.
Watanabe et al[1331]	2003	1b	RCT	(n=30) 1. oxymetazoline TID 2. placebo	Subjective nasal blockage, nPIF, airway resistance, airway volume	No significant nasal blockage or impaired decongestant response to oxymetazoline following 4-week treatment.
Morris et al[72]	1997	1b	RCT	(n=50) 1. daily oxymetazoline 2. intermittent oxmetazoline 3. placebo	Nasal airway resistance, subjective scaling of nasal patency, clinical examination	Evidence of rebound nasal congestion was found following 3 days of both daily and intermittent oxymetazoline treatment.
Yoo et al[83]	1997	2b	Individual cohort study	(n=10) daily oxymetazoline	Subjective history, physical exam, anterior rhinomanometry	All subjects remained responsive to oxymetazoline 4 weeks and 8 weeks after the study began.

LOE: level of evidence; RCT: randomized controlled trial; nPIF: nasal peak inspiratory flow; TID: three times daily

IX. B. 4. Leukotriene receptor antagonists (LTRA)

LTRAs have been studied and used in the treatment of AR. Montelukast is approved by the US FDA for the treatment of SAR in adults and children over 2 years of age, and for PAR in adults and children over 6 months of age. Several systematic reviews and meta-analyses of RCTs have demonstrated symptom reduction and improved QOL in patients treated with LTRA monotherapy compared to placebo.[1300,1332-1335] Nevertheless, in a clinical practice guideline on AR from the AAO-HNS there was a recommendation against LTRA monotherapy, citing decreased effectiveness compared to other first-line agents.[761]

Systematic review identified 28 studies, of which 19 were considered level 1 evidence, examining the use of LTRA monotherapy in AR. **[Table IX.B.4.]** Multiple systematic reviews[1300,1332-1335] and RCTs[1336-1344] demonstrated that LTRA monotherapy was superior to placebo at improving patient symptoms and QOL. This effect was consistent in studies of SAR,[1340-1344] PAR,[1339] and artificial allergen exposure.[1336-1338] Furthermore, in a double-blind RCT by Philip et al[1341] montelukast improved both AR and asthma disease-specific QOL in patients with concurrent SAR and asthma.

Despite multiple studies demonstrating superior effect of LTRA monotherapy over placebo in the treatment of AR, there is consistent evidence that LTRA is inferior to INCS.[1300,1333-1335,1345,1346] Multiple systematic reviews and meta-analyses have shown that INCS result in greater symptom reduction and QOL improvement compared to LTRA.[1300,1333-1335] A double-blinded RCT by Pullerits et al[1346] showed decreased numbers of activated tissue eosinophils in nasal mucosa biopsies in patients treated with intranasal beclomethasone compared to zafirlukast and placebo. There is conflicting evidence on the relative effect of LTRA compared to oral antihistamines, with two systematic reviews demonstrating that oral antihistamines have superior symptom reduction and QOL improvement[1300,1333] and a third study indicating equivalent effect.[1334] Moreover, a double-blind RCT by Mucha et al[1321] indicated that montelukast and pseudoephedrine yielded equivalent symptom reduction and QOL improvement. In that study, objective measurement of nasal peak inspiratory flow was not different between the montelukast and pseudoephedrine treatment groups.

In addition to less relative effectiveness compared to other agents, the AAO-HNS clinical practice guideline on AR cited increased costs of LTRA in the recommendation against this drug class as monotherapy in patients with AR without asthma.[761] Goodman et al[1347] examined the relative cost effectiveness of montelukast compared to several second-generation oral antihistamines. Montelukast was determined to have increased cost for relative effectiveness compared to levocetirizine, desloratadine, and branded and generic fexofenadine. The annual drug and incurred medical costs for montelukast were estimated to be $631.

LTRA monotherapy may be a useful alternative in rare patients with contraindications for both INCS and oral antihistamines, but this limits recommendations or options for these agents in general. In patients with concurrent AR and asthma, LTRA can contribute to symptom management of both respiratory diseases. LTRA monotherapy is not recommended as first-line treatment for patients with concurrent AR and asthma, although this may be a consideration in patients with contraindications to INCS.

- Aggregate Grade of Evidence: A (Level 1a: 6 studies; Level 1b: 17 studies; Level 2a: 2 studies; Level 2b: 3 studies; Level 4: 3 studies; *Table IX.B.4.*).
- Benefit: Consistent reduction in symptoms and improvement in QOL compared to placebo, as demonstrated in RCTs and systematic review of RCTs.
- Harm: Consistently inferior compared to INCS at symptom reduction and improvement in QOL in RCTs and systematic reviews of RCTs. Equivalent-to-inferior effect compared to oral antihistamines in symptom reduction and improvement of QOL.
- Cost: Annual incurred drug and medical costs estimated to be $631 for generic montelukast.
- Benefits-Harm Assessment: Preponderance of benefit over harm. LTRAs are effective as monotherapy compared to placebo. However, there is a consistently inferior or equivalent effect to other, less expensive agents used as monotherapy.
- Value Judgments: LTRAs are equivalent to oral antihistamine alone and more effective than placebo at controlling both asthma and AR symptoms in patients with both conditions. Control of AR symptoms with LTRAs, however, is less effective than INCS, and inferior or equivalent to oral antihistamines. Therefore, evidence is lacking to recommend LTRAs as first- or second-line monotherapy in the management of AR alone or in combination with asthma.
- Policy Level: Recommendation against as first line therapy for AR.
- Intervention: LTRAs should not be used as monotherapy in the treatment of AR but can be considered as second-line therapy, such as when INCS are contraindicated.

Table IX.B.4. Evidence for the use of leukotriene receptor antagonists as monotherapy in the treatment of allergic rhinitis (Level 1a and 1b studies only)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Devillier et al[1332]	2014	1a	SR of RCTs, with homogeneity	1. LTRA 2. SLIT 3. placebo	Symptoms	SLIT superior clinical effect to LTRA. LTRA with clinical effect compared to placebo.
Goodman et al[1347]	2008	1a	SR of RCTs, with homogeneity	1. montelukast 2. levocetirizine 3. desloratadine 4. fexofenadine	Symptoms, cost	Montelukast with higher incremental cost-effectiveness ratio than levocertirizine and desloratadine.
Grainger & Drake-Lee[1333]	2006	1a	SR of RCTs, with homogeneity	1. montelukast 2. oral antihistamine 3. INCS 4. placebo	Symptoms, QOL	Montelukast improved symptoms and QOL compared to placebo, and was inferior to oral antihistamines and INCS.
Rodrigo & Yanez[1334]	2006	1a	SR of RCTs, with homogeneity	1. LTRA 2. oral antihistamine 3. INCS 4. placebo	Symptoms, QOL	LTRA improved symptoms and QOL compared to placebo, was equally effective to oral antihistamine, and inferior to INCS.
Wilson et al[1300]	2004	1a	SR of RCTs, with homogeneity	1. montelukast 2. oral antihistamine 3. INCS 4. placebo	Symptoms, QOL	Montelukast improved QOL compared to placebo, and was inferior to antihistamines and INCS.
Gonyeau & Partisan[1335]	2003	1a	SR of RCTs, with homogeneity	1. montelukast 2. INCS 3. placebo	Symptoms	Montelukast was more effective than placebo in reducing symptoms, but was inferior to INCS.
Endo et al[1336]	2012	1b	RCT	1. pranlukast 2. placebo	Symptoms	Pranlukast prevented and reduced symptoms compared to placebo after artificial introduction of allergen.
Wakabayashi et al[1337]	2012	1b	RCT	1. pranlukast 2. placebo	Symptoms	Pranlukast reduced symptoms compared to placebo in children with artificial allergen exposure.
Day et al[1338]	2008	1b	RCT	1. montelukast 2. levocetirizine 3. placebo	Symptoms	Both montelukast and levocertirizine improved symptoms following artificial allergen exposures. Levocertirizine was more effective than montelukast.
Jiang[1348]	2006	1b	RCT	1. zafirlukast 2. loratadine	Symptoms, acoustic	All treatment groups had a significant reduction of pre-treatment symptoms. Zafirlukast was superior at reduction of nasal congestion. There were no

				3. loratadine + pseudoephedrine	rhinometry, rhinomanometry	differences in acoustic rhinometry and rhinomanometry between the 3 treatment groups.
Mucha et al[1321]	2006	1b	RCT	1. montelukast 2. pseuodephedrine	Symptoms, QOL, nasal peak inspiratory flow	Montelukast and pseudoephedrine had equivalent improvement of symptoms (except nasal congestion for which pseudoephedrine was more effective), QOL, and nasal peak inspiratory flow.
Patel et al[1339]	2005	1b	RCT	1. montelukast 2. placebo	Symptoms, QOL	Montelukast was more effective than placebo in reducing symptoms and improving QOL in patients with perennial allergic rhinitis
Chervinsky et al[1340]	2004	1b	RCT	1. montelukast 2. placebo	Symptoms, pollen count	Montelukast was more effective than placebo in reducing symptoms. The effect size was related to the amount of pollen exposure.
Philip et al[1341]	2004	1b	RCT	1. montelukast 2. placebo	Symptoms, rhinitis QOL, asthma QOL	Montelukast improved symptoms, rhinitis QOL, and asthma QOL compared to placebo in patients with concurrent seasonal allergic rhinitis and asthma.
Ratner et al[1345]	2003	1b	RCT	1. montelukast 2. fluticasone	Symptoms, QOL	Fluticasone was more effective than montelukast in reducing symptoms and improving QOL.
van Adelsburg et al[1342]	2003	1b	RCT	1. montelukast 2. loratadine 3. placebo	Symptoms, QOL	Montelukast was more effective than placebo in reducing symptoms and improving QOL. Montelukast not directly compared to loratadine.
van Adelsburg et al[1343]	2003	1b	RCT	1. montelukast 2. loratadine 3. placebo	Symptoms, QOL	Montelukast was more effective than placebo in reducing symptoms and improving QOL. Montelukast not directly compared to loratadine.
Philip et al[1344]	2002	1b	RCT	1. montelukast 2. loratadine 3. placebo	Symptoms, QOL, peripheral eosinophil count	Montelukast was more effective than placebo in reducing symptoms and peripheral eosinophil count, and improving QOL. Montelukast not directly compared to loratadine.
Pullerits et al[1346]	1999	1b	RCT	1. zafirlukast 2. beclomethasone 3. placebo	Symptoms, tissue eosinophilia	Zafirlukast was not different from placebo in symptom or tissue eosinophilia reduction. Both were inferior to intranasal beclomethasone.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; LTRA: Leukotriene receptor antagonist; SLIT: sublingual immunotherapy; INCS: intranasal corticosteroids; QOL: quality of life

IX. B. 5. Cromolyn

Disodium cromoglycate (DSCG) [synonyms: cromolyn sodium, sodium cromoglycate, disodium 4,4'-dioxo-5,5'-(2-hydroxytrimethylenedioxy)-di(4H-chromene-2-carboxylate)] was first used by ancient Egyptians for its spasmolytic properties. It is derived from the plant *Amni visnaga*. DSCG is a mast cell stabilizer that prevents histamine release. It impedes the function of chloride channels important in regulating cell volume and prevents extracellular calcium influx into the cytoplasm of the mast cell, thus preventing the degranulation of sensitized cells.[1349,1350] DSCG is best used prophylactically to prevent the onset of symptoms by interrupting the physiological response to nasal allergens.

DSCG was discovered over 50 years ago, and since that time other cromoglycate type agents (chromones) have been developed. The chromones have demonstrated the ability to inhibit the early phase and late phase reactions of asthma.[1351] Initial studies focused on histamine and cytokine release from mast cells. More recent studies have shown anti-allergy activity unrelated to mast cell activation, but rather through the inhibition of macrophages, eosinophils, monocytes, and platelets.[1352-1354]

DSCG can be used in an inhaled form as a prophylactic agent in the treatment of mild-moderate asthma, as a nasal spray to treat SAR, or as an ophthalmic solution to treat allergic or vernal conjunctivitis. DSCG may also be taken orally to control allergic reactions to certain foods. It can be used for patients 2 years and older but has a short half-life requiring dosing of 3-6 times daily.[1355] DSCG has an excellent safety profile, although the need for frequent dosing may affect compliance. Minor adverse effects include nasal irritation or burning, sneezing, epistaxis, and bad taste.[1355]

Most studies comparing DSCG directly to placebo have shown that it is effective in patients with SAR. **[Table IX.B.5.]** Studies on the efficacy of DSCG in PAR have been controversial.[1356-1360] In a recent RCT, Lejeune et al[1356] examined the role of DSCG in monosensitized PAR patients and found that DSCG resulted in significant reduction in symptom scores for nasal obstruction, discharge and sneezing compared to placebo. When compared to INCS, DSCG has been shown to be less effective.[1357,1361-1369] To date, there have been no direct comparisons between DSCG and intranasal antihistamines. Ultimately, the role of DSCG as a primary treatment for AR is limited given its lower efficacy when compared to INCS and potential compliance challenges secondary to frequent dosing regimen.

- Aggregate Grade of Evidence: A (Level 1b: 13 studies; Level 2b: 9 studies; *Table IX.B.5.*)
- Benefit: DSCG is effective in reducing sneezing, rhinorrhea and nasal congestion.
- Harm: Rare local side effects include nasopharyngeal irritation, sneezing, rhinorrhea, and headache.
- Cost: Low.
- Benefits-Harm Assessment: Preponderance of benefit over harm. Benefit is considered mild to moderate. Less effective than INCS.
- Value Judgments: Useful for preventative short term use in patients with known exposure risks.
- Policy Level: Option.
- Intervention: DSCG may be considered for the treatment of AR, particularly in patients known triggers who cannot tolerate INCS.

Table IX.B.5. Evidence for the use of disodium cromoglycate in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lejeune et al[1356]	2015	1b	DBRCT	PAR, adults: 1. DSCG QID (n=14) 2. placebo (n=7)	Symptom scores, nasal cytology, allergic mediators	DSCG performed better than placebo.
Meltzer[1370]	2002	1b	DBRCT	SAR, over 12 years old: 1. DSCG 4%, 1 spray q4-6 hours (n=580) 2. placebo (n=570)	Nasal symptoms	DSCG performed better than placebo.
Schuller et al[1371]	1990	1b	DBRCT	SAR, 12-65 years old: 1. nedocromil 1% (n=80) 2. DSCG 4%, 1 spray QID (n=7) 3. placebo (n=77)	Nasal symptoms	Nedocromil was equivalent to DSCG. Both performed better than placebo.
Chandra et al[1372]	1982	1b	DBRCT, crossover	SAR, 9-41 years old (n=47): 1. DSCG 4%, 1 spray q3-4 hours 2. placebo	Nasal symptoms, medication use	DSCG performed better than placebo.
Brown et al[1367]	1981	1b	RCT	SAR: 1. DSCG 2.6mg 6 times per day (n=29) 2. flunisolide 25µg BID (n=38)	Nasal symptoms	Flunisolide performed better than DSCG.
Craig et al[1373]	1977	1b	DBRCT	SAR (n=39): 1. DSCG 5.2mg 6 times per day (n=22) 2. placebo (n=17)	Nasal symptoms, medication use	No difference between DSCG and placebo.
Handelman et al[1374]	1977	1b	DBRCT	SAR, 6-51 years old: 1. DSCG 62.4 mg 6 times per day (n=45) 2. placebo (n=45)	Symptom score, medication use	DSCG performed better than placebo.
McDowell & Spitz[1358]	1977	1b	DBRCT, crossover	PAR, 17-71 years old (n=13): 1. DSCG 2.5mg 6 times per day 2. placebo	Nasal symptoms, cytology	No significant difference in majority of patients.
Nizami & Baboo[1375]	1977	1b	DBRCT, crossover	SAR, 7-59 years old (n=92): 1. DSCG 10mg QID 2. placebo	Nasal symptoms	DSCG performed better than placebo.
Posey & Nelson[1376]	1977	1b	DBRCT	SAR, 12-54 years old: 1. DSCG 4%, 6 times per day (n=17) 2. placebo (n=17)	Symptom score, medication use	No difference, except for in-season use of medications in DSCG group.
Warland & Kapstad[1359]	1977	1b	DBRCT, crossover	PAR, 15-57 years old (n=17): 1. DSCG 10mg QID 2. placebo	Nasal symptoms	No difference between DSCG and placebo.
Cohan et	1976	1b	DBRCT,	PAR, 16-37 years old:	Symptom score,	DSCG performed better than

al[1360]			crossover	1. DSCG 4%, 6 times per day 2. placebo	medication use	placebo.
Knight et al[1377]	1976	1b	DBRCT	SAR: 1. DSCG 10mg QID (n=35) 2. placebo (n=41)	Nasal symptoms	DSCG performed better than placebo.
Lange et al[1361]	2005	2b	RCT, no placebo	SAR, 18-65 years old: 1. MF 200µg QD (n=41) 2. levocabastine 200µg BID (n=40) 3. DSCG 5.6mg QID (n=42)	Symptom scores, nPIF	MF performed best.
Fisher[1362]	1994	2b	RCT, blinded, no placebo	SAR, 6-15 years old: 1. DSCG 31.2mg, 6 times per day (n=26) 2. budesonide BID, 400µg/day (n=30)	Nasal symptoms	Budesonide performed better than DSCG.
Bousquet et al[1363]	1993	2b	DBRCT, no placebo	SAR: 1. FP 200µg QD (n=110) 2. DSCG 5.2mg QID (n=108)	Nasal/ocular symptoms, medication use	FP better in all except nasal discharge. No difference in medication use
Welsh et al[1364]	1987	2b	RCT, blinded	1. BDP 2 sprays BID, 336µg/day 2. flunisolide 2 sprays BID, 200µg/day 3. DSCG 1 spray QID, 41.6mg/day 4. placebo	Symptom score, medication use	All medications were better than placebo. DSCG was the least effective.
Bjerrum & Illum[1365]	1985	2b	DBRCT, no placebo	SAR, 15-55 years old: 1. budesonide 200µg BID (n=22) 2. DSCG 5.2mg, 5 times per day (n=21)	Nasal symptoms	Budesonide was better than DSCG.
Morrow-Brown et al[1366]	1984	2b	RCT, no placebo	SAR, 11-71 years old: 1. BDP 2 sprays BID, 400µg/day (n=47) 2. DSCG 2.6mg, 6 times per day (n=39)	Symptom score, medication use	BDP performed better than DSCG. No difference in rescue medications.
Tandon & Strahan[1357]	1980	2b	DBRCT, crossover, no placebo	PAR, 13-45 years old (n=14): 1. BDP 50µg QID 2. DSCG 10mg QID	Nasal symptoms	BDP performed better than DSCG.
Wilson & Walker[1368]	1976	2b	RCT, no placebo	SAR, adults: 1. DSCG 10mg QID (n=10) 2. BV 100µg BID (n=10)	Nasal symptoms	BV performed better than DSCG.
Frankland and Walker[1369]	1975	2b	DBRCT, no placebo	SAR, adults: 1. DSCG 80µg, 6 times per day (n=14) 2. BV 100µg BID (n=18)	Nasal symptoms, nPIF	BV performed better than DSCG for symptoms. The 2 medications performed the same for nPIF.

LOE: level of evidence; DBRCT: double-blind randomized controlled trial; PAR: perennial allergic rhinitis; DSCG: disodium cromoglycate; QID: four times daily; SAR: seasonal allergic rhinitis; RCT: randomized controlled trial; BID: two times daily; MF: mometasone furoate; nPIF: nasal peak inspiratory flow; FP: fluticasone propionate; BDP: beclomethasone dipropionate; BV: betamethasone valerate

IX. B. 6. Intranasal anticholinergics

Ipratropium bromide (IPB) nasal spray acts by controlling watery nasal secretory output from seromucous glands. IPB is used primarily to reduce rhinorrhea and is effective in adults and children with perennial rhinitis and common cold.[1378,1379] It has a quick onset of action and short half-life administered up to 6 times per day, with less than 10% absorption over a range of 84 µg/day to 336 µg/day.[1380] Local side effects include nasal dryness, irritation, epistaxis and burning. Systemic side effects have not been observed with therapeutic dosing, as plasma concentrations of greater than 1.8 ng/ml are needed to produce systemic anticholinergic effects.[1380] However, care should be taken to avoid over-dosage that could lead to high serum concentrations of ipratropium.

All studies have shown that the use of IPB significantly controls rhinorrhea in children and adults with PAR. **[Table IX.B.6.]** The combined use with INCS have also been shown to be more effective than either agent alone, suggesting a role of IPB for patients with persistent rhinorrhea.[1381]

- Aggregate Grade of Evidence: B (Level 1b: 9 studies; Level 2b: 5 studies; *Table IX.B.6.*).
- Benefit: Reduction of rhinorrhea with topical anticholinergics.
- Harm: Local side effects include nasopharyngeal irritation, burning, headache, pharyngitis, epistaxis, nasal dryness, nasal congestion and dry mouth. Care should be taken to avoid over-dosage leading to systemic side effects.
- Cost: Low to moderate.
- Benefits-Harm Assessment: Preponderance of benefit over harm in patients PAR patients with rhinorrhea.
- Value Judgments: No significant benefits in controlling symptoms other than rhinorrhea Evidence for combined use with INCS is limited but encouraging for patients with persistent rhinorrhea.
- Policy Level: Option.
- Intervention: IPB nasal spray may be considered as an adjunct medication to INCS in PAR patients with uncontrolled rhinorrhea.

Table IX.B.6. Evidence for the use of ipratropium bromide in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Dockhorn et al[1381]	1999	1b	DBRCT	PAR, 8-75 years old: 1. IPB 0.03%, 2 sprays (42µg) TID + BDP 82µg BID (n=109) 2. IPB 0.03%, 2 sprays (42µg) TID (n=222) 3. BDP 82µg BID (n=222) 4. placebo (n=55)	Rhinorrhea	Combined use of IPB with BDP is more effective than either agent alone for controlling rhinorrhea.
Finn et al[1382]	1998	1b	DBRCT, crossover	PAR, 18-75 years old (n=205): 1. IPB 0.03% (42µg) TID + terfinadine 60mg PO BID 2. placebo + terfinadine	Nasal symptoms	Control of rhinorrhea and sneezing better in IPB + terbinafine. No differences in nasal congestion.
Kaiser et al[1379]	1998	1b	DBRCT	PAR, adults: 1. IPB 0.03% (42µg) TID 2. IPB 0.06% (84µg) TID 3. placebo	Nasal symptoms	High and low dose IPB resulted in significant reduction of nasal hypersecretion versus placebo.
Meltzer et al[1383]	1997	1b	DBRCT	PAR and perennial NAR, 6-18 years old: 1. IPB 0.03% 2 sprays (42 µg) BID (n=102) 2. placebo (n=102)	Nasal symptoms, medication use, QOL	In perennial NAR, IPB reduced symptoms. In PAR, a modest effect was seen
Gorski et al[1384]	1993	1b	DBRCT	PAR, 23-33 years old (n=18): 1. IPB 80µg QID 2. placebo	Sneezing, albumin and total protein in nasal lavage	IPB resulted in a decrease in albumin, total protein, eosinophil count and an increase in nasal reactivity to histamine with an increase in the number of sneezes.
Meltzer et al[1385]	1992	1b	DBRCT	PAR, 18-70 years old: 1. IPB 21µg (n=48) or 42µg (n=54), 1 spray TID 2. placebo (n=53)	Nasal symptoms, nasal cytology	IPB is effective in controlling rhinorrhea. No differences in other outcomes.
Sanwikarja et al[1386]	1986	1b	DBRCT, crossover	SAR or PAR (n=14), non-allergic perennial rhinitis (n=10), 18-49 years old: 1. IPB 80µg QID 2. placebo	Nasal symptoms	IPB has suppressive effects on sneezing and hypersecretion, but no influence on nasal airway resistance.
Schultz Larsen et al[1387]	1983	1b	RCT, crossover	PAR, 23-84 years old (n=20): 1. IPB 80µg QID 2. placebo	Nasal symptoms	IPB is effective in controlling rhinorrhea.
Borum et al[1388]	1979	1b	RCT, crossover	PAR, 18-82 years old (n=20): 1. IPB 1 puff 20µg QID	Nasal symptoms	IPB had a significant effect on rhinorrhea. No effect on other

				2. placebo		symptoms.
Kim et al[1378]	2005	2b	Prospective	Common cold, SAR or PAR; 2-5 years old (n=230) Allergy group: IPB 0.06 %, 1 spray (42µg) TID for 14 days (n=187)	Nasal symptoms	IPB is effective in controlling rhinorrhea.
Milgrom et al[1389]	1999	2b	RCT, blinded, no placebo	PAR, non-allergic perennial rhinitis, 6-18 years old: 1. IPB 0.03% nasal spray (42µg), 2 sprays BID (n=75) 2. BDP (n=71)	Nasal symptoms, QOL	Equally effective in controlling rhinorrhea and improving quality of life. BDP more effective in controlling sneezing.
Kaiser et al[1390]	1995	2b	Prospective	PAR, 18-75 years old (n=219): First six months: 0.06% IPB TID (84µg) 6 months to 1 year: lowest dose IPB controlling rhinorrhea	Nasal symptoms, medication use, QOL	IPB was effective in controlling rhinorrhea, congestion, postnasal drip and sneezing. Reduction in the use of medications and improvement in QOL.

LOE: level of evidence; DBRCT: double-blind randomized controlled trial; PAR: perennial allergic rhinitis; IPB: ipratropium bromide; TID: three times daily; BID: two times daily; BDP: beclomethasone dipropionate; NAR: non-allergic rhinitis; QOL: quality of life; QID: four times daily; SAR: seasonal allergic rhinitis; RCT: randomized controlled trial

IX. B. 7. Biologics

Biologics have been studied in the treatment of AR, specifically omalizumab, either alone or in combination with specific AIT. Omalizumab is a humanized antibody that binds to human IgE. No biologic is currently approved by the US FDA for the treatment of AR. One systematic review and meta-analysis of RCTs has demonstrated reduced symptoms, reduced rescue medication use and improved QOL in patients treated with omalizumab.[1391] However, the cost of omalizumab is very high, estimated to be over $18,000 year in the US.

Systematic review identified five level 1 evidence studies examining the use of omalizumab in AR. **[Table IX.B.7.]** Four RCTs[1392-1395] demonstrated that omalizumab monotherapy was superior to placebo at improving patient symptoms and QOL. The first RCT evaluating different delivery routes and dose-ranges did not show efficacy against ragweed-induced AR, but reported no significant adverse events associated with omalizumab.[1396] A second study randomized birch pollen-induced SAR patients to receive either 300mg of omalizumab (originally named rhumAb-E25) or placebo given 2 or 3 times over the season, depending on baseline IgE levels. RhemAB-E25 treatment significantly reduced nasal symptom severity scores, the average number of tablets of rescue antihistamines per day, the proportion of days with any SAR medication use, and all domains of QOL.[1392] A third study applied omalizumab, 50 mg, 150 mg, or 300 mg, versus placebo subcutaneously prior to ragweed season and repeated every 3 to 4 weeks during the pollen season dependent on the patient's baseline serum IgE.[1393] At the highest dose studied, 300 mg of omalizumab significantly reduced nasal symptom severity scores and rhinitis-specific QOL scores. A significant association was observed between IgE reduction and nasal symptoms and rescue antihistamine use. The frequency of adverse events was not significantly different between omalizumab and placebo groups.

Omalizumab was also studied in the treatment of PAR, significantly reducing the mean daily nasal severity score and the rescue medication, and improving QOL when given subcutaneously every 4 weeks for 16 weeks.[1394] Omalizumab therapy was well tolerated. Similarly, effectiveness and safety of subcutaneously injected omalizumab was shown in the treatment of Japanese cedar pollen-induced SAR.[1395] Omalizumab treatment markedly reduced serum free IgE and the clinical response to nasal allergen challenge in an open study, but did not affect IgE-secreting B cells and epsilon mRNA in nasal lavage fluid suggesting that treatment for 6 months does not significantly modulate synthesis of nasal IgE.[1397] The biologic also suppressed tryptase and ECP levels in nasal secretions in seasonal allergy.[1398] Omalizumab showed significantly greater improvements than suplatast tosilate, a selective T-helper type 2 cytokine inhibitor, in the treatment of SAR induced by Japanese cedar pollens.[1399]

In 4 trials, a combination of omalizumab with AIT was studied to determine whether combined therapy could provide better efficacy and lower adverse events than AIT alone. In children and adolescents with SAR to birch or grass pollen, combination therapy significantly reduced symptom load over AIT alone independent of the allergen.[1400] Anti-IgE monotherapy alone significantly diminished rescue medication use and reduced the number of symptomatic days. The combined treatment with AIT and anti-IgE showed superior efficacy on symptom severity compared with anti-IgE alone.[1401] Combination therapy may, therefore, be useful for the treatment of AR, particularly for polysensitized patients. Patients receiving omalizumab and rush ragweed AIT showed a significant improvement in severity scores during season compared with AIT alone.[1402] Although omalizumab carries some risk of

anaphylaxis itself, addition of omalizumab resulted in a significant decrease in risk of anaphylaxis caused by AIT. Combination therapy also significantly reduced the symptom load in HDM allergic subjects better than AIT monotherapy, and improved asthma control and QOL with respect to asthma and AR.[1403] These effects were limited to the combined treatment period.[1404]

There are no other published studies evaluating other biologics (anti-IL5, anti-IL4 or IL-4R) as monotherapy for AR. A combination therapy of anti-IL4 with suboptimal AIT provided no additional benefit over SCIT alone in suppressing the allergen-induced skin late-phase response.[1405]

Although there is consistent evidence that omalizumab monotherapy is superior to placebo in symptom reduction and QOL improvement in AR, the benefits are relatively small over pharmacotherapy. Omalizumab is superior in combination with AIT versus AIT alone and reduces the risk of anaphylaxis associated with AIT, but the costs of the treatment preclude a widespread use. The combination therapy might be indicated in selected patients who are polysensitized and highly sensitive.

- Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 5 studies; *Table IX.B.7.*)
- Benefit: Consistent reduction in symptoms and rescue medication as well as improvement in QOL in RCTs and systematic review of RCTs compared to placebo.
- Harm: Injection site reactions, possibility of anaphylactic reaction.
- Costs: High. Annual incurred drug costs estimated to be above $18,000 per year in the US.
- Benefits-Harm Assessment: No therapy option as omalizumab is not registered for treatment of AR alone. This review was limited to evaluation of AR only; comorbid asthma was not evaluated.
- Value Judgements: Omalizumab monotherapy is superior to placebo, but effects are small over pharmacotherapy. May be evaluated in exceptional cases of highly sensitive polysensitized individuals in combination with AIT.
- Policy Level: No indication for the treatment of AR alone.
- Intervention: Omalizumab should not be used as monotherapy in the treatment of AR but may be considered in combination with AR for highly sensitive poly-allergic rhinitis patients with increased risk of anaphylaxis. As omalizumab is not currently approved by the FDA for AR treatment, in the US this treatment approach would likely not be performed in routine clinical practice presently.

Table IX.B.7. Evidence for the use of omalizumab as monotherapy in the treatment of allergic rhinitis (Level 1a and 1b studies with clinical endpoints only)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Tsabouri et al[1391]	2014	1a	SR of RCTs, with homogeneity	1. omalizumab 2. placebo	Symptom score, rescue medication, QOL	Omalizumab was superior to placebo. Omalizumab was generally well tolerated.
Okubo et al[1395]	2006	1b	RCT	1. omalizumab 2. placebo	Symptom score, rescue medication	Efficacy and tolerability in cedar pollen AR.
Chervinsky et al[1394]	2003	1b	RCT	1. omalizumab 2. placebo	Symptom score, rescue medication, QOL	Efficacy and tolerability in PAR.
Casale et a[1393]	2001	1b	RCT	1. omalizumab 2. placebo	Symptom score, rescue medication, QOL	Dose-finding trial, 300mg dose effective in improving symptoms and QOL compared to placebo.
Adelroth et al[1392]	2000	1b	RCT	1. omalizumab 2. placebo	Symptom score, rescue medication, QOL	Omalizumab was significantly superior to placebo in improving symptoms and QOL. Well tolerated.
Casale et al[1396]	1997	1b	RCT	1. omalizumab 2. placebo	Symptom score, rescue medication, QOL	First dose-finding study, safety confirmed.

LOE: level of evidence; RCT: randomized controlled trial; QOL: quality of life; AR: allergic rhinitis; PAR: perennial allergic rhinitis

IX. B. 8. Nasal saline

Nasal saline is frequently utilized in the treatment of AR. However, the term "nasal saline" encompasses a wide variety of therapeutic regimens. These can include hypertonic saline, isotonic/normal saline, seawater, buffered or non-buffered solutions, and volumes varying from 300µl to 500ml per administration. Irrigation regimens are also used with varying frequency.

This review included only level 1 evidence published in the English language. The search identified 5 RCTs in adults[151,1406-1409] **[Table IX.B.8-1.]**, 6 RCTs in children[1410-1415] **[Table IX.B.8-2.]**, and 1 systematic review[1416] encompassing all ages (included in both Tables), which evaluated the efficacy of nasal saline in the treatment of AR.

In adults, all 5 studies found improvements in clinical outcomes with the use of various types of nasal saline. These studies varied in their evaluation of SAR versus PAR, as well as the type and volume of saline. Studies by Garavello et al[151] and Rogkakou et al,[1407] found that the addition of hypertonic saline significantly improved nasal symptoms and QOL compared to not using saline. Ural et al[1408] further compared the efficacy of hypertonic to isotonic saline irrigations, finding improved mucociliary clearance time with the isotonic solution. They postulated that in PAR, the rheologic properties of the mucus are enhanced most by isotonic saline, thus improving mucociliary clearance. Chusakul et al[1409] also identified that buffered isotonic saline with mild alkalinity had the greatest impact on reducing nasal symptom scores and was preferred by the most patients. Finally, Cordray et al[1406] found that Dead Sea saline spray had a significant improvement in the RQLQ compared to isotonic saline. Cordray and colleagues suggested that the magnesium in the Dead Sea saline may have anti-inflammatory properties, resulting in improved AR outcomes.[1406]

In the pediatric population, all studies evaluating either PAR or SAR found an improvement in nasal symptoms or QOL with the incorporation of nasal saline. Both studies by Garavello et al[1410,1411] showed a significant improvement after the addition of hypertonic saline irrigations TID when compared to no irrigations. Marchisio et al[1413] and Satchabudha et al[1414] further identified that hypertonic saline irrigations resulted in a greater improvement in nasal symptom scores in children versus isotonic saline. Finally, Li et al[1412] and Chen et al[1415] found an additive effect in the utilization of nasal saline spray as an adjunct to a nasal steroid spray when compared to either therapy independently.

The systematic review by Hermelingmeier et al[1416] included 10 studies of which 7 were RCTs evaluating both adult and pediatric patients. Several of these studies are also included above.[151,1406-1408,1410-1412] This review found that almost all studies showed an improvement in nasal symptoms from 3.1-70.5% with the addition of nasal saline. Additionally, they identified a 24.2-100% reduction in medication usage, as well as an improvement in QOL of 29.8-37.5%. This review also suggested that isotonic saline was more effective than hypertonic saline. Perhaps surprisingly, they found that nasal saline sprays resulted in greater symptom improvement than saline irrigations. Overall, they concluded that nasal saline was as effective as other frequently utilized AR pharmacologic treatments (i.e. nasal antihistamines, oral antihistamines, etc.) in treatment of both SAR and PAR.

Overall, there is substantial evidence to support the use of nasal saline as an adjunct treatment for SAR and PAR. It appears that in adults, a buffered isotonic spray may provide maximum benefit. However, in children, a hypertonic solution may be more effective. Some studies have suggested less intranasal irritation when using isotonic solutions rather than hypertonic. Hypotonic saline has not been

studied as a treatment for AR. Adding mild alkalinity (pH 7.2-7.4) to the solution may further improve tolerability.[1409] Although nasal saline has been shown to improve symptoms and QOL outcomes when used alone, it is often implemented as an adjunct to other therapies including nasal steroid, antihistamine sprays, or oral antihistamines. In both adults and children, nasal saline appears to have an additive effect when used in combination with other standard AR treatments. Further, nasal saline is of relatively low cost and has an excellent safety profile. While adverse effects are rare, they can include local irritation, ear pain, nosebleeds, headache, nasal burning, nasal drainage, and bottle contamination.[1417]

- Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 11 studies; *Tables IX.B.8-1. and IX.B.8-2.*). Lower level studies were not considered in this review.
- Benefit: Reduced nasal symptom scores, improved QOL, improved mucociliary clearance, well tolerated with excellent safety profile.
- Harm: Intranasal irritation, headaches, ear pain.
- Cost: Minimal.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Nasal saline should be used as an adjunct to other pharmacologic treatments for AR. Isotonic solutions may be more beneficial in adults, while hypertonic may be more effective in children.
- Policy Level: Strong recommendation.
- Intervention: Nasal saline is strongly recommended as part of the treatment strategy for AR.

Table IX.B.8-1. Evidence for the use of nasal saline in the treatment of allergic in adults

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hermelingmeier et al[1416]	2012	1a	SR and meta-analysis	SAR and PAR, adults and children	Nasal symptom score, medicine use, QOL	Nasal symptoms and medicine use decreased with the use of nasal saline. Adults benefit more than children.
Chusakul et al[1409]	2013	1b	DBRCT, crossover	AR: 1. non-buffered isotonic saline 2. buffered with mild alkalinity (pH 7.2-7.4) 3. buffered with alkalinity (pH 8.2-8.4)	Nasal symptom score	Nasal symptoms were improved from baseline only by buffered saline with mild alkalinity.
Garavello et al[151]	2010	1b	RCT, no blinding	SAR, pregnant women: 1. hypertonic saline irrigations TID 2. no irrigations	Nasal symptom score, oral antihistamine use	Hypertonic saline irrigations during pollen season improves nasal symptoms and decreases oral antihistamine use.
Ural et al[1408]	2008	1b	RCT, no blinding	PAR: 1. hypertonic saline irrigations BID 2. isotonic saline irrigations BID	Mucociliary clearance time.	Isotonic saline improved mucociliary clearance time.
Cordray et al[1406]	2005	1b	SBRCT	SAR: 1. Dead Sea saline spray 2. triamcinolone spray 3. placebo nasal saline spray	RQLQ	Dead Sea saline group had significant improvements but not as significant as triamcinolone group; no change in placebo group.
Rogkakou et al[1407]	2005	1b	RCT, no blinding	PAR: 1. hypertonic saline spray QID + cetirizine 2. cetirizine only	Nasal symptoms, QOL (Rhinasthma questionnaire)	The addition of hypertonic saline resulted in a significant improvement in symptoms and QOL.

LOE: level of evidence; SR: systematic review; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; QOL: quality of life; DBRCT: double-blind randomized controlled trial; AR: allergic rhinitis; RCT: randomized controlled trial; TID: three times daily; BID: two times daily; QID: four times daily; SBRCT: single-blind randomized controlled trial; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

Table IX.B.8-2. Evidence for the use of nasal saline in the treatment of allergic rhinitis in children

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hermelingmeier et al[1416]	2012	1a	SR and meta-analysis	SAR and PAR, adults and children	Nasal symptom score, medicine use, QOL	Nasal symptoms and medicine use decreased with the use of nasal saline. Adults benefit more than children.
Chen et al[1415]	2014	1b	RCT, no blinding	PAR: 1. steroid nasal spray daily 2. seawater spray BID 3. both	Nasal symptom score, nasal signs	All groups improved. Steroid spray plus seawater had more significant improvements than other arms.
Marchisio et al[1413]	2012	1b	SBRCT	SAR: 1. hypertonic saline irrigations BID 2. normal saline irrigations BID 3. no irrigations	Nasal symptom score, turbinate and adenoid hypertrophy, oral antihistamine use	Hypertonic saline was significantly more effective in improving symptom score, decreasing adenoid and turbinate hypertrophy, and decreasing duration of antihistamine use
Satdhabudha et al[1414]	2012	1b	DBRCT	AR: 1. buffered hypertonic saline irrigations BID 2. normal saline irrigations BID	TNSS, QOL (Rcq-36), oral antihistamine use	Greater improvement in symptoms with buffered hypertonic saline. No significant difference in QOL or antihistamine use at 4 weeks.
Li et al[1412]	2009	1b	RCT, no blinding	PAR: 1. steroid nasal spray daily 2. isotonic nasal saline irrigations BID 3. both	Nasal symptoms	All groups improved. Steroid spray plus saline irrigations had more significant improvement than other arms.
Garavello et al[1411]	2005	1b	RCT, no blinding	SAR: 1. hypertonic saline irrigations TID 2. no irrigations	Nasal symptom score, oral antihistamine use	Hypertonic saline irrigations during pollen season had significant improvement in nasal symptoms and reduction in oral antihistamine use after 5 weeks.
Garavello et al[1410]	2003	1b	RCT, no blinding	SAR: 1. hypertonic saline irrigations TID 2. no irrigations	Nasal symptom score, oral antihistamine use	Hypertonic saline irrigations during pollen season improves nasal symptoms and decreases oral antihistamine use.

LOE: level of evidence; SR: systematic review; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; QOL: quality of life; RCT: randomized controlled trial; BID: two times daily; SBRCT: single-blind randomized controlled trial; DBRCT: double-blind randomized controlled trial; AR: allergic rhinitis; TNSS: Total Nasal Symptom Score; TID: three times daily

IX. B. 9. Probiotics

The relationship between microbiome and development of atopy is complex and incompletely understood. *(See Section IV.G. Pathophysiology and Mechanisms – Microbiome for additional information on this topic.)* Preliminary data from observational studies suggest that microbial exposure, especially in infancy, shapes the gut and airway microbiome and affects subsequent Th2 or Th1 immunologic bias. Given the link between gut flora and atopy, manipulation of the microbiome via probiotic administration could theoretically lead to clinical improvement of allergic disease. Probiotics have been posited to elicit immunomodulatory effects on atopic disease via gut-associated lymphoid tissue. Stimulation of dendritic cells induces Th1 responses via IL-12 and interferon (IFN)-γ, upregulation of Treg cells via IL-10 and TGF-β, and suppression of Th2 pathways through downregulation of IL-4, sIgE, IgG1, and IgA.[1418]

The optimal timing of probiotic administration for the treatment of atopy is unknown. A meta-analysis of 17 double-blind RCTs demonstrated that probiotics in pregnancy and early infancy were associated with decreased incidence of eczema but not asthma or rhinosinusitis in early childhood.[1419] Many double-blind RCTs and randomized crossover studies have investigated the effects of probiotics on AR in older children and adults. **[Table IX.B.9.]** Meta-analyses of these studies have been published in 2015[1420] and 2016[1421] with positive results. Adverse events due to probiotics were rare and minor, including diarrhea, abdominal pain, and flatulence.

Guvenc et al[1421] performed a systematic review and meta-analysis of 22 double-blind RCTs comprising 2242 patients aged 2-65 years with SAR or PAR. Patients received daily probiotic or placebo for 4 weeks to 12 months as an adjuvant to standard allergy therapies; primary outcomes included Total Nasal/Ocular Symptom Scores and QOL. Secondary outcomes included specific nasal symptom scores and immunologic parameters. Seventeen trials demonstrated clinical benefit of probiotics, with improvement in TNSS (standardized mean difference [SMD] -1.23, $p<0.001$), TOSS (SMD -1.84, $p<0.001$), total QOL (SMD -1.84, $p<0.001$), nasal QOL (SMD -2.30, $p=0.006$) and ocular QOL (SMD -3.11, $p=0.005$). Subgroup analysis demonstrated improvement in clinical parameters for SAR and PAR. Th1:Th2 ratio was improved (SMD -0.78, $p=0.045$) in the probiotic group, with no difference in tIgE, sIgE, or eosinophil count.

Zajac et al[1420] published a systematic review and meta-analysis of 21 double-blind RCTs and two randomized crossover studies comprising 1919 adult and pediatric patients with SAR or PAR treated with 3 weeks to 12 months of probiotic versus placebo. A total of 26 level 1b studies analyzed by Guvenc et al[1421] and Zajac et al[1420] are included in **Table IX.B.9.** Zajac et al[1420] limited outcomes measures to validated QOL or symptom scores and immunologic variables; 17 studies demonstrated clinical benefit of probiotics in AR. Meta-analysis demonstrated improvement in RQLQ global score (SMD -2.23, $p=0.02$) and RQLQ nasal symptom score (SMD -1.21, $p<0.00001$). No effect was found for RTSS, tIgE, or sIgE.

The preponderance of data from meta-analyses and double-blind RCTs suggests a beneficial effect for probiotics in the treatment of SAR and PAR in both adults and children, but interpretation is limited by the heterogeneity of age and diagnosis, interventions, and outcomes included in the studies. Probiotics varied in dose, were delivered via milk, yogurt, powder or capsules, and included a number of diverse strains: 19 studies employed *Lactobacillus* species,[1422-1440] 6 studies

Bifidobacterium,[1061,1433,1437,1441-1443] and 1 study each *Tetragenococcus halophilus*,[1444] *Escherichia coli*[1445] and *Bacillus clausii*.[1446]

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 26 studies; *Table IX.B.9.*).
- Benefit: Improved nasal/ocular symptoms or QOL in most studies. Possible improvement in immunologic parameters (Th1:Th2 ratio).
- Harm: Low.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: Minimal harm associated with probiotics, but heterogeneity across studies makes magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific recommendation for treatment.
- Policy Level: Option.
- Intervention: Consider adjuvant use of probiotics for patients with symptomatic SAR and PAR.

Table IX.B.9. Evidence for the use of probiotics in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Guvenc et al[1421]	2016	1a	SR and meta-analysis	SAR and PAR, adults and children. Daily probiotic vs. placebo. 22 DBRCTs (n=2242)	Symptom scores, QOL, immunologic parameters	17 studies demonstrated clinical benefit of probiotics. Improvement in TNSS, TOSS, total QOL, nasal QOL, and ocular QOL.
Zajac et al[1420]	2015	1a	SR and meta-analysis	SAR and PAR, adults and children. Daily probiotic vs. placebo. 21 DBRCTs and 2 crossover studies, (n=1919)	Validated QOL or symptom scores, immunologic parameters	17 studies demonstrated clinical benefit of probiotics. Improvement in RQLQ global and nasal symptom scores.
Costa et al[1425]	2014	1b	DBRCT	SAR to grass pollen, adults (n=425). *Lactobacillus paracasei*-33 x 5 weeks	RQLQ, RTSS	Probiotic improved RQLQ.
Lin et al[1434]	2014	1b	DBRCT	PAR to HDM, children (n=60). *Lactobacillus paracasei HF.A00232* x 8 weeks	RTSS, PRQLQ	Probiotic improved PRQLQ, sneezing, ocular itching/swelling at 12 weeks.
Dolle et al[1445]	2013	1b	DBRCT	SAR to grass pollen, adults (n=34). *Escherichia coli Nissle* 1917 x 6 months	Symptom-medication score	No benefit.
Lin et al[1426]	2013	1b	DBRCT	PAR to HDM, children (n=199). *Lactobacillus salivarius* x 12 weeks	Specific symptom score, symptom-medication score, tIgE	Probiotic improved nasal, eye, medication scores.
Singh et al[1441]	2013	1b	DBRCT	SAR to grass pollen, adults (n=20). *Bifidobacterium lactis NCC2818* x 8 weeks	TNSS	Probiotic improved TNSS.
Lue et al[1422]	2012	1b	Randomized crossover	PAR, children (n=63). *Lactobacillus johnsonii EM1*	RTSS, PRQLQ	Probiotic improved RTSS.
Jan et al[1438]	2011	1b	DBRCT	PAR to HDM, children (n=240). *Lactobacillus gasseri* x 12 weeks	SCORing allergic rhinitis index. specific symptom score, symptom-medication score, tIgE, blood eosinophil count	No benefit.
Chen et al[1432]	2010	1b	DBRCT	SAR and PAR, children (n=105). *Lactobacillus gasseri A5* x 8 weeks	Subjective symptoms, tIgE	Probiotic decreased nasal symptoms.
Nagata et al[1431]	2010	1b	DBRCT	SAR to JCP, adults (n=55). *Lactobacillus plantarum #14* x 6 weeks	Symptom-medication score, tIgE, sIgE	Probiotic improved symptom-medication score and ocular itching.
Gotoh et	2009	1b	DBRCT	SAR, adults (n=107).	Symptom-medication	Probiotic improved symptom-

al[1439]				*Lactobacillus gasseri* x 8 weeks	score, RQLQ, tIgE, sIgE, blood eosinophil count, Th1:Th2 ratio	medication score.
Kawase et al[1427]	2009	1b	DBRCT	SAR to JCP, adults (n=40). *Lactobacillus GG and L. gasseri TMC0356* x 10 weeks	Mean symptom score, mean symptom-medication score, tIgE, sIgE	Probiotic improved nasal blockage and medication score.
Nishimura et al[1444]	2009	1b	DBRCT	PAR to HDM, adults (n=45). *Tetragenococcus halophilus Th221* x 8 weeks	Disease severity, TNSS, tIgE, sIgE	Probiotic improved TNSS at high dose.
Ouwehand et al[1433]	2009	1b	DBRCT	SAR to birch, children (n=47). *Lactobacillus acidophilus NCFM & Bifidobacterium lactis B1-04* x 4 months	Subjective symptoms	No benefit.
Yonekura et al[1435]	2009	1b	DBRCT	SAR to JCP, adults (n=116). *Lactobacillus paracasei KW3110* x 3 weeks	RQLQ, sIgE	Probiotic improved QOL when pollen scattering low.
Ivory et al[1440]	2008	1b	DBRCT	SAR to grass pollen, adults (n=20). *Lactobacillus casei* x 5 months	tIgE, sIgE, sIgG, cytokines	Probiotic decreased Th2 cytokines (IL-5, IL-6), sIgE, IFN-γ and increased sIgG.
Giovannini et al[1428]	2007	1b	DBRCT	SAR and PAR, children (n=187). *Lactobacillus casei* x 12 months	Time free of asthma/rhinitis, number of episodes of rhinitis, tIgE	Probiotic decreased annual rhinitis episodes.
Tamura et al[1429]	2007	1b	DBRCT	SAR to JCP, adults (n=120). *Lactobacillus casei Shirota* x 8 weeks	Symptom-medication score	No benefit.
Xiao et al[1061]	2007	1b	Randomized crossover	SAR to JCP, adults (n=24). *Bifidobacterium longum BB536* x 4 weeks	Subjective symptoms	Probiotic reduced throat and ocular symptoms.
Xiao et al[1442]	2006	1b	DBRCT	SAR to JCP, adults (n=40). *Bifidobacterium longum BB536* x 14 weeks	Subjective symptoms	Probiotic decreased ocular symptoms.
Xiao et al[1443]	2006	1b	DBRCT	SAR to JCP, adults (n=44). *Bifidobacterium longum BB536* x 13 weeks	Subjective symptoms	Probiotic improved rhinorrhea, congestion, composite scores.
Ciprandi et al[1446]	2005	1b	DBRCT	SAR, children (n=20). *Bacillus clausii* x 3 weeks	RTSS, medication use	Probiotic reduced medication use.
Ishida et al[1436]	2005	1b	DBRCT	PAR to HDM, adults (n=49). *Lactobacillus acidophilus L-92* x 8 weeks	Symptom-medication score, tIgE, sIgE	Probiotic improved nasal symptom-medication scores.
Peng & Hsu[1424]	2005	1b	DBRCT	PAR to HDM, children (n=90). *Lactobacillus paracasei* x30 days	Modified PRQLQ	Probiotic improved PRQLQ (frequency, level of bother).
Wang et al[1423]	2004	1b	DBRCT	PAR to HDM, children (n=90). *Lactobacillus paracasei-33* x 30 days	Modified PRQLQ	Probiotic improved PRQLQ (frequency, level of bother).
Aldinucci et	2002	1b	DBRCT	SAR and PAR, adults (n=20).	Subjective symptoms	Probiotic decreased nasal

al[1437]				*Lactobacillus acidophilus & Bifidobacterium* x 4 months		symptoms.
Helin et al[1430]	2002	1b	DBRCT	SAR to birch, adults and children (n=36). *Lactobacillus rhamnosus* x 5.5 months	RTSS; nose, eye, lung symptoms	No benefit.

LOE: level of evidence; SR: systematic review; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; DBRCT: double-blind randomized controlled trial; QOL: quality of life; TNSS: Total Nasal Symptom Score; TOSS: Total Ocular Symptom Score; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RTSS: Rhinitis Total Symptom Score; HDM: house dust mite; PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; tIgE: total immunoglobulin E; JCP: Japanese cedar pollen; sIgE: antigen-specific immunoglobulin E; sIgG: antigen-specific immunoglobulin G; IL: interleukin: IFN: interferon

IX. B. 10. Combination therapy

IX. B. 10. a. Oral antihistamine and oral decongestant

Oral antihistamines function as reversible competitive antagonists of the histaminic H_1 receptor and prevent the binding of histamine to its receptors. Oral decongestants, such as pseudoephedrine and phenylephrine, are alpha-adrenergic stimulatory drugs which bind to pre- and post-capillary blood vessels resulting in vasoconstriction of nasal mucosa.[1447] The unrelated biologic targets of these medications' mechanisms of action has been shown in RCTs to result in synergistic improvement in AR symptoms.[1448,1449]

The combination of an oral antihistamine along with an oral decongestant has been shown to be more effective than placebo in controlling sneezing, nasal itching, and reducing nasal congestion in patients with AR.[1044,1050,1052,1167,1450-1456] **[Table IX.B.10.a.]** Investigations by Kaiser et al[1450] found that both once-daily or twice-daily loratadine-pseudoephedrine were consistently superior to placebo in reducing total nasal and non-nasal symptom scores with significantly higher risk of insomnia and dry mouth in both antihistamine-decongestant arms compared to placebo. Additionally, Nathan et al[1451] reported in 2006 that cetirizine-pseudoephedrine reduced AR total symptom severity scores, asthma symptom severity scores, and improved asthma QOL scores significantly versus placebo. However, they found no significant changes in pulmonary function testing in patients receiving cetirizine-pseudoephedrine or placebo and they identified similar rates of discontinuation and adverse events in both treatment arms.

Oral antihistamine and oral decongestant combinations have also been shown to be more effective in controlling AR symptoms when compared to INCS or compared to treatment with either oral antihistamines or oral decongestants alone.[1050,1455,1457-1460] In 2005, Zieglmayer et al[1449] found that the combination of cetirizine with prolonged release pseudoephedrine was significantly superior to budesonide nasal spray for improving nasal congestion after exposure to HDM, as measured by anterior rhinomanometry and nasal imaging. The combination of second-generation oral antihistamines and pseudoephedrine has been shown to significantly reduce symptom scores in patients with SAR more than either drug alone.[1050,1455,1457-1462] Additionally, the type of second-generation antihistamine and medication dosing schedule does not seem to have a significant effect on efficacy.[1463,1464]

Oral decongestants have the benefit of relieving the symptoms of nasal congestion through their ability to vasoconstrict capillaries within the nasal mucosa; however, their mechanism of action can also result in unfavorable systemic adverse effects such as hypertension and urinary retention. Oral decongestants have also been linked to an increased incidence of specific birth defects including pyloric stenosis and endocardial cushion defects when utilized by pregnant women.[1465] Furthermore, decongestants are not recommended for children under 4 years of age secondary to the high risk of adverse drug events associated with utilization in this age group.[1466] Finally, oral decongestants have OTC sales restrictions secondary to their potential utilization in the production of methamphetamines. Therefore, caution must be applied in the utilization of these medications, particularly in children under 4 and patients who are pregnant or have a pre-existing cardiovascular condition, hypertension, or benign prostatic hypertrophy. Oral antihistamines are well tolerated, with a favorable risk-benefit ratio. However, caution should still be exercised as antihistamines have cardiac side effects, alter the

metabolism of other medicines, and have been linked to a higher incidence of adverse events and drug-drug interactions in the elderly.[216]

It is likely because of this significant risk of adverse events and propensity for interactions with other medications that the ARIA 2010 guidelines recommended against the routine treatment of AR with a combination oral decongestant and oral antihistamine.[1167] The 2010 ARIA document suggested that oral decongestants only be added in patients who are not controlled by antihistamines alone and are less averse to side effects or adverse reactions. Additionally, they suggested that oral decongestants be limited to utilization primarily as a rescue medication during periods of significant symptom exacerbations.

Overall, despite the available evidence verifying the efficacy of combination oral antihistamines and oral decongestants in improving AR symptoms, caution should still be exercised when prescribing this treatment, particularly in patients with cardiovascular or urologic co-morbidities.

- Aggregate Grade of Evidence: A (Level 1b: 21 studies; *Table IX.B.10.a.*)
- Benefit: Improved control of nasal congestion with combination of oral antihistamines and oral decongestants.
- Harm: Oral decongestants can cause significant adverse effects, particularly in patients with hypertension, cardiovascular disease, or benign prostatic hypertrophy. Additionally, these medications should not be used in children under 4 years of age or pregnant patients. This should be weighed against the potential benefits prior to prescribing.
- Cost: Low.
- Benefits-Harm Assessment: Harm likely outweighs benefit when used on a routine basis.
- Value Judgments: Combination therapy of oral antihistamines and oral decongestants can be helpful for relief of an acute exacerbation of AR, especially nasal symptoms, when exposed to triggers. Caution should be exercised regarding long-term use given the possibility of significant adverse effects.
- Policy Level: Option, particularly for acute exacerbations of nasal congestion.
- Intervention: Combination therapy with oral antihistamine and oral decongestant can provide effective reduction of nasal congestion symptoms in patients with AR, however recommend against chronic use given the significant side effect profile of oral decongestants.

Table IX.B.10.a. Evidence for oral antihistamine and oral decongestant combination therapy for the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Badorrek et al[1050]	2009	1b	RCT	(n=49) 1. cetirizine-pseudoephedrine 2. cetirizine 3. pseudoephedrine 4. placebo	Symptoms, nasal flow, nasal secretions	Cetirizine-pseudoephedrine was more effective than the other arms in improving nasal obstruction, nasal flow, and nasal secretions after controlled pollen exposures.
Grubbe et al[1462]	2009	1b	RCT	(n=598) 1. desloratadine-pseudoephedrine 2. desloratidine 3. pseudoephedrine	TSS (without nasal congestion), nasal congestion score	Combination therapy was significantly more effective then monotherapy in reducing symptoms, including nasal congestion.
Chen et al[1464]	2007	1b	RCT	(n=48) 1. loratadine-pseudoephedrine daily 2. loratadine-pseudoephedrine twice daily	TSS	Both groups showed significant improvement without significant difference between groups.
Chiang et al[1463]	2006	1b	RCT	(n=51) 1. cetirizine-pseudoephedrine 2. loratadine- pseudoephedrine	Nasal total symptom scores	Both groups had a significant improvement in symptoms with no statistically significant difference between groups.
Nathan et al[1451]	2006	1b	RCT	(n=274) 1. cetirizine-pseudoephedrine 2. placebo	Symptoms (total and asthma), PFTs, asthma QOL	Combination therapy significantly reduced symptoms of SAR, asthma symptom scores, and asthma QOL scores.
Chervinsky et al[1461]	2005	1b	RCT	(n=650) 1. desloratadine-pseudoephedrine 2. desloratidine 3. pseudoephedrine	TSS without nasal congestion, TSS with nasal congestion	Nasal congestion symptoms scores were significantly reduced with desloratadine-pseudoephedrine compared to monotherapy.
Pleskow et al[1460]	2005	1b	RCT	(n=1047) 1. desloratadine-pseudoephedrine 2, desloratadine 3. pseudoephedrine	TSS, morning instantaneous TSS, nasal congestion score	Combination therapy was more effective than either drug alone in reducing TSS and nasal congestion.
Zieglmayer et al[1449]	2005	1b	RCT	(n=36) 1. cetirizine + prolonged release pseudoephedrine 2. budesonide nasal spray	Rhinomanometry, nasal cavity images, nasal congestion	Oral cetirizine + pseudoephedrine was superior to budesonide in reducing nasal congestion when exposed to HDM.

Moinuddin et al[1467]	2004	1b	RCT	(n=72) 1. fexofenadine-pseudoephedrine 2. loratadine + montelukast	RQLQ, nasal symptoms, nPIF	Fexofenadine-pseudoephedrine and loratadine-montelukast were equally effective in improving RQLQ, total symptoms, and nPIF, except for the sleep domain (loratadine-montelukast better).
Berkowitz et al[1044]	2002	1b	RCT	(n=298) 1. fexofenadine-pseudoephedrine 2. placebo	Single exposure major symptom complex, total symptom complex, individual symptoms	Fexofenadine-pseudoephedrine was more effective in reducing all symptoms following a single exposure to allergen; onset of action: 45 minutes.
Stubner et al[1468]	2001	1b	RCT	(n=36) 1. cetirizine-pseudoephedrine 2. xylometazoline nasal spray	Nasal congestion by photographs and digital airflow, nasal secretions, nasal and ocular symptoms	Nasal congestion by photographs was similar between groups. Cetirizine-pseudoephedrine was significantly better in improving all subjective symptoms.
McFadden et al[1452]	2000	1b	RCT	(n=20) 1. loratadine-pseudoephedrine 2. placebo	Acoustic rhinometry, endoscopic inferior turbinate photography, QOL	Significant improvement in nasal edema and secretions and nasal/ocular symptoms of rhinoconjunctivitis in the treatment group compared to placebo.
Sussman et al[1457]	1999	1b	RCT	(n=651) 1. fexofenadine-pseudoephedrine 2. fexofenadine 3. pseudoephedrine	Total symptoms, nasal congestion	Combination therapy significantly more effective in improving total symptom score and nasal congestion, produced greater improvement in daily activities and work productivity.
Horak et al[1052]	1998	1b	RCT	(n=24) 1. cetirizine-pseudoephedrine 2. placebo	Nasal obstruction, nasal patency/airflow	Cetirizine-pseudoephedrine was significantly better than placebo in improving nasal obstruction and airflow.
Kaiser et al[1450]	1998	1b	RCT	(n=469) 1. loratadine-pseudoephedrine once daily 2. loratadine-pseudoephedrine twice daily 3. placebo	Total nasal and non-nasal symptom scores	Loratadine-pesudoephedrine (either dose) was superior to placebo in reducing symptom scores.
Serra et al[1453]	1998	1b	RCT	(n=40) 1. loratadine-pseudoephedrine 2. placebo	Nasal symptoms or signs, mean TSS	Combination drug was significantly better than placebo in improving signs and TSS; both placebo and combination drug improved nasal symptoms.

Corren et al[1454]	1997	1b	RCT	(n=193) 1. loratadine-pseudoephedrine 2. placebo	Nasal and chest symptoms, albuterol use, peak expiratory flow	Combination drug significantly reduced symptom scores and improved peak flow rates and FEV1 compared to placebo.
Grosclaude et al[1459]	1997	1b	RCT	(n=687) 1. cetirizine-pseudoephedrine 2. cetirizine 3. pseudoephedrine	5 daily symptoms: congestion, sneezing, rhinorrhea, nasal and ocular pruritus	Combination was significantly more effecting in controlling all symptoms and providing more comfortable days than either medication alone.
Bertrand et al[1458]	1996	1b	RCT	(n=210) 1. cetirizine-pseudoephedrine 2. cetirizine 3. pseudoephedrine	Daily symptom scores	Cetirizine-pseudoephedrine resulted in significantly reduced symptoms and more symptom free days than either drug alone.
Bronsky et al[1455]	1995	1b	RCT	(n=874) 1. loratadine-pseudoephedrine 2. loratadine 3. pseudoephedrine 4. placebo	Composite symptom scores – total, nasal and non-nasal	Combination drug was significantly superior to either drug alone or placebo in reducing symptom scores.
Grossman et al[1456]	1989	1b	RCT	(n=264) 1. loratadine-pseudoephedrine 2. placebo	4 nasal and 4 non-nasal symptoms	Treatment group had significantly lower nasal and non-nasal symptom scores than the placebo group.

LOE: level of evidence; RCT: randomized controlled trial; TSS: Total Symptom Score; PFT: pulmonary function test; QOL: quality of life; SAR: seasonal allergic rhinitis; HDM: house dust mite; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; nPIF: nasal peak inspiratory flow; FEV1: forced expiratory volume in 1 second

IX. B. 10. b. Oral antihistamine and intranasal corticosteroid

A combination of an oral antihistamine and INCS is often used in clinical practice for the treatment of AR. As previously mentioned, oral antihistamines function as a reversible competitive antagonist of the histamine H_1 receptor and thereby prevent the binding of histamine that is present in the circulation. The newer, second-generation agents, such as fexofenadine and cetirizine, are less sedating, have fewer adverse effects, and provide good control of sneezing, rhinorrhea, and nasal itching but with less effect on nasal congestion.[1448] Additionally, INCS, such as fluticasone or beclomethasone, have repeatedly been validated as an effective treatment option for AR while offering a good safety profile and low systemic absorption.[1448]

Several RCTs have examined the efficacy of combination therapy utilizing both an oral antihistamine and INCS and demonstrated no added benefit of combination therapy. **[Table IX.B.10.b.]** In 2000, Wilson et al[1469] demonstrated that oral cetirizine and intranasal mometasone were effective at improving nasal peak inspiratory flow rates as well as nasal symptoms and total daily symptoms after 4 weeks of use. However, the combination was not significantly better than cetirizine and placebo or cetirizine and montelukast. In a double-blinded crossover study, Barnes et al[1470] compared the combination of fluticasone and levocetirizine versus fluticasone and placebo and found, in most patients, that the benefits of an additional oral antihistamine to an effective nasal steroid regimen were not significant. Additionally, Ratner et al[1471] found that fluticasone monotherapy compared to fluticasone plus loratadine had comparable efficacy in nearly all clinician and patient rated symptoms. Finally, Di Lorenzo et al[1472] demonstrated similar results in patients with SAR noting that combination therapy did not appear to offer substantial improvement in daily nasal symptom scores or in reduction of nasal lavage inflammatory markers.

In contrast, a 2008 study by Pinar et al[1473] compared mometasone spray monotherapy to mometasone plus desloratadine and found that the combination therapy group had significantly better nasal symptom scores at the end of study week 2 and better QOL scores throughout the study. A recent systematic review and meta-analysis by Feng et al[1474] summarized the efficacy of the combination therapy of an oral antihistamine and INCS as compared to either therapy independently. They concluded that the combination demonstrated significant improvement in symptom scores in AR when compared to an oral antihistamine alone, but do not provide significant additional benefit when compared to monotherapy with an effective INCS.[1474] Limitations to this data include the fact that the studies did not control for variations in the specific oral antihistamines or INCS utilized and that the studies predominantly evaluated patients with SAR, excluding patients with PAR. Additionally, the conclusions of this meta-analysis are supported by the updated 2010 ARIA guidelines which also do not recommend the addition of an oral antihistamine to an effective INCS, in contrast to prior recommendations.[1167] It should also be noted that adverse effects of oral antihistamine and INCS combination therapies include drowsiness and dry mouth (from oral antihistamines) as well as epistaxis and nasal irritation (from INCS).

- Aggregate Grade of Evidence: B (Level 1b: 5 studies; *Table IX.B.10.b.*)
- Benefit: Reduction of nasal congestion with combination of oral antihistamines and INCS compared to oral antihistamines alone.

- Harm: Side effects include sedative properties of antihistamines, although significantly decreased with the newer second-generation agents. Side effects of topical INCS include nasal dryness and epistaxis, burning in the nose, and with prolonged usage, possible growth suppression in the pediatric population.
- Cost: Low.
- Benefits-Harm Assessment: Harm likely outweighs benefit of adding the oral antihistamine unless treating symptoms other than nasal symptoms.
- Value Judgments: Combination therapy of oral antihistamine and INCS can be helpful when managing the symptoms of nasal congestion.
- Policy Level: Option.
- Intervention: Combination therapy of INCS and oral antihistamine does not improve symptoms of nasal congestion over INCS use alone, and does risk the adverse effects of systemic antihistamine use.

Table IX.B.10.b. Evidence for the use of combination oral antihistamine and intranasal corticosteroids in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Pinar et al[1473]	2008	1b	RCT	(n=95) 1. mometasone furoate INCS 2. mometasone furoate INCS + desloratadine 3. mometasone furoate INCS + montelukast 4. placebo	TNSS, rhinoconjunctivitis Scores, nPIF	Combination therapy resulted in better nasal symptom scores at week 2 and better QOL scores than INCS monotherapy.
Barnes et al[1470]	2006	1b	DBRCT, crossover	(n=27) 1. fluticasone + oral cetirizine 2. fluticasone + oral placebo	TNSS, mRQLQ, nPIF, nasal nitric oxide	Nasal symptom scores are equivalent with combination therapy compared to INCS.
Di Lorenzo et al[1472]	2004	1b	DBRCT, double dummy	SAR, (n=100) 1. fluticasone INCS + cetrizine 2. fluticasone INCS 3. cetirizine + montelukast 4. placebo	DNSS, nasal lavage eosinophil count and ECP level	Combination therapy was equivocal to monotherapy INCS in reducing nasal symptoms in SAR.
Wilson et al[1469]	2000	1b	SBRCT	SAR, (n=38) 1. mometasone INCS + cetirizine 2. cetirizine 3. cetirizine and montelukast	nPIF, symptom diary card	Combination of oral cetirizine and mometasone INCS was not significantly better than cetirizine alone for SAR.
Ratner[1471]	1998	1b	DBRCT, double dummy	SAR, (n=600) 1. fluticasone INCS + lotratadine 2. loratadine 3. fluticasone INCS	Symptoms	Combination therapy, although significantly better than an oral antihistamine alone, offered no significant advantage over INCS alone.

LOE: level of evidence; RCT: randomized controlled trial; INCS: intranasal corticosteroid; TNSS: Total Nasal Symptom Score; nPIF: nasal peak inspiratory flow; QOL: quality of life; DBRCT: double-blind randomized controlled trila; mRQLQ: mini Rhinoconjunctivitis Quality of Life Questionnaire; SAR: seasonal allergic rhinitis; DNSS: Daily Nasal Symptom Score; ECP: eosinophil cationic protein; SBRCT: single-blind randomized controlled trial

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

Combination therapy with LTRA and oral antihistamines in the treatment of AR has been studied in a single systematic review[1300] and multiple RCTs.[1467,1472,1475-1483] **[Table IX.B.10.c.]** Combination therapy generally improved symptoms and QOL compared to placebo in multiple RCTs.[1472,1475,1479,1482,1483] The efficacy of combination therapy compared to monotherapy with either LTRA or oral antihistamine is less clear. In the systematic review by Wilson et al,[1300] combination therapy improved patient symptoms compared to either agent as monotherapy, but there were no differences in standardized QOL measures. A RCT by Cingi et al[1477] indicated that montelukast and fexofenadine combination therapy was superior at reducing symptoms and nasal resistance measured by rhinomanometry, compared to either fexofenadine alone or fexofenadine administered concomitantly with placebo. Several other RCTs, however, did not demonstrate a difference in symptom reduction between combination therapy and oral antihistamine monotherapy.[1475,1479,1482]

Several studies also examined the relative effectiveness of combination LTRA and oral antihistamine therapy compared to INCS. Combination therapy was generally less effective than INCS monotherapy,[1472,1479,1481] although some studies did not detect a statistically significant difference.[1300,1484] The systematic review by Wilson et al[1300] did not discern a difference in symptom reduction between LTRA and oral antihistamine combination therapy and INCS. In contrast, three RCTs showed that INCS resulted in improved nasal symptoms compared to treatment with the combination,[1472,1479,1481] in addition to decreased nasal mucosa eosinophil counts.[1472,1481]

There is conflicting evidence on whether combination therapy is more effective than oral antihistamine alone, and there appears to be relatively consistent evidence that INCS monotherapy is more effective at nasal symptom reduction than LTRA and oral antihistamine combination therapy. Therefore, combination therapy may be an option in patients whose symptoms are incompletely controlled with oral antihistamine monotherapy, and in whom INCS are not tolerated or contraindicated. This may be particularly useful in a subset of these patients with concurrent asthma. Montelukast may be effective at simultaneously reducing AR symptoms and improving asthma control.[1341]

Drug interaction and safety are an important consideration when using combination therapies. Reported adverse events for montelukast and loratadine in combination were similar to montelukast and loratadine monotherapy and placebo.[1485] The most common reported adverse events were headache (4.5%), fatigue (1.2%) and pharyngolaryngeal pain (1.2%). There were no changes of vital signs, electrocardiogram, or physical exam findings during the monitoring period.[1485] Combination LTRA and oral antihistamine therapy can be administered with minimal adverse events, and with similar frequency to either agent as monotherapy.

- Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 11 studies; Level 2b: 1 study; *Table IX.B.10.c.*)
- Benefit: Inconsistent evidence that combination LTRA and oral antihistamine were superior in symptom reduction and QOL improvement than either agent as monotherapy. Combination therapy is inferior in symptom reduction compared to INCS alone.
- Harm: No significant safety related adverse events from combination therapy.

- Costs: Generic montelukast was more expensive than either generic loratadine or cetirizine on a per dose basis, according to weekly NADAC data provided by CMS.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgements: Combination therapy of LTRA and oral antihistamines does not result in consistently improved AR symptoms compared to either agent alone. There are few reported safety-related adverse events from combination therapy. The addition of an LTRA may have a role in management of comorbid asthma.
- Policy Level: Option.
- Intervention: Combination therapy of LTRA and oral antihistamines is an option for management of AR, particularly in patients with comorbid asthma or those who do not tolerate INCS and symptoms are not well-controlled on oral antihistamine monotherapy.

Table IX.B.10.c. Evidence for the use of combination leukotriene receptor antagonist and oral antihistamine in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wilson et al[1300]	2004	1a	SR of RCTs, with homogeneity	1. LTRA + oral antihistamine 2. LTRA 3. oral antihistamine 4. INCS	Symptoms, QOL	Combination therapy improved symptoms vs either treatment alone. No differences in QOL measures. No difference in symptoms for combination therapy compared to INCS.
Ciebiada et al[1475]	2013	1b	RCT	1. montelukast 2. oral antihistamine 3. montelukast + oral antihistamine 4. placebo	Symptoms, ICAM-1 levels, eosinophilia	Active treatments were superior to placebo at reducing symptoms, ICAM-1 levels and eosinophilia. Active treatments were not statistically different from each other.
Yamamoto et al[1476]	2012	1b	RCT	1. montelukast + loratadine 2. montelukast + placebo	Symptoms	Combination therapy improved symptom scores, specifically sneezing and rhinorrhea.
Cingi et al[1477]	2010	1b	RCT	1. fexofenadine + montelukast 2. fexofenadine + placebo 3. fexofenadine	Symptoms, rhinomanometry	Combination therapy improved symptoms and decreased nasal resistance compared to fexofenadine alone or with placebo.
Li et al[1478]	2009	1b	RCT	1. fexofenadine + montelukast 2. fexofenadine	Symptoms, acoustic rhinometry, cytokine levels	Combination therapy improved symptoms, increased nasal volume by rhinometry. No difference in cytokine levels.
Lu et al[1479]	2009	1b	RCT	1. montelukast + loratadine 2. beclomethasone INCS 3. montelukast 4. loratadine 5. placebo	Symptoms, QOL	Combination therapy improved symptoms more than placebo or montelukast alone. There was no difference compared to loratadine alone. Combination therapy was inferior to beclomethasone INCS.
Watanasomsiri et al[1480]	2008	1b	RCT	1. montelukast + loratadine 2. loratadine + placebo	Symptoms, turbinate hypertrophy	No difference in symptoms with combination therapy vs antihistamine alone. Turbinate swelling significantly reduced with combination therapy.
DiLorenzo et al[1472]	2004	1b	RCT	1. montelukast + cetirizine 2. fluticasone INCS 3. fluticasone INCS + certirizine 4. fluticasone INCS + montelukast 5. placebo	Symptoms, peripheral eosinophilia, nasal eosinophil counts	Montelukast + cetirizine improved symptoms and decreased nasal eosinophil counts compared to placebo. Generally inferior to fluticasone INCS alone or in combination.

Moinuddin et al[1467]	2004	1b	RCT	1. montelukast + loratadine 2. fexofenadine + pseudoephedrine	Symptoms, QOL, nPIF	No significant difference between treatment groups for symptoms, QOL, and NPIF. Montelukast + loratadine reduced sleep domain symptoms.
Saengpanich et al[1481]	2003	1b	RCT	1. montelukast + loratadine 2. fluticasone INCS	Symptoms, nasal eosinophil count, nasal ECP level	No difference in total symptom score, but nasal symptoms reduced in the fluticasone group. Decreased eosinophil cell count and ECP level in the fluticasone group.
Nayak et al[1482]	2002	1b	RCT	1. montelukast + loratadine 2. montelukast 3. loratadine 4. placebo	Symptoms, QOL, peripheral eosinophilia	Combination therapy decreased symptoms and improved QOL compared to placebo. Effect did not reach statistical significance compared to monotherapy. Combination therapy decreased peripheral eosinophilia compared to placebo and loratadine only.
Meltzer et al[1483]	2000	1b	RCT	1. montelukast + loratadine 2. montelukast 3. loratadine 4. placebo	Symptoms, QOL	Combination therapy improved symptoms and QOL compared to placebo. Combination therapy not directly compared to monotherapy.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; LTRA: leukotriene receptor antagonist; INCS: intranasal corticosteroid; QOL: quality of life; ICAM: intercellular adhesion molecule; nPIF: nasal peak inspiratory flow; ECP: eosinophil cationic protein

IX. B. 10. d. Intranasal corticosteroid and intranasal antihistamine

The use of combination intranasal antihistamine and corticosteroid spray for AR has been well studied. One topical formulation is currently available in North America for intranasal use as a combination of azelastine hydrochloride and fluticasone propionate (AzeFlu). This agent is also designated in the literature as MP-AzeFlu or MP29-02, and is marketed in the US under the trade name Dymista. A systematic review of the English-language literature was performed for clinical trials of combination INCS and intranasal antihistamine for the treatment of AR. A total of 10 RCTs (9 double-blind, 1 non-blinded) evaluated combination therapy against either placebo or active control.[1486-1495] An additional 2 observational studies in the allowable search date range for this document reported outcomes of AzeFlu as a single treatment arm.[1496,1497] **[Table IX.B.10.d.]**

Outcome measures were predominantly patient-reported symptom scores or QOL assessments. The most common outcome measure was the TNSS (9 studies), which records the severity of runny nose, sneezing, itching and congestion. Other outcome measures included the TOSS (4 studies), a VAS (3 studies), the RQLQ (2 studies), the Pediatric RQLQ (1 study) and a threshold/discrimination/identification (TDI) score (1 study).

The minimum age of subjects in most included studies was 12 years or older. Study duration was 14 days of active treatment in most studies, except 1 study with a 3-month duration[1495] and 1 study with a 52-week duration.[1488] The number of subjects in each study ranged from 47 to 3398. Combination therapy with AzeFlu was compared to placebo in 6 studies, with primary outcomes showing superiority to placebo in all studies.[1486,1487,1489-1492] AzeFlu was compared to active treatment with fluticasone propionate monotherapy in 6 studies, all of which showed superiority of the combination therapy.[1488-1490,1492,1494,1495] Similarly, intranasal AzeFlu was compared to active treatment with azelastine hydrochloride monotherapy in 4 studies, all of which showed superiority of the combination therapy.[1489,1490,1492,1494] 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.[1493] One study found superiority of an experimental combination of solubilized azelastine and budesonide compared to either a suspension-type formulation of azelastine and budesonide or placebo.[1491]

Two studies evaluated children aged between 6-12 years old. Like findings in adults, AzeFlu showed superiority to placebo in improving symptoms and quality of life in children.[1486,1495] Several studies reporting time to onset found that AzeFlu had a more rapid effect compared to INCS alone.

Serious adverse effects were not reported in any study. Intranasal antihistamine and corticosteroid combination therapy was generally well tolerated, with the most commonly reported adverse effect being an unpleasant taste. Other reported adverse effects included somnolence, headache, epistaxis and nasal discomfort, all occurring in less than 5% of cases in each study. One study that compared combination therapy of fluticasone propionate with either azelastine or olopatadine reported more treatment-related events for the azelastine group (16/68) than the olopatadine group (7/67).[1493]

- Aggregate Grade of Evidence: A (Level 1b: 9 studies; Level 2b: 1 study; Level 2c: 2 studies; *Table IX.B.10.d.*)

- Benefit: Rapid onset, more effective for relief of multiple symptoms than either INCS or intranasal antihistamine alone.
- Harm: Patient intolerance, especially due to taste.
- Costs: Moderate financial burden. Average wholesale price of $202 USD per 23 gram bottle (1 month supply when used as labeled).
- Benefits-Harm Assessment: Preponderance of benefit over harm. Combination therapy with intranasal antihistamine and INCS is consistently more effective than placebo. Low risk of non-serious adverse effects.
- Value Judgments: Despite level 1 evidence demonstrating that combination spray therapy (INCS plus intranasal antihistamine) is more effective than monotherapy and placebo, the increased financial cost and need for prescription limit the value of combination therapy as a routine first-line treatment for AR.
- Policy Level: Strong recommendation for the treatment of AR when monotherapy fails to control symptoms.
- Intervention: Combination therapy with INCS and intranasal antihistamine may be used as second-line therapy in the treatment of AR when initial monotherapy with either INCS or antihistamine does not provide adequate control.

Table IX.B.10.d. Evidence for the use of combination intranasal corticosteroids and intranasal antihistamine in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Berger et al[1486]	2016	1b	DBRCT	1. AzeFlu 2. placebo	rTNSS, rTOSS, PRQLQ	AzeFlu superior to placebo for symptoms and QOL improvement in children; symptoms improved when children self-rate.
Meltzer et al[1487]	2013	1b	DBRCT	1. AzeFlu 2. placebo	rTNSS, rTOSS	AzeFlu superior to placebo for all symptoms.
Price et al[1488]	2013	1b	DBRCT	1. AzeFlu 2. fluticasone propionate	rTNSS, symptom-free days	AzeFlu superior to fluticasone for symptom reduction; faster onset.
Carr et al[1489]	2012	1b	DBRCT	1. AzeFlu 2. azelastine 3. fluticasone propionate 4. placebo	rTNSS, rTOSS, RQLQ	AzeFlu superior to either spray alone for symptom and QOL improvement; faster onset.
Meltzer et al[1490]	2012	1b	DBRCT	1. AzeFlu 2. azelastine 3. fluticasone propionate 4. placebo	rTNSS, rTOSS, RQLQ	AzeFlu superior to either spray alone for symptom and QOL improvement.
Salapatek et al[1491]	2011	1b	DBRCT	1. solubilized azelastine + budesonide (CDX-313) 2. azelastine + budesonide suspension 3. placebo	TNSS	Both treatments superior to placebo; CDX-313 superior to suspension-type spray for symptoms and speed of onset.
Hampel et al[1492]	2010	1b	DBRCT	1. AzeFlu 2. azelastine 3. fluticasone propionate 4. placebo	TNSS	AzeFlu superior to either spray alone; all treatments superior to placebo.
LaForce et al[1493]	2010	1b	DBRCT	1. AzeFlu 2. olopatadine + fluticasone propionate	TNSS	No difference between treatments.
Ratner et al[1494]	2008	1b	DBRCT	1. AzeFlu 2. azelastine 3. fluticasone propionate	TNSS	Combination superior to either agent alone.
Berger et al[1495]	2016	2b	RCT, non-blinded	1. AzeFlu 2. fluticasone propionate	Total symptom score	AzeFlu superior to fluticasone for children; faster onset.

Klimek et al[1496]	2016	2c	Prospective observational	AzeFlu	VAS	76% of subjects had symptom control after 14 days; significant improvement from baseline.
Klimek et al[1497]	2015	2c	Prospective observational	AzeFlu	VAS	Rapid symptom relief across all age groups.

LOE: level of evidence; DBRCT: double-blind randomized controlled trial; AzeFlu: combination spray of azelastine hydrochloride and fluticasone propionate; rTNSS: reflective Total Nasal Symptom Score; rTOSS: reflective Total Ocular Symptom Score; PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; QOL: quality of life; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; TNSS: Total Nasal Symptom Score; RCT: randomized controlled trial; VAS: visual analog scale

IX. B. 11. Non-traditional and alternative therapies

IX. B. 11. a. Acupuncture

In complimentary medicine, acupuncture has the distinction of being one of the oldest forms of healing arts practiced, with its origins dating back to the 6th-5th centuries BC.[1498] Traditional Chinese medicine holds to the concept that the body's vital energy (Qi) flows through a network of meridians beneath the skin.[1499] In a healthy state, the flow of the Qi is uninterrupted whereas disease states mark a disruption of the Qi. The aim of acupuncture is to stimulate acupuncture points (acupoints) with needles to recover equilibrium. Acupoints are specific anatomic points located along meridians that are believed to correspond to the flow of energy through the body.

There have been several blinded RCTs evaluating acupuncture as a treatment for AR. Acupuncture has an excellent safety profile with only minor side effects reported.[1500,1501] Some studies have shown acupuncture to influence allergic and inflammatory mediators including IgE and IL-10 levels in AR patients significantly more than controls,[1501,1502] suggesting a possible immunomodulatory effect. The clinical significance of these changes, however, remains to be seen.

Two meta-analyses addressing acupuncture have been performed. **[Table IX.B.11.a.]** The first, published in 2008 reviewed 7 RCTs and found a high degree of heterogeneity between studies with most studies being of low quality.[1500] No overall effects of acupuncture on AR symptom scores or use of relief medications were identified.[1500] A more recent meta-analysis of 13 studies had more favorable findings, demonstrating a significant reduction in nasal symptoms, improvement in RQLQ scores and decreased use of rescue medications in the group receiving acupuncture.[1501] This meta-analysis included 6 of the 7 studies in the 2008 review and 7 new studies. Again, a high level of heterogeneity between studies and varied quality of the studies was noted. Most important to note is that neither meta-analysis discussed the specific consideration of concomitant AR medication use during the trials, which is common in most acupuncture trials. The uncontrolled use of AR medications could have significantly impacted the outcomes in any of these studies and raises concerns when interpreting the results.

- Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 2b: 13 studies; *Table IX.B.11.a.*) Only level 1a studies are presented in the table.
- Benefit: Unclear, as one meta-analysis showed no overall effects of acupuncture on AR symptoms or need for rescue medications and a second meta-analysis showed an effect of acupuncture on symptoms, QOL and need for rescue medications.
- Harm: Needle sticks associated with minor adverse events including skin irritation, pruritis, erythema, subcutaneous hemorrhage, infection, and headache. Need for multiple treatments and possible on-going treatment to maintain any benefit gained.
- Cost: Cost of acupuncture treatment with multiple treatments required.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: The authors determined that the evidence was inconclusive but that acupuncture could be appropriate for some patients to consider as an adjunct therapy.
- Policy Level: Option.
- Intervention: In patients who wish to avoid medications, acupuncture may be suggested as possible therapeutic adjunct.

Table IX.B.11.a. Evidence for the use of acupuncture in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Feng et al[1501]	2015	1a	SR and meta-analysis	1. acupuncture 2. sham acupuncture	Nasal symptom scores, RQLQ scores, rescue medication use	Significant reduction in nasal symptoms, improvement in RQLQ scores and use of rescue medications with acupuncture.
Roberts et al[1500]	2008	1a	SR and meta-analysis	1. acupuncture 2. sham acupuncture	AR symptom scores, rescue medication use	No overall effect on AR symptom scores or need for rescue medications.

LOE: level of evidence; SR: systematic review; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; AR: allergic rhinitis:

IX. B. 11. b. Honey

A long-held belief has been that honey is effective in treating symptoms of AR; however, evidence in support of this is scarce. It is postulated that environmental antigens contained within locally produced honey could, when ingested regularly, lead to the development of tolerance in a manner similar to SLIT. It is important to note that heavy insect borne pollens do not meet Thomen's postulates, as they are not airborne and hence should not be able to induce allergic sensitivity.[818] Studies in animals have demonstrated the ability of honey to suppress IgE antibody responses elicited against different allergens and to inhibit IgE mediated mast cell activation.[1503-1505] As yet, these same effects have not been tested for in humans; however, studies in humans have demonstrated various anti-inflammatory properties of honey which point to a potential benefit for its use in the treatment of AR.[1506,1507]

There have been two randomized, double-blind, placebo-controlled trials and one RCT evaluating honey in the treatment of AR. **[Table IX.B.11.b.]** The studies differed in geographic location, length of honey treatment, dose of honey and timing regarding specific allergy seasons. One double-blind trial and one RCT showed a significant decrease in total symptom scores in the treatment group compared to control.[1508,1509] The RCT additionally reported fewer number of severe symptom days and decreased need for antihistamines in the honey group.[1509] Contradicting these findings, a randomized, double-blind, placebo-controlled trial by Rajan et al[1510] found no benefit of honey ingestion compared to controls for the relief of AR symptoms. Of note, it has been reported that higher doses (50-80g daily intake) of honey are required to achieve health benefits from honey[1511] and only the study by Asha'ari et al[1508] dosed patients at that level.

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 1 study; *Table IX.B.11.b.*)
- Benefit: Unclear, as studies have shown differing results. Honey may be able to modulate symptoms and decrease need for antihistamines.
- Harm: Some patients stopped treatment because they could not tolerate the level of sweetness. Some patients could have an allergic reaction to honey intake, and in rare instances,

anaphylaxis. Use of this therapy in pre-diabetics and diabetics would likely need to be avoided out of concern for elevated blood glucose levels.

- Cost: Cost of honey; low.
- Benefits-Harm Assessment: Balance of benefit and harms.
- Value Judgments: Studies are inconclusive and heterogeneous.
- Policy Level: No recommendation due to inconclusive evidence.
- Intervention: None.

Table IX.B.11.b. Evidence for the use of honey in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Asha'ari et al[1508]	2013	1b	RDBPCT	1. honey 2. placebo	AR symptom scores	Improvement in overall and individual AR symptoms with honey.
Rajan et al[1510]	2002	1b	RDBPCT	1. locally collected, unpasteurized, unfiltered honey 2. nationally collected, pasteurized, filtered honey 3. placebo	Daily AR symptoms, rescue medication use	No significant difference in AR symptoms or need for rescue medication.
Saarinen et al[1509]	2011	2b	RCT	1. birch pollen honey 2. regular honey 3. no honey	Daily AR symptoms, number of asymptomatic days, rescue medication use	Birch pollen honey significantly lowered total symptom scores and decreased use of rescue medications. Honey groups had significantly more asymptomatic days.

LOE: level of evidence; RDBPCT: randomized double-blind placebo-controlled trial; AR: allergic rhinitis; RCT; randomized controlled trial

IX. B. 11. c. Herbal therapies

Like acupuncture and honey, herbal remedies have been used for the treatment of various physical ailments, including AR, world-wide for thousands of years. This area of complementary/alternative medicine is an attractive alternative to mainstream medicine for patients who wish to avoid traditional pharmacotherapy or who have not tolerated various anti-allergic medications in the past. There are a vast number of studies looking at the effectiveness of numerous herbs and herbal supplements in the treatment of AR, however, most are small and of poor quality. Those herbal remedies that have been subjected to more rigorous study are summarized in **Table IX.B.11.c.**

Given the lack of robust and repeated large double-blind randomized placebo-controlled trials on any one herbal remedy, no evidence based recommendations can be made supporting the routine use

of any one herb or compound and this should be considered an area requiring further research before any such recommendations can be made.

- Aggregate Grade of Evidence: Uncertain.
- Benefit: Unclear, but some herbs may be able to provide symptomatic relief.
- Harm: Some herbs are associated with mild side effects. Also, the safety and quality of standardization of herbal medications is unclear.
- Cost: Cost of herbal supplements; variable.
- Benefits-Harm Assessment: Unknown.
- Value Judgments: The authors determined that there is a lack of sufficient evidence to recommend the use of herbal supplements in AR.
- Policy Level: No recommendation.
- Intervention: None.

Table IX.B.11.c. Evidence for the use of herbal therapies in the treatment of allergic rhinitis

Herb	Mechanism of action	Evidence	Side effects
Astragalus membranaceus	Unknown	RDBPCT comparing 80mg daily x 6 weeks showed significant improvement in rhinorrhea, changes in TSS, and QOL.[1512]	Pharyngitis, rhinosinusitis
Aller-7	Possibly through antioxidant and anti-inflammatory pathways[1513-1515]	2 RDBPCTs showed some relief of symptoms with Aller-7. However, there were some contradictory findings.[1516]	Dry mouth, gastric discomfort
Benifuuki green tea	Inhibits type I and type IV hypersensitivity reactions[1517,1518]	RDBPCT showed 700mL Benifuuki green tea daily significantly reduced AR symptoms, improved QOL, and suppression of peripheral eosinophils.[1519]	None reported
Biminne	Unknown	RDBPCT found 12 weeks of Biminne significantly reduced sneezing.[1520]	Not reported
Butterbur (*Petasites hybridus*)	Inhibits leukotriene and histamine synthesis and mast cell degranulation[1521]	3 RDBPCTs showed Butterbur effective in alleviating symptoms, attenuating nPIF recovery, and reducing maximum % nPIF decrease from baseline after adenosine monophosphate challenge. Butterbur similar to antihistamine for improving QOL and symptom relief.[1516] 1 RDBPCT demonstrated no benefit for nPIF, symptoms, or QOL.[1516]	Hepatic toxicity, headache, gastric upset
Capsaicin	Thought to desensitize and deplete sensory C-fibers[1522,1523]	No evidence of a therapeutic effect of intranasal capsaicin in AR.[694,1524]	Mucosal irritation, burning
Cinnamon bark, Spanish needle,	Inhibits production of prostaglandin D2[1525]	RDBPCT showed 450 mg CG TID comparable to loratadine 10 mg in symptom reduction. CG prevented	None reported

acerola (ClearGuard)		increase in prostaglandin D2 release following nasal allergen challenge.[1525]	
Grape Seed Extract	Contains catechin monomers which may inhibit allergen-induced histamine release[1526]	RDBPCT showed no benefit of 100 mg Grape seed extract BID on nasal symptoms, need for rescue medications or QOL.[1527]	None reported
Nigella sativa (Black seed)	Inhibited histamine release from rat macrophages.[1528] Thymoquinone may inhibit Th2 cytokines and eosinophil infiltration in airways.[1529]	2 RDBPCTs showed *N. sativa* capsules and 1 RDBPCT showed *N. sativa* nasal drops improve AR symptoms.[1530-1532] 1 RDBPCT did not find significant differences between treatment and placebo.[1530]	Gastrointestinal complaints with oral intake. Nasal dryness with topical drops.
Perilla frutescens	Polyphenolic phytochemicals such as Rosmarinic acid inhibit inflammatory processes and the allergic reaction.[1533-1536]	RDBPCT showed 50 mg or 200 mg *P fruescens* enriched for rosmarinic acid did not significantly improve symptom scores.[1537]	None reported
RCM-101	Inhibits histamine release and prostaglandin E2 production[1538,1539]	RDBPCT showed 4 tablets of RCM-101 TID for 8 weeks significantly improved symptom scores and RQLQ.[1540]	Mild gastrointestinal side effects
Spirulina	Reduces IL-4 levels,[1541] inhibits histamine release from mast cells[1542]	RDBPCT showed 2000 mg/day Spirulina significantly improved sneezing, rhinorrhea, congestion and nasal itching.[1543]	Not reported
Ten-Cha (*Rubus suavissimus*)	Inhibits cyclooxygenase activity and histamine release by mast cells[1544]	RDBPCT showed no significant improvement in symptom scores, RQLQ, or need for antihistamine with 400 mg daily of Ten-Cha extract.[1545]	None Reported
TJ-19*	Inhibits histamine signaling and IL-4 and IL-5 expression in a rat model[1546]	RDBPCT showed 3 g TJ-19 TID significantly improved sneezing, stuffy nose and runny nose.[1547]	Not reported
Tinofend (*Tinospora cordifolia*)	Possibly through anti-inflammatory effects[1548]	RDBPCT showed 300mg Tinofend x 8 weeks significantly improved multiple AR symptoms and a significant decrease in eosinophil, neutrophil and goblet cell counts on nasal smear.[1548]	Leukocytosis
Urtica dioica (stinging nettle)	*In vitro*: antagonist/negative agonist activity against Histamine-1 receptor, inhibits mast cell tryptase, prevents mast cell degranulation, inhibits prostaglandin formation[1549]	1 RDBPCT showed symptom improvement over placebo at 1 hour.[1550] 1 systematic review showed no significant intergroup differences.[1516]	Not reported

RDBPCT: randomized double blind placebo controlled trial; TSS: Total Symptom Score; QOL: quality of life; AR: allergic rhinitis; nPIF: nasal peak inspiratory flow; CG: ClearGuard; TID: three times daily; BID: two times daily; RQLQ: Rhinoconjunctivitis Quality of Life Qustionnaire; IL: interleukin; *not available in the US as it contains ephedra

IX. C. Surgical treatment

AR is a medical disease, but at times may become refractory to medical management. Surgery for AR is primarily aimed at reducing nasal obstruction and/or rhinorrhea, with the contributing structures being the nasal septum and turbinates.[1551] Vidian neurectomy is historically a surgical technique that also sought to overcome chronic and intractable rhinitis.

No Cochrane review of septoplasty or vidian neurectomy for allergic patients currently exists. A Cochrane review of turbinate reduction in allergic patients refractory to medical management was explored, but was unable to identify any qualifying studies (selection criteria stringently required randomized controlled trials of inferior turbinate surgery versus continued medical treatment for proven AR, or comparisons between one technique of inferior turbinate surgery versus another technique, after maximal medical treatment).[1552] Physicians must, therefore, rely upon less scientifically rigorous data when deciding upon surgery for AR patients.

The role of septoplasty for the treatment of nasal obstruction in AR is poorly understood. The nasal septum is not a major contributor to allergic disease because it does not experience the extent of dynamic change the turbinate tissue does, and therefore, there is a paucity of literature investigating septoplasty alone to improve nasal patency in AR. The nasal septal swell body may serve to alter nasal airflow and humidification, but no literature exists to implicate a role in AR.[1553] Karatzanis et al[1554] found that subjective improvement in patients undergoing septoplasty was higher in those without AR than those with it. For this reason, a cautious approach to the management of nasal septal deviation in AR is warranted. On the other hand, Kim found that AR patients undergoing septoplasty with turbinoplasty felt more relief of nasal obstruction then those undergoing turbinoplasty alone.[1555] **[Table IX.C.]**

In contrast to the septum, the inferior turbinates are a prime target of allergic effects, characterized by vasodilation of capacitance vessels leading to engorgement, in turn causing nasal obstruction and congestion. Although surgery will not eliminate the inflammatory origins of AR, additional patency of the nasal cavity reduces the effects of edematous mucosa. From a surgical standpoint, inferior turbinate reduction is the most beneficial treatment for nasal obstruction in AR refractory to medical therapy.[1552] The inferior turbinate consists of three primary components: a mucosal covering, a submucosal layer (containing the capacitance vessels), and a bony center. Surgery is typically aimed at the submucosa or bone, or total/partial turbinectomy which involves removal of all three components.

The submucosal tissue can be reduced through direct removal (e.g., submucous bony resection or microdebrider submucosal resection) or energy applied to damage tissue with subsequent remodeling (e.g., cautery, radiofrequency, laser, Coblation™). These various techniques have substantial support in the literature. Mori et al[1556] reported on long term outcomes on patients undergoing submucous bony resection over a 5-year follow-up period and noted a significant improvement in symptoms and nasal allergen responses. Additionally, QOL was enhanced in postoperative patients and maintained long term. Microdebrider submucous reduction targets the cavernous tissue surrounding the bony turbinate. Advantages include real-time suction with precise tissue removal. Compared to submucosal bony resection, data suggests improved mucociliary time due to less tissue trauma.[1557]

Laser turbinate reduction seeks to induce scarring in the submucosa, though the overlying superficial mucosal layer is transgressed in the process. Caffier et al[1558] reported on the effects of diode laser turbinoplasty in 40 patients with AR. Statistically significant improvements occurred in rhinomanometry and nasal obstruction, rhinorrhea, sneezing, and nasal pruritus. The improvement in nasal obstruction was sustained at 2 years.[1558]

In radiofrequency ablation (RFA) for nasal obstruction, a probe is inserted directly into the inferior turbinate to deliver a low-frequency energy, causing ionic agitation of tissues.[1559] The thermal effect is limited to the submucosal layer, which preserves surface epithelium and ciliary function.[1560] Following RFA, coagulative necrosis occurs first, with scar contracture and tissue retraction occurring later in the healing process. Over time, portions of the fibrotic scar undergo resorption and the submucosal scar will adhere to the bony periosteum, which reduces turbinate bulk and renders it less susceptible to edema and engorgement.[1560,1561] In the first long term study of its kind, Lin et al[1562] published a report on 101 patients who were followed up to 5 years postoperatively after undergoing RFA turbinoplasty for the treatment of AR. Six-month and 5-year response rates were 77.3% and 60.5%, respectively, and statistically significant improvement was achieved in nasal obstruction, rhinorrhea, sneezing, itchy nose, and itchy eyes.[1562] Coblation™ technology relies on electrodissection by molecular activation. This technology can similarly target the submucosal layers. Siméon et al[1563] investigated the efficacy of Coblation™ on 9 AR patients with a mean age of 12.7 years. Favorable decreases in nasal resistance, pruritus, sneezing, hyposmia, and rhinorrhea were observed and sustained at 6 month follow-up.[1563] RFA and Coblation™ procedures are well-tolerated with minimal adverse effects and can be safely performed in the operating room or the outpatient office setting.

Bony outfracture seeks to shift the bony skeleton of the inferior turbinate laterally into the inferior meatus, thereby creating more breathing space. Aksoy et al[1564] found statistically significant reductions in the distance between the inferior turbinate and the lateral nasal wall after outfracture in 40 patients. This effect was sustained at 6 months postoperatively, which suggests that lateralization persists.[1564] Radical turbinate excision might overcome obstruction, but, at the cost of dryness and possibly empty nose syndrome.[1565]

Vidian neurectomy is an older technique that seeks to damage the parasympathetic nerve impulses to the nasal cavity. Tan et al[1566] found significant improvement in QOL measures in a prospective group undergoing vidian neurectomy over septoplasty/partial turbinectomy or medical management groups. This technique is considered more effective for non-allergic patients and seeks to primarily address severe rhinitis.[1567] Posterior nasal nerve section may also be considered for recalcitrant rhinorrhea; this technique aims to avoid the dry eye complications of vidian neurectomy.[1568]

Recent publications have identified isolated middle turbinate polypoid edema or frank polyps to have a significant correlation with inhalant allergy, especially in more severe cases.[785,786] In cases where the polypoid changes in the middle turbinate are significant enough to cause nasal obstruction, conservative recontouring of the middle turbinate(s) can reduce nasal obstructive symptoms.

To summarize, surgical treatment of the septum, inferior and/or middle turbinates, and possibly vidian/posterior nasal neurectomy may be considered in both allergic and non-allergic patients. Outcomes of these various techniques are variable in patients with AR.

- Aggregate Grade of Evidence: C (Level 1a: 1 study; Level 1b: 1 study; Level 2b: 1 study; Level 3b: 4 studies; Level 4: 5 studies; *Table IX.C.*)
- Benefit: Improved postoperative symptoms and nasal airway.
- Harm: Possible septal perforation, empty nose syndrome, nasal dryness, mucosal damage, epistaxis.
- Cost: Office versus operating room associated procedural costs.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Properly selected patients can experience an improved nasal airway with judicious surgical intervention.
- Policy Level: Option.
- Intervention: Turbinate reduction with or without septoplasty may be considered in AR patients that have failed medical management, and have anatomic features which explain symptoms of nasal obstruction.

Table IX.C. Evidence for surgery in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Jose & Coatesworth[2]	2010	1a	SR of RCTs	Turbinate reduction in refractory AR	No studies qualified as RCT.	No conclusions could be made.
Chen et al[1557]	2008	1b	RCT	AR patients undergoing IT: 1. microdebrider submucous resection 2. bony resection	VAS, anterior rhinomanometry, saccharin transit time	Significant improvement in all parameters for both treatment groups at 1, 2 and 3 years.
Passali et al[1236]	1999	2b	RCT	AR patients undergoing IT: 1. electrocautery 2. cryotherapy 3. laser ablation 4. submucosal resection without lateral displacement 5. submucosal resection with lateral displacement 6. turbinectomy	Rhinomanometry, acoustic rhinometry, mucociliary transport time, secretory IgA levels, symptom scores	Submucosal resection with lateral displacement of the IT results in the greatest increase in nasal airflow and nasal respiratory function with the lowest risk of long-term complications.
Tan et al[1566]	2012	3b	Observational cohort	AR patients undergoing: 1. Vidian neurectomy 2. turbinectomy and/or septoplasty 3. medical treatment	QOL outcomes	All subjects improved, but improvement in Vidian neurectomy group exceeded group undergoing turbinectomy and/or septoplasty.
Kim et al[1555]	2011	3b	Case-control	AR patients undergoing: 1. septoplasty with IT turbinoplasty 2. IT turbinoplasty alone	Mean rescue medication score, Rhinasthma Questionnaire	Significant improvement in both groups but less obstruction in septoplasty group.
Karatzanis et al[1554]	2009	3b	Case-control	Septoplasty in patients with or without AR	NOSE scores, anterior rhinomanometry	Non-AR subjects showed more improvement than AR subjects
Mori et al[1556]	2002	3b	Observational cohort	AR patients undergoing IT submucous turbinectomy	Standard symptom score, rhinometry, nasal challenge	Significant improvement seen at 1 and 3 years.
Caffier et al[1558]	2011	4	Case series	AR patients undergoing mucosal laser reduction, 95% to IT.	Rhinomanometry and VAS	Objective and subjective improvement up to 2 years.
Aksoy et al[1564]	2010	4	Case series	AR patients undergoing IT outfracture	CT sinus at pre-, and 1 and 6 months post-operative	Statistically significant reductions were noted in the angle and distances in all sections.

Lin et al[1562]	2010	4	Case series	AR patients undergoing IT radiofrequency turbinoplasty	Symptoms per VAS	Statistically significant reductions were noted in obstruction, rhinorrhea, sneezing, itching.
Siméon et al[1563]	2010	4	Case series	Children with AR undergoing IT coblation turbinoplasty	Rhinomanometry, VAS, PRQLQ	All improved per PRQLQ.
Li et al[1561]	1998	4	Case series	AR patients undergoing IT radiofrequency turbinoplasty	Questionnaires and VAS	21 of 22 showed improved symptoms at 8 weeks.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; AR: allergic rhinitis: IT: inferior turbinate; VAS: visual analog scale; IgA: immunoglobulin A; QOL: quality of life; NOSE: Nasal Obstruction Symptom Evaluation score; CT: computed tomography; PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire

IX. Management

IX. D. Allergen immunotherapy (AIT)

In addition to allergen avoidance and numerous pharmacotherapy options, AIT is frequently considered in the management of AR. AIT involves scheduled administration of allergen extracts at effective doses with the goal of instituting a sustained immunologic change. AIT effectiveness is often measured through control of allergy symptoms and reduction in allergy medication use. The following section reviews the specifics of allergen extract units and standardization, allergen extract adjuvants and modifications, subcutaneous and sublingual immunotherapy (SCIT, SLIT), as well as less traditional types of immunotherapy.

IX. D. 1. Allergen extract units, potency, and standardization

Historically, allergy testing began with pollen grains placed directly on the conjunctiva,[1569,1570] but as skin testing and SCIT became the diagnostic and immunotherapy treatment methods of choice, injectable allergen extracts were required. Inhaled allergenic particles are composed of a complex heterogeneous mixture of allergenic and non-allergenic proteins and macromolecules. Allergen extracts are created by collecting raw material from a particular species of plant, mold, or animal and then using a solution to extract proteins from the source.[1571]

There are multiple sources of variance in allergen extracts. There is biologic variability in the raw material, and proteins can vary in antigenicity and composition; furthermore, the relative amounts of allergenic proteins may vary.[1572,1573] Impurities in the source materials, such as mold growing on pollen granules or bacteria on cat pelts, may also be immunogenic even if non-viable. Variation occurs in the collection and processing of the raw material.[1573] There is variability in the extraction process with different manufacturers using different techniques including filtration, extraction, sterilization, and preservation.[1571,1572,1574,1575] Only a very small fraction of the proteins extracted are allergenic.[1571] Given that the protein composition of allergen extracts is not known, producing and labeling allergen extracts that are safe and effective is challenging.

Units and potency. Allergen extracts are labeled with an assortment of units that provide an indirect indication of the allergen content of the extract. Most allergen extracts are labeled in units that do not convey information about biological composition or potency. There are multiple types of units that can be grouped into non-standardized, standardized, or proprietary. The difference between standardized and non-standardized extracts is discussed later this section.

Potency of an allergen can have different meanings. Potency sometimes refers to the allergenicity of a source material's proteins or the biologic activity. For example, grass pollens are generally more potent than tree pollens. The typical grass-allergic person would have a larger clinical reaction to grass pollen than a tree-allergic person to the same amount of tree pollen. However, a measure of potency of an allergen extract may also just refer to the strength or concentration measured in units.

Non-standardized allergen extracts. Most allergen extracts available in the US are non-standardized. Allergen extracts are regulated by the Center of Biologics Evaluation and Research under the FDA in the US.[1576] Allergen extracts are required to list the biologic source, a potency unit, and an expiration date.

- Weight/volume (w/v) – Weight/volume refers to the ratio of grams of dry raw material to milliliters of extract solvent. Commonly this is 1/20 w/v, which means that for every 1 gram of raw material (pollen for example) there is 20 mL of extract solvent. This does not provide direct information about the amount of allergenic proteins in the allergen extract nor its biologic activity. However, it implies a reproducible methodology was employed.[1571]
- Protein Nitrogen Units (PNUs) – This is the second most common non-standardized unit currently used in the US. PNU refers to an assay of the precipitable protein nitrogen by phosphotungstic acid which correlates with the total protein. While most of the protein is non-allergenic, the total protein is another method to quantitate an allergen extract's content.[1571]

In Europe, many manufacturers use proprietary units and internal quality controls which must utilize a validated assay.[1572] This European manufacturer-based quality control is known as "In House Reference Preparation".[1573] However, the European Medical Agency has been developing a standardized framework based on protein homology rather than source species.[1577] The EU is also developing additional allergen standards with the WHO starting with Bet v 1 and Phl p 5a.[1577]

Standardized allergen extracts. In the US, standardized allergen extracts are tested by the manufacturer to be within a reference range (70-140%) when compared to a standard provided by the Center of Biologics and Research (US government). The government's standard is referenced to the reactivity in highly allergic individuals creating a standard of biologic activity.

The Center of Biologics and Research creates the standard extract through testing in known "highly allergic" individuals. They use serial intradermal three-fold titrations and measure potency by how many dilutions are needed to produce a flare reaction of a certain size. The size is determined by measuring the largest diameter and adding the length of a line 90 degrees to the largest diameter line. The orthogonal sums are plotted for each dilution and a best fit line drawn. The concentration that corresponds to where the orthogonal sum of the flare is 50mm ($ID_{50}EAL$) determines the units listed in either Allergy Units (AU) or Biologic Allergy Units (BAU). AU is used for dust mites. A mean $ID_{50}EAL$ of 14 3-fold dilutions is defined as 100,000 BAUs/mL and 12 3-fold dilutions 10,000 BAUs/mL.[1577]

The FDA allergen standards are compared to the produced allergen extracts by the manufacturers. The process is different for extracts where the major allergen reactivity correlates with overall allergen reactivity (cat and ragweed) than for extracts that do not have a major allergen that correlates as strongly. A major allergen is defined as a specific protein epitope that more than 50% of individuals allergic to that species react. If there is a major allergen that correlates strongly with the population's clinical reactivity, the manufacturer can compare their extract to the standard extract by gel electrophoresis with the gel having monoclonal IgG antibodies to the major allergen protein. If there is not a single allergen that correlates well with the reactivity of the population, the manufactured extract and the standard are compared through competition ELISA using pooled serum IgE from known

allergic subjects. The manufacturer's extract must fall within a 70-140% range of the FDA's reference.[1576] The amount of major allergen is sometimes listed in mcg/mL, Fel d 1 units (cat), or Antigen E units (ragweed). Standardized inhalant allergens within the United States include cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, short ragweed, and multiple grass species.[1577]

Some allergen extracts in Europe use the Nordic method where 10,000 biologically standardized units/mL is comparable to a skin reaction elicited by 10 mg/mL of histamine.[1577]

In conclusion, an international consensus has not been established for allergen units or standardization of allergen extracts. While standardization and transparent potency assays increase manufacturing costs, it is widely agreed that greater standardization and consistency across manufacturers would be beneficial. Variations in allergen extracts between manufacturers may discourage medical providers from changing between vendors reducing the effect of price on competition. The multitude of allergen extract units and variability also complicates the interpretation and application of published studies between the US, the EU, and other countries. The WHO has identified allergen standardization as a problem and the EU funded a project known as CREATE, "Development of Certified Reference Materials for Allergenic Products and Validation of Methods for the Quantification."[1578] But as of 2017, multiple allergen units are still in use worldwide.

IX. D. 2. Modified allergen extracts

The goal of AIT is to suppress the underlying inflammatory diathesis and induce a state of clinical tolerance to the relevant allergen. This thereby attenuates, if not completely arrests, the inflammation that manifests as AR. Traditional AIT with native, unmodified extracts is successful but has several limitations. Immunotherapy can lead to adverse reactions which rarely can be life-threatening. Besides the risks, allergen extracts have significant production costs with limitations of availability and consistency between batches. Variations exist in pharmaceutical-produced native extracts in the allergen amounts, potencies, and immunogenicity of individual allergen molecules that cannot be controlled in the manufacturing process.[1579]

New advances in AIT have focused on redirecting the untoward allergic diathesis through upregulation of T- and B-regulatory cells, restoring the balance between Th2 and Th1 cell subtypes, and establishing T-cell immune tolerance. The use of recombinant-derived allergens, synthetic peptides, allergoids, and adjuvants has been sought to provide safer, more consistent, readily available, and effective allergens compared to commercially available native extracts.[1580-1582] **[Table IX.D.2-1.]**

The laboratory production of allergens allows for modification of extracts and epitope structures that aim to enhance immunogenicity while decreasing the risk of adverse reactions. Clinical studies have reported outcomes for AIT using recombinant-produced molecules, synthetically-produced peptides, and modifications of allergens via allergoids with adjuvant molecules or through denaturing of proteins.

Recombinant allergens. Recombinant-derived allergens are produced by cloning of native allergen proteins with use of recombinant DNA technology. The allergy protein is reverse transcribed to yield a complimentary DNA molecule which can then be transferred into bacteria which produce copies of the

incorporated DNA. This technique allows for controlled production of a high-yield product with consistent structure. Immunotherapy trials with recombinant allergens has been reported for birch pollen and timothy grass pollen. **[Table IX.D.2-2.]** Recombinant birch AIT demonstrated equivalent clinical outcomes to native birch extract and improved symptoms over placebo.[1583-1585] Recombinant timothy grass AIT showed improved outcomes compared to placebo with a good safety profile.[805,1586] Recently, a recombinant peptide carrier fusion grass vaccine has reported positive outcomes with a B-cell epitope-based vaccine for immunotherapy of grass pollen allergy.[798]

- Aggregate Grade of Evidence for birch: B (Level 1b: 3 studies; Level 2b: 1 study).
- Aggregate Grade of Evidence for timothy grass: B (Level 1b: 3 studies).
- These studies of recombinant allergens for birch and timothy grass demonstrate safety and efficacy.

Peptide constructs. Synthetic peptides for immunotherapy are linear fragments of amino acids that correspond to T-cell epitopes. These fragments lack the secondary and tertiary structure that activate IgE receptors, but can induce immunologic tolerance by targeting allergen-specific T-cells to induce tolerance. The premise with synthetic peptides is that the lack of IgE activation will eliminate the risk of IgE-mediated adverse reaction while preserving the immunogenicity that leads to desensitization. AIT trials with synthetic peptides have been reported for cat, birch, and ragweed allergens. **[Table IX.D.2-2.]** Overall, studies have shown mixed outcomes from synthetic peptides with some peptide molecules resulting in an increase in late adverse reactions. The recently completed large-scale multicenter field trial (clinicaltrials.gov NCT01620762) with cat peptide failed; however, as of this writing, the HDM peptide study is ongoing.[1587,1588] Newer peptide constructs under investigation include overlapping peptides that reproduce the entire sequence of the naturally-occurring allergen in an attempt to cover all T-cell epitopes and natural peptide fragments that cover a broad panel of epitopes.[1589]

- Aggregate Grade of Evidence for cat: B (Level 1b: 5 studies).
- Aggregate Grade of Evidence for birch: Indeterminate, based on only 1 Level 1b study.
- Aggregate Grade of Evidence for ragweed: B (Level 1b: 1 study; Level 2b: 1 study).

Allergoids and polymerized allergens. Allergoids are chemically modified allergens which were developed for improved immunotherapy protocols via accelerated dosing and decreased side effects. Initial attempts at development of an allergoid by partial denaturing of the allergenic moiety with formalin resulted in reduced allergenicity; however, concurrent reduction in the immunogenicity of the allergoids, as defined by IgG antibody production, was seen.[1590] Studies using a glutaraldehyde-linked polymerization of allergens for grass and ragweed allergens demonstrated efficacy and tolerability.[1591,1592] However, standardization criteria and production factors negatively impacted regulatory approval in the US. Clinical trials for allergoids employing ragweed, grass, and HDM allergens have been reported. Promising early results are seen for these allergoids. In addition, more recent work has focused on depigmented allergoid constructs, which are currently in use in Europe.[1593,1594] **[Table IX.D.2-2.]**

- Aggregate Grade of Evidence for ragweed: B (Level 1b: 1 study; Level 2b: 1 study).
- Aggregate Grade of Evidence for grass: B (Level 1b: 7 studies).
- Aggregate Grade of Evidence for HDM: Indeterminate, based on only 1 Level 2b study.
- Allergoid or polymerized allergen products have been approved in Europe but none has received US FDA approval.

Adjuvant constructs. The addition of molecules (adjuvants) to the native allergen has been attempted to improve desensitization protocols. Alum was the first adjuvant to gain acceptance in AIT. Early studies with alum-precipitated extracts demonstrated an augmented immunologic response. However, alum induced an initial IgE immune response which hindered its therapeutic application.[1595] Clinical trials with adjuvants have been reports for ragweed, grass, and HDM allergens. **[Table IX.D.2-2.]**

Creticos reported the proof-of-concept study for using bacterial DNA (CpG oligonucleotide synthetically derived from mycobacterium bovis) to upregulate an immunostimulatory response to allergen through the corresponding ligand (TLR ligand) on a specific class of regulatory dendritic cells.[1596] The TLR-9 agonist was administered in a 2-year double blind placebo controlled study of ragweed-allergic subjects immunized with a 6-injection regimen administered prior to the initial ragweed season. A similar magnitude of effect versus placebo was observed over both ragweed seasons indicating that the vaccine conferred meaningful long-term efficacy (clinical and immune tolerance) over 2 ragweed seasons.[1596] Subsequent large scale multicenter trials were not able to satisfy regulatory approval requirements and this specific product is not going forward in development.[1597] However, the field of adjuvant approaches to immunization is moving forward.

A TLR-4 adjuvant is also currently in clinical development. This construct is comprised of monophosphoryl lipid A, derived from detoxified lipopolysaccharide of gram negative bacterium (*Salmonella minnesota*, a TLR-4 inducing adjuvant), and formulated with pollen allergoids absorbed onto microcrystalline tyrosine. This compound reduces IgE-mediated allergenicity but preserves immunogenicity. A large grass study showed significant improvement in symptom and medication scores versus placebo with subgroup analysis showing greater benefit in patients with more severe symptoms.[1598] An abbreviated ragweed trial showed clinical effect in the primary endpoint versus placebo.[1066]

These studies of adjuvant-modified extracts demonstrate potential for improved immunotherapy protocols; however, several challenges remain. Each of the modified extracts requires robust clinical outcomes data to demonstrate short and long-term improvement in both efficacy and safety over conventional allergenic extracts.

- Aggregate Grade of Evidence for ragweed: B (Level 1b: 3 studies).
- Aggregate Grade of Evidence for grass: B (Level 1b: 2 studies).
- Aggregate Grade of Evidence for HDM: Indeterminate, based on only 1 Level 2b study.

In summary, a wide variety of immunotherapeutic agents are currently undergoing clinical development with the goal of improving safety and achieving immune tolerance with long-lasting

therapeutic efficacy. This new generation of vaccines includes recombinant allergens, peptide constructs, allergoids/polymerized allergens, and adjuvant constructs – each of which must undergo rigorous clinical evaluation to demonstrate acceptable safety and meaningful clinical outcomes that meet regulatory guidelines for approval. For some of the studied preparations, there appears to be improvement over placebo and comparable outcomes to native allergens. The TLR-9 agonist trial showed 2 years of efficacy post discontinuation of drug. However, some peptide molecules demonstrated increased late reactions as well as mixed clinical outcomes depending on the preparation. Allergoids, adjuvants, and peptides have also shown efficacy in multi-year clinical trials. There is insufficient evidence to make recommendations based on the low number of studies for each preparation and lack of long-term outcomes, as no study has examined outcomes for longer than a 2-year period.

Table IX.D.2-1. Modified allergen immunotherapy constructs*

Injectable Immunotherapy Approaches
Recombinant Allergens (SQ)
Peptide Constructs (ID)
Chemical modifications (SQ)
Alum salts (SQ)
Allergoids / Polymerized allergens
Adjuvant Constructs (SQ; IM)
DNA Vaccines
TLR-9 (CpG oligonucleotides) (SQ)
- linked to allergen; co-combined
- Nanoparticle-based VLPs (Viral-like particles)
TLR-4 (MPL) (SQ)

SQ: subcutaneous; ID: intradermal; IM: intramuscular; TLR: toll-like receptor; CpG: cytosine phosphorylated to guanine; VLP: viral-like particles; MPL: monophosphoryl lipid A. *Modified and used with permission; from: Creticos PS. Allergen Immunotherapy: Vaccine Modification; Immunol Allergy Clin N. Am. 2016 (36); 103-124.

Table IX.D.2-2. Evidence for the use of recombinant, peptide, allergoid/polymerized, and adjuvant allergen immunotherapy

Recombinant Allergens						
Study	**Year**	**LOE**	**Study design**	**Study groups**	**Clinical endpoint**	**Conclusion**
Zieglmayer et al[798]	2016	1b	RDBPCT	1. recombinant peptide vaccine with grass epitopes at 3 doses 2. control	Total nasal symptoms scores, ocular symptoms, skin tests	Improvement in primary endpoint for two higher doses but not the lower dose.
Nony et al[1584]	2015	1b	RDBPCT	1. 12.5 μg cGMP-grade rBet v 1 SLIT 2. 25 μg cGMP-grade rBet v 1 SLIT 3. 50 μg cGMP-grade rBet v 1 SLIT 4. placebo	Symptom scores, medication scores	SLIT with rBet v 1 resulted in a significant decrease of symptom score and medication score vs placebo.
Meyer et al[1063]	2013	1b	RDBPCT	1. rBet v 1-FV in multiple doses 2. placebo	Symptom scores, change in IgG1 and IgG4	All dosing regimens were more effective than placebo.
Klimek et al[1585]	2012	1b	RDBPCT	recombinant timothy grass antigens (Phl p 1, Phl p 2, Phl p 5a, Phl p 5b, Phl p 6) 1. Study groups: 20 μg, 40 μg, 80 μg, 120 μg protein 2. placebo	Primary: systemic allergic reactions. Secondary: Improvement in symptoms, conjunctival provocation test	Recombinant allergens safe and effective even at high protein levels.
Pauli et al[1583]	2008	1b	RDBPCT	1. recombinant birch pollen allergen 2. licensed birch pollen extract 3. natural purified birch pollen allergen 4. placebo	Symptoms, immunologic markers	Recombinant allergens were safe and effective for 2 seasons.
Jutel et al[1586]	2005	1b	RDBPCT	1. recombinant timothy grass antigens (Phl p 1, Phl p 2, Phl p 5a, Phl p 5b, Phl p 6) 2. placebo	Symptoms, medication use, RQLQ, immunologic markers, conjunctival provocation test.	Recombinant allergens safe and effective over two grass seasons.
Klimek et al[805]	2015	2b	Open RCT	1. recombinant birch extract (rBet v 1-FV) 2. native birch extract	Symptom scores, IgG levels	Both were safe and equally efficacious over 2 seasons.
Peptide Constructs						
Study	**Year**	**LOE**	**Study design**	**Study groups**	**Clinical endpoint**	**Conclusion**
Spertini et al[1589]	2016	1b	RDBPCT	1. Bet v 1-derived contiguous overlapping peptides 50 μg 2. Bet v 1-derived contiguous overlapping peptides 100μg 3. placebo	Combined rhinoconjunctivitis symptom and medication scores, QOL	Improved symptom, medication, and QOL scores in both treatment groups vs placebo.

Couroux et al[1599]	2015	1b	RDBPCT	1. Cat-PAD 8 doses 3 nmol 2. Cat-PAD 4 doses 6 nmol 3. control	Rhinoconjunctivitis symptom scores 2 years after start of treatment, symptom scores after challenge	Significant reduction in symptoms was observed in the 6 nmol dose group but not the other groups.
Patel et al[1065]	2013	1b	DBPCT	1. Fel d 1-derived peptide 8x3nmol 2 weeks apart 2. Fel d 1-derived peptide 4x6nmol 4 weeks apart 3. 8x placebo	Total rhinoconjunctivitis score at 20 weeks and 52 weeks	Durable treatment effect at 1 year with best regimen 4x6nmol at 4 weeks apart.
Purohit et al[1600]	2008	1b	DBPCT	1. pre-seasonal Bet v 1 primer 2. pre-seasonal Bet v 1 fragments 3. placebo control	Primary: symptom medication scores. Secondary: skin and nasal sensitivities, immunoglobulins, adverse reactions.	No significant difference in symptom and medication scores between the groups.
Oldfield et al[1601]	2002	1b	RCT	1. Fel d 1 peptide 90 μg 2. placebo	Development of late respiratory reaction	Increase in late respiratory reaction with treatment. Tolerance may develop with continued treatment.
Maguire et al[1602]	1999	1b	RCT	1. 75 μg /dose SC Allervax Cat peptide 2. 750 μg /dose SC Allervax Cat peptide 3. placebo	Improvement in pulmonary function, adverse events	Improvement in pulmonary function. Increased incidence of late adverse reaction.
Norman et al[1603]	1996	1b	RDBPCT	1. 7.5 μg Allervax CAT peptide 2. 75 μg Allervax CAT peptide 3. 750 μg Allervax CAT peptide 4. placebo	Nose, lung, and symptom scores during live cat exposure	Dose response was observed at highest dose, resulting in the most significant decrease in lung and nasal symptoms upon cat exposure.
Litwin et al[1604]	1991	2b	Placebo controlled trial	1. pre-seasonal ragweed 2. pre-seasonal ragweed peptide fragments 3. histamine placebo control	Symptom-medication scores	Subjects receiving the peptide fragment preparation had improved scores vs other groups.
Allergoids/Polymerized Allergens						
Study	**Year**	**LOE**	**Study design**	**Study groups**	**Clinical endpoint**	**Conclusion**

Klimek et al[1605]	2014	1b	DBPCT	1. cluster immunotherapy with grass/rye polymerized antigen	Combined symptom and medication score, rescue medication use, total rhinoconjunctivitis symptom score	Improvement in symptoms and medication usage compared to placebo.
Pfaar et al[1594]	2013	1b	DBPCT	1. mixed depigmented polymerized birch and grass pollen extract 2. placebo	Combined symptom and medication score	Significant reduction in median combined scores at year 2 compared to placebo.
Pfaar et al[1593]	2012	ib	DBRCT	1. pre-seasonal depigmented polymerized grass pollen SCIT 2. placebo	Combined symptom and medication score	Significantly improved combined scores in peak season at year 2 compared to placebo.
Corrigan et al[1606]	2005	1b	DBPCT	1. pre-seasonal grass pollen allergoid (low dose) 2. pre-seasonal grass pollen allergoid (high dose) 3. placebo	Combined symptom and medication score	Pre-seasonal grass pollen allergoid resulted in significantly improved symptom and medication score compared to placebo.
Bousquet et al[1607]	1990	1b	RDBPCT	1. low-dose grass pollen allergoid 2. high-dose grass pollen allergoid 3. placebo	Symptom and medication scores during pollen season	Significant reduction in symptom and medication scores for both treatment groups compared to placebo.
Bousquet et al[1608]	1989	1b	RDBPCT	1. unfractionated grass pollen allergoid 2. high molecular weight grass pollen allergoid 3. standardized grass pollen extract 4. placebo	Clinical symptoms: rhinitis, conjunctivitis, asthma	High molecular weight and pollen extract were most effective, followed by unfractionated allergoid. All better than placebo.
Grammer et al[1592]	1983	1b	RDBPCT	1. pre-seasonal polymerized whole grass 2. placebo	Blocking antibodies, daily symptom scores	Significant elevations in blocking antibodies and decrease in symptoms scores in treatment group.
Grammer et al[1591]	1982	1b	DBPCT	1. pre-seasonal polymerized ragweed 2. placebo 3. no treatment	IgE and blocking antibodies, daily symptom scores	Significant elevations in blocking antibodies and decrease in symptoms scores in treatment group.

Pfaar et al[1609]	2016	2b	RCT	1. mite allergoid SCIT 6667 AUeq/ml 2. mite allergoid SCIT 20000 AUeq/ml 3. mite allergoid SCIT 50000 AUeq/ml 4. mite allergoid SCIT 100000 AUeq/ml 5.placebo	Clinical response to a titrated nasal provocation test	All doses above 20,000 AUeq/ml showed improved efficacy compared to placebo.
Norman et al[1590]	1981	2b	Open trial	1. allergoid ragweed (formaldehyde treated) 2. allergen ragweed	Daily symptom and medication scores	Significant improvement of allergoid over allergen.
Adjuvant Constructs						
Study	**Year**	**LOE**	**Study design**	**Study groups**	**Clinical endpoint**	**Conclusion**
Patel et al[1066]	2014	1b	RDBPCT	1. four weekly injections of short ragweed pollen allergoid adsorbed to L-tyrosine monophosphoryl lipid A 2. placebo	rhinoconjunctivitis symptoms after exposure in a chamber	Significant improvement in symptom scores in the treatment group.
Dubuske et al[1598]	2011	1b	RCT	1. pre-seasonal grass modified allergen tyrosine adsorbate monophosphoryl lipid A 2. placebo	Symptom and medication scores.	Significant improvement in subjects with severe symptoms and long-standing symptoms with treatment.
Creticos et al[1596]	2006	1b	RDBPCT	1. ragweed Amb a 1- phosphorothioate oligodeoxyribonucleotide conjugate (TLR-9 agonist) 2. placebo	Symptoms, immune changes, adverse reactions	Efficacious, benefits lasted for 2 more seasons.
Tulic et al[1610]	2004	1b	RCT	1. Amb a 1-oligodeoxyribonucleotide conjugate 2. placebo	Primary: symptom and medication scores. Secondary: tissue markers of inflammation.	No difference in primary endpoint after 1 season, chest symptoms were better in the treatment group after the second season.
Drachenberg et al[1611]	2001	1b	RDBPCT	1. pre-seasonal tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing 3-deacylated monophosphoryl lipid 2. placebo	Symptom scores, medication scores, skin reactivity, IgG and IgE antibodies	Significant improvement in nasal, ocular, and combined symptom and medication scores in treatment group.
Senti et al[1612]	2009	2b	Open trial	10 weekly injections of dust mite with A-type CpG oligodeoxynucleotides with virus-like particles	Symptoms, conjunctival provocation, skin prick tests, IgG and IgE levels	Significant reduction in symptoms, improved conjunctival tolerance, increase in IgG, and decreased skin reactivity.

LOE: level of evidence; RDBPCT: randomized double blind placebo controlled trial; SLIT: sublingual immunotherapy; Ig: immunoglobulin; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RCT: randomized controlled trial; QOL: quality of life; DBPCT: double blond placebo controlled trial; SCIT: subcutaneous immunotherapy; TLR: toll-like receptor

IX. D. 3. Subcutaneous immunotherapy (SCIT)

AIT is a treatment for IgE-mediated sensitivity to environmental allergens.[101,1613,1614] SCIT involves the injection of increasing doses of an extract of the allergen in question, followed by repeated injections of the top or maintenance dose for periods of 3-5 years, to reduce symptoms on exposure to that allergen. SCIT has been practiced for over a century using aqueous extracts of the naturally occurring allergens.[1615] SCIT has been shown to be effective for AR, allergic asthma and sensitivity to hymenoptera venom, along with demonstrated benefit in selected patients with AD. Although meta-analyses conclude that AIT is effective, this positive judgment of efficacy (and safety) should be limited to products tested in the clinical trials. It is incorrect to make a general assumption that "AIT is effective" since this may lead to the clinical use of products that have not been properly studied.[1614,1616] However, as currently practiced, SCIT has the drawbacks not only of the prolonged period of treatment and multiple visits to health care facilities but also the ever-present risk of systemic reactions. There are now attempts to overcome these limitations by modifying the native allergens or using recombinant technology to produce extracts that are less reactive with sIgE allowing higher dosing with greater safety and shorter courses of treatment.[1615] *(See Section IX.D.2. Modified Allergen Extracts for additional information on this topic.)*

Two US health care agencies have recently commissioned systematic reviews of the medical literature on the use of AIT in AR.[1617,1618] **[Table IX.D.3-1.]** The National Institute for Health Research commissioned an update of the 2007 Cochrane Review of AIT for SAR[1617] and the Agency for Healthcare Research and Quality commissioned a systematic review of the use of SCIT and SLIT for the treatment of AR and bronchial asthma.[1618] The first of these systematic reviews found highly significant differences in favor of SCIT over placebo for improvement of symptoms and medication use for treatment of AR, as well as for improvement in the rhinitis QOL, all with a p-value of <0.00001.[1617] The second systematic review found high quality evidence for SCIT, compared to placebo, improving rhinitis and rhinoconjunctivitis symptoms and QOL, with moderate quality of evidence for reduction in medication use for treating AR.[1618] A third systematic review using the EBRR methodology found that SCIT for SAR and PAR has Aggregate Grade of Evidence A and recommended SCIT for SAR or PAR patients not responsive to medical therapy, whose symptoms significantly affect QOL.[1619]

A search of the Embase, MEDLINE, and Cochrane Library databases for systematic reviews and randomized controlled clinical trials yielded a recent otolaryngology clinical practice guideline for allergic rhinitis[761] and an International Consensus on Allergy Immunotherapy[1577,1620] as well as 5 double-blind, placebo-controlled trials of SCIT in AR that were published since the previously discussed systematic reviews. **[Table IX.D.3-1.]** All five of these trials were conducted with aldehyde-modified natural pollen extracts (allergoids).[1593,1594,1605,1621,1622] These trials all support the efficacy of SCIT in treating AR.

Patient selection. There are three therapeutic options for patients with AR: avoidance, pharmacotherapy and immunotherapy. The evidence supporting avoidance is reviewed in *Section IX.A.* of this document. Pharmacotherapy is discussed in *Section IX.B.* There are two primary reasons to consider AIT.[101,1623] One is that addition of AIT to pharmacotherapy alone will likely result in a more pronounced decrease of symptoms (even after a short course of AIT). The second relates to the failure of pharmacotherapy to

alter the underlying immunologic process. Patients may choose AIT largely to obtain a lasting benefit, prevent the progression of AR to bronchial asthma, or prevent new sensitizations.[1624-1626]

Contraindications for AIT. The 2015 EAACI Position Paper noted contraindications for instituting SCIT for AR.[1627] Absolute contraindications were poorly controlled or uncontrolled asthma, active autoimmune disorders, and malignant neoplasm. Relative contraindications were partially controlled asthma, autoimmune diseases in remission, cardiovascular disease and use of beta-adrenergic blocking agents. The Allergy Immunotherapy: Practice Parameters 3rd Update, on the other hand, found no substantive evidence that immunotherapy is harmful in patients with autoimmune diseases.[1623] The Practice Parameters also list pregnancy as a contraindication to initiating SCIT.[1623] It may, however, be continued if the patient is on maintenance dosing.

Extracts. In the US most pollen, dander, insect and fungal extracts are available either in a buffered saline with phenol or in 50% glycerin. The exception is those extracts that have been standardized by the US FDA which only come in 50% glycerin. There is one line of alum-precipitated extracts, consisting solely of pollen extracts. In Europe, on the other hand, alum-precipitated extracts are commonly employed and there is increasing use of allergoid extracts consisting of natural allergens partially denatured by mixture with an aldehyde.[1593,1594,1605,1621,1622,1628] *(See Section IX.D.1. Allergen Extract Units, Potency, and Standardization and Section IX.D.2. Modified Allergen Extracts for additional information on this topic.)*

Dosing. The beneficial results of SCIT have been repeatedly shown to be dependent on administering a sufficient maintenance dose of each extract with each maintenance injection.[1609,1629-1631] Reduction of the effective maintenance dose by 90-95% causes partial or complete loss of efficacy.[1632] The results of many double-blind, placebo-controlled studies have been utilized to formulate the recommendations for dosing in **Table IX.D.3-2.**, adapted from the Immunotherapy Practice Parameters 3rd Update.[1623]

Mono- versus polysensitization. In most large studies of AR, 80-85% of the subjects are sensitized to more than one unrelated allergen. Analysis of some of these studies has shown that the polysensitized subjects respond as well to (sublingual) AIT as those with sensitivity only to the administered allergen.[1633] There is no immunological rationale why this should be different in subcutaneous AIT, but this specific question is an important unmet need which should be addressed in future trials.[1634] [28]

Single- versus multiple-allergen AIT. It is the common practice among US allergists to include in their treatment multiple allergen extracts to which the patient is sensitized. A recent survey of 670 patients in 6 practices found a mean of 18 allergen extracts in their treatment.[1635] [29] On the other hand, European guidelines recommend treating with the single most troublesome allergen identified clinically,[1636] or if more than one extract is to be given they should be given at separate sites with at least 30 minutes in between administration.[32] Scientific support for the US allergists' approach of using multiple allergen mixtures for SCIT can be found in four double-blind, placebo controlled studies, two in patients with AR,[1629,1637] one in children with asthma,[1630] and one in patients with both rhinitis and asthma[1638] all of which demonstrated significant improvement in patients receiving mixtures of multiple, unrelated

allergen extracts. However, a recent review concluded that multiallergen immunotherapy in polysensitized patients, whether delivered sublingually or subcutaneously, requires more supporting evidence from well-designed, well-powered double blind, placebo controlled clinical trials to validate its efficacy in practice.[1634]

Mixing. If multiple-allergen mixtures are to be used for SCIT, there are several considerations, in addition to ensuring that each extract in the mixture is at a concentration that will provide an effective dose when delivered with the maintenance injection. These considerations are: 1) avoiding mixing extracts with strong proteolytic activity with extracts whose allergens are susceptible to this activity, 2) paying attention to allergenic cross-reactivity, 3) using preservatives that are appropriate for the allergens.[1632]

All fungal and some insect body extracts (but not US HDM extracts) have strong proteolytic activity to which many pollen, mite and animal dander allergens are susceptible.[1639] Fungal and cockroach extracts should not be mixed, but fungal extracts can be combined.[1640]

Plant pollens contain some allergens that are like the allergens of unrelated plants (pan-allergens) but generally the major allergens are unique. When the appropriate allergens are available in the testing panel, the use of molecular diagnosis or CRD can be of great use in differentiating cross-reactivity due to pan-allergens from that due to multiple related major allergens. *(See Section VIII.F.6. Component Resolved Diagnosis for additional information on this topic.)* When the patient is sensitized to the major allergens of botanically related plants there are two approaches that can be employed.[1641] One approach is to only include the locally most important member of a related group (such as ragweed or northern pasture grasses); the other approach is to use a mixtures of related allergen extracts, but treating it as if it were one allergen.[1641]

Diluents. Diluents containing 50% glycerin are excellent at maintaining extract potency and are used in the US routinely for extracts with high protease activity.[1639,1642] The drawback to using extracts with high glycerin content is that they cause pain when injected.[1633] A phenol-saline extract containing 0.3% human serum albumin is well tolerated and, in the absence of high proteolytic activity, is an excellent diluent that may be used routinely for making dilutions for initiation of SCIT in the US.[1643]

Regimens. For reasons of safety, SCIT is initiated at a dilution of the final dose and built up usually with weekly injections of increasing amounts and concentrations over a period of weeks or even months. Once maintenance doses are achieved, the interval between injections can be increased but usually not beyond 4 weeks with aqueous extracts used in the US,[1623] but up to 4-6 weeks for depot extracts as used in Europe.[1614]

Venue for administering SCIT. SCIT in allergy practices in the US is associated with a rate of severe systemic reactions of 0.1%.[1644] For this reason the Immunotherapy Practice Parameters 3rd Update state that injections should be given only in a medical facility where prompt recognition and treatment of anaphylaxis is assured and patients should remain under observation for at least 30 minutes following the injection.[1623] This is in line with the European perspective.[32] There is a company in the US that promotes the practice of home administration of SCIT.[1645] Their protocol calls for administration of

relatively low doses of SCIT several times per week resulting in a cumulative dose that approaches that recommended in the Practice Parameters. However, there is evidence to suggest that it is the size of the individual dose rather than the cumulative amount administered that determines efficacy,[1646] and no blinded studies have been offered to support the efficacy of this low-dose approach.

Accelerated SCIT administration. To shorten the length of the build-up, cluster dosing is sometimes employed. Two or three injections are given on each visit on non-consecutive days, with a 30-minute waiting between injections. If visits are twice weekly, maintenance dosing can be achieved in 4 weeks[1647] or even after a shorter period depending on the product administered and schedule followed.[1648] A retrospective analysis of rates of systemic reactions in a large, multi-physician practice[1649] and a double-blind randomized trial[1650] showed no increase in the rate of systemic reactions in patients, comparing cluster to conventional regimens. Another (open) trial supports these findings.[1651]

Rush regimens administer many injections per day on consecutive days, typically achieving maintenance dosing in one to three days. Even with the use of premedication, there is an increased rate of systemic reactions compared to conventional dosing.[1652]

Mechanism of action. In general, the immunologic response to SCIT involves two sequential steps. The first is a generation of regulatory T-cells secreting IL-10 and TGF-β, leading to a switch from IgE to IgG4 antibody formation.[1653,1654] With continued AIT the Treg response declines and an immune deviation from Th2 to Th1 responses dominates.[1577,1653] *(See Section IV. Pathophysiology and Mechanisms for additional information on this topic.)*

Modification of disease. An advantage of SCIT over pharmacotherapy is that it alters the underlying immunologic response towards that which is seen in non-allergic individuals.[1654] The results of this alteration in the underlying immune response by SCIT can be seen clinically in the reduction in new sensitizations, in the progression from AR to asthma, and in the persisting benefit following an adequate course of therapy.

In children, adolescents and young adults, who are sensitized only to the allergen being administered, the development of new sensitizations is reduced not only during AIT but for several years following completion of the course of AIT.[1625,1626] A similar protective effect has not been demonstrated in patients polysensitized at the initiation of AIT.

SCIT has also been shown to prevent the progression from AR to asthma. Two-hundred five children, sensitized to grass, birch or both, and showing no evidence of asthma during an observational year, were treated with timothy and/or birch SCIT for 3 years, or standard pharmacotherapy alone, and observed for an additional 7 years after completion of SCIT in an open trial.[1624] The risk for developing asthma was significantly reduced at the end of SCIT and persisted for the seven years of follow-up. The database of the German National Health Insurance was used to follow patients with AR without asthma who were or were not placed on AIT in 2006.[1655] During five-year follow-up, those patients who received AIT (90% on SCIT) were significantly less likely to have developed asthma.

Duration of treatment and persistence of treatment effect. Regarding persistence of benefit, a double-blind, randomized study was conducted in patients with AR who had received 3 or 4 years of SCIT with

timothy grass extract.[1656] Subjects were randomized to continue maintenance SCIT or receive placebo for three years. There was no difference in symptom/medication scores over the three grass pollen seasons between those receiving and not receiving timothy extract injections. In another trial, grass SCIT was discontinued in 108 grass sensitive patients who had responded well to the treatment after 3 or 4 years of SCIT.[1657] The patients were followed through up to 4 grass pollen seasons looking for relapse. Approximately 30% relapsed by the third grass pollen season, with few more subsequently relapsing.

In the two studies in the preceding section,[1656,1657] three or four years of SCIT with grass extract induced remissions that persisted in most of the subjects for at least 3 years. There are only a few studies that look at longer or shorter periods of treatment. A study that compared 3- or 5-years of SCIT with HDM extract found significant improvement after 3 years but added clinical improvement in rhinitis after 5 years of SCIT.[1658]

Safety. Information regarding the occurrence of fatal reactions to SCIT was obtained retrospectively by the Immunotherapy Committee of the AAAAI by periodic surveys of its members from 1985 to 2001[1659,1660] and by an on-line website since 2008.[1644] The earlier retrospective surveys suggested that a fatal reaction occurs with every 2 to 2.5 million injection visits.[1659,1660] The on-line survey elicited information on two fatal reactions in 28.9 million injection visits which was thought to represent an improvement due to more careful monitoring of patients with asthma.[1644] The rate of systemic reactions has remained steady with 1.9% of patients experiencing a systemic reaction, most mild, but with 0.08% experiencing a grade 3 and 0.02% a grade 4 reaction.[1644] The occurrence and size of local reactions do not predict the occurrence of a systemic reaction with the next injection.[1661,1662]

Cost effectiveness. SCIT can be administered for 3-5 years with continuing relief of symptoms for years after discontinuation. Pharmacotherapy, on the other hand, must be continued indefinitely, since it has no disease modifying activity. Because of this difference, the initial higher cost of SCIT may be offset by the continuing benefit after it is stopped. This factored into a decision-making analysis that suggested if a patient with SAR requiring nasal steroids 6 months per year is seen before age 41 years, the cost will be less in the long term if they are placed on SCIT.[1663] [62] If the patient has perennial need for nasal steroids, and they are less than 60 years of age, the most cost effective approach is SCIT. Another cost-effectiveness analysis found that SCIT for SAR may be more effective and less expensive than pharmacotherapy from the societal perspective when costs of productivity loss are considered.[1664] A retrospective study compared US Medicaid treated adults and children who were newly diagnosed with AR and were or were not placed on AIT. Eighteen month follow-up revealed 30% and 42% health care cost savings, respectively, in the AIT treated patients.[1665]

- Aggregate Grade of Evidence for SCIT in the treatment of AR: A (Level 1a: 3 recent studies listed; Level 1b: 5 recent studies listed; *Table X.D.3-1.*) Of note, due to the large body of literature supporting SCIT as a treatment for AR, only recent systematic reviews and select double-blind, placebo-controlled RCTs are included in Table X.D.3-1, as these achieve an Aggregate Grade of Evidence of A.

- Benefit: Improvement in symptoms and decreased need for rescue medication. Decreased likelihood of progression from AR to bronchial asthma. Persistent benefit for years after completion of 3-5 years of SCIT.
- Harm: Inconvenience of multiple visits to a medical facility to receive injections. Potential for systemic reactions, including anaphylaxis.
- Cost: Cost for preparation of allergen extract for treatment. Cost of visits to medical facilities to receive injections.
- Benefits-Harm Assessment: Benefit greater than harm for patients who cannot obtain adequate relief with symptomatic treatment and whose symptoms extend more than a few weeks each year.
- Value Judgments: Patients who can obtain adequate relief of symptoms with medication must decide if the short-term increased cost and inconvenience of SCIT is compensated for by the long term persisting clinical benefit and relief from need to take medication. Pharmacoeconomic studies suggest that in the long term, SCIT is cost effective over symptomatic therapy.
- Policy Level: Strong recommendation for SCIT in patients unable to obtain adequate relief with symptomatic therapy.
- Intervention: SCIT should be recommended to the AR patient who cannot obtain adequate relief from symptomatic medication for significant periods of time each year and to those who would benefit from its secondary disease-modifying effects (prevention of bronchial asthma and new sensitization), particularly children and adolescents.

Table X.D.3-1. Recent systematic reviews and selected RDBPCTs for the use of SCIT in allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lin et al[1618]	2013	1a	Systematic review	Rhinoconjunctivitis and/or asthma, adults and children	Efficacy, effectivenss, safety. Symptoms, medication use, QOL.	Rhinitis or rhinoconjunctivitis. - Symptoms (n=1734): Strength of evidence high for SCIT. - Medication use (n=564): Strength of evidence moderate for SCIT. - QOL (n=532): Strength of evidence high for SCIT.
Meadows et al[1617]	2013	1a	Systematic review	SAR, adults and children.	Clinical effectiveness, cost effectiveness. Symptoms, medication use, QOL.	- Symptoms (n=659 active, 525 placebo): SMD -0.65, p<0.00001 favoring SCIT. - Medication use (n=621 active, 483 placebo): SMD -0.55, p<0.00001 favoring SCIT. - QOL (n=955): SMD -0.53, p<0.00001, a 0.74-unit reduction in RQLQ compared with placebo.
Purkey et al[1619]	2013	1a	Systematic review	SAR and PAR, adults and children, level 1b evidence, single-extract AIT	Symptoms, medication use, QOL	SCIT for SAR and PAR has Aggregate Grade of Evidence A. SCIT is recommended for SAR or PAR patients not responsive to medical therapy, whose symptoms significantly affect QOL.
Bozek et al[1622]	2016	1b	RDBPCT	SAR (n=55), age 65-75 years. Maintenance dose 26.3 µg Phl p 5.	Combined symptom-medication score	Third year combined symptom-medication score reduced 41% from baseline (p=0.004) & 37% versus placebo.
Klimek et al[1605]	2014	1b	RDBPCT	SAR (n=102), age 18-75 years. Maintenance dose 24 µg Gp 1 plus Gp 5.	Symptoms, medication use	Reduction in symptoms: 34% (p=0.004). Reduction in medication use: 40% (p=0.004).
Pfaar et al[1594]	2013	1b	RDBPCT	SAR (n=269), age 12-70 years. Maintenance dose Bet v 1 6.75 µg & Phl p 5 15.75 µg.	Symptom-medication score	Symptom-medication score reduced for grass & birch pollen seasons: 1st year 21% (NS), 2nd year 19.4% (p=0.0385).
Rajakulasingam[1621]	2012	1b	RDBPCT	SAR (n=37), ages 22-54 years. Maintenance dose 25.2 µg group 5.	Symptom improvement from baseline year	Improvement from baseline year of ≥2/10 in symptoms: active 65%, placebo 35% (p=0.024).
Pfaar et al[1593]	2012	1b	RDBPCT	SAR (n=179), age 11-69 years. Maintenance dose 31.5 µg Phl p 5.	Symptom-medication score	Symptom-medication score reduced: 1st year 16% (p<0.01), 2nd year 37% (p<0.01).

RDBPCT: randomized double-blind placebo-controlled trial, SCIT: subcutaneous immunotherapy; LOE: level of evidence; QOL: quality of life; SAR: seasonal allergic rhinitis; SMD: standardized mean difference; RQLQ: Rhinconjunctivitis Quality of Life Questionnaire; PAR: perennial allergic rhinitis

Table X.D.3-2. Recommended dosing for SCIT*

Allergenic extract	Labeled potency or concentration	Probable effective dose range	Range of estimated major allergen content in US licensed extracts
House dust mites: *D. farinae* *D. pteronyssinus*	3,000, 5,000, 10,000, 30,000 AU/mL	500-2,000 AU	10,000 AU/mL 20-160 µg/mL Der p1, Der f 1 2-180 µg/mL Der p 2, Der f 2
Cat hair	5,000, 10,000 BAU/mL	1,000-4,000 BAU	10,000 BAU/mL 20-50 µg/mL Fel d 1
Grass, standardized	100,000 BAU/mL	1,000-4,000 BAU	100,000 BAU/mL 425-1,100 Phl p 5
Bermuda	10,000 BAU/mL	300-1,500 BAU	10,000 BAU/mL 141-422 Cyn d 1 µg/mL
Short ragweed	1:10 w/v, 1:20 w/v 100,000 AU/mL	6-12 µg Amb a 1 or 1,000-4,000 AU	1:10 w/v 300 µg/mL Amb a 1
Acetone precipitated (AP) dog	1:100 w/v	15 µg Can f 1	80-400 µg/mL Can f 1
Nonstandardized dog extracts	1:10w/v to 1:20 w/v	15 µg Can f 1	0.5-10 µg/mL Can f 1
Nonstandardized pollen extracts	1:10 to 1:40 w/v or 10,000 to 40,000 PNU/mL	0.5 of 1:100 or 1:200 w/v	Not available
Nonstandardized fungal, cockroach extracts	1:10 to 1:40 w/v or 10,000 to 40,000 PNU/mL	Highest tolerated dose	Not available

SCIT: subcutaneous immunotherapy; AU" allergy units; BAU: bioequivalent allergy units; w/v: weight by volume

*Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127:S1-55.[1623]

IX. D. 4. Sublingual immunotherapy (SLIT)

SLIT is an alternative application variant of SCIT, which was first practiced over a century ago by Noon et al.[1570,1666] The first double-blind placebo-controlled trial with SLIT wasn't conducted until 1986 by Scadding et al[1667] in London, UK. After that, only several small trials were conducted until the beginning of the new millennium, when several 'big trials' finally demonstrated the clinical efficacy and safety of SLIT. Since then, many high-quality SLIT trials have been reported. As a result, the actual evidence for SLIT appears to be at least as solid as that for SCIT. The literature on SLIT for AR/rhinoconjunctivitis is vast and several good meta-analyses and systematic reviews have been published over the past decade, the decision was made to primarily analyze results from these reviews and to complement them with findings from large randomized trials published during 2016. **[Table X.D.4-1.]**

Efficacy in adults. Most systematic reviews and meta-analyses show a low to moderate efficacy of SLIT over placebo (SMD=0.30-0.50), and this approaches high efficacy with longer treatment[1668] (greater than 12 months' treatment SMD=0.70). It must be considered that all patients, both those in the SLIT and the placebo arms, have open access to rescue medication, and that SLIT results in an efficacy on top of the symptom improvement obtained with rescue medication.

Efficacy in children. Over five years ago, Dutch colleagues analyzed systematic reviews of SLIT in children and concluded that the methodological quality should be improved. They especially questioned the heterogeneity of the included trials and the risk of bias.[1669] Roder et al[1670] also determined in 2008 that there was not enough evidence to support the usefulness of SLIT in children. These flaws have been improved in recent studies. There is strong[1671] evidence that grass pollen SLIT tablets in children reduce symptoms of AR. The evidence for aqueous SLIT is moderate.[1672] The evidence for HDM SLIT is of moderate-low quality.

Efficacy of SLIT over pharmacotherapy. For PAR, SLIT with HDM tablets is more effective than any single pharmacotherapy, including antihistamines, antileukotrienes and INCS.[1673] For SAR grass and ragweed tablet SLIT is almost as effective as INCS and more effective than the other pharmacotherapies.[1673] These data had already been confirmed for the SLIT grass pollen tablets by a previous meta-analysis; in this publication the separate analysis of the 5-grass tablet showed its superiority over all pharmacotherapy treatments.[1332]

Efficacy of SLIT compared to SCIT. Several investigators have tried to compare the efficacy of SLIT against that of SCIT. Most meta-analyses are based on indirect comparisons, as there are only a very few direct head-to-head randomized trials comparing both treatments; therefore, the evidence that SCIT is more effective than SLIT is weak. Also in children, SCIT seems more effective than SLIT, but again the quality of evidence is low.[1672]

Safety. Rare systemic and serious adverse events have been reported with SLIT, but in general, meta-

analyses found SLIT to be safer than SCIT. In the complete data-set of systemic reviews there were 7 reports of the use of epinephrine in the SLIT group and one case of eosinophilic esophagitis with a grass pollen SLIT tablet. There was no administration of epinephrine in trials outside of the US. A 2012 review by Calderon et al[1674] estimated the anaphylaxis rate of SLIT to be 1 per 100 million doses, or 1 per 526,000 treatment years. Grass pollen SLIT tablets are just as safe in AR patients with and without mild asthma.[1675] Starting SLIT in-season appeared to be safe. Although there were 2 serious treatment-related adverse events with co-seasonal SLIT initiation, none required epinephrine administration.[1676] In the US, the FDA requires patients be prescribed an epinephrine autoinjector and the first dose be given in the physician's office for those on SLIT tablets. Continuing AIT during pregnancy did not augment the incidence of adverse outcomes during delivery nor alter the risk of developing atopic disease in the offspring. No conclusion can be drawn regarding the safety of starting SLIT in a pregnant woman, due to lack of cases.[1677]

Preventative effects. There are no systematic reviews specifically addressing the preventative effects of SLIT that fall within the allowable search date range of this ICAR:AR document. The preventative effect SLIT on asthma development was investigated in an open RCT by Marogna et al[1678] involving 216 children treated with SLIT for 3 years. Mild persistent asthma was less common in patient treated with SLIT than patients receiving only pharmacotherapy. In a double-blind RCT involving 812 children with grass pollen-induced rhinoconjunctivitis, after 3 years of therapy with SQ-standardized grass pollen tablet, children in the treatment group presented a reduced risk of developing asthma compared to placebo group at 2-year follow-up (OR 0.71, $p< 0.05$).[1679] Although these findings are interesting, the overall strength of evidence for the prevention of asthma in SLIT studies is low at present, though the evidence for asthma symptom and medication reduction is high.

Developing new allergen sensitizations frequently occurs in the natural history of respiratory allergy. Preventative effects of AIT on the onset of new sensitizations is often discussed. However, currently available SLIT data for prevention of new allergen sensitivities is also limited. The above referenced Marogna et al[1678] study did note that the rate of new sensitizations was low, corresponding to 3.1% of SLIT treated patients and to 34.8% of controls, with an OR of 16.85 to develop new sensitizations in controls. Another study by Marogna et al[1680] prospectively evaluated the long-term effect of SLIT given for 3, 4, or 5 years in 78 SLIT patients versus 12 controls. Over a 15-year follow-up, all the control subjects developed new allergen sensitivities, while this occurred in less than 25% of the patients receiving SLIT (21% in treated for 3 years, 12%, in treated for 4 years, and 11% in treated for 5 years, respectively).

Cost-effectiveness. The meta-analysis comparing the efficacy and cost-savings of the 5-grass SLIT tablet versus the timothy grass SLIT tablet has several flaws, as some trials were reported in several publications and thus these publications should be analyzed as one. More importantly, the outcome variables and the precise definition of the pollen season vary between the timothy grass SLIT tablet and the 5-grass SLIT tablet trials, so direct comparison of outcomes should not be done, as was reviewed in detail previously.[1681,1682] The 5-grass SLIT tablet ($1003 Canadian dollar) was associated with cost savings against year-round SCIT (+$2471), seasonal SCIT (+$948) and the timothy grass SLIT tablet (+$1168)

during the first year of therapy and still during the second and third year of treatment. The higher costs for SCIT were due to the elevated indirect costs from missing working hours and transportation costs due to in-office SCIT administration. The higher costs for the timothy grass SLIT tablet were due to the year-round dosing versus the pre/co-seasonal 6-month total dosing of 5-grass SLIT tablet.

A UK meta-analysis of costs showed that SCIT and SLIT may be cost-effective compared with standard pharmacotherapy for 6 years (when considering a threshold of pound 20,000-30,000 per QALY). The investigators were not able to establish a clear difference between SCIT and SLIT in cost-effectiveness.[1617]

Additional data from double-blind placebo-controlled trials. Some of the most important recent trials with data that add to the already presented systematic reviews are listed here:

- High dose tree pollen aqueous SLIT was effective in reducing symptom-medication scores in children in a high-quality double-blind placebo-controlled trial.[1683]
- Double-blind placebo-controlled trials with ragweed SLIT reduced the combined symptom-medication score when administered as drops[1684,1685] and as tablets, particularly at the high dose.[1686,1687]
- In a small double-blind placebo-controlled trial of moderate-high quality, Alternaria SLIT for AR (and asthma) was shown to be effective in significantly reducing the AR combined symptom-medication score.[1688]
- As for the SLIT HDM tablets, a dose-effect for a reduction in AR symptoms-medication scores has been shown in three double-blind placebo-controlled trials.[1064,1689] One trial demonstrated a significant difference and a symptom score reduction of 29% only in those patients with more moderate-severe disease.[799]
- Moderate evidence for efficacy of dual grass pollen-HDM SLIT after 12 months of treatment and 1 year after discontinuation.[1690]
- Multi-allergen SLIT has been tested in a single-center, double-blind, placebo-controlled trial with timothy grass monotherapy, timothy grass plus 9 other pollen allergens, or placebo. Only the timothy grass monotherapy group showed statistically significant improvement in the nasal challenge test, titrated SPT, sIgE (reduction) and IgG4 (increase). Due to very low pollen season, there were no differences in symptom-medication scores between any of the groups.[1691] Additional study on multi-allergen SLIT is needed.

Aggregate grade of evidence and recommendations. In **Table X.D.4-2.** the grade of evidence is shown and how this leads to recommendations in the decision-making concerning SLIT.

- Aggregate Grade of Evidence: A (Level 1a: 10 studies; Level 1b: 3 studies; Level 2a: 11 studies; Level 3a: 1 study; *Table X.D.4-1.*).
- Benefit: SLIT improved patient symptom scores, even as add-on treatment on top of rescue medication. SLIT reduced medication use. The effect of SLIT lasts for at least 2 years after a 3-year course of high dose therapy. Benefit is generally higher than with single-drug

pharmacotherapy; however, it is possibly somewhat less than with SCIT. Although a very recent high-quality head-to-head trial did not show a statistically significant difference in efficacy between SCIT and SLIT, this evidence is not presented here, as the publication date is outside the review period for this manuscript.[797]

- Harm: Minimal harm with very frequent, but mild, local adverse events. Very rare systemic adverse events. SLIT seems to be safer than SCIT.
- Cost: Intermediate, SLIT becomes cost-effective compared to pharmacotherapy after several years of administration. Data on cost of SLIT compared to SCIT is variable.
- Benefits-Harm Assessment: Benefit of treatment over placebo is small, but tangible, and on top of improvement with medication. Lasting effect at least 2 years off treatment. Minimal harm with SLIT, greater risk for SCIT.
- Value Judgments: SLIT improved patient symptoms with low risk for adverse events.
- Policy Level:
    - Use of SLIT: grass pollen tablet, ragweed tablet, HDM tablet, tree pollen aqueous solution – Strong recommendation.
    - Alternaria SLIT – Recommendation.
    - Epithelia SLIT – Option.
    - Dual SLIT in bi-allergic patients – Recommendation.
- Intervention: We recommend high dose tablet or aqueous SLIT be administered in patients (adults and children) with SAR and/or PAR who wish to reduce their symptoms and their medication use. SLIT can be continued safely in the pregnant patient.

Table X.D.4-1. Evidence for the use of SLIT in the treatment of allergic rhinitis – systematic reviews and meta-analyses from the last decade*

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion*
Di Bona et al[815]	2015	1a	Meta-analysis of RCTs	SLIT grass pollen tablets vs placebo for SAR	Symptom & medication score	Small improvement in symptom and medication scores vs placebo: (SMD -0.28; CI -0.37 to -0.19; p<0.001) and (SMD -0.24; CI -0.31 to -0.17; p<0.001) Adverse events: 7/2259 SLIT patients were given epinephrine.
Leatherman et al[1692]	2015	1a	Systematic review of RCTs for SLIT doses	SLIT for AR versus placebo	Doses of the effective vs doses of non-effective SLIT	Wide dose ranges between studies. For certain antigens, effective and non-effective dose ranges often overlap. For other allergens: insufficient data.
Devillier et al[1332]	2014	1a	Meta-analysis of RCTs	Pollen SLIT vs pharmacotherapy vs placebo for SAR	Relative clinical impact**	Clinical impact: 5-grass pollen tablet > INCS > timothy grass pollen tablet > montelukast > antihistamines
Makatsori et al[1693]	2014	1a	Systematic review of RCTs	SLIT versus placebo	Drop-out rates in SLIT and placebo groups	No tendency for a skewed drop-out ratio between SLIT and placebo groups. Confirms trial results are unbiased and SLIT appears to be safe.
Meadows et al[1617]	2013	1a	Meta-analysis of RDBPCTs, cost analysis	SCIT and SLIT vs placebo for SAR	Several efficacy variables, costs	Symptom reduction with SCIT and SLIT is greater than placebo.
Lin et al[1694]	2013	1a	Systematic review of RCTs	Aqueous SLIT vs placebo for SAR (and asthma)	Symptom & medication scores	Moderate evidence aqueous SLIT reduces symptoms and medication use in AR/ARC.
Radulovic et al[1695]	2011	1a	Meta-analysis of RDBPCTs	SLIT vs placebo for AR	Symptom & medication scores	SLIT vs placebo: Reduction in symptoms (SMD -0.49) and medication use (SMD -0.32). No epinephrine use.
Di Bona et al[1696]	2011	1a	Meta-analysis of RDBPCTs	Grass pollen SLIT vs placebo for SAR (and asthma)	Symptom & medication scores	SLIT vs placebo: Reduction in symptoms (SMD -0.32) and medication use (SMD -0.33). No epinephrine use.
Durham et al[1673]	2016	1b	Pooled analysis from RCTs	SAR: grass or ragweed SLIT tablet vs. pharmacotherapy. PAR: HDM SLIT tablet vs. pharmacotherapy.	Total Nasal Symptom Score	SAR: SLIT numerically greater than montelukast and antihistamine; almost equal to mometasone furoate INCS. PAR: SLIT effect numerically greater than all pharmacotherapy.

Maloney et al[1675]	2015	1b	Pooled analysis from RCTs	Grass SLIT tablet vs placebo. Grass SLIT in AR patients with (24%) and without (76%) mild asthma.	Treatment related AE frequency	Severe asthma-related adverse events due to treatment in 6/120 SLIT and 2/60 placebo. No difference between the 2 groups. Both adults and children were included.
Creticos et al[1676]	2016	2a	Systematic review	Patients treated with SLIT, started in-season, vs out-of-season vs placebo	Serious treatment-related AE, systemic AE discontinuations	11 SLIT trials (n=2668 subjects total). No epinephrine administration. 0-4% systemic AE with in- vs 0% out-season initiation. 2 serious treatment-related AE with co-season SLIT initiation.
Oykhman et al[1677]	2015	3a	Systematic review of cohort studies	Pregnant women with vs without SLIT or SCIT and their off-spring. 422 pregnancies continuing AIT and 31 starting AIT.	Pregnancy outcome, allergy in offspring	No difference in prematurity, proteinuria, hypertension, congenital malformations, perinatal death. No fetal complications of 10/453 systemic reactions to SCIT. No altered risk of developing atopic disease in off-spring.
SLIT or SCIT: Children only						
Larenas-Linnemann et al[1671]	2013	2a	Systematic review of RCTs	Children with AR and/or asthma treated with SLIT vs placebo/open controls	Symptom & medication scores	Strong evidence that grass pollen SLIT in children reduces symptoms of AR. Moderate-low evidence for HDM SLIT.
Roder et al[1670]	2008	2a	Systematic review of RCTs	Children 0-18 years with AR: any form of AIT vs placebo	Symptom & medication scores	Insufficient evidence that AIT in any form has a positive effect on AR in children.
SLIT versus SCIT						
Chelladurai et al[1697]	2013	1a	Systematic review of RCT	SCIT vs SLIT (and vs placebo) in AR	Symptom & medication scores	Low grade evidence favors SCIT over SLIT for AR symptom & medication reduction. Moderate evidence for nasal & eye symptom reduction.
Di Bona et al[1698]	2012	1a	Meta-analysis based comparison	Grass pollen SCIT – placebo vs grass pollen SLIT – placebo in SAR	SMD of symptom & medication scores	SCIT more effective than SLIT (drops) and SLIT (tablet) for symptom and medication score reduction.
Nelson et al[1699]	2015	1b	Network meta-analysis of RCTs	Grass pollen SLIT tablets vs placebo.	Symptom & medication scores	Symptom and medication scores with SCIT, SLIT tablets and drops all reduced vs. placebo, except for symptom score with SLIT drops.

				Grass pollen SLIT drops vs placebo. Grass pollen SCIT vs placebo.		
Aasbjerg et al[1700]	2015	2a	Systematic review of RCTs, product information, registry	AR patients receiving Phleum pratense SCIT, SLIT drops or SLIT tablets vs placebo. (Including 314 children.)	Safety data	Many products without structured collection of safety data. General safety assessment: SLIT safer than SCIT.
Dranitsaris & Ellis[1701]	2014	2a	Systematic review of RCTs & indirect comparison	Timotht grass tablet, 5-grass tablet, grass pollen SCIT vs placebo in SAR	Efficacy, safety, cost for Canadian setting	Symptoms: all IT treatments better than placebo. Costs for 5-grass tablet greater than costs for timothy grass tablet and SCIT.
Calderon et al[1702]	2013	2a	Systematic review of RCTs	Patients allergic to HDM, with AR and asthma, treated with HDM SCIT vs SLIT vs placebo	Symptom score, IT schedule, dosing	Improved symptom score vs placebo was observed more frequently for SCIT. Data is weak as the basic treatment parameters vary widely.
Dretzke et al[1703]	2013	2a	Systematic review of RCT & indirect comparison	SCIT and aqueous SLIT vs placebo, SCIT vs SLIT in AR	Symptom & medication scores	Trend favoring SCIT over SLIT for AR symptom & medication score reduction. No conclusive results.
SLIT vs SCIT: Children only						
Kim et al[1672]	2013	2a	Systematic review of RCTs & indirect comparison	Children with SAR (asthma): Aqueous SLIT vs SCIT vs placebo for SAR (and asthma)	Symptom & medication scores	In children, moderate evidence that SLIT improves AR symptoms and medication use, low evidence that SCIT is superior to SLIT for both outcomes.
Hoeks et al[1704]	2008	2a	Systematic review of RCTs and OCTs	SCIT vs placebo, SLIT vs placebo in children with asthma/ARC	Symptom & medication scores	Not enough evidence because of poor quality of the studies.

SLIT: sublingual immunotherapy; LOE: level of evidence; RCT: randomized controlled trial; SAR: seasonal allergic rhinitis; SMD: standardized mean difference; CI: 95% confidence interval; AR: allergic rhinitis; INCS: intranasal corticosteroid; RDBPCT: randomized double-blind placebo-controlled trial; SCIT: subcutaneous immunotherapy; ARC: allergic rhinoconjunctivitis; PAR: perennial allergic rhinitis; HDM: house dust mite; AE: adverse event; AIT: allergen immunotherapy
* Only outcomes with statistically significance are mentioned here.
** Clinical impact score = season-long nasal or total symptom scores: 100 x (scorePlacebo – scoreActive)/scorePlacebo

Table X.D.4-2. Aggregate grades of evidence for specific SLIT issues

Issue	Aggregate grade of evidence	Direction of impact	Magnitude of impact*	Recommendation, considering: harm and cost
SLIT is effective for AR symptom reduction in adults	A	Yes	Low impact	Strong recommendation
	LOE: Lin 1a; Radulovic 1a; Di Bona (2 studies) 1a; Nelson 1b; Calderon 2a.			
SLIT is effective for AR symptom reduction in children	B	Yes	Low impact	Recommendation
	LOE: Kim 2a; Larenas-Linnemann 2a. Not enough evidence: Roder 2a.			
SLIT is safe for the treatment of AR in adults	A	Yes	-------	Safety profile is very good
	Many of the systematic reviews (1a and 2a) included safety evaluation. Makatsori 1a: same drop-out rates SLIT vs placebo.			
SLIT is safe for the treatment of AR in children	B	Yes	-------	Safety profile is very good
	The systematic reviews (Kim, Larenas-Linnemann, Roder: all 2a) included safety evaluation. Makatsori 1a: same drop-out rates SLIT vs placebo.			
SCIT is more effective than SLIT	A	Yes	Weak evidence	Recommendation
	LOE: Chelladurai 1a; Dretzke 2a; Calderon 2a; Kim 2a. Grass pollen tablets/drops vs SCIT: Di Bona 2012 1a; SCIT = grass pollen tablets only, drops slightly less effective Nelson 1b.			
SLIT is safer than SCIT	B	Yes	Weak evidence	Recommendation
	LOE: Aasbjerg 2a			
The total cost of SLIT is less than SCIT	A	Yes	Moderate evidence	Recommendation
	LOE: Meadows 1a (UK setting); Dranitsaris 2a (Canadian setting)			
It is safe to continue SLIT during pregnancy	B	No added risk.	Moderate evidence	Recommendation
	LOE: Oykman 3a			
It is safe to start SLIT during the season	B	Sightly added risk.	Moderate evidence	Option
	LOE: Creticos 2a			
Tablet SLIT is more effective than pharmacotherapy. Exception in SAR: INCS are as *efficacious* as tablet SLIT.	A	Yes	Moderate: antihistiamine, montelukast	Recommendation

			Weak: INCS	
	LOE: Devillier 1a (pollen tablet SLIT); Durham 1b (grass pollen or ragweed tablet SLIT).			
SLIT is cost-effective in the 1st year	B	No	Moderate evidence	Option (considering its long-term benefit)
	LOE: Meadows 1a; Dranitsaris 2a			
SLIT is cost-effective after several years of treatment	B	Yes	Weak-moderate	Recommendation
	LOE: Meadows 1a; Dranitsaris 2a			
SLIT has a long-term effect beyond 3-years' application	B	Yes	Moderate evidence	Recommendation
	LOE: Durham 2012[1705] 2b, Didier 2015[1706] 2b			
SLIT with grass-pollen is effective for SAR	A	Yes	Low impact	Strong recommendation**
	LOE: Di Bona (2 studies) 1a; Nelson 1b; Durham 1b.			
SLIT with tree-pollen is effective for SAR	A	Yes	Moderate effect	Strong recommendation**
	LEO: Valovirta 2006[1683] 1b			
SLIT with ragweed-pollen is effective for SAR	A	Yes	Moderate effect	Strong recommendation**
	LOE: Durham 2016, Nolte 2013, Creticos 2013, 1b (tablet ragweed); Creticos 2014 (drop ragweed); Skoner 2010 (drop ragweed) 1b			
SLIT with HDM is effective for AR	A	Yes	Low impact	Strong recommendation**
	LOE: Nolte 2015, Bergmann 2014, Mosbech 2015 all 1b; Calderon 2a			
SLIT with epithelia is effective for AR	-------	No data	No data	Option
	No separate data in the systematic reviews/meta-analyses; no recent trials			
SLIT with fungi is effective for AR	B	Yes	Weak evidence	Option
	No separate data in the systematic reviews/meta-analyses. Cortellini 2010[1688] 1b			

SLIT: sublingual immunotherapy; AR: allergic rhinitis; LOE: level of evidence; SCIT: subcutaneous immunotherapy; INCS: intranasal corticosteroids; SAR: seasonal allergic rhinitis

* For those variables with meta-analysis: according to Cohen's classification: low impact SMD 0.2-0.5, moderate 0.5-0.8, high above 0.8. For those with only systematic review: strength of evidence.

** considering the added long-term post-treatment effect and the possible preventive effects on the development of asthma and new sensitizations.

IX. D. 5. Transcutaneous/epicutaneous immunotherapy

Transcutaneous or epicutaneous immunotherapy is a non-invasive form of AIT that consists of the application of allergens to the skin. The epidermis is rich in APCs while being less vascularized potentially reducing the risk for systemic reaction.[1707,1708] To improve delivery of antigens through the stratum corneum to the immune cells of the epidermis and dermis, different techniques have been used: scarification or scratching of the skin, tape stripping, microneedle arrays, and sweat accumulation through the application of a patch.[1709] Epicutaneous immunotherapy has recently been investigated in a mouse model using nanoparticles containing an allergen encoding DNA.[1710] Records of allergen administration via the skin date back to 1926, where 29 patients with hay fever received intradermal pollen extract administrations; all benefited after only 3 doses without significant side effects.[1711] The first RCT was in 2009. To date, four clinical trials using this procedure have been published. **[Table IX.D.5.]**

In a single-center, placebo-controlled, double-blind trial, 37 adults with positive SPT and nasal challenge to grass pollen were randomized to treatment with allergen (n=21) or placebo patches (n=16).[1712] Treatment was started one month before the 2006 pollen season. The skin was tape-stripped 6 times; patches were applied weekly for 12 weeks, and removed 48 hours later. Patients were assessed before, at the beginning of, and after the 2006 pollen season, and followed up before (n=26) and after (n=30) the pollen season of 2007. The primary outcome was nasal provocation test with grass extract; secondary outcomes included a rhinitis questionnaire, medication use, and adverse events. In grass immunotherapy treated patients, nasal challenge test scores significantly decreased in the first ($p<0.001$) and second year ($p=0.003$). In placebo-treated patients, scores decreased after year 1 ($p=0.03$), but the effect diminished in year 2 ($p=0.53$). However, the improvement of nasal provocation test scores was not significantly better in the treatment versus placebo groups. Patients in the treatment arm had improvement in subjective symptom scores, both after the pollen seasons of 2006 ($p=0.02$) and 2007 ($p=0.005$). Eczema at the application site was significantly higher in the treatment arm, and there were no serious adverse events.

A second single-center double-blind RCT treated 15 children with grass transcutaneous immunotherapy and 15 children with placebo.[1713] The adhesive patch was placed weekly from February to April 2008, and removed after 24 hours. There were no significant differences in prick tests between groups before and after treatment. Both groups had an increase in symptoms, but the treatment group had lower rhinorrhea, nasal obstruction, dyspnea, and ocular tearing. The treatment group had a significant reduction in antihistamine use ($p=0.019$). There were no systemic or local reactions.

A third single-center, double-blind placebo-controlled trial, published by the same authors enrolled 132 adults with grass pollen allergic rhinoconjunctivitis.[1714] Patients received placebo, low, medium and high dose grass extract treatment (n=33 in each arm). Weekly for 6 weeks, starting one month prior to the initiation of the 2008 pollen season, patches were applied with subsequent removal after eight hours. SPT and conjunctival provocation tests were done at baseline, and after the pollen seasons of 2008 and 2009. Ninety-three of 132 patients were included in the efficacy analysis. The primary endpoint was subjective rhinoconjunctivitis symptoms using a VAS. Five months after application of the first patch, all treatment and placebo groups improved. One year later, only the high-dose treatment group had improved compared to control ($p=0.017$); symptoms were reduced by more

than 30% (2008 pollen season) and 24% (2009 pollen season) compared with placebo. There were no differences in rescue medication use, SPTs or CPTs. Local reactions were more frequent with higher doses and improved with subsequent applications. Systemic reactions leading to discontinuation of treatment occurred in 11 patients (8.3%) within 45 minutes of patch application; reactions were milder (grade 1-2) and did not require treatment with epinephrine.

A fourth single-center, double-blind placebo-controlled trial, published by the same authors enrolled 98 adults with grass allergic rhinoconjunctivitis; 48 received grass patches and 50 received placebo.[1715] Treatment consisted of six weekly patches kept on for 8 hours. After treatment in the year 2009, median rhinitis symptoms improved by 48% in the treatment group versus 10% in the placebo group (p=0.003); a year later, this was 40% compared to 18% for placebo (p=0.43). There was no change in combined symptom and medication scores. CPT scores improved after the first year in the treatment group but not the placebo group. In the first year, allergen-specific IgG4 increased in the treatment group, while allergen-specific IgE decreased in the placebo group; there was no difference in both measures compared to baseline in the second year. Eight systemic reactions led to study exclusion. The authors concluded that this treatment strategy may have a potential role in treating IgE-mediated allergies, but further research was needed to find an optimal regimen that balances efficacy and safety.

- Aggregate Grade of Evidence: B (Level 1b: 4 studies; *Table IX.D.5.*)
- Benefit: Transcutaneous immunotherapy resulted in limited and variable improvement in symptoms, medication use, and allergen provocation tests in patients with AR or conjunctivitis.
- Harm: Transcutaneous immunotherapy resulted in systemic and local reactions. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous immunotherapy.
- Cost: Unknown.
- Benefits-Harm Assessment: There is limited and inconsistent data on benefit of the treatment, while there is a concerning rate of adverse effects. Three out of 4 studies on this topic were published by the same investigators from 2009-2015.
- Value Judgments: Transcutaneous immunotherapy could offer a potential alternative to SCIT and SLIT, but further research is needed.
- Policy Level: Recommend against.
- Intervention: While transcutaneous immunotherapy may potentially have a future clinical application in the treatment of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a significant rate of adverse reactions. Given the above and the availability of alternative treatments, transcutaneous immunotherapy is not recommended presently.

Table IX.D.5. Evidence for the use of transcutaneous/epicutaneous immunotherapy in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Senti et al[1715]	2015	1b	RDBPCT	Adults. 1. grass patches (n=48) 2. placebo patches (n=50)	Subjective symptoms, conjunctival provocation test	Symptom score improved in the treatment arm in year 1, but was not significantly different from control in year 2. Conjunctival provocation improved in the treatment group. Systemic reactions occurred in 7 treatment (14.6%) and 1 control patients.
Senti et al[1714]	2012	1b	RDBPCT	Adults. 1. placebo patches (n=33) 2. low-dose grass patches (n=33) 3. medium-dose grass patches (n=33) 2. high-dose grass patches (n=33)	Subjective symptoms, medication use, SPT, conjunctival provocation test	Symptoms improved only in the highest dose group. There was no difference in medication use, SPT, or conjunctival provocation test. Local reactions were common. Systemic reactions occurred in 8.3% of patients.
Agostinis et al[1713]	2009	1b	RDBPCT	Children. 1. grass patches (n=15) 2. placebo patches (n=15)	SPT endpoint, subjective symptoms, antihistamine use	No difference in SPT endpoint. Treatment group had less rhinoconjunctivitis symptoms and antihistamine use.
Senti et al[1712]	2009	1b	RDBPCT	Adults. 1. grass patches (n=21) 2. placebo patches (n=17)	Nasal provocation test, subjective symptom score	No significant difference in nasal provocation test. Subjective symptoms score improved. More local reactions (eczema) in treatment group.

LOE: level of evidence; RDBPCT: randomized double blind placebo controlled trial; SPT: skin prick test

IX. D. 6. Intralymphatic immunotherapy

Intralymphatic immunotherapy (ILIT) is a novel method for AIT, where allergen is injected directly into lymph nodes.[1716] The major advantages of this route of allergen application are the markedly reduced duration of immunotherapy treatment (both time spent and number of visits) and the much lower amount of allergen required to achieve results. This lower dose of allergen also confers a lower risk of adverse allergic side effects.

Clinical trials have illustrated that a reduction in AR symptoms can be achieved with just three doses of injected allergen, with a dosage interval of one month.[1716-1720] **[Table IX.D.6.]** This contrasts with subcutaneous application, where up to seventy doses may be needed over a five-year period. ILIT involves the injection of allergen directly into inguinal lymph nodes under ultrasound guidance.

Five of the clinical trials published to date have compared ILIT with placebo. In 2008, Senti et al[1716] compared ILIT to SCIT and not to placebo. All trials have used aluminum hydroxide-adsorbed antigen as the vaccine. Most trials[1716,1718-1721] used commercially available grass pollen or birch pollen allergen extract as the antigen. One trial[1717] used recombinant major cat dander allergen fused to a translocation sequence and to part of the human invariant chain generating a modular antigen transporter, or "MAT", vaccine.

The general protocol for administration was three injections with 1,000 standardized quality units (SQ-U) of aluminum hydroxide-adsorbed allergen at four week intervals. Variations to this included a shorter dose interval in one trial[1721] and no translation of allergen quantities into SQ-U in the trial using recombinant major cat dander allergen.[1717]

Of the six trials published thus far, five have demonstrated clinical efficacy and safety.[1716-1720] In total, 127 patients have received active treatment and 45 patients have received placebo. Witten et al[1721] demonstrated immunological changes with ILIT, but no improvement in symptoms. Of note, the dose interval in this trial was shorter than in the trials that demonstrated clinical efficacy, with allergen administered at two-week intervals instead of four-week intervals.

The greatest variation between the trials to date is in the selection of clinical endpoints and the measurement of clinical outcomes, as illustrated in **Table IX.D.6.** All trials have used subjective measures to define clinical endpoints, most commonly in the form of symptom questionnaires.

Given the reduction in treatment duration, allergen dose, financial burden relative to SCIT, and the low risk of adverse effects, ILIT is a promising new therapy for AR. Before ILIT is integrated into clinical practice, a well-designed pharmaco-economic evaluation of ILIT vs SCIT and larger RCTs are needed, as well as further studies investigating the impact of treatment protocol on outcomes.

- Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 4: 1 study; *Table IX.D.6.*)
- Benefit: Reduced treatment period, reduced number of injections, reduced dose of allergen injected, decreased risk of adverse events.
- Harm: Risk of anaphylaxis.
- Cost: ILIT might be associated with reduced costs relative to SCIT (reduced time, reduced financial burden for patients and health care provider). Application requires training.
- Benefits-Harm Assessment: Balance of benefit over harm for ILIT relative to SCIT.

- Value Judgments: ILIT appears to be efficacious in the treatment of AR. Preliminary data indicates that, relative to SCIT, the burden of treatment on the patient and on the health care system is lower.
- Policy Level: Option, pending additional studies.
- Intervention: While the research is promising, further studies are needed before ILIT can be translated into routine clinical practice.

Table IX.D.6. Evidence for the use of intralymphatic immunotherapy in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hylander et al[1719]	2016	1b	RCT, blinded	Birch- or grass-pollen-induced AR (n=36): 1. aluminum hydroxide adsorbed, depot birch- or grass-pollen vaccine 2. placebo	Seasonal allergic symptoms by VAS, safety of injections, nasal symptom score following nasal provocation test, IgE and IgG4 levels, inflammatory cells, rescue medication use	ILIT is effective and safe; results in a marked reduction of seasonal allergic symptoms.
Patterson et al[1720]	2016	1b	RCT, blinded	Adolescents, grass-pollen-induced AR (n=15): 1. aluminum hydroxide-adsorbed grass pollen extract 2. 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[1718]	2013	1b	Pilot study and RCT, blinded	Birch-pollen/grass-pollen-induced AR (pilot n=6; RCT n=15): 1. Three intralymphatic inguinal injections of 1000 SQ-U birch pollen or grass pollen 2. placebo	Seasonal allergic symptoms by VAS, SPT, validated rhinitis QOL questionnaire	ILIT is effective and safe.
Witten et al[1721]	2013	1b	RCT, blinded	Grass pollen-induced AR (n=45): 1. 6 injections of 1000 SQ-U of depot grass pollen extract, minimal interval of 14 days 2. Three injections of 1000 SQ-U followed by 3 placebo injections 3. Six placebo injections	Combined symptom and medication score, global seasonal assessment, RQLQ	ILIT produced immunological changes but no improvement in symptoms.

Senti et al[1717]	2012	1b	RCT, blinded	Cat-dander-induced AR (n=20): 1. MAT-Fel d 1 2. placebo (saline in alum)	Immunological parameters, systemic adverse effects, nasal provocation test, 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[1716]	2008	2b	RCT, open	Grass pollen-induced AR (n=165): 1. Three 0.1-ml injections with 1,000 SQ-U of aluminum hydroxide-adsorbed grass pollen extract injected into lymph node at day 0 and after 4 and 8 weeks 2. 54 subcutaneous injections over 3 years (cumulative dose of 4,031,540 SQ-U).	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.
Schmid et al[1722]	2016	4	Pilot study, open, no control group	Grass-pollen-allergy-induced AR (n=7): 1. Three injections of 1000 SQ-U of allergen, dose interval 23-36 days	Combined symptom and medication score, RQLQ, number of IgE+ and IgE- plasmablasts specific for grass	ILIT may induce allergen specific plasmablasts. Confirms an effect on provocation of mast cells in skin and nasal mucosa during the ensuing winter.

LOE: level of evidence; RCT: randomized controlled trial; AR: allergic rhinitis; VAS: visual analog scale; Ig: immunoglobulin; ILIT: intralymphatic immunotherapy; SQ-U: standardized quality units; SPT: skin prick test; QOL: quality of life; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; MAT: modular antigen transporter

IX. D. 7. Alternative forms of immunotherapy

Oral, nasal, and inhaled (intra-bronchial) AIT represent alternate options for the treatment of AR, with primarily historical significance.[1623] While alternative forms of AIT have been evaluated in an effort to avoid the local discomfort and resource utilization associated with SCIT, the adoption of SLIT has largely replaced these methods.[1623]

Non-injectable, alternative immunotherapies involve the topical absorption of allergen extracts via oral/gastrointestinal, nasal, or inhalational exposures. SLIT, intralymphatic, and epicutaneous routes are reviewed separately in this document. Double-blind placebo-controlled studies have evaluated oral/gastrointestinal immunotherapy for the treatment of birch,[1723] cat,[1724] and ragweed[1725] sensitivity, without a significant decline in nasal symptoms, improvements in provocation testing, or reductions in medication utilization. Additionally, oral/gastrointestinal allergen administration requires extract concentrations approaching 200 times greater than SCIT, and is associated with adverse gastrointestinal side effects.[1623,1724] However, the efficacy of oral/gastrointestinal immunotherapy has been demonstrated for the treatment of food hypersensitivity, where this approach remains investigational.[1726]

Oral mucosal immunotherapy (OMIT) is an alternative form of AIT that is distinctly different from SLIT and oral/gastrointestinal strategies. OMIT utilizes a glycerin-based toothpaste vehicle to introduce antigen to high-density antigen processing oral Langerhans cells in the oral vestibular and buccal mucosa.[1727] Theoretical benefits include induction of immune tolerance with lower antigen concentrations, decreased local side effects and higher adherence versus SLIT.[1728] A recently completed pilot study of OMIT versus SLIT identified clinically meaningful improvements in disease-specific QOL measures with a significant rise in specific IgG4 over the first six months of treatment.[1729] No adverse events were reported, and there were no significant differences between outcome measures for both treatment arms.[1729] Additional study is needed to define the role of OMIT in the treatment of AR.

Local nasal immunotherapy has been established as an effective approach for the treatment of pollen and HDM sensitivity.[1730] However, high rates of local adverse reactions limit patient compliance, with one prior study finding that 43.9% of treated children abandoned this treatment option within the first year of therapy.[1731] High quality studies of inhaled/intra-bronchial immunotherapy for the treatment of AR have not yet been completed, with current studies limited to the treatment of allergic asthma.[1732] In light of these findings, including poor compliance and limited efficacy, oral/gastrointestinal, nasal, and inhaled immunotherapies have limited utility in the current treatment of AR, while OMIT represents an emerging alternative to SCIT and SLIT.

IX. D. 8. Combination omalizumab and subcutaneous immunotherapy

In consideration of combination therapy with concurrent biological omalizumab and AIT, each intervention targeting different mechanisms in the early allergic cascade. AIT desensitizes the body's response to a specific antigen, with alteration of the Th1/Th2 balance and induction of T-cell anergy.[1623] Omalizumab indiscriminately targets the humoral effector of allergic inflammation, with use of a humanized monoclonal antibody to block unbound IgE.[1623] While both modalities have independently demonstrated efficacy as treatment options for PAR, improved strategies are needed, especially in patients with multiple sensitizations.[1733]

Two benefits of combination therapy have been described: decreased incidence of AIT-associated systemic allergic reactions and improved control of AR symptoms.[1400-1402,1734-1736] Anaphylaxis is a persistent concern with AIT, with incidence of reported systemic reactions as high as 65% following rush protocols.[1737,1738] Omalizumab pretreatment has therefore been evaluated as a strategy to improve AIT tolerance, with positive findings. Two multi-center, randomized, placebo-controlled studies have evaluated the incidence of AIT-induced systemic allergic reactions following pretreatment with omalizumab.[1402,1736] **[Table IX.D.8.]** Massanari et al[1736] evaluated 248 patients with moderate persistent asthma receiving omalizumab pretreatment or placebo prior to cluster AIT, an accelerated AIT build-up schedule. A significantly lower incidence of systemic and respiratory-related reactions was reported among the omalizumab group, with an improved likelihood of reaching maintenance therapy compared to the group without preventive treatment with this biological. Casale et al[1402] evaluated 123 adult patients with ragweed induced AR receiving omalizumab prior to one-day rush AIT, finding a 5-fold decreased risk of systemic allergic reactions with omalizumab pretreatment (odds ratio 0.17). Further outcomes included significant improvement in daily symptom scores among patients receiving combination therapy (continued omalizumab + AIT) versus AIT alone. Additional study of AIT for the treatment of food[1739] or insect venom[1740,1741] hypersensitivity has also demonstrated improved safety with omalizumab pretreatment.

The efficacy of combination therapy for the treatment of AR has been further evaluated by several iterative analyses of a single RCT.[1400,1401,1735] Kuehr et al[1400] evaluated 221 adolescents (6-17 years) with moderate to severe AR and sensitization to birch and grass pollen. Using a randomized, controlled design, the effectiveness of combination therapy was evaluated during sequential birch and grass pollen seasons, with comparison of AIT +/- concurrent omalizumab. Significant findings included superiority of combination therapies versus AIT alone, with 48% reduction in symptom load (sum of mean daily symptom severity score plus mean daily rescue medication use) during an entire pollen season and 80% reduction in median rescue medication score. Two additional studies report unique findings generated by this trial.[1401,1735] Rolinck-Werninghaus et al[1401] completed a subgroup analysis of study patients receiving specific AIT +/- concurrent omalizumab during the matched grass season. Results included decreased symptoms scores and rescue medication usage for patients receiving combination versus either therapy alone. Kopp et al[1735] evaluated a subgroup of 92 children, with findings of decreased leukotriene (LTC4, LTD4 and LTE4) release among patients receiving combination therapies following *in vitro* antigen stimulation of collected blood cells. An unrelated study by Klunker et al[1734] provides further evidence for the efficacy of combination therapy, with *in vitro* demonstration of inhibition of allergen-specific IgE binding for 42 weeks after discontinuation of combination therapy

(versus 30 weeks with omalizumab alone).

While a prior study has estimated the cost of omalizumab (1,253 EUR/patient/month) and AIT therapies (425 EUR/patient/year), evaluation of economic and productivity outcomes has not been completed for patients undergoing combination therapy.[1401] Finally, omalizumab has been associated with anaphylactic reactions in 0.09 to 0.2% of patients, with current recommendations to monitor patients for 30 minutes following administration.[1742,1743]

- Aggregate Grade of Evidence: B (Level 1b: 4 studies, plus 2 additional iterative analyses of a parent study; *Table IX.D.8.*)
- Benefit: Improved safety of accelerated cluster and rush AIT protocols, with decreased symptom and rescue medication scores among a carefully selected population.
- Harm: Financial cost and risk of anaphylactic reactions.
- Cost: Moderate to high.
- Benefits-Harm Assessment: Propensity of benefit over harm.
- Value Judgments: Combination therapy increases the safety of AIT, with decreased systemic reactions following cluster and rush protocols. Associated treatment costs and likelihood of systemic reactions must be considered, with greater consideration for omalizumab pretreatment prior to higher-risk AIT protocols. While two high-quality RCTs have demonstrated improved symptom control with combination therapy over AIT or omalizumab alone, not all patients will require this approach. Rather, an individualized approach to patient management must be considered, with evaluation of alternative causes for persistent symptoms, such as unidentified allergen sensitivity. The current evidence does not support the utilization of combination therapy for all patients failing to benefit from AIT alone.
- Policy Level: Option, based on current evidence. However, it is important to note that omalizumab is not currently approved by the US FDA for the treatment of AR.
- Intervention: Omalizumab may be offered as a premedication prior to induction of cluster or rush AIT protocols. Combination therapy is an option for a carefully selected patient with persistent symptomatic AR following AIT. An individualized approach to patient management must be considered. In addition, as omalizumab is not currently approved by the FDA for AR treatment, in the US this treatment approach would likely not be performed in routine clinical practice presently.

Table IX.D.8. Evidence for the combination of omalizumab and subcutaneous immunotherapy in the treatment of allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Massanari et al[1736]	2010	1b	RCT	Adults with poorly controlled moderate persistent allergic asthma: 1. omalizumab pretreatment + cluster AIT 2. placebo + cluster AIT	Incidence of systemic allergic reactions	Omalizumab pretreatment is associated with a lower incidence of systemic allergic reactions and higher likelihood of reaching maintenance AIT dose.
Klunker et al[1734^]	2007	1b	RCT	Adults with ragweed induced AR: 1. AIT-ragweed + omalizumab 2. AIT-ragweed alone 3. omalizumab alone 4. placebo	Ragweed hypersensitivity via IgE-FAB assay, allergen-specific IgG4	Combination therapy enhanced the inhibition of sIgE binding for 42 weeks after discontinuation.
Casale et al[1402 ^]	2006	1b	RCT	Adults with ragweed induced AR: 1. omalizumab pretreatment + RIT 2. omalizumab pretreatment + placebo [IT] 3. placebo [omalizumab] + RIT 4. placebo for both interventions	Daily symptom severity, incidence of adverse events	Pretreatment with omalizumab resulted in a 5-fold decrease in risk of RIT associated anaphylaxis. Combination therapy is associated with significant reduction in symptom severity versus AIT alone.
Rolinck-Werninghaus et al[1401 #]	2004	1b	RCT	Subgroup analysis of Kuehr et al[1400] study	Daily symptom severity, rescue medication use	Combination therapy is associated with reduced symptom severity and rescue medication scores.
Kopp et al[1735 #]	2002	1b	RCT	Subgroup analysis of Kuehr et al[1400] study	*In vitro* leukotriene release following antigen stimulation	Combination therapy is associated with reduced leukotriene release following antigen stimulation.
Kuehr et al[1400 #]	2002	1b	RCT	Children and adolescents with SAR and: 1. AIT-birch + omalizumab 2. AIT-birch + placebo 3. AIT-grass + omalizumab 4. AIT-grass + placebo	Daily symptom severity, rescue medication use	Combination therapy is clinically superior to either component monotherapy, with reduced symptom severity and rescue medication scores.

LOE: level of evidence; RCT: randomized controlled trial; Ig: immunoglobulin; AIT: allergen immunotherapy; AR: allergic rhinitis; IgE-FAB: IgE-facilitated allergen binding; sIgE: antigen-specific IgE; RIT: rush immunotherapy; SAR; seasonal allergic rhinitis

^ = Immune Tolerance Network Group; # = omalizumab rhinitis study group

X. Associated conditions

Several medical conditions have been associated with AR, with varying prevalence dependent upon the specific comorbidity. In contrast, certain conditions are often associated with allergy or AR by conjecture, yet the available literature fails to identify a close association. This section examines various medical conditions that have a potential association with AR, specifically examining the evidence that supports or refutes the association

X. A. Asthma

X. A. 1. Asthma definition

Asthma is a heterogeneous and complex disease, perhaps better characterized as a syndrome with overlapping phenotypes. The definition of asthma has evolved over the past several decades, combining clinical symptoms, examination findings and functional parameters. When analyzing current international or national asthma guidelines,[1744-1747] all include respiratory symptoms such as cough, shortness of breath, wheezing or chest tightness and the presence of a variable expiratory airflow limitation that needs to be documented from bronchodilator reversibility testing or bronchial hyper-reactivity tests (e.g. methacholine test or other tests such as inhaled histamine, mannitol, exercise, or eucapnic hyperventilation). All guidelines also include the statement that symptoms and airflow limitation characteristically vary over time and in intensity and may resolve spontaneously or in response to medication. Discussion of chronic airway inflammation is included in all guideline documents. This has been characterized by several important cellular elements including mast cells, eosinophils, T-cells, macrophages, and neutrophils, but none of the guidelines require demonstration of inflammation by invasive or non-invasive methods. The Global Initiative of Asthma guidelines[1744] specify that asthma is *usually* associated with bronchial hyper-responsiveness but highlight that demonstration of airway hyper-responsiveness and inflammation are not necessary or sufficient to make the diagnosis. Asthma is also classified by severity (i.e. mild, moderate, severe) and by persistence (i.e. intermittent vs persistent); however, the specific definitions of these categories vary dependent upon the specific guideline. Since asthma is defined as a heterogeneous disease, or rather as a syndrome, there appear to exist significant and variable etiologies that may manifest in similar phenotypes. Consequently, in the last decade, the definition of asthma has sought to include recognizable clusters of clinical and/or pathophysiological characteristics to more accurately characterize endotypes that exist.[1748,1749]

X. A. 2. Asthma association with allergic and non-allergic rhinitis

Most patients with asthma (both allergic and non-allergic) also have rhinitis, whereas 10% to 40% of patients with AR have comorbid asthma.[101,1167] Asthma and allergy may have similar underlying pathogenesis and immunologic mechanisms. IgE-mediated inflammation can involve both the upper and lower airways, suggesting an integration of the involved areas of the airway. This pattern of similarities gave rise to the concept of the unified airway model, which considers the entire respiratory system to

represent a functional unit that consists of the nose, paranasal sinuses, larynx, trachea, and distal lung.[1750]

Some, but not all, studies suggest that asthma is more common in patients with moderate-to-severe persistent rhinitis than in those with mild rhinitis.[25,1751-1753] Other large studies found a link between the severity and/or control of both diseases in children and adults.[1754-1758] Adults and children with asthma and documented concomitant AR experience more asthma-related hospitalizations and doctors' visits and also incur higher asthma drug costs than adults with asthma alone.[1759-1764] **[Table X.A.2.]** Concerning changes in prevalence of rhinitis and asthma, some studies have demonstrated a parallel increasing prevalence of asthma and rhinitis,[1765,1766] whereas others have not.[1767-1775] It appears that in regions of highest prevalence, the proportion of subjects suffering from asthma or rhinitis may be reaching a plateau.

Rhinitis and asthma are closely associated and thus AR should be evaluated in asthmatic patients, and likewise, the possibility of a diagnosis of asthma should be evaluated in patients with AR.

- Aggregate Grade of Evidence: C (Level 3b: 7 studies; *Table X.A.2.*).

Table X.A.2. Evidence for the association between asthma, allergic rhinitis and non-allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ohta et al[1754]	2011	3b	Case series	Asthmatic patients (n=26,680)	Rhinitis and asthma diagnosis	Rhinitis is common in asthma and impairs asthma control.
Valero et al[1756]	2009	3b	Case series	Patients with AR (n=3225)	Rhinitis comorbidities	Asthma was influenced by skin sensitization and severity of AR.
Ponte et al[1755]	2008	3b	Case series	Patients with severe asthma (n=557)	Asthma severity	Moderate/severe rhinitis is a strong predictor for greater severity of asthma.
Bousquet et al[25]	2005	3b	Case-control	Patients consulting ENT & allergy specialists for AR (n=591) vs. controls (n=502)	Presence of asthma	Asthma prevalence increases with duration and severity of rhinitis.
Leynaert et al[1753]	2004	3b	Cohort	International cross-sectional study of representative samples of young adults (n=3000)	Rhinitis and asthma diagnosis	Association between asthma and rhinitis was not fully explained by atopy.
Linneberg et al[1752]	2002	3b	Cohort	Follow-up on two occasions eight years apart (n=734)	Rhinitis and asthma in patients sensitized to pollen	AR and allergic asthma are manifestations of the same disease.
Bresciani et al[1757]	2001	3b	Case series	Patients with severe steroid-dependent asthma (n=35)	Sinonasal disease	Frequency of rhinosinusitis in patients with mild-to-moderate or severe steroid-dependent asthma is similar.

LOE: level of evidence; AR: allergic rhinitis; ENT: ear, nose and throat

X. A. 3. Rhinitis as a risk factor for asthma

AR and NAR are risk factors for developing asthma. This has been demonstrated in several large epidemiological studies. **[Table X.A.3.]** The Children's Respiratory Study[597] showed that physician-diagnosed AR during infancy is independently associated with a doubling of the risk of developing asthma at age 11. In children and adults, AR is a risk factor for asthma according to a 23-year follow-up of college students.[1776] These studies were confirmed by other studies.[458,1764,1777-1786] Some of these studies showed that rhinitis is a significant risk factor for adult-onset asthma in both atopic and non-atopic subjects.[1779,1780,1783] Therefore, rhinitis is a risk factor independent of allergy for developing asthma in both adults[1779,1780,1783] and children.[597] In adulthood, the development of asthma in patients with rhinitis is often independent of allergy, whereas in childhood, it is frequently associated with allergy,[597,1785] as almost all asthma in children is allergic.

Asthma and AR also share common risk factors. Sensitization to allergens is probably the most important. Most inhaled allergens are associated with nasal[1787] and bronchial symptoms, but in epidemiologic studies, differences have been observed (e.g. in pollen allergy). Some genetic polymorphisms are different in the case of AR and asthma. Other risk factors for asthma such as gender, obesity, viral infections in infancy, exposure to tobacco smoke (passive smoking or active smoking), diet or stress are not found as common risk factors for AR. Outdoor or indoor air pollution is still a matter of debate as risk factor for AR or NAR.[101] In summary, AR and NAR are risk factors for developing asthma.

- Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 3b: 11 studies; *Table X.A.3.*)

Table X.A.3. Evidence for allergic rhinitis as a risk factor for asthma

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Guerra et al[1779]	2006	2a	Nested case-control study	Longitudinal cohort	Asthma onset	Rhinitis is a significant risk factor for adult-onset asthma in both atopic and non-atopic subjects.
Wright et al[597]	1994	2a	Cohort	Birth cohort	Respiratory symptoms at age 6	Asthma in the child (OR: 4.06, CI: 2.06-7.99)
Ibáñez et al[1764]	2013	3b	Cross-sectional study	Children with AR	Associated diseases	Asthma was present in 49.5% of patients with AR.
Jarvis et al[458]	2012	3b	Cross-sectional study	General population	Self-reported current asthma	Asthma was associated with chronic rhinosinusitis.
Rochat et al[1785]	2010	3b	Cohort	Birth cohort	Wheezing onset	AR is a predictor for subsequent wheezing onset.
Shaaban et al[1783]	2008	3b	Cohort	Population-based study	Frequency of asthma	Rhinitis, even in the absence of atopy, is a powerful predictor of adult-onset asthma.
Shaaban et al[1784]	2007	3b	Cohort	General population	Changes in bronchial hyper-responsiveness in non-asthmatic subjects	AR was associated with increased onset of bronchial hyper-responsiveness.
Burgess et al[1786]	2007	3b	Cohort	General population	Incident of asthma in preadolescence, adolescence, or adult life	Childhood AR increased the likelihood of new-onset asthma
Bodtger et al[1777]	2006	3b	Cohort	Population-based	Rhinitis onset	Asymptomatic sensitization, but not NAR, was a significant risk factor for later development of AR.
Porsbjerg et al[1781]	2006	3b	Cohort	Random population sample	Prevalence of asthma	Presence of bronchial hyper-responsiveness and concomitant atopic manifestations in childhood increase the risk of developing asthma in adulthood.
Toren et at[1780]	2002	3b	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[1778]	2000	3b	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[1776]	2000	3b	Cohort	Follow-up of students	Asthma development	Allergic asthma depends on: elevated IgE, eosinophilia, airway hyper-responsiveness, exposure to allergens, and the predominance of the Th2 pathway of immunologic reactions.

LOE: level of evidence; OR: odds ratio; CI: 95% confidence interval; AR: allergic rhinitis; NAR: non-allergic rhinitis; IgE: immunoglobulin E

X. A. 3. Treatment of allergic rhinitis and its effect on asthma

The 2015 AR clinical practice guideline from the AAO-HNS has highlighted the overlap of AR and asthma, specifically recommending that clinicians should assess for and document associated medical comorbid conditions including asthma.[761] The guidelines also review and consider the impact of comorbid asthma on treatment decisions for AR, though the action statements may not apply to AR with comorbid asthma. However, there is a body of evidence to suggest that AR therapies, including INCS,[1296,1788-1790] oral antihistamines,[1791,1792] LTRAs,[7,1793,1794] and AIT[1672,1788,1795,1796] may benefit both conditions. Some of the most promising results in altering the course of allergic inflammation common to AR and asthma have been seen with AIT.[1678,1797,1798] Given this increased understanding of the relationship between AR and asthma as similar inflammatory processes affecting the upper and lower airways, respectively, the importance of understanding the overlap of AR treatment with the treatment of asthma is increasingly evident. The studies reviewed in this section are limited to prospective randomized trials to minimize inherent biases and weaknesses of retrospective studies.[1794]

Allergen avoidance. Allergen avoidance is often advocated for allergy treatment, specifically for AR and allergic asthma.[7] Despite the intuitive acceptance of this and reasonable biological plausibility, the evidence for benefit of avoidance and environmental control measures in AR with associated asthma is limited. A Cochrane review examining randomized trials of subjects with asthma who underwent chemical or physical methods to reduce HDM allergen found no benefit with these methods.[1799] Single allergen avoidance or elimination plans such as removing or washing pets, mattress coverings, removing carpeting, and use of HEPA filters have shown limited evidence-based clinical benefit for reducing asthma and/or AR symptoms.[101,1799,1800] However, there is theoretical benefit of reducing allergen exposure, a paucity of data on multimodality approaches to reduce allergen load, and minimal negatives to attempting these various techniques; therefore, allergen avoidance could be considered as part of a multifactorial approach in the management of asthma associated with comorbid AR.[1801,1802] *(See Section IX.A. Management – Allergen Avoidance for additional information on this topic.)*

Pharmacotherapy: Oral H1 Antihistamines. We identified 6 RCTs which specifically evaluated oral H_1 antihistamines for the treatment of asthma in the context of coexistent AR. **[Table X.A.3-1.]** There are many oral H_1 antihistamine medications, but cetirizine and loratadine are the two most highly studied second-generation antihistamines used concomitantly in AR and asthma. There is biologic plausibility for a role of antihistamines in the treatment of allergic asthma, as elevated histamine levels after allergen challenge are associated with bronchoconstriction responses in acute asthma episodes. Cetirizine also has bronchodilatory effects which are significant both as monotherapy as well is in combination with albuterol.[1803] Despite improvement in asthma symptoms, objective measures using pulmonary function testing and peak expiratory flow have failed to demonstrate significant improvements.[1804-1806] Alternatively, there is growing evidence that antihistamines may have a preventive effect on the development of asthma in atopic patients, as shown in the Early Treatment of the Atopic Child trial.[1807] Briefly, atopic infants were treated with 18 months of cetirizine and followed for the development of asthma. While analysis of the entire group found no significant difference between cetirizine and placebo treated patients, subgroup analysis revealed approximately 50% reduced risk of developing

asthma among certizine-treated patients with grass pollen and HDM sensitivities. The authors hypothesize that variation in key genes related to histamine regulation may explain these differences.[1807,1808] *(See Section IX.B.1.a. Management – Oral H_1 Antihistamines for additional information on this topic.)*

Pharmacotherapy: Oral Corticosteroids. Oral corticosteroids are an effective component of the asthma treatment algorithm, particularly for cases which are inadequately controlled with bronchodilators and inhaled corticosteroids.[1809] They are also effective for symptoms of rhinitis.[1247] However, oral corticosteroids have significant side-effects, especially with increasing duration of use.[7] Because of the side effect profile associated with these medications, they are not recommended for the routine treatment of AR, and utilization is only recommended for select cases after thorough discussion of the associated risks and benefits. *(See Section IX.B.2.a. Oral Corticosteroids for additional information on this topic.)*

Pharmacotherapy: Intranasal Corticosteroids. In the 1980s, topical INCS were reported to improve asthma symptoms in patients with coexistent AR and asthma.[1364,1810] Since then, it has been shown that very little intranasally administered corticosteroid reaches the lung (approximately 2%), suggesting this effect on the lower airway may be related to its intranasal effects.[1788,1811] We have identified two meta-analyses and 12 RCTs that address this potential "unified airway" effect of INCS on asthma. **[Table X.A.3-2.]** A 2003 Cochrane review evaluated the efficacy of INCS on asthma outcomes in patients with coexistent rhinitis, finding no significant improvement in asthma outcomes with the use of INCS.[1295] Heterogeneity in study designs may have limited the findings of this meta-analysis and explain the discrepancy of the results compared to high-quality RCTs. Alternatively, a 2013 systematic review and meta-analysis of the efficacy of INCS for asthmatics with concomitant AR demonstrated improvements in asthma outcomes with the use of INCS compared to placebo, but a lack of further improvement with INCS as an addition to inhaled corticosteroids.[1296] Interestingly, patients with concomitant AR and asthma who received training on the proper use of INCS and education on the relationship of AR and asthma demonstrated significant reductions in asthma symptoms and albuterol use compared to patients receiving INCS without additional education.[1812] This demonstrates the importance of patient instruction for both therapy evaluation and future trial design. *(See Section IX.B.2.c. Management – Intranasal Corticosteroids for additional information on this topic.)*

Pharmacotherapy: Leukotriene Receptor Antagonists. LTRAs (montelukast and zafirlukast) have demonstrated benefit for the treatment of both asthma and AR, consistent with efficacy in addressing inflammation in the "unified airway".[1813] **[Table X.A.3-3.]** In 2008, the ARIA group reviewed the evidence for effectiveness of montelukast in treating patients with asthma and AR, finding improvement of both nasal and bronchial symptoms as well as reduction of β–agonist use.[101] In fact, the LTRAs are the only class of medications specifically described in the 2008 AR management guide for primary care physicians, and in the full ARIA report, as effective for both asthma and AR.[101,1814] The 2010 ARIA update further supports the recommendation of LTRAs for both AR and asthma, but specifies that LTRAs are not recommended over other first-line therapies for the respective conditions (i.e. it is better to treat asthma and AR with both a nasal and inhaled steroid, than try to treat both with an LTRA). A more

recent review in 2015 also identified some utility of LTRAs for patients with concomitant AR and asthma.[1802] Despite this evidence, the limited additional benefit and added cost leads to a strong recommendation (based on moderate quality evidence) for inhaled glucocorticoids over LTRAs for single-modality treatment of asthma in patients with comorbid AR.[1167] Based on the summarized RCTs, an evidence-based recommendation is made for LTRAs not to be used as monotherapy for AR, but LTRAs may be considered as part of the treatment of comorbid asthma and AR. *(See Section IX.B.4. Management – Leukotriene Receptor Antagonists for additional information on this topic).* **[Table X.A.3-3.]**

Pharmacotherapy recommendations for the treatment of AR with coexisting asthma:

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 23 studies). Antihistamines (Level 1b: 6 studies; *Table X.A.3-1.*). INCS (Level 1a: 2 studies; Level 1b: 12 studies; *Table X.A.3-2.*). LTRA (Level 1b: 5 studies; *Table X.A.3-3.*).
- Benefit: Pharmacotherapy improves subjective and objective severity of asthma in patients with coexistent AR. Patient education and training on medication use improves compliance and benefits for INCS, and likely all patient-administered pharmacotherapy.
- Harm: Pharmacotherapy other than systemic steroids - minimal harm with rare mild adverse events such as drowsiness. No serious adverse events reported in the studies reviewed. Systemic corticosteroids have significant side-effects.
- Cost: Generally low cost for pharmacotherapy.
- Benefits-Harm Assessment: There is a benefit over placebo for asthma treatment, though no significant benefit is seen over standard asthma pharmacotherapy. Risks of routine use of systemic corticosteroids generally outweighs the benefits, though short courses for acute indications (e.g. asthma exacerbation) have a favorable likelihood of benefit relative to harm.
- Value Judgments: Pharmacotherapy for AR may also benefit asthma symptoms and objective parameters of pulmonary function in patients with coexisting asthma and AR, however, the benefit for asthma should be considered a positive side-effect rather than an indication for use as there appears to be limited benefit compared to standard asthma therapy.
- Policy Level: Use of pharmacotherapy other than systemic steroids: Recommended use for optimal control of AR, with potential additional benefit for coexistent asthma, though not recommended for primary intent of asthma treatment. Use of systemic corticosteroid: Not recommended for routine use in AR with comorbid asthma due to unfavorable risk-benefit profile, though certain situations may indicate a short course (e.g. acute asthma exacerbation).

Biologics: omalizumab. Omalizumab is an anti-IgE mAb that binds free-IgE, preventing interactions with high-affinity IgE receptors and resulting in receptor downregulation on inflammatory cells.[1815] Omalizumab has demonstrated effectiveness separately for asthma as well as AR.[1393,1815-1818] Despite a number of studies evaluating omalizumab in AR or asthma,[1815,1819] there is only one double blind RCT which specifically evaluates the efficacy of omalizumab in patients with concomitant moderate-to-severe asthma and persistent AR.[1820] Additionally, another study evaluates omalizumab as an adjunct to SCIT,[1403] with both studies showing a reduction in symptoms as well as an improvement in QOL

measures. **[Table X.A.3-4.]** The 2010 ARIA update makes a conditional recommendation of using a mAb against IgE, such as omalizumab for treatment of asthma in patients with both AR and asthma, where there is a clear IgE-dependent allergic component and failure of other maximal therapy.[1167] Additional biologics, including anti-IL5, anti-IL4, and IL-4 receptor mAbs, are currently in varying stages of development/emergence with positive findings for the treatment of asthma and other atopic diseases. Additional evaluation is needed to further evaluate their role for the treatment of coexistent AR and asthma. *(See Section IX.B.7. Management – Biologics for additional information on this topic.)*

Biologics recommendations for the treatment of AR with coexisting asthma:

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; *Table X.A.3-4.*). Grade A evidence with multiple 1b RCTs and 1a reviews exist for asthma and AR individually, but only one double blind RCT specifically evaluating omalizumab versus placebo in patients with concurrent conditions.
- Benefit: Decreased asthma exacerbations, decreased symptom scores, and improvement in disease-specific QOL in patients with coexisting asthma and AR.
- Harm: There is evidence for acceptable safety for use up to 52 weeks.[1821] Potential longer term harm unknown. Minor events such as mild injection site reactions are reported. Possibility of anaphylaxis.
- Cost: Substantially higher cost than conventional therapy for asthma and AR.
- Benefits-Harm Assessment: Benefits appear to outweigh potential harm for the treatment of more severe/persistent coexistent AR and asthma.
- Value Judgments: Added benefit of omalizumab as therapy for patients with AR and asthma which is uncontrolled despite maximal conventional interventions. However, given the significant increased cost associated with omalizumab, the value of this therapy is likely greatest for patients with severe asthma and symptoms that persist despite usual therapies.
- Policy Level: Omalizumab is recommended for those patients with clear IgE-mediated allergic asthma with coexistent AR who fail conventional therapy. The significant additional cost of this therapy should be considered in evaluating its value.

Allergen immunotherapy. Both SCIT and SLIT have been shown to improve the control of comorbid AR conditions, such as asthma.[1618,1788,1822] **[Table X.A.3-5.]** AIT also appears to prevent the development of asthma.[1678,1797,1798] The efficacy of SLIT for AR has been confirmed by several systematic reviews.[1694,1695,1823] Both SCIT and SLIT have been shown to be efficacious for AR, though there is ongoing debate as to whether one form is superior.[1697,1703] AIT is also thought to help halt the progression of allergic disease, including prevention of new allergic sensitivities and the development of asthma.[1624,1626,1678,1797,1798,1824-1826] AIT also appears to have long lasting effects even after discontinuing treatment, unlike pharmacotherapy. Such promising results have led to a 2010 ARIA update statement recommending both SCIT and SLIT for the treatment of asthma in patients with AR and asthma.[1167] Recent systematic reviews demonstrate that SCIT and SLIT reduce both asthma and rhinitis symptoms, as well as medication use.[1694,1822] These evidence-based reviews also demonstrate strong evidence for the utility of SCIT and SLIT in the treatment of asthma alone in studies that did not specifically address

the condition of combined asthma and AR.[1694,1822] Evidence for AIT (SCIT and SLIT) for asthma in context of comorbid asthma and AR, is reviewed in **Table X.A.3-5.** *(See Section IX.D.Management – Immunotherapy for additional information on this topic.)*

Allergen immunotherapy recommendations for the treatment of AR with coexisting asthma:

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 4 studies; Level 2b: 1 study; *Table X.A.3-5.*)
- Benefit: AIT (both SCIT and SLIT) has demonstrated benefit in concomitant AR and asthma, with decreased symptoms, rescue medication use, and bronchial hyper-responsiveness, as well as reduced development of asthma in patients with AR only.
- Harm: Local site reactions are common and there is potential for anaphylactic events with any form of AIT.
- Cost: Increased cost compared to standard therapy for AR and asthma, though the potential to treat the underlying disease process and prevent progression of disease could reduce long-term costs.
- Benefits-Harm Assessment: Significant evidence to support the use of AIT for patients with AR and asthma, as well as the potential utility of AIT for preventing progression of allergic disease from AR to the development of allergic asthma. Harms are generally limited to minor local reactions, though there is a potential risk of anaphylaxis. Benefits appear to outweigh potential harm, given that anaphylaxis is rare.
- Value Judgments: There appears to be unique value in AIT, as this therapy treats the underlying pathology of AR and asthma, with potential to halt the progression of allergic disease. The unique benefits of this therapy are of value, despite some uncertainty of their true magnitude.
- Policy Level: AIT (SCIT and SLIT) is recommended for treatment of AR with asthma in patients following an appropriate trial of medical therapy, and may also be considered for the benefit of preventing progression of AR to asthma in patients with AR only, and for whom AIT is otherwise indicated.

Table X.A.3-1. Evidence for oral H1 antihistamines for the treatment of asthma in the context of coexistent allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Pasquali et al[1827]	2006	1b	DBRCT	Persistent AR and asthma (n=50): 1. levocetirizine 5mg 2. placebo	Daily rhinitis and asthma symptoms, QOL by Rhinasthma questionnaire and SF-36	Rhinitis and asthma symptoms reduced with levocetirizine. Rhinasthma QOL score reduced with levocetirizine. No differences in SF-36.
Baena-Cagnani et al[1828]	2003	1b	DBRCT	SAR and asthma (n=924): 1. desloratadine 5mg 2. montelukast 10mg 2. placebo	TASS, FEV1, β-agonist medication use	Desloratadine versus placebo: reduction in mean TASS, improvement in FEV_1, reduction in average β-agonist medication use. Desloratadine versus montelukast: No differences.
Berger et al[1829]	2002	1b	DBRCT	AR and asthma (n=326): 1. desloratadine 5mg 2. placebo	TSS, asthma symptom scores, β-agonist medication use	Desloratadine reduced rhinitis symptoms, asthma TSS, and β-agonist medication use
Aubier et al[1804]	2001	1b	DBRCT, crossover	SAR and asthma (n=12): 1. cetirizine 2. placebo	BHR (measured as methacholine PD_{20}). NBI (measured using peak expiratory flow meter and calculated as [oral peak flow – nasal peak flow] divided by oral peak flow).	BHR: increase with cetirizine NBI: reduced with cetirizine compared to placebo at 6 h
Aaronson[1830]	1996	1b	DBRCT	AR and perennial asthma (n=28): 1. cetirizine 20 mg daily 2. placebo	Daily rhinitis and asthma symptoms, medication use, PEFR, PC_{20}, PFTs, asthma management	Cetirizine reduced asthma and rhinitis symptoms. No difference in albuterol use. No difference in PFTs, PC_{20}, and patient PEFRs. No difference in asthma management. *
Grant et al[1831]	1995	1b	DBRCT	AR and asthma (n=186): 1. cetirizine 10 mg daily 2. placebo	Rhinitis and asthma symptoms, pulmonary function by spirometry	Improvement in asthma symptoms with cetirizine. No differences in objective measures.

LOE: level of evidence; DBRCT: double blind randomized controlled trial; AR: allergic rhinitis; QOL: quality of life; SF-36: The Short Form Health Survey; SAR: seasonal allergic rhinitis; TASS: Total Asthma Symptom Severity Score; FEV1: forced expiratory volume in 1 second; TSS: Total Symptom Score; BHR: bronchial hyperresponsiveness; NBI: Nasal Blocking Index; PEFR: peak expiratory flow rate; PC_{20} and PD_{20}: provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV1 (also described as $PD_{20}FEV_1$); PFT: pulmonary function test. *Note small sample size and no power-analysis or sample size calculation which limits interpretation of negative findings.

Table X.A.3-2. Evidence for intranasal corticosteroids for the treatment of asthma in the context of coexistent allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lohia et al[1296]	2013	1a	SR and meta-analysis	18 RCTs (n=2162): 1. INCS spray vs placebo 2. INCS spray plus oral inhaled CS vs. oral inhaled CS alone 3. nasal inhaled CS vs placebo	Asthma symptoms, rescue medication use, FEV1, PEF, PC_{20}, QOL	INCS improved FEV1, PC_{20}, asthma symptom scores, and rescue medication use. No asthma outcome changes with INCS plus oral inhaled CS vs oral inhaled CS alone. Nasal inhaled CS improved PEF.
Taramarcaz & Gibson[1295]	2003	1a	Meta-analysis	14 RCTs with 3 interventions: 1. INCS vs placebo 2. INCS vs conventional asthma treatment 3. INCS plus conventional vs conventional alone	Asthma symptoms and β-agonist use, asthma exacerbation events, QOL, FEV1, PEF, PC_{20}, and PD_{20}, inflammatory markers	Non-significant symptom improvement INCS vs placebo. No difference in FEV1, PEF, PC_{20}, and PD_{20}.
Jindal et al[1832]	2016	1b	RCT, single-blind	AR and asthma (n=120): 1. FP INCS 200µg twice daily 2. montelukast 10mg at night	Symptom scores of rhinitis and asthma, PEF	Reduction in asthma symptom severity score and increased in PEF with FP INCS vs montelukast.
Kersten et al[1789]	2012	1b	DBRCT	AR and mild-to-moderate exercise exacerbated asthma (n=32): 1. fluticasone furoate INCS 2. placebo	Change in exercise induced decrease in FEV1, change in AUC of the FEV1 curve, ACQ score, PAQLQ score, FeNO	Exercise induced decrease in FEV1 reduced with FP. No difference in FEV1, ACQ, PAQLQ, FeNO.
Baiardini et al[1833]	2010	1b	DBRCT	Moderate/severe persistent AR with intermittent asthma (n=47): 1. MF INCS 200 µg per day 2. placebo	QOL by GS; symptom scores; Rhinasthma scores of RAI, LA, and UA[a], rescue asthma medication use	GS score reduction with MF INCS. LA score decreased with MF INCS. No difference MFNS vs placebo for rescue meds
Nair et al[1834]	2010	1b	DBRCT, double-dummy, 3-way crossover	Persistent AR and asthma (n=25): 1. inhaled FP 100 µg, inhaled placebo, placebo nasal spray, 2. inhaled FP 100 µg, inhaled placebo, FP INCS 3. inhaled FP 500 µg, inhaled placebo, placebo nasal spray	Methacholine PC_{20}, FeNO, PNIF, FEV1, asthma and rhinitis QOL	Improvement of PC_{20} in all groups. No PC_{20} improvement with INCS and inhaled steroid vs inhaled FP alone. No change in Asthma QOL. FeNO and PNIF reduced only with INCS.
Agondi et al[1835]	2008	1b	DBRCT	AR and asthma (n=33): 1. Bdp INCS 400 µg per day 2. placebo nasal spray	Rhinitis and asthma symptom scores, rescue medication use, BHR (histamine provocation)	Changes with Bdp INCS vs placebo: asthma symptoms reduced, decrease in rescue medication use, BHR reduced

Pedroletti et al[1836]	2008	1b	DBRCT	Perennial rhinitis and allergic asthma (n=40): 1. MF INCS 2. placebo	FeNO, ECP in nasal lavage, PEF, FEV1	No difference of FeNO for MF INCS vs placebo. Nasal ECP reduced. No difference in PEF or FEV1.
Dahl et al[1837]	2005	1b	DBRCT, double dummy	Pollen-induced AR and asthma (n=262): 1. FP INCS 200 µg daily + inhaled FP 250 µg bid 2. FP INCS + inhaled placebo 3. Intranasal placebo + inhaled FP 4. Intranasal and inhaled placebo	Asthma and AR symptoms, PFTs, methacholine BHR, PEF	Increased PEF for FP INCS + inhaled FP vs other groups. PEF increase for inhaled FP vs no inhaled FP. FEV1 higher with inhaled FP. Increased BHR with FP INCS; no increase with inhaled FP.
Nathan et al[1838]	2005	1b	RCT, plus open-label	SAR and persistent asthma (n=863): 1. FP INCS 200 µg 2. montelukast 10 mg 3. placebo All received inhaled FP-salmeterol.	Daily PEF, daily asthma and AR symptoms, rescue albuterol use	FP INCS improved nasal symptoms. No asthma outcome improvement with FP INCS addition to inhaled FP-salmeterol.
Stelmach et al[1839]	2005	1b	DBRCT	PAR and mild-to-moderate persistent asthma (n=59): 1. Bdp INCS 400 µg + inhaled placebo 2. placebo nasal spray and inhaled Bdp 1,000 µg 3. Bdp INCS 400 µg and inhaled 1,000 µg daily	Asthma and AR symptom scores, PEF, FEV1 and BHR (PC_{20}), proxy indicators of asthma-related morbidity (work absence, emergency department visits, etc)	Reductions of AR and asthma symptoms in all groups. No change PEF or BHR. Increased FEV1 for inhaled Bdp. Asthma morbidity reduced for all
Thio et al[1840]	2000	1b	DBRCT	Two grass pollen seasons of treatment (Season 1, n=21; season 2, n=67): 1. FP INCS 200 µg daily 2. placebo nasal spray 3. Bdp INCS 400 µg	Asthma scores, rescue use of salbutamol, ethacholine PD_{20}, FEV1	No difference in asthma scores or rescue salbutamol for all groups. PD_{20} not significantly different. FEV1 increased with FP and BDP in season 2.
Watson et al[1811]	1993	1b	DBRCT, crossover	AR and controlled asthma (n=21): 1. Bdp INCS 100 µg twice daily, then placebo 2. Placebo nasal spray, then Bdp INCS 100 µg twice daily	Asthma and rhinitis symptoms, PC_{20}, Bdp deposition*	No difference of all asthma symptoms with Bdp. PC_{20} improved with Bdp. Evening asthma symptoms reduced with Bdp.
Corren et al[1788]	1992	1b	DBRCT	Mild SAR and asthma (n=18):	Nasal and chest symptoms, NBI, BHR (PC_{20})	PC_{20} decreased over pollen season with placebo, not Bdp. Morning NBI

				1. Placebo nasal spray (vehicle of Bdp formulation) 2. Bdp INCS		decreased with placebo, improved with Bdp. No difference in symptoms.

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; INCS: intranasal corticosteroid; CS: corticosteroid; FEV1: forced expiratory volume in 1 second; PEF: peak expiratory flow; PC_{20} and PD_{20}: provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV1 (also described as $PD_{20}FEV_1$); QOL: quality of life; AR: allergic rhinitis; FP: fluticasone propionate; DBRCT: double blind randomized controlled trial; AUC: area under the curve; ACQ: Asthma Control Questionnaire; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; FeNO: fraction of exhaled nitric oxide; MF: mometasone furoate; GS: [a]Rhinasthma global summary (GS) includes scores from the three categories of RAI, LA, and UA (RAI: respiratory allergy impact; LA: lower airway; UA: upper airway); PNIF: peak nasal inspiratory flow; Bdp: beclamethasone dipropionate; ECP: eosinophil cationic protein; PFT: pulmonary function test; BHR: bronchial hyper-responsiveness; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; NBI: Nasal Blocking Index. *Radiolabeled Bdp < 2% deposition in lungs, 20%-50% in nasal cavity, and 48%-78% swallowed in 1993 Watson et al. study.

Table X.A.3-3. Evidence for leukotriene receptor antagonists for the treatment of asthma in the context of coexistent allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Katial et al[1841]	2010	1b	RCT	SAR and asthma (n=1385): 1. FP-salmeterol inhaled 100/50 µg twice daily 2. FP-salmeterol inhaled 100/50 µg twice daily + FP INCS 200 µg daily 3. FP-salmeterol inhaled 100/50 µg twice daily + montelukast 10 mg daily 4. montelukast 10 mg daily	PEF, rescue albuterol use, asthma and rhinitis symptoms	No additional improvements in asthma with montelukast plus FP-salmeterol. FP-salmeterol associated with improvement in all outcome measures vs montelukast.
Price et al[1842]	2006	1b	DBRCT Analysis of COMPACT trial data	Asthma symptoms despite inhaled corticosteroid. Subgroup with coexistent AR. (n=889) 1. montelukast + budesonide 2. double dose budesonide	Improvement in morning PEF compared to baseline	Least-squares mean difference of morning PEF greater increase from baseline in montelukast + budesonide vs double dose budesonide. *
Nathan et al[1838]	2005	1b	RCT, plus open-label	SAR and persistent asthma (n=863): 1. FP INCS 200 µg 2. montelukast 10 mg 3. placebo All received inhaled FP-salmeterol.	Daily PEF, daily asthma and AR symptoms, rescue albuterol use	FP INCS improved nasal symptoms. No asthma outcome improvement with FP INCS addition to inhaled FP-salmeterol.
Philip et al[1341]	2004	1b	DBRCT	SAR and asthma (n=831): 1. monelukast 10 mg daily 2. placebo	Rhinitis symptoms, RQLQ, global evaluations of	Global evaluation of asthma by patients and physicians improved with

					asthma, β-agonist medication use	montelukast. Reduction in β-agonist medication use montelukast.
Baena-Cagnani et al[1828]	2003	1b	DBRCT	SAR and asthma (n=924): 1. desloratadine 5mg 2. montelukast 10mg 2. placebo	TASS, FEV1, β-agonist medication use	Montelukast versus placebo: reduction in mean TASS, improvement in FEV_1, reduction in average β-agonist medication use. Desloratadine versus montelukast: No differences.

LOE: level of evidence; RCT: randomized controlled trial; FP: fluticasone propionate; INCS: intranasal corticosteroid; PEF: peak expiratory flow; DBRCT: double blind randomized controlled trial; COMPACT: Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy; AR: allergic rhinitis; SAR: seasonal allergic rhinitis; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; TASS: Total Asthma Symptom Severity Score; FEV1: forced expiratory volume in 1 second

Table X.A.3-4. Evidence for omalizumab for the treatment of asthma in the context of coexistent allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kopp et al[1403]	2009	1b	DBRCT	AR and seasonal asthma. All patients received SCIT. (n=140) 1. SCIT + omalizumab 2. 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, improved QOL by ACQ and AQLQ. No difference in rescue medication use. No difference in FEV1 or mean PEF.
Vignola et al[1820]	2004	1b	DBRCT	Moderate-to-severe persistent AR and allergic asthma (n=405): 1. omalizumab 2. placebo	Asthma exacerbations, disease-specific QOL by AQLQ and RQLQ, rescue medication use, symptom scores, patient and investigator GETE, inhaled corticosteroid use, FEV1, FVC, and morning PEF	Omalizumab: reduced asthma exacerbations; increased AQLQ and RQLQ; reduced asthma symptoms; increased FEV1, FVC, and PEF. No difference in β-agonist use.

LOE: level of evidence; DBRCT: double blind randomized controlled trial; AR: allergic rhinitis; SCIT: subcutaneous immunotherapy; PEF: peak expiratory flow; GETE: Global Evaluation of Treatment Effectiveness; ACQ: Asthma Control Questionnaire; QOL: quality of life; AQLQ: Asthma Quality of Life Questionnaire; RQLQ: Rhinoconjunctivtis Quality of Life Questionnaire; PFT: pulmonary function test; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity

Table X.A.3-5. Evidence for allergen immunotherapy for the treatment of asthma in the context of coexistent allergic rhinitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion

Erekosima et al[1822]	2014	1a	SR	Systematic review of 61 RCTs (26 specifically asthma and rhinitis): 1. SCIT vs placebo 2. SCIT vs pharmacotherapy	1. Asthma and rhinitis/conjunctivitis symptoms 2. Asthma and rhinitis/conjunctivitis medication use 3. Safety of SCIT	1. Symptoms reduced with SCIT[a] 2. Medication use reduced with SCIT[a] 3. Most adverse reactions mild.
Lin et al[1694]	2013	1a	SR	Systematic review of 63 RCTs (SCIT and SLIT). 1. SLIT vs placebo 2. SLIT vs pharmacotherapy	1. Asthma and rhinitis/conjunctivitis symptoms 2. Combined medication use plus symptoms	1. Symptoms reduced with SLIT[b] 2. Medication plus symptom scores reduced with SLIT[b]
Marogna et al[1678]	2008	1b	RCT	Rhintis with/without intermittent asthma (n=216): 1. Pharmacotherapy 2. Pharmacptherapy plus SLIT*	Development of persistent asthma (not at baseline), symptom and medication scores, 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[1798]	2004	1b	RCT	Rhinoconjunctivitis, no asthma (n=97): 1. SLIT, maintenance 3 years 2. Standard symptomatic treatment, no SLIT	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.
Möller et al[1797]	2002	1b	RCT	Rhinoconjunctivitis with or without asthma (n=191): 1. SCIT 2. Control (no injections)	Development of asthma (if none at trial start), BHR by PC_{20}, VAS of symptoms	Asthma incidence greater in controls. BHR improved with SCIT after 1 yr pollen season.
Grembiale et al[1795]	2000	1b	DBRCT	HDM AR and BHR to methacholine (n=44): 1. SCIT 2. placebo	BHR by PD_{20}, serum IgE levels, rescue medicaiton use, additional visits for symptoms, development of asthma	BHR increased with SCIT. No HDM IgE difference. Increased medication use and visits with placebo. No difference of asthma incidence.
Inal et al[1825]	2007	2b	Open, non-randomized, prospective, parallel group	HDM AR and/or mild-to-moderate asthma (n=147): 1. SCIT 2. Medication only	Asthma and rhinitis medication use, positive HDM skin test, development of asthma	Decreased asthma medication use with SCIT. Improved atopy scores with SCIT. Asthma incidence nearly half with SCI.T

LOE: level of evidence; SR: systematic review; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; BHR: bronchia hyper-reactivity; PC_{20} and PD_{20}: provocation 'concentration' or 'dose' of methacholine causing a 20% decrease in FEV1 (also described as $PD_{20}FEV_1$); VAS: visual analog scale; DBRCT: double blind randomized controlled trial; HDM: house dust mite; AR: allergic rhinitis; IgE: immunoglobulin E; [a]Strength of evidence moderate to high, for asthma-focused studies and rhinitis-focused studies, respectively; [b]The strength of evidence is moderate for both comparisons; *SLIT administered as sublingual drops of standardized allergen for a build-up phase and then continued for maintenance phase

X. B. Rhinosinusitis

AR may be associated with rhinosinusitis in several clinical settings. In general, AR is regarded as a disease-modifying factor for rhinosinusitis.[1] Rhinosinusitis may be broadly divided into ARS, RARS, CRSwNP, or CRSsNP. The association between each of these forms of rhinosinusitis with AR will be discussed individually below. Of note, many of these studies used SPT or *in vitro* testing for confirmation of allergic disease. While positive testing does indicate evidence of sensitization, this does not necessarily correlate with allergic nasal disease.[1843] Given the paucity of literature exclusively discussing AR and rhinosinusitis (versus allergy and rhinosinusitis), this literature will be included.

AR is thought to be a potential risk factor for the development of rhinosinusitis in general. Exposure to allergens in allergic patients has been associated with increased eosinophilia in the maxillary sinus.[1844,1845] In addition, the majority of ragweed allergic patients (60%) display abnormal opacification of CT scans of the paranasal sinuses in peak allergic seasons.[1846] These CT findings persist despite symptom resolution outside the allergic season.[1846] These studies do not always delineate whether ARS, RARS, or CRS is the form of rhinosinusitis associated with AR.

Allergic rhinitis and acute rhinosinusitis. In addition to these more general studies, evidence exists to support the concept of an increased risk of ARS with AR. There is a significantly higher incidence of ARS in both children and adult patients with a history of AR.[1847,1848] Children with AR are also more likely to experience orbital complications of ARS compared to those without AR, especially in pollinating seasons.[1849] A mouse model has also shown that ongoing nasal allergy is associated with worsened episodes of ARS.[1850,1851] Available data supports an association between AR and ARS. However, AR is thought to be a disease-modifying or risk-modifying factor rather than a causative one. There are no studies examining the effects of treating AR on the risk of developing an episode of ARS. For example, it is unclear whether treating AR decreases the incidence of ARS. Future study may help clarify the interaction between AR and ARS. **[Table X.B-1.]**

- Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 2b: 1 study; Level 3a: 1 study; Level 3b: 1 study; *Table X.B-1.*).

Allergic rhinitis and recurrent acute rhinosinusitis. The potential link between AR and RARS is an extension of the link between AR and ARS. The increase in sinonasal inflammation associated with AR is proposed to increase mucosal edema, sinus ostium obstruction and the retention of sinus secretions.[1] This environment may support secondary bacterial overgrowth and subsequent ARS or RARS.[1] Two studies have specifically examined the association between RARS and AR, with a focus on potentially altered innate immunity. The results of these two studies are conflicting. One study suggests there is a decrease in the antimicrobial properties of sinonasal secretions in patients with RARS and AR compared to AR only patients as well as control patients.[1852] The second study identified an up-regulation in toll-like receptor 9 expression, suggesting increased resistance to bacterial infection rather than susceptibility.[1853] Further study is required to define the association between AR and RARS. **[Table X.B-2.]**

- Aggregate Grade of Evidence: D (Level 2b: 2 studies; conflicting evidence; *Table X.B-2.*).

Allergic rhinitis and chronic rhinosinusitis without nasal polyposis. CRS is a condition of the sinonasal cavity characterized by persistent inflammation. The cause of the inflammation varies from patient to patient. As AR is a cause of sinonasal inflammation, many have suspected there may be an association with the pathogenesis of CRS. However, there are no controlled studies examining the role of AR in the development of CRSsNP. Additionally, there are no studies showing that the treatment or control of allergic disease alters the progression of CRSsNP, or vice versa.[1] Given the varied pathophysiology of CRSsNP, it is challenging to determine the association between allergy and CRSsNP. Wilson et al[1854] performed a systematic review of allergy and CRS, excluding studies that did not differentiate between CRSsNP and CRSwNP. Their review found four studies that supported an association between allergy and CRSsNP and five that did not.[1854] Because the relationship remains unclear, allergy testing is listed as an option in CRSsNP patients based on the theoretical benefit of identifying and treating comorbid allergic disease.[1,1854] **[Table X.B-3.]**

- Aggregate Grade of Evidence: D (Level 1b: 1 study; Level 3a: 1 study; Level 3b: 8 studies; conflicting evidence; *Table X.B-3.*). Adapted from Wilson et al.[1854]

Allergic rhinitis and chronic rhinosinusitis with nasal polyposis. The pathogenesis of CRSwNP is strongly associated with Th2-mediated inflammation.[1] Additionally, nasal polyps in CRSwNP have high levels of tissue eosinophilia, as well as mast cells and basophils.[1] AR follows a similar inflammatory pathway and this suggests there may be a pathophysiologic similarity between CRSwNP and AR. Wilson et al[1854] examined the association between allergic disease and CRSwNP. Again, the evidence was conflicting. Ten studies supported an association while seven did not. One study had equivocal findings.[1854] Since this review, Li et al[1855] examined the association between atopy and CRSwNP and concluded that there was no correlation between atopy status and disease severity.[1855] They did note that atopy-positive patients were younger than atopy-negative patients.[1855] Despite some overlapping pathophysiologic features between allergic disease and CRSwNP, conflicting evidence exists and there is no clear association between AR and CRSwNP. Allergy testing is once again an option in CRSwNP patients based on the theoretical benefit of identifying and treating comorbid allergic disease.[1,1854] **[Table X.B-4.]**

- Aggregate Grade of Evidence: D (Level 2b: 1 study; Level 3a: 1 study; Level 3b: 15 studies; Level 4: 4 studies; conflicting evidence; *Table X.B-4.*). Adapted from Wilson et al.[1854]

In summary, AR has a moderate level of evidence supporting an association with ARS (Level C). Regarding RARS, CRSsNP and CRSwNP, the preponderance of evidence does not support an association, though the evidence is highly conflicting. The available literature is also limited as it often assumes patients who test positive on allergy testing have nasal allergic disease and may not differentiate between systemic allergy and nasal allergy. Further study is needed to determine the association between AR and rhinosinusitis, as well as the impact treating one process has on the progression of the other. However, the diagnosis and treatment of comorbid allergic disease is an option in rhinosinusitis

patients balancing the cost and low evidence with the low risk of allergic rhinosinusitis treatment and the theoretical benefits of reducing allergic sinonasal inflammation.[1]

Table X.B-1. Evidence for an association between allergic rhinitis and acute rhinosinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Rantala et al[1856]	2013	2a	Cross-sectional	Atopic and non-atopic adults age 21-63 years (n=1008)	Upper and lower respiratory tract infections	Individuals with atopic disease had higher risk of developing URTI, including RS.
Chen et al[1848]	2001	2a	Questionnaire	Children in Taiwan (n=8723)	Rhinosinusitis	Children reporting allergy are more likely to have RS.
Holzmann et al[1849]	2001	2b	Retrospective review	Children with orbital complications of ARS (n=102)	Prevalence of AR	Orbital complications are more common in allergy season.
Frerichs et al[1857]	2014	3a	SR	Allergic and non-allergic patients	Prolonged course (>4 weeks) of RS	No significant increase in prolonged RS in AR patients.
Savolainen[1847]	1989	3b	Case-control	Acute maxillary sinusitis with and without allergy (n=224)	ARS	Prevalence of AR 25% and 16.5% in non-AR patients.

LOE: level of evidence; URTI: upper respiratory tract infection; RS: rhinosinusitis; ARS: acute rhinosinusitis; AR: allergic rhinitis; SR: systematic review;

Table X.B-2. Evidence for an association between allergic rhinitis and recurrent acute rhinosinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Melvin et al[1853]	2010	2b	Prospective cohort	(n=21) 1. allergic patients with RS 2. allergic-only patients	Expression of TLR9 in sinonasal epithelium	Increased expression of TLR9 in allergic patients with RS
Kalfa et al[1852]	2004	2b	Cross-sectional	(n=47) 1. allergic patients with RS 2. allergic-only patients 3. non-allergic controls	Nasal secretion levels of EDN and lysozyme levels	Allergic patients with RS have elevated levels of EDN and decreased lysozyme levels

LOE: level of evidence; RS: rhinosinusitis; TLR9: toll like receptor 9; EDN: eosinophil-derived neurotoxin

Table X.B-3. Evidence for allergic rhinitis and chronic rhinosinusitis without nasal polyposis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Baroody et al[1844]	2008	1b	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[1854]	2014	3a	SR	CRSsNP with or without allergy	Association between CRSsNP and allergy	Conflicting evidence with no clear association.
Tan et al[1858]	2011	3b	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[1859]	2009	3b	Prospective case series	CRSsNP with or without allergy (n=115)	CT scores	No difference in CT scores.
Gelincik et al[1860]	2008	3b	Prospective case series	CRSsNP with or without allergy (n=66)	Prevalence of CRSsNP in allergic and non-allergic rhinitis patients	CRSsNP was equally prevalent in allergic (43%) and non-allergic (50%) rhinitis patients.
Kirtsreesakul & Ruttanaphol[1861]	2008	3b	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[1862]	2006	3b	Prospective case series	CRSsNP with or without allergy (n=193)	Lund-Mackay CT scores and symptoms scores	Allergy was not associated with CT findings or symptoms scores.
Alho et al[1863]	2004	3b	Prospective case series	CRSsNP with or without allergy (n=48)	CT findings during viral URTI, incidence of *S. aureus* sensitization	Allergic patients had higher CT scores and higher incidences of *S. aureus* sensitization.
Van Zele et al[1864]	2004	3b	Prospective case-control	CRSsNP with or without allergy (n=31)	Rates of *S. aureus* colonization	No difference in colonization rates.
Berrettini et al[1865]	1999	3b	Prospective case-control	CRSsNP with or without allergy (n=77)	CT scan findings, nasal endoscopy, nasal swabs, rhinomamometry	Increased CT evidence of sinusitis in allergy (68%) versus non-allergic (33%) patients.

LOE: level of evidence; RCT: randomized controlled trial; CRSsNP: chronic rhinosinusitis without nasal polyposis; SR: systematic review; CT: computed tomography; URTI: upper respiratory infection

Table X.B-4. Evidence for allergic rhinitis and chronic rhinosinusitis with nasal polyposis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Houser & Keen[1866]	2008	2b	Retrospective case series	CRSwNP with or without allergy (n=373)	Nasal polyposis	AR is associated with the development of nasal polyposis.
Wilson et al[1854]	2014	3a	Systematic review	CRSwNP with or without allergy	Association between CRSwNP and allergy	Conflicting evidence with no clear association.
Al-Qudah[1867]	2016	3b	Prospective cohort study	CRSwNP compared to CRSsNP (n=155)	Rates of food sensitivity	No difference between allergic and non-allergic patients.
Li et al[1855]	2016	3b	Prospective cohort	CRSwNP with or without allergy (n=210)	Nasal endoscopy, CT scores, serum inflammatory markers	No difference in allergic and non-allergic patients.
Gorgulu et al[1868]	2012	3b	Prospective case-control	CRSwNP compared to controls (n=60)	Rate of allergen sensitivity	No difference between allergic and non-allergic patients.
Lill et al[1869]	2011	3b	Prospective case-control	CRSwNP compared to controls (n=50)	Rates of food sensitivity	Higher rate of milk sensitivity in CRSwNP.
Tan et al[1858]	2011	3b	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[1870]	2009	3b	Prospective case-control	CRSwNP compared to controls (n=190)	Rates of allergy compared to control	Higher rates of allergy in CRSwNP compared to controls.
Collins et al[1871]	2006	3b	Prospective case-control	CRSwNP compared to controls (n=40)	Rates of food sensitivity	Higher rates of food sensitivity in CRSwNP.
Van Zele et al[1864]	2004	3b	Prospective case-control	CRSwNP compared to CRSsNP and controls (n=55)	Rates of *S. aureus* colonization	Higher rates of colonization in CRSwNP.
Kirtsreesakul[1872]	2002	3b	Prospective cohort	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.
Voegels et al[1873]	2001	3b	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[1874]	2001	3b	Prospective case-control	CRSwNP compared to non-polyp controls (n=68)	Rates of *Candida* and house dust sensitivity	Higher rates of sensitivity in CRSwNP.
Asero & Bottazzi[1875]	2000	3b	Prospective case-control	CRSwNP compared to allergic controls (n=20)	Rates of *Candida* sensitivity	Higher rates of sensitivity in CRSwNP.
Pang et al[1876]	2000	3b	Prospective case-control	CRSwNP compared to controls (n=80)	Rates of food sensitivity	Higher rates of food sensitivity in CRSwNP.
Pumhirun et al[1877]	1999	3b	Prospective case-control	CRSwNP compared to controls (n=40)	Incidence of house dust and cockroach allergy	Higher rates of allergy in CRSwNP compared to controls.

Keith et al[1878]	1994	3b	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 increase symptom scores and serum inflammatory markers.
Pearlman et al[1859]	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[1879]	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[1880]	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[1881]	2006	4	Prospective case series	CRSwNP with or without allergy (n=180)	Endoscopy, CT scores	No difference between allergic and non-allergic patients.

LOE: level of evidence; CRSwNP: chronic rhinosinusitis with nasal polyposis; AR: allergic rhinitis; CRSsNP: chronic rhinosinusitis without nasal polyposis; CT computed tomography

X. C. Conjunctivitis

Although the burden of illness (impaired QOL) associated with allergic conjunctivitis (AC) is well established, this condition is often under recognized and consequently undertreated except when it is most severe.[1882] Its frequent association with AR contributes to the substantial burden associated with AR. Although this association is well recognized clinically, its extent remains poorly defined due to methodologic differences and deficiencies of the studies which have examined this association in the literature. Further compounding this problem is the phenotypic diversity of both AR and AC, and the observation that very few studies have adequately characterized the phenotypes of their study populations. Additionally, many epidemiologic studies are limited by being based solely on questionnaire results rather than on objective clinical evidence of allergic sensitization.

The largest data source regarding the AR-AC association derives from the ISAAC study, a worldwide study established in 1991 with the aim of investigating the epidemiology and etiology of asthma, rhinitis and atopic dermatitis in each country, using standard methodology including questionnaire and SPT. ISAAC has reported the prevalence of AC symptoms in 257,800 children aged 6 to 7 years in 91 centers in 38 countries and 463,801 children aged 13 to 14 years in 155 centers in 56 countries. Although the ISAAC survey was not validated for the diagnosis of AC, ISAAC studies support the frequent association of AR with itchy-watery eyes, reporting that ocular symptoms affect approximately 33-50% of children with AR.[1883] **[Table X.C.]**

The best evidence of disease association derives from studies of AR patients assessed for the prevalence of AC as a comorbidity.[1884-1890] The evidence suggests that AR is associated with 35-74% prevalence of AC and that among patients with AC, the prevalence of AR may be as high as 97%.

To summarize, there is a substantial body of evidence which supports AC as a frequently occurring comorbidity of AR, particularly in children. Not only is this disease association common, but ocular allergy symptoms also contribute significantly to the QOL impairment associated with AR. It is not surprising, therefore, that ocular symptoms of allergic rhinoconjunctivitis are among the most common symptoms which cause patients to seek allergy treatment.[1891] It is advisable, when assessing patients with AR, to also assess for ocular symptoms and to consider treatment specific to providing relief of AC.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3a: 2 studies; Level 3b: 3 studies; *Table X.C.*)

Table X.C. Evidence for an association between allergic rhinitis and allergic conjunctivitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kim et al[1884]	2016	2b	Cross-sectional survey	General population: 14,356 students, health screening 2010-2014. "Korean International Study of Asthma and Allergies in Childhood" AR defined as symptoms + SPT positivity.	SPT positivity, AR prevalence, prevalence of comorbidities	Most common comorbid allergic diseases associated with AR: pollen allergy (37.0%), AC (34.5%).
Han et al[1889]	2015	2b	Cohort	1,020 children total, 338 with AR "The Allergic Rhinitis Cohort Study for Kids (ARCO-kids)"	SPT, questionnaire, endoscopic examination. Evaluation of risk factors for AR.	History of AC identified as risk factor for AR (OR: 14.25, CI: 4.99-40.74)
Alexandropoulos et al[1885]	2012	3a	Case series	Adult non-random patients referred to a Clinical Immunology outpatient clinic 2001-2007 (n=1,851). AR defined according to ARIA.	SPT, questionnaire, sIgE. Evaluation of risk factors for AR.	AR prevalence was 38.4%. AC identified as risk factor for AR (OR: 6.16, CI: 4.71-8.06).
Navarro et al[1890]	2009	3a	Cross-sectional	n=4991 patients selected by referral for allergy evaluation	Characteristics of patients with AR.	AR prevalence was 55%. 65% had associated AC.
Almaliotis et al[1888]	2010	3b	Retrospective case series	n=448 subjects selected by clinic referral and diagnosis of AC by ophthalmologist	SPT, questionnaire. Evaluation of comorbidities of ocular allergy.	70% of patients with AC also had AR. Symptoms of ocular allergy are very common in patients with AR and asthma.
Gradman & Wolthers[1886]	2006	3b	Retrospective survey	n=458 children (5-15 years) selected from a secondary pediatric outpatient clinic with diagnosis of AC, asthma, AR, or eczema	Prevalence of AC in children with rhinitis, asthma and eczema.	Prevalence of AC in children with rhinitis: 42%. Prevalence of AR in children with AC: 97%.
Kosrirukvongs et al[1887]	2001	3b	Case series	n=445 patients (mean age 24.5 +/- 16.3 years) with a history of itching, foreign body sensation, lacrimation and red eyes. No control group.	Skin test. Evaluation of clinical features and risk factors of various AC types.	73.8% of patients with perennial AC had associated AR. Most common allergen sensitization was HDM.

LOE: level of evidence; AR: allergic rhinitis; SPT: skin prick test; AC: allergic conjunctivitis; OR: odds ratio; CI: 95% confidence interval; ARIA: Allergic Rhinitis and its Impact on Asthma; sIgE: allergen-specific IgE; HDM: house dust mite

X. D. Atopic dermatitis (AD)

AD is a chronic and/or relapsing skin disorder characterized by pruritus, scratching, and eczematous lesions.[1892] Its burden of illness, impact on QOL and complications are substantial.[1893] AD commonly presents as the first manifestation of atopy in infants and children who later develop AR and/or asthma, a pattern that has been referred to as "the atopic march."[1894]

Although the association between AR and AD has long been clinically recognized, the extent of this association remains poorly defined due to methodologic differences and limitations of the studies that have examined this association.[537,556,636,1895-1912] **[Table X.D.]** Further compounding this problem is the phenotypic diversity of both AR and AD, and the observation that very few studies have adequately characterized the phenotypes of their study populations. Additionally, many epidemiologic studies are limited by being based purely on questionnaire results rather than objective evidence of allergic sensitization, such as SPT or *in vitro* testing.

The largest data source regarding AR-AD association comes from the ISAAC study, investigating the epidemiology and etiology of asthma, rhinitis and AD using standard methodology including questionnaires, SPT, and flexural dermatitis examination.[1895] ISAAC reported the prevalence of AD symptoms in 256,410 children aged 6-7 years in 90 centers from 37 countries, and 458,623 children aged 13-14 years in 153 centers from 56 countries. These studies indicate that AD is a major public health problem worldwide, affecting approximately 5-20% of children aged 6-7 and 13-14 years.[1896] While longitudinal studies demonstrate improvement or resolution of AD with age,[1897] increasing severity of AD has been shown to correlate with an increased risk of developing AR, with prevalence of AR among people with AD ranging from 15-61%.[1898-1900]

The best evidence of disease association derives from studies which compare the incidence and/or prevalence of AR in populations with and without AD. In this regard, the limited evidence available suggests that AD is associated with a 2-fold increase in AR among people with AD compared with the normal population.[1901] In this study, among those children with present or past AD, 60.8% reported AR compared to 31% in subjects without AD.

- Aggregate Grade of Evidence: C (Level 2b: 4 studies; Level 3b: 15 studies; Level 4: 1 study; *Table X.D.*).

Table X.D. Evidence for the association between allergic rhinitis and atopic dermatitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Mortz et al[1901]	2015	2b	Prospective cohort	The Odense Adolescence Cohort Study (TOACS). - Cross-sectional study (n=1501 8th-graders) - 15-year retention cohort (n=899)	Questionnaire, interview, clinical exam, serum IgE, patch test, SPT. Persistence of AD, comorbidities	Lifetime prevalence of AD was 34.1%. 60.8% prevalence of AR in those with AD vs. 31% in those wihtout AD. Subjects with AD were twice as likely to develop AR.
Sybilski et al[1902]	2015	2b	Cross-sectional	- Questionnaire (n=22,703 Polish subjects). - Medical evaluation (n=4,783 patients).	Questionnaire (response rate 64.4%), SPT with 15 aeroallergens. Diagnosis of AD and comorbidities.	AD identified in 3.91% of subjects. Comorbidities of AD included AR in 26.17%. Association of AD with rhinitis subtypes: 9.5% with perennial vs. 9.3% with seasonal and 9.6% with polyvalent vs. 9.0% monovalent sensitization
Lowe et al[1907]	2007	2b	Prospective birth cohort	n=620 infants with family history of atopic disease. 71.5% had sufficient data for anlalysis.	SPT, interview. Risk of AR development amongst infants with atopic AD vs. those with non-atopic AD.	Children with atopic eczema had a substantially greater risk of AR (OR 2.91; CI 1.48-5.71). In children with eczema within the first 2 years of life, SPT can provide information on the risk of AR.
Kusel et al[1909]	2005	2b	Prospective birth cohort	(n=263), 75.3% of the 263 followed for the full 5 years.	SPT at 6 months, 2 years, 5 years. Evaluation of risk factors for eczema in relation to atopic status.	Persistent eczema significantly associated with AR (OR 2.8; CI 1.5-5.3). AR significantly associated with AD (OR 3.5; CI 1.7-7.1). AR not associated with nonatopic dermatitis.
Schneider et al[1900]	2016	3b	Cohort	n=1,091 infants age 3-18 months with AD followed for 3 years.	Development of comorbidities in patients with AD.	18.5% of patients developed AR. Mean age at onset was 2.4±1.3 years for AR. Comorbidities developed more often in infants with greater baseline AD severity.
Bozek & Jarzab[1903]	2013	3b	Cross-sectional	n=7,124 Polish participants; mean age 66-67 years; 70% participation	Questionnaire, examination, SPT, tIgE, sIgE Epidemiology of of allergic disease in an elderly Polish population.	1.6% had AD/eczema (CI 1.1-2.0). 12.6% had SAR (CI 10.8-14.6). 17.1% had PAR (CI 15.9-19.7).

Batlles-Garrido et al[537]	2010	3b	Cross-sectional	n=1143 participants; 10 and 11-year-old school children; 49.8% response rate. Part of ISAAC II study.	Homologated questionnaire, SPT. Assessment of prevalence, severity, and factors linked to rhinitis.	Prevalence of "rhinitis" during the previous year: 8.9%. Concomitant with atopic eczema: 3.5%. Significant association between "rhinitis" and atopic eczema (OR 1.98; CI 1.36–2.88).
Batlles-Garrido et al[1905]	2010	3b	Cross-sectional	n=1143 participants; 10 and 11-year-old school children; 49.8% response rate. Part of ISAAC II study.	Homologated questionnaire, SPT, physical examination. Assessment of prevalence, severity, and factors linked to atopic eczema.	Prevalence of atopic eczema: 11.4%. Risk factors was severe rhinitis (OR 7.7; CI 1.79-33).
Peroni et al[1906]	2008	3b	Cross-sectional	n=1402 preschool children aged 3-5 years; response rate 92%. Part of ISAAC study.	SPT. Assessment of prevalence of AD, comorbidities and risk factors.	Rhinitis symptoms present in 32.2% AD children. Allergic sensitization to egg, cat, grass pollen and mites, presence of symptoms of rhinitis, and family history of atopy were risk factors for AD.
Karaman et al[1908]	2006	3b	Cross-sectional	n=1217 children in 3rd, 4th, and 5th grade in Izmir, Turkey; response rate 57.6%. ISAAC II methodology.	Questionnaire, physical exam ination, SPT. Prevalence and etiologic factors of asthma, rhinitis, and eczema.	Prevalence of physician-diagnosed AR: 17%. Prevalence of physician-diagnosed eczema: 4.9%. Atopic sensitization prevalence: 8.8%; HDM sensitization most frequent.
Kuyucu et al[556]	2006	3b	Cross-sectional	n=2774 Turkish school children aged 9-11; response rate: 89.2%. ISAAC II questionnaire.	Questionnaire, SPT (subset), lexural dermatitis.	Prevalence of ever rhinitis: 36.3%, current rhinitis: 30.6%, ever hay fever: 8.3%. SPT positivity: 20.4% among children with current rhinitis. Flexural dermatitis significantly associated with current rhinitis.
Yemaneberhan et al[1911]	2004	3b	Cross-sectional	n=12,876 participants; 95% of those eligible took part in the survey.	Questionnaire, SPT (subset). Prevalence of AD symptoms, association with rhinitis symptoms.	Lifetime cumulative prevalence of AD symptoms: 1.2%. AD symptoms strongly associated with rhinitis symptoms (OR 61.94; CI 42.66-89.95).
Peroni et al[636]	2003	3b	Cross-sectional	n=1402 preschool children age 3-5 years; response rate: 92%. ISAAC questionnaire.	Questionnaire, SPT. Comparison of disease associations between rhinitic and nonrhinitic children.	Prevalence of rhinitis in the last 12 months: 16.8%. Rhinitic children had significantly more AD (22.9% vs. 13.9%, P<0.001).

Rhodes et al[1898]	2002	3b	Longitudinal cohort	n=100 infants from atopic families followed for 22 years; 63% retained at last follow-up.	Examination, SPT, tIgE, bronchial hyper-responsiveness to inhaled histamine. Development of allergic rhinitis and asthma	Prevalence of AD peaked at 20% of children by 1 year of age, declined to 5% at end of the study. AR prevalence slowly increased over time from 3% to 15%.
Min et al[1912]	2001	3b	Cross-sectional	n=71,120 randomly selected subjects from Korean otolaryngology clinics	Questionnaire, examination, SPT, serum allergy test.	Prevalence of PAR in tertiary referral hospitals in Korea is 3.93%. Associated atopic dermatitis in 20.9% subjects with PAR.
Gustafsson et al[1899]	2000	3b	Longitudinal cohort	n=94 children with AD followed for 8 years	tIgE, sIgE, SPT. Evaluation of development of AR and asthma.	AD improved in 84 of 92 children; 45% developed AR. Severity of AD was a risk factor for subsequent development of AR. Consistent with atopic march.
Ozdemir et al[1913]	2000	3b	Cross-sectional	n=1603 college students in Eskisehir, Turkey; 94.5% response rate.	Questionnaire, physical examination and SPT (subset) Determine prevalence of asthma, AR, AD.	Eczema rate: 5.4% among females, 6.3% among males. Rhinitis symptoms: 11.1% among females, 8.9% among males.
Garcia-Gonzalez et al[1914]	1998	3b	Cross-sectional	n=365 students from Malaga, Spain.	Interview, SPT, tIgE, sIgE. Evaluation of prevalence of atopic disease.	19.9% suffered from rhinoconjunctivitis, and 0.8% AD.
Leung & Ho[1915]	1994	3b	Cross-sectional	n=2208 secondary school students; response rate over 87%.	Questionnaire, SPT (subset). Evaluation of prevalence of asthma and allergic disease.	Hayfever prevalence: Hong Kong 15.7%, Kota Kinabalu 11.2%, San Bu 2.1%. Eczema prevalence: Hong Kong 20.1%, Kota Kinabalu 7.6%, San Bu 7.2%.
Kidon et al[1910]	2005	4	Prospective case series	n=175 newly diagnosed AR patients; predominantly Chinese; mean age 7.9.	Questionnaire, SPT. Relative risk of sensitization and associated risk factors.	Prevalence of AD: 48%. SPT positive for HDM in 85%. Children with AR and concomitant AD show preferential sensitization to Dermatophagoides mites.

LOE: level of evidence; IgE: immunoglobulin E; SPT: skin prick test; AD: atopic dermatitis; AR: allergic rhinitis; OR: odds ratio; CI: 95% confidence interval; tIgE; total immunoglobulin E; sIgE: antigen-specific immunoglobulin E; SAR: seasonal allergic rhinitis; par: perennial allergic rhinitis; ISAAC: International Study of Asthma and Allergies in Childhood; HDM: house dust mite

X. E. Food allergy and pollen-food allergy syndrome (PFAS)

Approximately 5-8% of patients with pollen allergy will develop a PFAS.[1916] Patients with pollen allergies may have allergy-related manifestations after consuming specific fruits, vegetables, nuts or spices. The prevalence of pollen-food allergies varies with the type of pollen. As many as 70% of patients with birch allergy will manifest a food-related sensitivity.[1917] PFAS is an IgE-mediated reactivity, which occurs in the oral mucosa, leading to itching, stinging pain, angioedema, and rarely systemic symptoms. The term, "oral allergy syndrome" (OAS), has also been frequently used and refers to a pollen-food allergy that occurs only at the level of the oral mucosa. OAS is, therefore, a specific manifestation of the broader PFAS. The symptoms of OAS manifest because of IgE specific for the offending pollen cross-reacting with highly homologous proteins found in a variety of fruits, vegetables and nuts. The most common example of this cross-reactivity in western populations is birch pollen and apples. **Table X.E-1.** lists common pollen allergens with plant-derived foods that may demonstrate cross-reactivity. These pollen-food relationships have been observed clinically and are also demonstrated at a molecular level through identification of the homologous amino acids, cross-reactive carbohydrate determinants and lipid transfer proteins. The birch-apple syndrome is due to the high homology of the major birch allergen Bet v 1 and the apple allergen Mal d 1.[1918]

The diagnosis of PFAS is typically established by a detailed history and physical exam. The history should be guided by an understanding of the patient's underlying pollen allergy and foods that share highly homologous proteins. The clinician should elicit a detailed history of the allergic response including any systemic symptoms and history of anaphylaxis. The estimated rate of systemic reaction from a pollen-food allergy is 10% and the estimated rate of anaphylaxis is 1.7% to 10%.[1742,1919,1920] Systemic symptoms are the manifestation of an allergic response by organ systems that have not come into direct contact with the ingested food and include: urticaria, nasal congestion, sneezing, flushing, wheezing, cough, diarrhea and hypotension. The gold standard for establishing a diagnosis of PFAS is a double-blind food challenge. However, this is difficult to perform because of the bias inherent to the appearance, texture and taste of foods.[1921] Oral food challenge, SPT and food-specific IgE levels have also been used to establish the diagnosis. The diagnostic approach should be guided by the patient's history and severity of allergic response.

The standard recommendation for the treatment of PFAS has been elimination of the offending food. Patients should be counseled on the risk for systemic and anaphylactic reactions. Patients with a history of systemic or anaphylactic reactions should be provided with an epinephrine auto-injector. The proteins responsible for PFAS are often labile and may be denatured by heat. The denatured proteins are typically not cross-reactive with the pollen IgE. Therefore, pollen-associated foods may become edible when heated. In one study, food challenges were performed with cooked apple, carrot, or celery in patients with atopic dermatitis and birch pollen allergy who had OAS and dermatologic symptoms upon ingestion of the raw foods. Cooked versions of the offending foods did not cause oral allergy symptoms.[1922] However, some patients did manifest a late eczematous skin reaction, which was likely T-cell-mediated. **[Table X.E-2.]**

There is also one RCT in a group of 30 patients evaluating the use of an antihistamine to reduce PFAS symptoms, which demonstrated a clinically significant reduction in allergy symptoms compared to

placebo when ingesting offending foods.[1923] The antihistamine used in this study, astemizole, has been removed from the market due to QT interval prolongation on electrocardiogram.

There have been several studies evaluating the effect of targeted immunotherapy for pollen allergy at reducing PFAS symptoms. The results are mixed. Several small cohort studies and RCTs have shown an increased tolerance to the offending food when patients are treated with pollen specific immunotherapy.[1916,1924-1926] However, one RCT failed to demonstrate any improved tolerance to apple in birch allergic patients treated with birch specific immunotherapy compared to placebo.[1921] One study evaluating the persistence of tolerance for apple after birch immunotherapy demonstrated that some patients had an increased apple tolerance for up to 30 months after immunotherapy. However, there was no statistically significant difference between the immunotherapy and control groups.[1927] Immunotherapy is not currently recommended for the sole purpose of treating PFAS. Patients receiving immunotherapy for the treatment of pollen allergies should be counseled on the potential but unsubstantiated benefit for improved food tolerance.

- Aggregate Grade of Evidence: B (Level 2b: 8 studies; Level 4: 1 study; *Table X.E-2.*)

Table X.E-1. Pollen-food allergy cross-reactivity[1928]

Pollen	Food
Birch	apple, pear, sweet cherry, peach, plum, apricot, almond, celery, carrot, potato, kiwifruit, hazelnut, mango
Japanese cedar	tomato
Mugwort	celery, carrot, mango, spice
Grass	melon, watermelon, tomato, potato, kiwifruit, orange, peanut
Ragweed	melon, watermelon, cantaloupe, zucchini, cucumber, banana
Plane	hazelnut, apple, lettuce, corn, peanut, chickpea

Table X.E-2. Evidence for the role of pollen allergy in pollen-food allergy syndrome

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Inuo et al[1916]	2015	2b	Cohort	Children with AR to JCP and tomato sensitization (n=23, age 6-17	Basophil activation by tomato and JCP extract, IgE and IgG4 levels against tomato and JCP antigens	Tomato-specific basophil activation decreases after JCP-based SCIT, suggesting efficacy in treating PFAS symptoms in patients with JCP AR.
Bohle et al[1922]	2006	2b	Case-control	Patients with birch pollen allergy and OAS	Oral challenge and basophil activation assays	T-cell cross-reactivity occurs independently of IgE cross-reactivity. The view that cooked pollen-related foods can be consumed without allergologic consequences should be reconsidered.
Bolhaar et al[1925]	2004	2b	RCT	Patients with PFAS (birch-apple, n=25) randomized to: 1. AIT 2. pharmacologic intervention	Double-blind placebo-controlled food challenge and SPT	Birch pollen AIT decreases allergy to foods containing homologous allergens (apple).
Skamstrup Hansen et al[1921]	2004	2b	RCT	Patients with birch allergy (n=74) randomized to: 1. SLIT 2. SCIT 3. placebo	Oral challenge with apple before and after treatment	AIT was not accompanied by a significant decrease in the severity of allergy to apple compared with placebo.
Asero[1927]	2003	2b	Case-control	1. birch pollen allergic patients with apple tolerance after completing injection AIT (n=30) 2. birch pollen allergic patients without apple allergy (n=57)	Prevalence of apple allergy at 30 months by symptoms or SPT	Most patients have propensity for apple re-sensitization. No significant difference between in prevalence of PFAS between test group and controls at 30 months. In some patients, pollen AIT can exert a long-lasting effect on PFAS.
Asero[1924]	1998	2b	Case-control	Patients with PFAS (birch-apple, n=75) assigned to: 1. AIT 2. no intervention	Oral apple challenge and SPT at 12, 24, and 36 months of AIT	AIT with birch pollen extracts effectively reduces clinical apple sensitivity and skin reactivity in most cases after 1 year of treatment.
Bircher et al[1929]	1994	2b	Case-control	Serum samples from: 1. patients with pollen allergy (n=274) 2. patients with cat allergy (no pollen allergy, n=36)	Presence of IgE for 6 pollen associated foods	There is a high prevalence of food specific IgE in pollen allergic patients, but not in non-pollen allergic patients.

				3. patients with no allergies (n=55)		
Bindslev-Jensen et al[1923]	1991	2b	RCT	Patients with PFAS (birch-hazelnut, n=30) randomized to: 1. antihistamine 2. placebo	Symptom score (0-5 rating) with hazelnut provocation before and after 2 weeks of treatment	Treatment with antihistamine (astemizole) significantly reduced (but did not eliminate) the severity of local symptoms after ingestion of hazelnuts compared to placebo.
Mauro et al[1926]	2011	4	Cohort	Patients with birch allergy (n=30) randomized to: 1. SLIT 2. SCIT	Oral challenge with apple before and after treatment	Different doses of birch extract may be necessary to induce apple tolerance amongst patient with birch-apple PFAS.

LOE: level of evidence; AR: allergic rhinitis; JCP: Japanese cedar pollen; Ig: immunoglobulin; SCIT: subcutaneous immunotherapy; PFAS: pollen-food allergy syndrome; OAS: oral allergy syndrome; RCT: randomized controlled trial; AIT: allergen immunotherapy; SPT: skin prick test; SLIT: sublingual immunotherapy

X. F. Adenoid hypertrophy

In children, adenoid hypertrophy (AH) and AR may exhibit similar symptoms including nasal obstruction and rhinorrhea. The potential relationship between AR and AH is explored in this section. Adenoid enlargement most commonly begins during infancy; it continues through the first five to six years of life and involutes with puberty.[1930,1931] Symptomatic AH affects an unknown percentage of children and may contribute to a range of symptoms including nasal obstruction, nasal drainage, sleep disturbance, increased episodes of rhinosinusitis, increased lower respiratory tract infections, worsened asthma, and eustachian tube dysfunction.[1930,1932]

Case series evaluating the relationship between AH and allergic sensitization fall into two main categories: 1) cohorts of children with allergic conditions assessed for AH or 2) children identified with AH assessed for allergy sensitization. These may not represent the same populations.

Three studies assessing allergic children found a higher rate of AH than controls (when present). In 2015, 1322 children (mean age 5.9 +/- 3.3 years) treated for "allergic conditions" were compared to 100 age-matched children with no allergic disease for AH. They found AH was more prevalent in the allergic group (12.4%) than controls (3%) ($p<0.0001$). AH was statistically associated with AR and cigarette smoke exposure ($p=0.004$).[1933] Similarly, Dogru et al[1934] found that among 566 children with AR the prevalence of AH was 21.2% (no control group). Additionally, they reported that children with both AH and AR had a higher frequency of persistent rhinitis ($p<0.05$), moderate/severe rhinitis ($p=0.005$), and nasal congestion ($p=0.001$) than those with AR alone. The AR-only group had a higher prevalence of asthma ($p=0.037$) and "itchy nose" (0.017). In another study, adenoid size in seasonally allergic children was assessed by Modrynski et al,[1935] concluding that seasonal adenoid enlargement was observed in birch pollen allergic children more than controls not allergic during the tree pollen season. The increased adenoid size resolved after pollen season in the study group, and the seasonal increase in adenoid size was not observed in birch-allergic children treated co-seasonally with topical nasal steroid and antihistamines. The study was small (n=67 among four groups) and did not state whether it was blinded. **[Table X.F.]**

Exposure and sensitization to mold and AH has been specifically examined. Atan Sahin et al[1936] compared 242 children living in a less humid environment to 142 children living on the more humid Turkish Mediterranean coast. Mite-sensitive children in the coastal group had an increase in AH ($p=0.01$). Those living in the more humid coastal location demonstrated increased mold and pollen sensitization but no significant correlation with adenoid hypertrophy was found. In contrast, Huang et al[1937] compared 315 children with AH and AR to age-matched controls with AR-alone. There was a higher prevalence of positive skin tests to molds in the AH group (p 0.013 to <0.0001). Dogru et al[1934] also reported an increased sensitization to *Alternaria* in children with both AH and AR compared to AR alone ($p=0.032$), although a statistical correction for multiple variables was not described.

In studies where children were recruited by nasal obstruction, the degree of AH sometimes showed either no relationship or an inverse relationship with the prevalence of allergy sensitization. Cassano et al[1931] reported that the prevalence of specific inhalant IgE sensitization decreased as the AH increased: AH first degree (37% sensitized), AH second degree (35% sensitized), AH third degree (19% sensitized). Karaca et al[1938] did SPT on 82 children who presented with upper airway obstruction to an otolaryngology clinic and compared allergy sensitization to radiographic adenoid size and clinically

assessed tonsil size. They concluded that there was not a statistically significant association with adenoid size (p=0.195) and a negative correlation with tonsil size (p=0.045). The methods are vague on how the correlation was performed with tables showing percentages of "negative" SPT and the text incongruently stating "all of the cases were positive for at least one of the 14 allergens".[1938] Ameli et al[1939] assessed 205 children (mean age 6.7 years) with nasal endoscopy and SPT and found an association between negative SPT and adenoid volume (p<0.0001). In an exception to the previously noted studies, Sadeghi-Shabestari et al[1940] compared 117 children aged 1-14 years with adenotonsillar hypertrophy to 100 controls of similar age for allergen SPT, total IgE and smoking parents. They reported 70.3% of the adenotonsillar hypertrophy group had a positive SPT compared to 10% of the control group (p=0.04); however, they included SPTs for foods (highest positive allergen subgroup) and latex.

In a study that is difficult to categorize by recruitment, 155 children (mean age 8.7 years) referred from Pediatric Allergy to Otolaryngology were assessed by rigid nasal endoscopy and SPT. Children on allergy medication were excluded. They observed a negative correlation between AH and allergen positivity (r=-0.208, p=0.009).[1941]

Immunologic evidence of allergy in adenoid tissue is limited in the literature. Ni et al[1942] found a higher Th17/Treg ratio in adenoid tissue from children with AR than controls. Masieri et al[1943] reported Th1 gene expression in non-allergic adenoid tissue, Th1 & Th2 gene expression in adenoid tissue in those with AR treated with antihistamines, and a down regulation in Th1 and Th2 gene expression in adenoid tissue from children treated with SLIT. Both studies were small.

Treatment studies are also limited. One retrospective, uncontrolled study (n=47) reported improvement in rhinitis symptoms in similar percentages for both AR (86%) and NAR (76%) after adenoidectomy.[1944] The effect of INCS on reducing nasal obstruction in the setting of AH, independent of allergy, has been demonstrated in systematic reviews,[1932,1945] but whether this is due to decrease in adenoid size is less clear and blinded studies are uncommon.[1946]

In conclusion, there is a trend among allergic children who are assessed for AH to have increased prevalence AH compared to non-allergic controls. However, when children are selected for upper airway obstruction and then assessed for inhalant allergy sensitivity, a consistently increased prevalence of allergic sensitivity is not found. One potential explanation for this discrepancy is that symptomatic AH peaks in younger children than pediatric AR, with the allergic cohorts having a higher average age. This is supported in the literature by Pagella et al[1947] who retrospectively reviewed records of children referred to Otolaryngology for nasal symptoms (n=795). They found an association between allergy and AH in children aged 8-14 years (p=0.0043), but not for children aged 1-7 years (p=0.34).

- Aggregate Grade of Evidence: C (Level 4: 11 studies; *Table X.F.*)

Table X.F. Evidence for the association between allergic rhinitis and adenoid hypertrophy

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Dogru et al[1934]	2017	4	Retrospective, cross-sectional, non-randomized	1. AR 2. AR plus AH	Symptoms, allergen sensitivities, allergy comorbidities	The AR plus AH group had more severe symptoms than the group with AR alone.
Atan Sahin et al[1936]	2016	4	Case-control	Children from humid vs. less humid locations	AH, SPT, IgE, vitamin D	High humidity group had higher prevalence of AH, higher IgE levels, and an association between AH and SPT for dust mite.
Eren et al[1941]	2015	4	Consecutive cohort	155 children referred to Otolaryngology from Pediatric Allergy	Nasal endoscopy and SPT	There was a negative correlation between AH and SPT positivity (r=-0.208, p=0.009).
Evicimk et al[1933]	2015	4	Retrospective, cross-sectional, non-randomized	1. AR 2. no AR	AH, cigarette exposure, gender, age, family history of allergy, asthma, SPT	AH was more prevalent in the AR group. Cigarette smoke exposure was associated with AH.
Pagella et al[1947]	2015	4	Retrospective case series	Otolaryngology clinic for nasal symptoms (1-7 years, n=582; 8-14 years, n=213)	Allergy testing (n=169), endoscopic adenoid size, clinical symptoms	In the whole population: AH and AR not associated age 1-7 yrs (p=0.34), AH and AR associated with age in 8-14 year-old group (p=0.0043).
Ameli et al[1939]	2013	4	Consecutive cohort	205 children with persistent upper airway obstruction	Nasal endoscopy and SPT	Adenoid volume and % with no associated allergy (p<0.001)
Karaca et al[1938]	2012	4	Case series	Children with upper airway obstruction (n=82)	Radiographic AH, clinical tonsillar hypertrophy, allergy sensitivity	Negative correlation: SPT and tonsil hypertrophy. No correlation: SPT and AH.
Sadeghi-Shabestari et al[1940]	2011	4	Cohort	1. adenotonsillar hypertrophy (n=117) 2. no adenotonsillar hypertrophy (n=100)	SPT for food, inhalant and latex	Adenotonsillar hypertrophy and positive SPT 70.3%. No adenotonsillar hypertrophy and positive SPT 10%. (p=0.04)
Modrzynski & Zawisza[1935]	2007	4	Prospective unblinded controlled	1. tree sensitive (n=28) 2. mugwort sensitive (n=14) 3. non-atopic (n=15) 4. tree sensitive "treated" (n=10)	Acoustic rhinometry, endoscopic adenoid exam	Increased adenoid size in birch allergic children during pollen season, decreased after pollen season and prevented by allergy phamacotherpy.

Cassano et al[1931]	2003	4	Cohort (recruitment not specified)	Children with nasal obstruction (n=98, age 3-14 years)	Nasal endoscopy. "Allergic rhinitis was diagnosed by prick test and RAST in 22 patients" (20.9%)	% with "allergy" decreased with increasing adenoid size. Statistical significance not calculated.
Huang & Giannoni[1937]	2001	4	Case-control	1. AR 2. AR plus AH	SPT, otitis media, sinusitis, lower respiratory tract infection, second hand smoke, sleep disordered breathing	Higher prevalence of mold SPT positivity and lower respiratory tract infection (in some age groups) in AR plus AH group

LOE: level of evidence; AR; Allergic rhinitis; AH: adenoid hypertrophy; SPT: skin prick test; IgE: immunoglobulin E

X. Associated conditions
X. G. Otologic conditions

Eustachian tube dysfunction. Ear symptoms are commonly experienced by patients with AR. Ear fullness and pressure, otalgia, popping or other sounds during swallowing, and transient hearing loss can all be manifestations of Eustachian tube dysfunction. The Eustachian tube opens into the nasopharynx and is in direct continuity with the upper respiratory tract. Inflammation of the nasal mucosa may involve the torus tubarius or Eustachian tube mucosa, resulting in obstruction that leads to negative pressure as middle ear gases are resorbed. Frequent sniffing or swallowing during nasal obstruction may transmit negative pressure to the middle ear space. The frequently observed clinical association of Eustachian tube symptoms and AR is corroborated by high level evidence that demonstrates that in AR patients, nasal challenge with histamine or relevant aeroallergens results in transient Eustachian tube obstruction.[1948-1950] These studies used the 9-step inflation-deflation swallow test of Eustachian tube function developed by Bluestone and Cantekin.[1951] The development of negative middle ear pressure after allergen challenge corresponds with increases in nasal airway resistance.[1952] AR appears to increase the incidence of Eustachian tube dysfunction relative to control populations,[1953] and natural pollen exposure has been associated with negative middle ear pressures[1954] and defects in Eustachian tube opening.[1955] This body of evidence supports a direct causal role for AR in some cases of Eustachian tube dysfunction. **[Table X.G-1.]**

- Aggregate Grade of Evidence: C (Level 1b: 3 studies; Level 2b: 1 study; Level 3b: 1 study; Level 4: 2 studies; *Table X.G-1.*)

Otitis media. The role of allergy as a causative factor in otitis media has not been clearly demonstrated. Historically, allergy was considered an important etiologic factor in otitis media. However, as clinical definitions have become more stringent and evidence expectations have evolved, it has become apparent that a clear etiopathogenic connection between AR and otitis media is yet to be demonstrated. Investigations into the connection between these two conditions have examined the evidence for type 1 IgE-mediated inflammation in the middle ear space, epidemiologic associations between the two conditions, and the effect of allergy treatment on otitis outcomes. The middle ear mucosa may behave in a manner similar to nasal mucosa and be a site of local IgE-mediated inflammatory reactions.[1956-1958] However, direct intranasal allergen challenge in allergic subjects does not appear to cause otitis media.[1948-1950] Studies of the epidemiologic association of AR or atopy and otitis media with effusion (OME) are widely discordant. Some studies have found no significant difference in allergic sensitization or clinical allergy in OME patients compared to control groups,[1959,1960] while others have shown a dramatically increased prevalence of IgE sensitization or clinical allergy in OME patients,[1961-1964] or that AR is an independent risk factor for the development of OME.[1965] Finally, some studies suggest a nearly universal association of OME and allergic disease.[1966-1970] These inconsistencies in the literature are likely related to highly selected patient populations in specialty practices, variability in allergy test methods, and the problems incumbent in identifying appropriate control groups. Thus, the relationship of allergy and OME remains unclear. **[Table X.G-2.]**

In general, randomized placebo-controlled trials have shown that INCS do not improve OME outcomes.[1971-1973] Also, a Cochrane systematic review found no benefit of antihistamines and/or decongestants in the treatment of OME. Thus, traditional medical treatments for AR do not appear to be an effective option for OME and recent otitis media CPGs recommend against the use of these agents.[1974] Additional investigation is needed to discern the effect of allergy on the incidence or natural history of OME and to determine if AIT has beneficial effects.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3b: 3 studies; Level 4: 11 studies; *Table X.G-2.*)

Inner Ear Disease. Meniere's disease is characterized by recurring episodes of tinnitus, hearing loss, aural fullness and vertigo. The basic pathophysiologic defect in Meniere's disease appears to be a dysregulation of endolymph in the inner ear (endolymphatic hydrops).[1975] An immunologically-mediated disturbance in fluid handling by the endolymphatic sac has been postulated as one cause for the disease.[1976] The notion that "allergy" of the inner ear is a cause of Meniere's disease predates our modern understanding of type 1 IgE-mediated hypersensitivity, and is still evoked as a possible causative or contributing factor for the disease in some individuals. Indeed, AR has been postulated as a cause of inner ear dysfunction,[1977] and a connection between allergy and inner ear disorders such as Meniere's disease is plausible based on compiled circumstantial evidence. Derebery and colleagues have published studies suggesting that inhalant and food allergies are more common in Meniere's patients,[1978] and that allergy treatment including AIT results in improved Meniere's disease symptoms.[1979,1980] However, these studies generally provide low grade evidence, and aside from one small study that also found a higher prevalence of IgE-mediated hypersensitivity in Meniere's patients, [1981] these findings have not been duplicated by others. Case-control studies examining total serum IgE levels have provided conflicting results.[1981,1982] A few small studies have shown changes in objective parameters such as the electrocochleographic summating potential/action potential (SP/AP) ratio in response to aeroallergen or food challenge in Meniere's patients.[1983,1984] Overall, the evidence supporting a connection between type 1 IgE-mediated hypersensitivity and Meniere' disease is of low grade, with substantial defects in study design. **[Table X.G-3.]**

- Aggregate Grade of Evidence: C (Level 3b: 4 studies; Level 4: 4 studies; *Table X.G-3.*))

Table X.G-1. Evidence for the role of allergic rhinitis in Eustachian tube dysfunction

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Skoner et al[1950]	1987	1b	Double blind crossover with provocation (histamine)	1. AR (n=5) 2. control (n=5)	Inflation-deflation swallow test of ET function	All AR subjects had ET obstruction after challenge.
Skoner et al[1949]	1986	1b	Cohort with intervention (HDM nasal provocation)	HDM sensitive AR subjects with normal ET function	Inflation-deflation swallow test of ET function	55% of ears developed ET obstruction after provocation.
Friedman et al[1948]	1983	1b	Double blind crossover, nasal provocation (pollen insufflation)	8 adult AR subjects with ragweed or timothy grass allergy	Inflation-deflation swallow test of ET function	Allergen intranasal challenge induces transient ET obstruction
Osur et al[1955]	1989	2b	Cohort	Children with AR, ragweed sensitive (n=15)	9-step ET function test	60% of children developed ET obstruction during ragweed season.
Lazo-Saenz et al[1953]	2005	3b	Case-control	1. AR (n=80) 2. control (n=50)	Tympanometry	AR pts had negative pressure. 15% of AR children had type B or C tympanograms.
Knight et al[1954]	1992	4	Cohort	SAR patients	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.
O'Connor et al[1952]	1984	4	Cohort	Children with AR (n=37)	Middle ear pressure and nasal airway resistance after pollen challenge	69% of children had negative middle ear pressure after challenge.

LOE: level of evidence; AR: allergic rhinitis; ET: Eustachian tube; HDM: house dust mite; SAR: seasonal allergic rhinitis; ETD: Eustachian tube dysfunction

Table X.G-2. Evidence for the role of allergic rhinitis in otitis media

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Yeo et al[1960]	2007	2b	Cohort with control group	1. OME (n=123 children) 2. controls (n=141 children)	History, SPT	AR was present in in 28% of OME group vs. 24% of control.
Caffarelli et al[1959]	1998	2b	Cohort with control group	1. AR and OME (n=172, 4-14 years) 2. controls (n=200)	SPT and tympanogram for all subjects	Equal rates of sensitization between OME group and controls.
Chantzi et al[1961]	2006	3b	Case-control	1. OME (n=88 children) 2. controls (n=80 children)	Allergy history and tests	IgE sensitization is independent risk factor for OME.
Corey et al[1964]	1994	3b	Case-control	1. OME (n=89 children) 2. controls (n=59 children)	RAST	Positive RAST: 61% in OME group vs. 41% in controls

Borge[1963]	1983	3b	Case-control	1. serous OM (n=89) 2. controls (n=67)	Allergy history and testing	41% of serous OM patients had perennial rhinitis vs. 11% of controls.
Kreiner-Moller et al[1965]	2012	4	Case series	6 year-old children (n=262)	Assessment for OME and allergy	39% of cohort had OME. OR of 3.36 for AR and OME.
Hurst[1966]	2008	4	Cohort	1. OME patients treated with AIT (n=89) 2. OME patients not treated with AIT (n=21)	Resolution of effusion or drainage at 2-8 year follow-up	100% of OME had positive allergy tests; 85% of AIT treated patients cured.
Alles et al[1969]	2001	4	Cohort	3-8 year-old children with OME	Assessment of AR, Asthma, eczema	57% with positive SPT, almost all with rhinitis.
Hurst[1967]	1996	4	Cohort	1. OME (n=73) 2. controls (n=16)	Allergy tests, effusion, ECP	Allergies in 97% of COME
Hurst[1968]	1990	4	Cohort	20 OME patients, all allergic: 17 treated with AIT, 3 untreated controls	AIT or food elimination diet	All pts treated with AIT or food elimination resolved.
Tomonaga et al[1962]	1988	4	cohort	259 children with OME; 605 nasal allergy; 104 controls	Allergy testing; tympanometry	50% of OME cases had nasal allergy vs. 17% control.
Bernstein et al[1956]	1985	4	Cohort	100 patients with OME: 35 allergic, 65 non-allergic	Total and specific IgE in MEE and serum	23% of allergic OME patients had evidence of local IgE.
Bernstein et al[1957]	1983	4	Cohort	77 children with recurrent OME and history of myringotomy tubes	Allergy evaluation, serum, nasal, MEE total IgE	Higher levels of IgE in MEE of allergic children
Bernstein et al[1958]	1981	4	cohort	41 patients with OME: 20 allergic, 21 non-allergic	Total and specific IgE in MEE and serum	15% of allergic OME cases had evidence of local IgE.
McMahan et al[1970]	1981	4	Case series	119 COME patients	RAST test	93% of COME positive to inhalant allergens

LOE: level of evidence; OME: otitis media with effusion; SPT: skin prick test; AR: allergic rhinitis; RAST: radioallergosorbent test; OM: otitis media; AIT: allergen immunotherapy; COME: chronic otitis media with effusion; IgE: immunoclobulin E; MEE: middle ear effusion

Table X.G-3. Evidence for the role of allergic rhinitis in inner ear disease

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Singh et al[1977]	2011	3b	Case-control	1. AR (n=30) 2. controls (n=20)	Audiometry, OAE, ABR	AR subjects had evidence of inner ear dysfunction.
Keles et al[1981]	2004	3b	Case-control	1. Meniere's disease (n=46) 2. controls (n=46)	Peripheral blood lymphocyte populations, cytokines,	Menieres patients are more likely to have positive allergy test. 41%

					allergen-specific and total IgE levels	Menieres patients had elevated total IgE.
Derebery and Berliner[1978]	2000	3b	Case-control	1. Meniere's disease (n=734) 2. controls (n=172)	Allergy symptoms, history questionnaire	Meniere's disease patients have more AR and food allergy.
Hsu et al[1982]	1990	3b	Case-control	1. Meniere's disease (n=42) 2. controls (n=18)	Serum total IgE	No difference in serum total IgE between groups.
Derebery[1979]	2000	4	Cohort	1. Meniere's disease treated with AIT and diet (n=113) 2. controls (n=24)	Self-reported symptoms via post treatment survey	Allergy treatment reduced tinnitus and vértigo.
Gibbs et al[1983]	1999	4	Case series	7 patients with Meniere's and inhalant allergy	Change in ECoG after allergen challenge	57% of subjects had >15% change in SP/AP ratio after challenge.
Derebery and Valenzuela[1980]	1992	4	Cohort	93 Meniere's disease patients with suspected allergy	intradermal test, *in vitro* allergy tests, serum IgE, provocative food testing, AIT response	82% had normal serum IgE; AIT improved vertigo in 62%
Viscomi and Bojrab[1984]	1992	4	Cohort	5 patients with Meniere's disease and AR	Allergen challenge with intracutaneous provocative food test. >15% change in SP/AP ratio on ECoG, provocation of Meniere's symptoms	6/27 intracutaneous food challenges had induction of aural symptoms and >15% change in SP/AP ratio

AR: allergic rhinitis; LOE: level of evidence; OAE: oto-acoustic emissions; ABR: auditory-brainstem response; IgE: immunoglobulin E; AIT: allergen immunotherapy; ECoG: electrocochleography

X. H. Cough

Cough is a sudden reflex used to clear the breathing passage of any foreign particles or irritants. There is evidence that vagal afferent nerves regulate an involuntary cough; yet, there is also cortical control of this overall visceral reflex.[1985] Cough is often considered a comorbidity of AR. The rhinobronchial reflex is one of the mechanisms that may explain the ability of stimuli on the nasal mucosa, such as an allergen, to result in direct bronchospasm.[1986] The role of descending secretions (post-nasal drip) from the upper to lower airways is another theory. While many practitioners link post-nasal drainage to cough, there is very little evidence to support this. When functioning normally, the vocal folds protect the lower airways from upper airway secretions and foreign bodies. Thirdly, a direct mechanism due to diffuse inflammation and activation of eosinophils may be responsible for the common upper and lower airway manifestations. The American College of Chest Physicians evidence-based clinical practice guidelines on cough suggest the term upper airway cough syndrome, rather than post-nasal drip syndrome, when discussing a cough originating from the upper airway due to the varying possible causes.[1985]

AR and asthma may coexist and may indeed produce a continuum of the same airway disease.[1167] Associations with cough in AR patients can relate to their underlying asthma or a seasonal asthma during peak pollen season. The Asia Pacific Burden of Respiratory Diseases study, a 1000-person cross sectional observational study, revealed that cough was the primary reason for a visit to the physician for patients with asthma and or COPD. However, AR patients were more likely to present with classic watery, sneezing, runny nose. The study however did find that 33.5% of patients were diagnosed with combinations of respiratory disease; the most frequent was asthma and AR.[1987,1988] **[Table X.F.]**

While patients with AR that have concomitant chest symptoms such as cough often do have asthma, seasonal asthma and/or a nonspecific bronchial hyper-reactivity, many studies show generalized inflammation of the upper airways extending to the lower airways. There is a complex interplay between cells and inflammatory cytokines and hence one should consider the upper and lower airways as a single unique functional unit.[1986] The key pathogenic mechanism is the inflammation of the upper airways with extension to the lower airways and the induction of a systemic dysregulation via a complex interaction between cells and inflammatory cytokines.[1986]

Many patients with AR and cough do not have the diagnostic airflow obstruction or the reversibility of forced expiratory volume in 1 second (FEV1) following bronchodilator administration to make a diagnosis of asthma.[1167] Krzych-Falta et al[1989] performed a nasal challenge in 30 patients with AR. Extra-nasal symptoms were noted, including a cough and breathlessness, especially in those with PAR. In 2000, Chakir et al[1990] performed histochemical tests on bronchial biopsies of patients with AR but without current or history of asthma. They demonstrated increased numbers of lymphocytes, eosinophil recruitment and IL-5 expression in the bronchial mucosa after exposure with natural pollen.[1990] This 2000 study followed a prior investigation of deposition of type I and III collagens and fibronectin by bronchial myofibroblasts in AR patients.[1991] This is suggestive of an active structural remodeling of the lower airways in AR patients that is similar to asthma patients but less severe. In addition, Buday et al[1992] demonstrated that guinea pigs sensitized to HDM had a significantly enhanced cough response compared to those that were not sensitized; however, airway resistances did not change. This study is relevant to humans, since the neurophysiology of the vagus nerve in the guinea pig is thought to be

closest to humans. These studies demonstrate that AR, unrelated to asthma, can indeed result in bronchial inflammation, possible lower airway remodeling and ultimately a symptom of cough.

A largescale cross-sectional, multinational observational study set out to determine the symptom of cough as it relates to respiratory diseases in the Asia-Pacific region. With over 5,250 patients enrolled, the study found that 47% of patients with AR frequently reported cough as a symptom; however, only 11% of these patients had cough as the main reason for seeking medical care.[1993] The numbers were 61% and 33%, respectively, for patients with asthma and cough. In a prospective study with 2,713 AR patients, He et al[1994] found the occurrence of comorbidities, including cough, to gradually increase from mild intermittent, to mild persistent, to moderate-severe intermittent, and moderate-severe persistent AR.[1994]

There is low level evidence that associates AR with cough or, more commonly, cough as a comorbidity of AR.[1990-1992] The severity of AR may affect its manifestation towards upper airway cough syndrome.[1994] AR is often a comorbidity with asthma which also has an increased correlation with cough. The exact pathways and mechanisms by which the unified airway functions continue to unfold.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3b: 2 studies; Level 4: 4 studies; Level 5: 1 study; *Table X.H.*).

1 **Table X.H. Evidence for the association between allergic rhinitis and cough**

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
He et al[1994]	2016	2b	Cohort, prospective nonrandomized	AR patients (n=2,713)	sIgE, questionnaire	*D. pteronyssinus* was the most common offending allergen. The occurrence cough increased with increasing AR severity.
Passali et al[1986]	2011	2b	Individual cohort	159 patients from 9 otolaryngology and pulmonary centers	Standardization of diagnostic approach for rhino-bronchial syndrome	Increased frequency of rhino-bronchial síndrome with allergic disease (37.9% vs 20.9%). Cough was a frequent symptom (96%).
Krzych-Falta et al[1989]	2015	3b	Case-control	1. AR (n=30) 2. control (n=30)	Safety evaluation of nasal allergen challenge	In early phase of allergic reaction, extra-nasal symptoms were observed (cough, breathlessness), especially in PAR patients.
Chakir et al[1991]	1996	3b	Case-control	1. nonasthmatic subjects with SAR (n=8) 2. allergic asthmatics (n=6) 3. controls (n=5)	Immunohistochemical analysis of the distribution of collagens, laminin, and fibronectin in bronchial biopsy specimens	Content of type I and III collagens was increased in rhinitic subjects compared with controls, suggesting active structural remodeling in the lower airways of AR patients.
Cho et al[1993]	2016	4	Case series	Patients ages ≥18 years with asthma, AR, COPD, or rhinosinusitis (n=5250)	Patient and physician surveys	Report of cough symptom: COPD (73%), followed by asthma (61%), rhinosinusitis (59%), AR (47%). Cough as the main reason for seeking medical care: COPD (43%), asthma (33%), rhinosinusitis (13%), and AR (11%).
Ghoshal et al[1988]	2016	4	Case series	Patients ages ≥18 years with asthma, AR, COPD, or rhinosinusitis (n=1000)	Survey regarding symptoms, healthcare resource utilization, work productivity, activity impairment. Cost analysis.	Asthma was the most frequent primary diagnosis followed by AR, COPD, and rhinosinusitis. 33.5% patients were diagnosed with combinations of the four respiratory diseases.
Lin et al[1987]	2016	4	Case series	Patients ages ≥18 years with asthma, AR, COPD, or rhinosinusitis (n=1001)	Survey regarding symptoms, healthcare resource utilization, work productivity, activity impairment.	AR was the most frequent primary diagnosis (31.2%). Cough was the primary reason for the medical visit for patients with asthma and COPD. Nasal symptoms were the primary reasons for AR and rhinosinusitis.
Chakir et al[1990]	2000	4	Case series	Adults with SAR, non-asthmatic (n=12)	Immunohistochemistry and cytokine expression of bronchial biopsy specimens.	Natural pollen exposure is associated with an increase in lymphocyte numbers, eosinophil recruitment and IL-5 expression

						in the bronchial mucosa of non-asthmatic subjects with SAR.
Buday et al[1992]	2016	5	Bench research	30 guinea pigs divided into the HDM-sensitized group, OVA-sensitized group, and control group	Symptoms of AR induced by intranasal application of 15 µl 0.5 % HDM and cough challenges with citric acid. Airway resistance measurements.	Both HDM and OVA-sensitized groups showed a significantly enhanced nasal reactivity and cough response compared with controls. The airway resistance data did not show significant differences.

LOE: level of evidence; AR: allergic rhinitis; sIgE: allergen-specific immunoglobulin E; PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; COPD: chronic obstructive pulmonary disease; IL: interleukin; HDM: house dust mite; OVA: ovalbumin

X. I. Laryngeal disease

AR has been implicated as a cause of laryngeal disease. However, further understanding of its precise role has been limited. While previous research has provided anecdotal evidence of a relationship between the two, establishing a causal relationship between AR and laryngeal dysfunction had proven difficult due to a lack of safe and effective models for studying the larynx.[1995] Findings of laryngeal inflammation have largely been attributed to laryngopharyngeal reflux (LPR), but various etiologies may contribute to laryngeal dysfunction.

Vocal dysfunction can have a significant psychosocial impact on patients, including those with AR. Several studies have reported higher Voice Handicap Index (VHI) scores in patients with AR compared to control subjects.[1996-1999] Dysphonia is particularly disturbing for professional voice users. Singers with self-perceived voice issues were 15% more likely to have AR than singers without vocal complaints.[2000] The likelihood of AR increased as the number of vocal symptoms increased.[2000] When comparing patients with AR and NAR to control patients, Turley et al[2001] found that dysphonia was more prevalent in patients with asthma. A prior study had similar overall findings in patients with AR while controlling for asthma.[2002] Studies have reported the adverse effects of AR on voice-related QOL, and Turley et al validated this by showing that patients who reported poor rhinitis-related QOL on questionnaires also had poor voice-related QOL and more severe chronic laryngeal symptoms.[1996,1998,2001] The greater the degree of allergen load, the greater severity of vocal symptoms.[1999] Overall, patients with vocal dysfunction have a higher than anticipated incidence of AR and vice versa.[1999,2001,2002] **[Table X.I.]**

Allergic laryngitis can be difficult to distinguish from other laryngeal inflammatory disorders, including LPR, due to the limitations of current diagnostic methods, which overall have poor specificity and inter-rater reliability. In a study of patients presenting with voice complaints, Randhawa et al[2003] noted that two-thirds of patients were diagnosed with allergies whereas only one-third were diagnosed with LPR. However, allergy testing may be positive in up to 46% of the general population.[2004] Laryngeal findings in AR and LPR can be indistinguishable and include laryngeal edema, excessive mucus, vocal fold erythema, and arytenoid erythema.[1995,2005] A study by Eren et al[2005] supported this diagnostic challenge in demonstrating no significant difference in the appearance of the larynx between allergy-positive and LPR-positive subjects; however, thick endolaryngeal mucus has been shown to be a predictor of allergy. Belafsky and colleagues examined the effects of *Dermatophagoides* on the laryngeal mucosa of guinea pigs and found an increase in eosinophilia compared to those exposed to saline, which provides some support for etiologies other than reflux contributing to laryngeal disease.[2006,2007] In contrast, Krouse et al[1998] were unable to demonstrate a difference in acoustic and speech aerodynamic testing or videostroboscopic evaluation between allergic patients compared to control subjects.

Despite anecdotal evidence implicating the role of allergic laryngitis in laryngeal dysfunction, there have been limited studies demonstrating a direct causal relationship between the two. Three studies with similar design evaluated the symptoms and laryngeal appearance and function in patients with proven allergies exposed to direct laryngeal stimulation by the nebulized allergen *Dermatophagoides pteronyssinus.*[2008-2010] Initially, Reidy et al[2009] were unable to find any significant difference between antigen and placebo challenged subjects on any of the evaluated measures, including VHI, Sinus Symptoms Questionnaire, laryngoscopic findings, and acoustic and speech

aerodynamic testing. In a subsequent study, Dworkin et al[2010] increased the concentration of allergen in the antigenic suspension and noted an increase in endolaryngeal mucus in addition to coughing and throat clearing. The study was terminated prematurely due to adverse pulmonary reactions attributed to the higher antigen concentration, and it is possible that the lower airway reactivity contributed to the visualized endolaryngeal mucus.[2010] Roth et al[2008] then performed a study using similar methods but isolated the larynx by utilizing a nose clip to ensure oral inhalation and by eliminating patients with reactive airways based on methacholine challenge testing. They demonstrate an apparent causal relationship between allergen stimulation and impaired vocal function.[2008]

There is mounting evidence suggesting a relationship between AR and laryngeal dysfunction. There have not been consistently reported laryngeal findings specific to allergic laryngitis, though thick endolaryngeal mucous should raise suspicion for allergy as a cause. Although its exact role in the pathophysiology of laryngitis has yet to be fully elucidated, AR should be considered in the differential diagnosis of patients with vocal complaints as it may have implications on treatment of laryngeal disease.

- Aggregate Grade of Evidence: C (Level 2b: 8 studies; Level 3a: 1 study; Level 3b: 4 studies; Level 4: 5 studies; *Table X.I.*).

Table X.I. Evidence for an association between allergic rhinitis and laryngeal disease

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Roth et al[2008]	2013	2b	RCT	Patients responding to an advertisement	Effect of allergen on larynx	Relationship between allergen exposure and impaired vocal function independent of asthma or nasal exposure.
Dworkin et al[2010]	2009	2b	RCT	Adults testing positive for HDM allergy: 1. *D. pteronyssinus* challenge 2. placebo challenge	Effect of allergen on larynx	Laryngeal abnormalities occurred secondary to lower respiratory stimulation.
Krouse et al[1998]	2008	2b	Prospective cohort	1. HDM allergy, (+) skin test 2. No HDM allergy	Effect of allergen on larynx	Significant changes in VHI in patients with HDM allergy. Findings present among subjects without symptomatic LPR/GERD.
Millqvist et al[1996]	2006	2b	Case-control	1. birch pollen allergy 2. control	Prevalence of vocal dysfunction	Statistically significant differences in VHI between allergic patients and controls.
Reidy et al[2009]	2003	2b	RCT	1. *D. pteronyssinus* challenge 2. placebo challenge	Effect of allergen on larynx	No significant differences between antigen and placebo exposed subjects on any measure.
Roth & Ferguson[1995]	2010	3a	Systematic review	Relationship of allergy and laryngeal disease	not applicable	Further investigations into mechanisms mediating laryngeal response to allergy are necessary.
Brook et al[2011]	2015	3b	Retrospective case-control	1. atopic patients 2. non-atopic patients	Endoscopic findings in AR	Findings within the nasopharynx, rather than the larynx, are predictive of positive atopic status.
Koc et al[1997]	2014	3b	Case-control	1. AR patients 2. control	Laryngeal findings in AR	AR patients had higher incidence of dysphonia and mean VHI.
Turley R et al[2001]	2011	3b	Case-control	1. patients with rhinitis symptoms, (+) and (–) allergy tests 2. patients without rhinitis	Prevalence of dysphonia	Patients with AR or NAR had higher prevalence of dysphonia versus controls. Patients with worse rhinitis symptoms had worse voice-related QOL and more severe chronic laryngeal symptoms.
Hamdan et al[2000]	2006	3b	Retrospective case-control	1. singers without vocal symptoms 2. singers with vocal symptoms	Symptom prevalence	Incidence of AR in singers is high. Occult allergies may affect professional voice.
Brook et al[2004]	2016	4	Retrospective case series	Patients undergoing *in vitro* allergy testing	Symptom prevalence	Yield of *in vitro* allergy testing for laryngeal symptoms comparable to other common allergy testing indications.
Eren et al[2005]	2014	4	Case series	Patients referred from allergy clinic with SPT testing	Laryngeal findings in AR and LPR	Thick endolaryngeal mucus was a predictor of allergy. No association between allergic sensitization and presence of LPR. No significant difference in laryngeal appearance between allergy-positive and LPR-positive individuals
Randhawa et al[2003]	2010	4	Case series	Patients with primary voice disorder or globus sensation	Prevalence of AR and LPR	Three times as many patients had allergies compared with LPR, no statistical signigicance.

Randhawa et al[1999]	2010	4	Cross sectional	Patients presenting to rhinology clinic, no prior voice-related symptoms	Allergy and vocal dysfunction association	The degree of allergen load correlates with the severity of vocal symptoms, as per an increase in score on the VHI.
Simberg et al[2002]	2007	4	Cross sectional	1. allergy patients in AIT program 2. non-allergic controls	Symptom prevalence	Individuals with allergies had more severe vocal symptoms than non-allergic controls. Patients who had undergone AIT >2 years had fewer symptoms.
Jackson-Menaldi et al[2012]	1997	4	Prospective cohort	Subjects referred to voice center with a voice problem	Association between AR, LPR, laryngeal findings	Could not determine causative relationship between allergy and vocal symptoms.
Belafsky et al[2006]	2015	5	Bench research	Guinea pigs exposed to: 1. saline (allergen control) + filtered air (pollution control) 2. HDM + filtered air 3. saline + combustion particulates 4. HDM + combustion particulates	Mean eosinophilic profile in the glottic, subglottic, tracheal epithelium and submucosa	Iron soot and HDM resulted in eosinophilia in glottic, subglottic, and tracheal epithelium and submucosa.
Mouadeb et al[2007]	2009	5	Bench research	Guinea pigs exposed to intranasal HDM for 9 weeks	Histopathologic findings	Twice as much eosinophilia in supraglottis in animals exposed to HDM versus saline.

LOE: level of evidence; RCT: randomized controlled trial; HDM: house dust mite; VHI: Voice Handicap Index; LPR: laryngopharyngeal reflux; GERD: gastroesophageal reflux; AR: allergic rhinitis; NAR: non-allergic rhinitis; QOL: quality of life; SPT: skin prick test; AIT: allergen immunotherapy

X. J. Eosinophilic esophagitis

Eosinophilic esophagitis is an allergic inflammatory condition of the esophagus with infiltration of eosinophils. Symptoms include dysphagia, heartburn, and vomiting. Several studies have examined the prevalence of clinician-diagnosed AR and aeroallergen sensitization in patients with eosinophilic esophagitis (EoE). **[Table X.J.]** Among both pediatric and adult patients with EoE, it has consistently been found that 50 to 75 percent have AR.[2013-2020] Although many of these studies were case series, the consistency of the findings strongly suggests that most patients with EoE have comorbid AR.

The evidence for an association between environmental allergies and EoE pathogenesis is less clear. A few case series, among both children and adults, have observed seasonal peaks of EoE diagnosis in the spring and summer.[2021-2023] One of these studies found that EoE diagnosis was correlated with grass pollen counts.[2021] Another showed that esophageal eosinophilia on biopsies was least intense in the winter.[2023] There is one reported case of a pediatric EoE patient whose symptoms flared seasonally, in whom biopsies revealed moderate to severe esophageal eosinophilia during pollen seasons with no or mild inflammation in winter months, with no change in diet.[2024] Another case report described resolution of esophageal eosinophilia in a pediatric patient with EoE and dust mite sensitization after a course of high-dose dust mite immunotherapy.[2025] Therefore, there is very limited observational data suggesting a potential association between aeroallergens and EoE pathogenesis, but more study is needed.

- Aggregate Grade of Evidence: C (Level 3a: 1 study; Level 4: 12 studies; *Table X.J.*)

1 **Table X.J. Evidence for the association between allergic rhinitis and eosinophilic esophagitis**

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Evidence of AR prevalence in patients with EoE						
Furuta et al[2015]	2007	3a	Systematic review	Adult and pediatric patients with EoE	Demographic and clinical characteristics	50-80% had AR and sensitization to aeroallergens
Spergel et al[2013]	2009	4	Case series	Pediatric patients with EoE (n=562)	Demographic and clinical characteristics	68% were atopic and 43% had AR
Roy-Ghanta et al[2014]	2008	4	Case series	Adult patients with EoE (n=23)	Demographic and clinical characteristics	78% had allergic rhinitis; 86% were sensitized to aeroallergens
Assa'ad et al[2016]	2007	4	Case series	Pediatric patients with EoE (n=89)	Demographic and clinical characteristics	79% were sensitized to environmental allergens
Plaza-Martin et al[2017]	2007	4	Case series	Pediatric patients with EoE in Spain (n=14)	Demographic and clinical characteristics	93% had AR and sensitization to aeroallergens
Sugnanam et al[2018]	2007	4	Case series	Pediatric patients with EoE in Australia (n=45)	Demographic and clinical characteristics	93% had AR
Remedios M et al[2019]	2006	4	Case series	Adult patients with EoE in Australia (n=26)	Demographic and clinical characteristics	77% were atopic and 54% had AR
Guajardo et al[2020]	2002	4	Case series	Adult and pediatric patients with EoE in worldwide registry (n=39)	Demographic and clinical characteristics	64% had AR
Evidence for role of aeroallergens in EoE pathogenesis						
Ramirez & Jacobs[2025]	2013	4	Case report	A pediatric patient with EoE and dust mite allergy treated with dust mite immunotherapy	Eosinophils on esophageal biopsies	Resolution of esophageal eosinophilia was observed after course of dust mite immunotherapy
Moawad et al[2021]	2010	4	Case series	Adult patients with EoE (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[2022]	2009	4	Case series	Adult patients with EoE (n=41)	Season of EoE diagnosis	68% diagnosed in spring and summer versus 32% in fall and winter
Wang et al[2023]	2007	4	Case series	Pediatric patients with EoE (n=234)	Season of EoE diagnosis and biopsy findings by season	Significantly fewer patients diagnosed with EoE in Winter versus spring, summer, and fall; least intense esophageal eosinophilia in winter
Fogg et al[2024]	2003	4	Case report	Pediatric patient with EoE	Seasonal biopsy findings	Increased esophageal eosinophilia during pollen seasons

LOE: level of evidence; AR: allergic rhinitis; EoE: eosinophilic esophagitis

X. K. Sleep disturbance and obstructive sleep apnea

Nasal congestion is reported by as many as 90% of AR patients.[2026] Nocturnal nasal congestion can significantly affect sleep quality. Nasal obstruction due to AR has been well established as a cause of sleep disruption.[707,714,2026] One population-based survey study of children with AR identified sleep disturbance due to AR as a significant factor affecting health-related QOL.[2027] Diminished sleep quality resulting from AR has been shown to negatively impact work performance and productivity.[2028] Another population-based study found that patients with AR were more likely to report suffering from insomnia, snoring and sleep apnea than control groups.[727] The severity of AR symptoms was also shown to affect the duration of sleep, frequency of daytime somnolence and sleep latency. The influence of AR on sleep is multifactorial. Upper airway resistance, biochemical and hormonal effects, and pharmacologic interventions all play a role in altering sleep. A large population-based survey of AR patients demonstrated a strong correlation between AR disease severity and sleep disturbance.[679] The study showed that increasing severity of AR symptoms caused worse sleep quality.

When establishing a diagnosis of AR, the impact of allergy symptoms on sleep should be assessed by detailed history. There are several different instruments, which have been used to assess the impact of AR on sleep. These include: the ESS, Stanford Sleepiness Score, Jenkins Questionnaire, Pittsburgh Sleep Quality Index, University of Pennsylvania Functional Outcomes of Sleep, Sleep scale from the Medical Outcome Study, Sleep Disorders Questionnaire, The Pediatric Sleep Questionnaire, and The Pediatric Daytime Sleepiness Scale. These metrics may be useful in establishing baseline symptoms and monitoring a response to treatment.

There have been several studies that have investigated the relationship between AR and sleep-disordered breathing (SDB). **[Table X.K.]** SDB refers to a spectrum of conditions including primary snoring, upper airway resistance syndrome, and obstructive sleep apnea. In a population-based analysis, Young et al[714] found that moderate-to-severe SDB were 1.8 times more frequent in participants with nasal congestion due to allergy. In a small case series of patients with SAR who underwent repeat PSG, patients with symptomatic AR had an average 1.7 obstructive apneas per hour of sleep that decreased to 0.7 per hour when patients were symptom free.[718] A 2011 case-control study assessing differences in polysomnography between persistent AR sufferers and healthy controls found no statistically significant difference in apnea-hypopnea index (AHI) between the two groups.[720] There were modest differences in sleep efficiency, arousal index, and snoring time.

A standard approach to the treatment of AR should help to decrease or alleviate the symptoms that adversely impact sleep. Medications that act to treat nasal congestion are typically effective at improving sleep quality. INCS have been shown to improve nasal congestion, daytime somnolence, and sleep quality.[2029] INCS are also thought to improve sleep quality by reducing pro-inflammatory cytokines, which have been shown to negatively impact sleep.[2030] There have been five RCTs assessing the efficacy of ICS on nasal congestion and sleep.[673,706,707,1275,1276] The results of all five studies demonstrated an improvement in sleep quality and sleep-related QOL metrics. A meta-analysis by Weiner et al[1297] found that INCS were more effective than oral antihistamines at treating nasal blockage, although there was no significant differences between treatments on nasal resistance.

The pharmacologic interventions used in the treatment of AR may also have consequences on sleep. The first generation H_1 antagonists are known to cause sedation due to the capability of crossing

the blood-brain barrier and acting as a depressant on the central nervous system leading to drowsiness.[2031] While this may be a desirable side effect at bedtime, it is an undesirable consequence for daytime symptom management. The second-generation H_1 antagonists have less propensity for crossing the blood-brain barrier and are therefore less sedating. Fexofenadine and loratadine are reported as the least sedating oral antihistamine treatment options.[2032,2033] Patients should be counseled regarding the potential for sedation when taking oral H_1 antihistamines. There has been one RCT study looking at pseudoephedrine (taken in the morning) and the impact on sleep quality, daytime somnolence, and fatigue. The study found no significant negative or positive impact on all measures compared to placebo.[2030] There was a statistically significant beneficial effect on nasal congestion.

The impact of AR on sleep should be assessed by history, sleep and QOL questionnaires and careful physical examination. A standard treatment algorithm for symptomatic management of AR should be effective at improving the symptoms which adversely affect sleep. INCS are the most effective pharmacologic therapy for alleviating nasal congestion. Patients treated with oral antihistamines should be mindful of the potential for sedation.

- Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 2c: 5 studies; Level 3b: 7 studies; Level 4: 2 studies; *Table X.K.*)

Table X.K. Evidence for an association between allergic rhinitis and sleep disturbance

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Yamada et al[673]	2012	1b	RCT	PAR, adults (n=57)	ESS and RQLQ	INCS mometasone significantly improves nasal symptoms, QOL, sleep quality, and upper airway condition.
Meltzer et al[1276]	2010	1b	RCT	PAR, adults (n=30)	PSG, ESS, RQLQ-S and WPAI-AS	INCS mometasone improves nasal symptoms and sleepiness.
Craig et al[1275]	2003	1b	RCT	AR, adults (n=32)	PSG, ESS, RQLQ, direct sleep questions in daily diary	Improvement in NC and sleep with treatment with topical nasal fluticasone
Hughes et al[706]	2003	1b	RCT	PAR, adults (n=22)	ESS, SSS, FOSQ, RQLQ	INCS budesonide improved daytime fatigue, somnolence and quality of sleep.
Craig et al[707]	1998	1b	RCT	PAR, adults (n=20)	Direct sleep questions in daily diary	Improvement in congestion and sleep with treatment with INCS flunisolide.
Sherkat et al[2030]	2011	2b	RCT	AR, adults (n=14)	ESS, PSQI, FOSQ, RQLQ, NRQLQ, Pennsylvania Quality of Life, direct sleep questions in daily diary	Sleep quality is not significantly affected by pseudoephedrine.
Colas et al[726]	2012	2c	Population-based	AR, adults (n=2,275)	PSQI RQLQ, direct sleep questions based on Epworth scale	Moderate-severe AR and NC are associated with worse sleep quality.
Meltzer et al[2027]	2009	2c	Population-based	AR, children (n=1,004)	Direct sleep questions by telephone interviews	AR disrupts the pattern and quality of sleep.
Bousquet et al[2028]	2006	2c	Population-based	AR, adults (n=3,052)	Jenkins Questionnaire, RQLQ, WPAI-AS	The severity of the AR has more effect on QOL and sleep, than the duration (intermittent/persistent).
Leger et al[727]	2006	2c	Population-based	AR, adults (n=591)	ESS, Sleep Disorders Questionnaire, Score for Allergic Rhinitis	All dimensions of sleep were impaired by AR, and more impaired in severe AR than in mild AR.
Young et al[714]	1997	2c	Population-based	Adults (n=4,927)	PSG, direct sleep questions	Moderate-to-severe SDB was 1.8 times more frequent in participants with NC due to allergy.
Ishman et al[2034]	2012	3b	Case-control	AR, children (n=21)	PSQ, PDSS, Obstructive Sleep Apnea-18	AR children have higher SDB and sleepiness scores.
Meng et al[720]	2011	3b	Case-control	PAR, adults (n=98)	PSG	Differences in most PSG parameters including sleep efficiency, arousal index, and snoring time, statistically significant (though clinically modest).

Yuksel et al[2035]	2009	3b	Case-control	SAR, children (n=14)	PSQI and Actigraphy	Sleep dysfunction scores, sleep latency and fragmentation index are significantly higher in the AR group.
Benninger & Benninger[2036]	2009	3b	Case-control	AR, adults (n=701)	RSDI and sleep question by RSDI	AR has a significant negative impact on sexual function, sleep and fatigue.
Meltzer et al[2037]	2009	3b	Case-control	AR, adults (n=7,024)	MOS-Sleep and mRQLQ	AR adversely affects QOL and sleep parameters.
Shedden[2026]	2005	3b	Case-control	AR, adults and children (n=2,355)	Direct sleep questions	>80% with NC affected in some way at night, primarily causing them to wake up or made it difficult to fall asleep.
Stuck et al[731]	2004	3b	Controlled trial	SAR, adults (n=50)	ESS, SF-36, PSG	SAR increases daytime sleepiness, and worsens QOL.
Stull et al[682]	2009	4	Case series	AR, adults (n=404)	MOS-Sleep, NRQLQ, WPAI-AS, PANAS-X	Those with more severe NC or ocular symptoms report poorer scores on sleep domains.
McNicholas et al[718]	1982	4	Case- series	SAR, adults (n=7)	PSG	In patients with SAR, obstructive sleep apneas are more frequent during a period of symptomatic nasal obstruction.

LOE: level of evidence; RCT: randomized controlled trial; PAR: perennial allergic rhinitis; ESS: Epworth Sleepiness Scale; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; INCS: intranasal corticosteroid; QOL: quality of life; AR: allergic rhinitis; PSQI: Pittsburgh Sleep Quality Index; FOSQ: Functional Outcomes of Sleep; NRQLQ: Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire; PSG: polysomnogram; RQLQ-S: Standardized Rhinoconjunctivitis Quality of Life Questionnaire; WPAI-AS: Work Productivity and Activity Impairment Questionnaire - Allergy-Specific; NC: nasal congestion; SSS: Stanford Sleepiness Score; SDB: sleep didordered breathing; PSQ: Pediatric Sleep Questionnaire; PDSS: Pediatric Daytime Sleepiness Scale; SAR: seasonal allergic rhinitis; RSDI: Rhinosinusitis Disability Index; MOS-Sleep: Sleep Scale from the Medical Outcomes Study; mRQLQ: mini- Rhinoconjunctivitis Quality of Life Questionnaire; SF-36: Medical Outcomes Study 36-item Short Form health survey; PANAS-X: Positive and Negative Affect Schedule-Expanded Form

XI. Knowledge gaps and research opportunities

The existing literature related to AR is quite deep in certain areas but notably lacking in othes. **[Table XI.]** We continue to see more and more citations related to AR every year, yet the process undertaken to produce this ICAR:AR document has identified some important knowledge gaps. The sections below highlight the need for future research related to specific aspects of AR.

XI. A. Epidemiology and Risk Factors

Studies have previously been undertaken to determine the prevalence of AR in various parts of the world. While the data from these studies is often quoted, it is limited by its methodology relating primarily to surveys (sometimes complemented by allergen sensitivity testing). Our world is better connected by technology today than it had been previously. We should leverage these capabilities to better understand the epidemiology of AR. Research opportunities include:

- Improved understanding of the incidence and prevalence of AR and its phenotypes (i.e. SAR, PAR, IAR, PER) worldwide.
- Improved understanding of AR variation by geographic region, patient age, and sex.
- Evaluation of climate change and its effect on the pattern and degree of allergen exposure.

Our understanding of the risk factors for the development of AR should also be improved. While certain areas (i.e. early childhood exposure to pets as a risk factor vs protective factor) have seen numerous articles published, the data is highly conflicting. In other areas, such as early exposure to pollens and mites, the data is more limited. Genetic studies provide some notable evidence for potential AR risk but functional data needs to be expanded. Research opportunities include:

- Understanding the role of candidate gene alterations in the pathophysiology of AR via functional characterization.
- Investigation of epigenetic mechanisms to provide a functional explanation between gene-environment interactions and AR disease development.
- Improved understanding of environmental exposures as a risk/protective factor for AR disease development, especially in diverse geographic locations.
- Further study of the role of pollutants and tobacco smoke in the development of AR and in the severity of allergic rhinitis symptoms.
- Greater elucidation of the environmental risk factors and protective factors for AR, particularly exposure to pets, HDM, and breastfeeding.
- Longitudinal study evaluating risk factor reduction and its effect on the incidence of AR.

XI. B. Evaluation and Diagnosis

Evaluation of the patient with suspected AR classically relies on a thorough history, often reinforced by findings on physical examination. The diagnosis is further supported with skin or *in vitro* testing methods. These techniques have been rather dependable, provided objective testing is correlated to the patient's clinical symptoms and not used in isolation to determine a treatment plan, as there are distinct differences between sensitization and clinical allergy. As newer testing methods gain their footing, we have the opportunity to bring them to widespread clinical practice with solid supporting evidence. Research opportunities include:

- Improved characterization of newer testing techniques (i.e. nasal sIgE, BAT) in larger populations to provide standardization for incorporation into mainstream clinical practice.
- Need for comparative studies for IDT and single dilution intradermal testing.
- Further study of the role of single intradermal testing after a negative prick test.
- Development of standardized testing and interpretation of testing for LAR, as well as further defining the clinical utility of testing.
- Further elicudation of clinical uses for CRD in patient management.
- Need for international consensus on allergen units in antigen standardization.

XI. B. Management

There are several options for management of the AR patient. Allergen avoidance and EC strategies are often discussed, yet high-level evidence is frequently lacking, especially as it relates to AR symptom control. Many pharmacotherapy options have very high LOEs, which is helpful as we strive to choose the best drug options to control patient symptoms. SCIT and SLIT also have very high LOEs in general, yet specific issues related to AIT management could be bolstered with additional evidence. Research opportunities include:

- Improved understanding of the impact of EC strategies on AR symptom control and rescue medication use, especially for cockroach, pet, and pollen allergens.
- Improved understanding of the polyallergic AR patient and appropriate AIT regimens in this population.
- Improved understanding and characterization of ILIT for possible routine clinical application.
- Further study of comparative efficacy/effectiveness of SLIT versus SCIT.
- Further study of AIT with multiple allergens.
- Improved understanding of cost effective management for optimal AR control and the use of multimodality therapy, including combinations of pharmacotherapy and AIT.
- Further study of the comparative effectiveness of various AR treatments.

XI. B. Associated conditions

The evidence supporting an association between AR and numerous other conditions is weak or conflicting. There is clearly a need to better define the relationship between AR and several of the comorbidities identified in this document (especially rhinosinusitis, otitis media with effusion, cough, laryngeal disease, and eosinophilic esophagitis), and to further delineate the role that AR treatment has for potential improvement of associated conditions.

Conclusion. In summary, the authors of ICAR:AR have worked to collate the best external evidence for various aspects of AR, providing evidence grades and recommendations where appropriate. From this evidence, knowledge gaps and research opportunities have been identified. It is our sincere hope that the ICAR:AR document will be a reference for understanding the current AR evidence and a springboard for future investigation.

Table XI. Aggregate grades of evidence and recommendation levels

Topic	# of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
Risk factors for AR				
Genetics	5 (GWAS)	C	-----	Some genes have been associated with development of AR and other atopic diseases.
In utero or early exposure (mites)	6	C	-----	Data inconclusive.
In utero or early exposure (pollen)	2	C	-----	Data inconclusive.
In utero or early exposure (animal dander)	39	C	-----	Data inconclusive.
In utero or early exposure (fungal allergens)	13	C	-----	Data inconclusive.
Restricted diet (during pregnancy and early childhood)	5	A	-----	Maternal diet restriction while child the is *in utero* does not influence the development of AR. Food allergy during childhood is a risk factor for AR.
Pollution	14	C	-----	Data inconclusive.
Tobacco smoke	9	A	-----	Most studies found no association between active or passive tobacco smoke exposure and AR. Specific patient populations and temporal variations (i.e. length of exposure) should be further evaluated.
Socioeconomic status	10	C	-----	Most studies show an association between high SES and AR, but this is not a consistent finding across all studies.
Potential protective effect on the development of AR				
Breastfeeding	2 (SRs)	C	Option	Option for breastfeeding for the specific purpose of AR prevention. In general, breastfeeding has been strongly recommended due to its multiple beneficial effects.
Pet exposure	6	C	-----	No evidence that pet avoidance in childhood prevents AR later in life. Early pet exposure, especially dog exposure in non-allergic families early in childhood, may be protective.
Microbial diversity ("Hygiene Hypothesis")	15	B	-----	Microbial diversity of the skin, airways and gut is important for the prevention of sensitization and allergic disease in populations.
Disease burden				

Quality of life	33	B	Recommendation	AR has significant effects on general and disease-specific QOL Treatment of AR is recommended to improve QOL.
Effect on sleep	46	B	Recommendation	AR has significant negative effects on sleep. Treatment of AR is recommended to decrease sleep disturbance.
Evaluation and diagnosis				
Clinical examination (history and physical)	4	D	Recommendation	Despite the lack of studies to address clinical examination in the diagnosis of AR, history taking is essential and physical examination is recommended. Multiple prior guideline documents support this recommendation.
Nasal endoscopy	5	D	Option	Evidence does not support the routine use of nasal endoscopy for diagnosing AR. However, it may be helpful in ruling out other causes of symptoms.
Radiologic imaging	0	N/A	Recommend against	Radiologic imaging is not recommended for the diagnosis of AR.
Use of validated survey instruments	10	A	Strong recommendation	Validated survey instruments can be used to screen for AR, follow treatment outcomes, and as an outcome measure for clinical trials.
Skin prick testing	8	B	Recommendation	SPT is recommended for evaluation of allergen sensitivities in appropriately selected patients. The practitioner may decide whether skin or *in vitro* sIgE testing is best in an individual patient.
Skin intradermal testing	17	B	Option	Intradermal testing may be used to determine specific airborne allergen sensitization for individuals suspected of having AR.
Blended skin testing techniques	5	D	Option	MQT is a skin testing technique that may be used to determine a safe starting dose for AIT.
Serum total IgE (tIgE)	15	C	Option	Serum tIgE is an option to assess atopic status.
Serum antigen-specific IgE (sIgE)	7	B	Recommendation	Serum sIgE testing is recommended for evaluation of allergen sensitivities in appropriately selected patients. The practitioner may decide whether skin or *in vitro* sIgE testing is best in an individual patient.
Correlation between skin and *in vitro* testing	19	B	-----	Studies differ regarding the concordance of various allergy testing methods.

Nasal sIgE	24	C	Option	Nasal sIgE is an option in patients with suspected or known LAR to aid in diagnosis or guide therapy.
Basophil activation test	12	B	Option	BAT may be used for diagnosis when first-line tests are discordant, and for monitoring response to AIT.
Nasal provocation testing	4	C	-----	NPT has been employed for diagnosis of occupational rhinitis and LAR.
Nasal cytology	4	C	-----	Nasal cytology is an investigational tool, rather than diagnostic.
Nasal histology	11	B	-----	Nasal histology is used for research on the pathophysiology of AR but is not routinely used in clinical practice for the diagnosis of AR.
Management – avoidance measures and environmental controls				
House dust mite	12	B	Option	Concomitant use of acaricides and EC measures is an option for the treatment of AR.
Cockroach	11	B	Option	Combination of physical measures (bait traps, house cleaning) and education is an option for AR management related to cockroach exposure.
Pets	3	B	Option	Pet avoidances and EC strategies are an option for AR related to pets.
Pollen and occupational allergens	3	B	Option	Pollen and occupational allergen avoidance by EC strategies are an option for the treatment of AR.
Management – pharmacotherapy				
Oral H1 antihistamines	21	A	Strong recommendation	Newer-generation oral H1 antihistamines are strongly recommended for the treatment of AR.
Oral H2 antihistamines	6	B	No recommendation	Available data does not adequately address the question of benefit in the treatment of AR.
Intranasal antihistamines	44	A	Recommendation	Intranasal antihistamines many be used as first- or second-line therapy for the treatment of AR.
Oral corticosteroids	9	B	Recommend against	Due to the risks of oral steroid use, along with the availability of other pharmacotherapy options, this therapy is not recommended for routine AR management.
Injectable corticosteroids	13	B	Recommend against	Due to the risks of injectable steroid use, along with the availability of other pharmacotherapy options, systemic or intraturbinate injection of corticosteroids is not recommended for the routine treatment of AR.

Intranasal corticosteroids	53	A	Strong recommendation	INCS should be used as first-line therapy in the treatment of AR.
Oral decongestants	9	B	Option Recommend against	Option for pseudoephedrine for short-term treatment of AR symptoms. Recommend against phenylephrine, as it has not been shown to be superior to placebo.
Topical decongestants	4	B	Option	Option for topical IND use in the short-term for nasal decongestion. Chronic use carries a risk of RM.
Leukotriene receptor antagonists	31	A	Recommend against	LTRAs should not be used as monotherapy in the treatment of AR.
Cromolyn (DSCG)	22	A	Option	DSCG may be considered in the treatment of AR, particularly for patients with known triggers who cannot tolerate INCS.
Intranasal anticholinergic (IPB)	14	B	Option	IPB nasal spray may be considered as an adjunct to INCS in PAR patients with uncontrolled rhinorrhea.
Omalizumab	6	A	No indication	Omalizumab is not approved by the US FDA for the treatment of AR alone.
Nasal saline	12	A	Strong recommendation	Nasal saline is strongly recommended as part of the treatment strategy for AR.
Probiotics	28	A	Option	Probiotics may be considered in the treatment of AR.
Combination: oral antihistamine and oral decongestant	21	A	Option	Option, particularly for acute exacerbations with a primary symptom of nasal congestion.
Combination: oral antihistamine and INCS	5	B	Option	Combination equivocal over either drug alone.
Combination: oral antihistamine and LTRA	13	A	Option	Combination is an option for AR management, particularly in patients with comorbid asthma who do not tolerate INCS and are not well-controlled on oral antihistamine monotherapy.
Combination: INCS and intranasal antihistamine	12	A	Strong recommendation	Strong recommendation for combination therapy when monotherapy fails to control AR symptoms.
Acupuncture	15	B	Option	In patients who wish to avoid medications, acupuncture many be suggested as a possible therapeutic adjunct.
Honey	3	B	No recommendation	Studies are inconclusive and heterogeneous.

Herbal therapies	-----	-----	No recommendation	Multiple different herbs studied, with few studies for each specific therapy. Results are inconclusive.
Surgical treatment	12	C	Option	Turbinate reduction may be considered in AR patients with nasal obstruction who have failed medical management.
Management – allergen immnuotherapy				
Subcutaneous immunotherapy	8	A	Strong recommendation	Strong recommendation for SCIT in patients unable to obtain adequate relief from pharmacotherapy and those who would benefit from secondary disease-modifying effects.
Sublingual immunotherapy	25	A	Strong recommendation*	Strong recommendation for SLIT in patients unable to obtain adequate relief from pharmacotherapy. *Specific recommendations for various SLIT preparations and treatment effects given in Section IX.D.4.
Trans/epicutaneous immunotherapy	4	B	Recommend against	Limited studies show variable effectiveness, along with adverse reactions. Trans/epicutaneous immunotherapy is not recommended for AR treatment.
Intralymphatic immunotherapy	7	B	Option	Pending additional studies, ILIT may be a viable option for AR treatment in the clinical population.
Associated conditions				
Asthma – association with rhinitis	7	C	-----	Asthma is associated with AR and NAR.
Asthma – rhinitis as a risk factor	13	C	-----	AR and NAR are risk factors for developing asthma.
Asthma – benefit of AR treatment	-----	------	-----	See Section X.A.4. for specific recommendations.
Acute rhinosinusitis	5	C	-----	AR is thought to be a disease-modifying factor for ARS.
Recurrent acute rhinosinusitis	2	D	-----	Data inconclusive.
Chronic rhinosinusitis without nasal polyps	10	D	-----	Conflicting evidence for/against an association.
Chronic rhinosinusitis with nasal polyps	21	D	-----	Conflicting evidence for/against an association.
Conjunctivitis	7	C	-----	AC is a frequently occurring comorbidity of AR.
Atopic dermatitis	20	C	-----	There is evidence for an association between AR and AD.
Food allergy and PFAS	12	B	-----	There is evidence for a link between pollen allergy and PFAS.
Adenoid hypertrophy	11	C	-----	Data inconclusive.
Otologic conditions – Eustachian tube dys.	7	C	-----	There is a causal role for AR in some cases of ETD.

Otologic conditions – otitis media	16	C	-----	Relationship between AR and OTE is unclear.
Otologic conditions – Meniere's disease	8	C	-----	Evidence for an association is of low grade, with substantial defects in study design.
Cough	9	C	-----	Low level evidence for an association between AR and cough.
Laryngeal disease	18	C	-----	There is some evidence for an association between AR and laryngeal disease.
Eosinophilic esophagitis	13	C	-----	Limited observational data suggests a potential association between aeroallergens and EoE pathogenesis.
Sleep disturbance and OSA	20	B	-----	Sleep disturbance is associated with AR.

AR: allergic rhinitis; GWAS: genome-wide association studies; SES: socioeconomic status; SR: systematic review; QOL: quality of life; SPT: skin prick test; sIgE: antigen-specific immunoglobulin E; MQT: Modified Quantitative Testing; AIT: allergen immunotherapy; tIgE: total immunoglobulin E; LAR: local allergic rhinitis; BAT: basophil activation test; NPT: nasal provocation testing; EC: environmental controls; INCS: intranasal corticosteroids; IND: intranasal decongestants; RM: rhinitis medicamentosa; LTRA: leukotriene receptor antagonist; DSCG: disodium chromoglycate; IPB: ipratropium bromide; PAR: perennial allergic rhinitis; US: United States; FDA: Food and Drug Administration; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; ILIT: intralymphatic immunotherapy; NAR: non-allergic rhinitis; ARS: acute rhinosinusitis; AC: allergic conjunctivitis; AD: atopic dermatitis; PFAS: pollen-food allergy syndrome; ETD: Eustachian tube dysfunction; OTE: otitis media with effusion; EoE: eosiniphilic esophagitis

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