

Current Evidence in Allergic Rhinitis Brought to you by the ARS/AAOA Education Committees

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International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis

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Section I pg. 113 Introduction

- ▶ There is a wide variety in the type and quality of the growing literature on allergic rhinitis (AR)
- ▶ The International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) was developed to summarize the best evidence relating to AR.
- ▶ More than 100 international authors evaluated the evidence using a structured review process.



Introduction

- ▶ This document summarizes findings of meta-analyses and other systematic reviews to provide recommendations based on the best AR evidence
- ▶ High value placed on strength of evidence
- ▶ Similar to the 2016 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS), this is not a clinical practice guideline or meta-analysis
- ▶ **Practitioners are able to use this evidence-based knowledge to provide support for treatment**



Section II Methods

II.A. pg. 114 Topic development

- ▶ The 2011 Rudmik and Smith evidence-based review with recommendations (EBRR) method was utilized as the foundation for ICAR:AR
- ▶ AR was divided into 103 topics/content areas
- ▶ Section topics were assigned to senior authors who reviewed the literature using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standardized guidelines

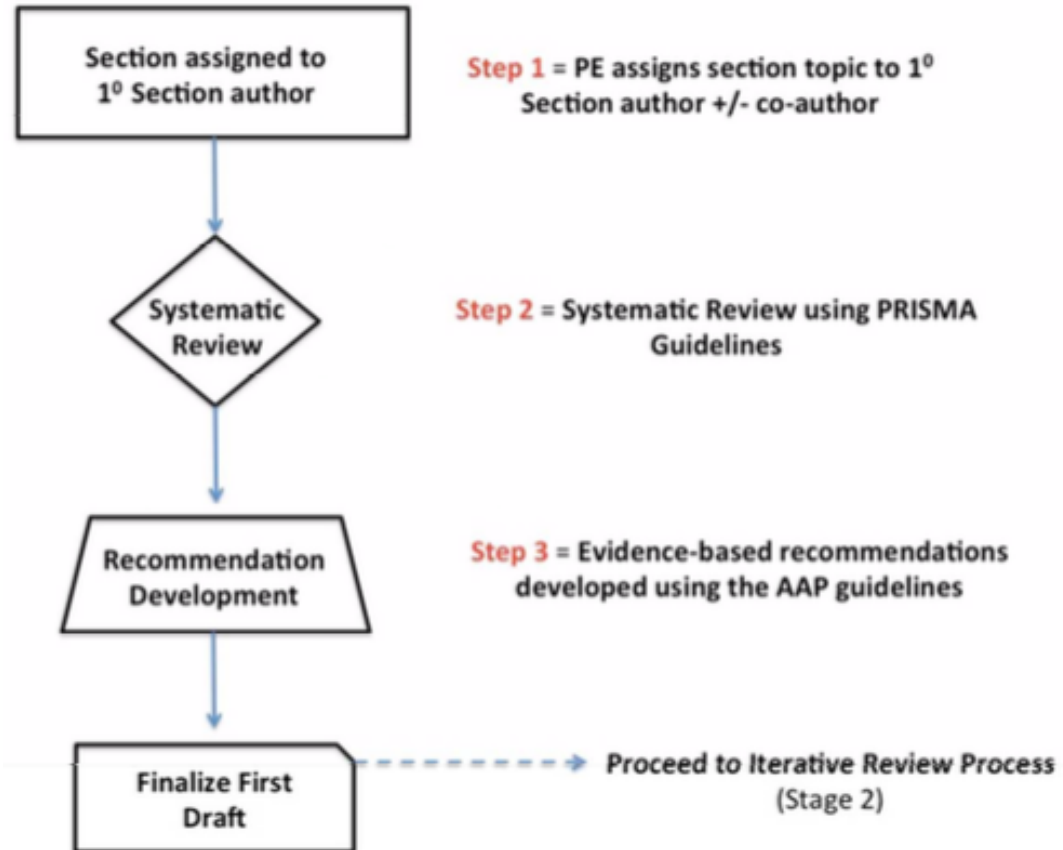


Topic development

- ▶ An aggregate level of evidence was produced for each topic guidelines from the American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM)
- ▶ A recommendation using the AAP SCQIM guidelines was then produced



Topic development



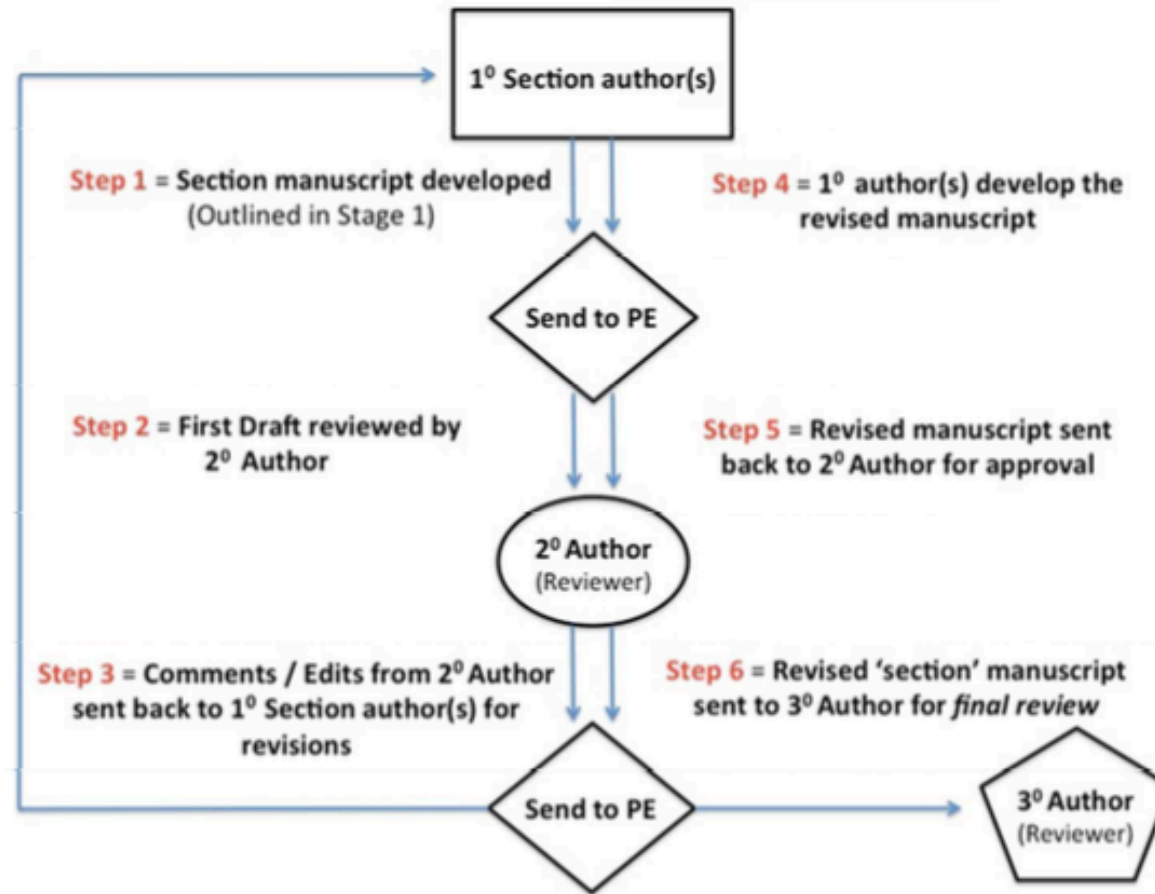
Section II Methods

II.B. pg. 115 Iterative review

- ▶ Each section underwent a two-stage online iterative review process using two independent reviewers
- ▶ The purpose was to evaluate the completeness of the identified literature and ensure any EBRR recommendations were appropriate
- ▶ The first draft was reviewed by a first reviewer and changes were agreed upon by the author and first reviewer
- ▶ The same process was employed with the revised section and a second reviewer
- ▶ All changes were then agreed upon by the initial authors and both assigned reviewers



Iterative review



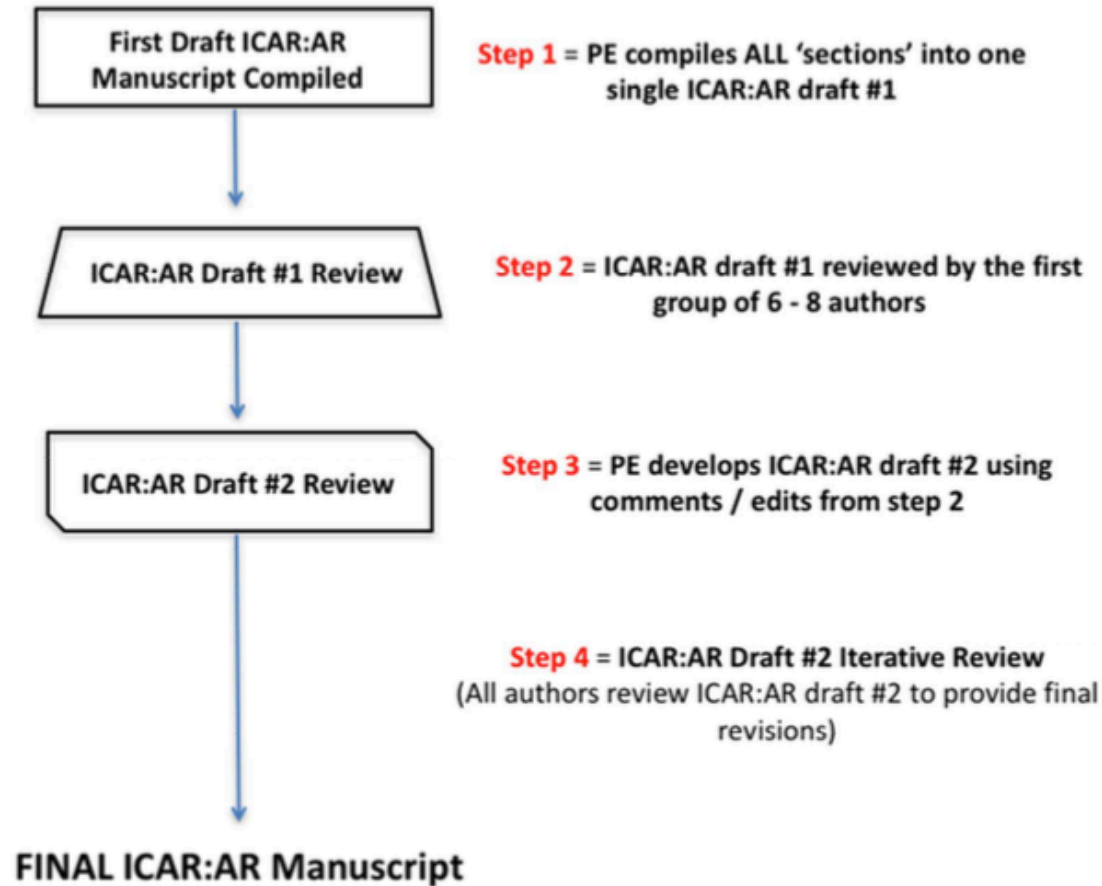
Section II Methods

II.C. pg. 115 ICAR statement development

- ▶ After each topic's content was reviewed and consensus was reached amongst the author and two iterative reviewers, the principal editor compiled all topics into one ICAR:AR statement
- ▶ The first draft underwent additional reviews by 6-8 authors



ICAR statement development



Section II Methods

II.D. pg. 116 Limitations of methods and data presentation

- ▶ Search results by each individual author may demonstrate some variability despite specific and detailed search instructions
- ▶ This document may not present every study published on every topic
 - ▶ Only high quality studies or systematic reviews are listed, especially for topics with extensive literature



Section III Definition and differential diagnosis:

III.A. pg. 117 Allergic rhinitis definition

- ▶ AR is an immunoglobulin E (IgE)-mediated inflammatory nasal condition resulting from allergen introduction in sensitized individuals
- ▶ AR includes the following 3 cardinal symptoms defined in 1929: sneezing, nasal obstruction, and mucus drainage
- ▶ AR results from an overactive response of T helper (Th) 2 lymphocytes which may initiate a systemic, IgE-driven reaction



Section III Definition and differential diagnosis: III.A. pg. 117 Allergic rhinitis definition

- ▶ In atopic individuals, exposure to allergens may prompt antigen-specific IgE production
- ▶ Re-introduction of the allergen triggers early and late-stage reactions
 - ▶ Early stage → within minutes. nasal itching, nasal congestion, and rhinorrhea
 - ▶ Late stage → 4-8 hours later; nasal blockage, hyposmia, increased secretions, and nasal hyper-responsiveness



Section III. Definition and Differential Diagnosis

III.B pg. 117 Allergic rhinitis classification

- ▶ Allergic Rhinitis Classification
 - ▶ ARIA proposed classification - can be confusing
 - ▶ Seasonal Allergic Rhinitis (SAR)
 - ▶ Perennial Allergic Rhinitis (PAR)
 - ▶ Recommended Update:
 - ▶ Intermittent Allergic Rhinitis (IAR) (<4 days/week or <4 consecutive weeks)
 - ▶ Persistent Allergic Rhinitis (PER) (>4 days/week or >4 consecutive weeks)
 - ▶ Severity
 - ▶ Based on disturbances in quality of life (QOL), sleep, exercise tolerance, productivity, and social functioning
 - ▶ Mild or Moderate-Severe



Sensitization vs clinical allergy

- ▶ Monosensitization³¹
 - ▶ Sensitization to 1 allergen
- ▶ Monoallergy
 - ▶ Single sensitizing agent causing clinical allergy symptoms
- ▶ *In vivo* and *in vitro* results must be carefully interpreted in the context of patient symptoms
- ▶ Component-resolved diagnosis testing (in vitro)
 - ▶ More objective means of identifying clinically relevant allergens
 - ▶ Better distinguishes true co-sensitization from polysensitization due to cross-reactivity
- ▶ Polysensitization
 - ▶ Sensitization to 2 or more allergens
- ▶ Polyallergy
 - ▶ Affirmed clinical symptoms to 2 or more sensitizing allergens



Section III Definition and Differential Diagnosis

III.C. pg. 118 Allergic rhinitis differential diagnosis

- ▶ 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
- ▶ NARES
- ▶ Vasomotor rhinitis (nonallergic rhinopathy)
- ▶ Age-related rhinitis (ie, elderly)
- ▶ Empty nose syndrome
- ▶ Atrophic rhinitis
- ▶ Autoimmune, granulomatous, and vasculitic rhinitis
- ▶ Rhinosinusitis



Section III. Definition and Differential Diagnosis

III.C.1 pg. 118 Drug-induced rhinitis

Neurogenic/ Neuromodulator

- ▶ **α antagonists**
 - ▶ α -1: doxazosin, silodosin, prazosin, tamsulosin, alfuzosin, indoramin;
 - ▶ α -1, α -2: phentolamine
- ▶ **Presynaptic α -2 agonists**
 - ▶ Clonidine, methyldopa, guanfacine, piribedil
- ▶ **β -antagonists**
 - ▶ β -1: metoprolol, atenolol, bisoprolol;
 - ▶ - β -1, β -2: pindolol;
 - ▶ - β -1, β -2, α -1: carvedilol, labetalol
- ▶ **Presynaptic depletion norepinephrine stores**
 - ▶ Guanethidine
- ▶ **Phosphodiesterase Inhibitors**
 - ▶ PDE-3 - Cilostazol
 - ▶ PDE-5 - Sildenafil, tadalafil, vardenafil
 - ▶ Non-specific - Pentoxifylline
- ▶ **ACE inhibitors**

Local Inflammatory

- ▶ NSAIDs, ASA, Ketorolac

Illicit intranasal drug use

- ▶ Cocaine, narcotics, antidepressants, anticholinergics, psychostimulants

Idiopathic

- ▶ **Psychotropics**
 - ▶ Chlorpromazine, thioridazine, amitriptyline, alprazolam, reserpine, risperidone, mianserin
- ▶ **Immunomodulators**
 - ▶ Cyclosporine
- ▶ **Hormones**
 - ▶ Estrogen, oral contraceptives
- ▶ **Antihypertensives**
 - ▶ Amiloride, chlorothiazide, hydralazine, hydrochlorothiazide
- ▶ **Other**
 - ▶ Gabapentin, ginkgo biloba

Section III. Definition and Differential Diagnosis

III.C.2 pg. 120 Rhinitis medicamentosa

Rhinitis Medicamentosa (RM)

- ▶ Induced by prolonged use of topical intranasal decongestant (IND) - exact mechanism unknown
- ▶ Triad
 - ▶ Prolonged IND use
 - ▶ Constant nasal obstruction
 - ▶ Poor shrinkage of nasal mucosa
- ▶ Physical exam
 - ▶ Mucosal edema, erythema and hyperemia
- ▶ Studies suggest IND use should be discontinued after 3 days to avoid RM
- ▶ Intranasal corticosteroids - only treatment with demonstrable improvement in rebound symptoms^{62,76,77}



Section III. Definition and Differential Diagnosis

III.C.3 pg. 121 Occupational rhinitis

Occupational Rhinitis (OR)

- ▶ Inflammatory condition of the nasal mucosa
 - ▶ Intermittent or persistent nasal congestion, sneezing, rhinorrhea, itching, and/or hypersecretion
- ▶ Attributable to a particular work environment
 - ▶ not encountered outside the workplace
 - ▶ typically involves occupational exposure to high molecular weight (HMW) (more common) or low molecular weight (LMW) agents
- ▶ HMW-associated occupational rhinitis
 - ▶ 3x more prevalent than occupational asthma
 - ▶ often precedes asthma onset



Occupational rhinitis

► Diagnosis

- Clinical and occupational history, identify high risk occupational exposures
- Examination, including anterior rhinoscopy and nasal endoscopy
- SPT and/or in vitro sIgE assessment for suspected HMW agent if available
- Nasal provocation test (NPT) with suspected agent in lab setting = gold standard
- Suggestive history + exposure to HMW agent(s) + negative immunologic tests + positive NPT may suggest local allergic rhinitis (LAR)
- Unified airway theory - testing including spirometry, measurement of nonspecific airway hyperresponsiveness, and measurement of bronchial inflammation by exhaled NO



Occupational rhinitis

► Treatment

- Early identification and prevention reduces risk of development of occupational asthma
- Avoidance or reduction of exposure
- Nonspecific allergic/nonallergic rhinitis pharmacotherapy
- Specific immunotherapy may be available (HMW agents with available extracts)



Section III: Definition and differential diagnosis

III.C.4. pg. 122 Chemical rhinitis

- ▶ Some chemical exposures can cause congestion, rhinorrhea, nasal discomfort, post nasal drainage, headache or epistaxis
- ▶ Can be occupational, household, or leisure (ie pool chlorine)
- ▶ Generally caused by larger particles, as smaller particles pass through nasal passages
- ▶ Not IgE related in general
- ▶ Some chemicals can cause immunologic sensitization (diisocyanates, acid anhydrides, some platinum salts, reactive dyes, glutaraldehyde, plicatic acid, and chroamine)



Section III: Definition and differential diagnosis

III.C.5. pg. 122 Smoke-induced rhinitis

- ▶ Environmental smoke exposure is associated with chronic rhinitis symptoms
- ▶ Serum cotinine levels can correlate with symptoms
- ▶ Not IgE mediated
- ▶ Can be neurogenic and irritant components in the pathophysiology
- ▶ Not all patients react but those who do can have subjective symptoms (congestion, rhinorrhea, sneezing), and objective increases in nasal resistance
- ▶ Nasal symptoms after exposure may last hours to days



Section III: Definition and differential diagnosis

III.C.6. pg. 123 Infectious rhinitis

- ▶ Infectious rhinitis can be acute or chronic, viral or bacterial
- ▶ Sneezing and itching are indicative of non-infectious etiologies
- ▶ Mucosal inflammation, purulent rhinorrhea, cervical lymphadenopathy or pharyngeal erythema are associated with infectious rhinitis
- ▶ Children average 6 episodes of rhinitis a year while adults have 2-3
- ▶ Symptoms persisting beyond 10 days may be attributable to bacterial infection



Section III: Definition and differential diagnosis

III.C.7. pg. 124 Rhinitis of Pregnancy and Hormone-Induced Rhinitis

- ▶ Defined as nasal congestion and rhinorrhea that lasts for 6 weeks of pregnancy and resolves within 2 weeks of delivery
- ▶ Affects up to 22% of pregnancies
- ▶ Typically starts in the 2nd trimester
- ▶ Can be an exacerbation of pre-existing rhinitis (allergic or non)
- ▶ Etiology thought to be due to hormones or physiologic pregnancy-related changes
- ▶ Treatment has limited evidence
 - ▶ Head of bed elevation, exercise, and nasal dilator strips have been recommended
 - ▶ Hypertonic saline effective
 - ▶ Little evidence for intranasal corticosteroids
- ▶ Any condition that affects hormone levels can causes similar symptoms (puberty, menarche, perimenopausal)



Section III: Definition and differential diagnosis

III.C.8. pg. 124 Food and alcohol induced Rhinitis

- ▶ Food induced rhinitis is low in prevalence (<1% of population), but involves symptoms after ingestion of triggers
- ▶ Food induced rhinitis is a nonimmunologic reaction
- ▶ Generally considered a reflex response from a cholinergic and adrenergic response of the nose
 - ▶ Gustatory rhinitis
- ▶ Rarely the only manifestation of a food allergy
- ▶ May predate the development of other sensitivities, and associated with elevated total IgE



Food and alcohol induced Rhinitis

- ▶ Pollen food allergy syndrome (oral allergy syndrome)- oropharyngeal swelling, itching, tingling after eating certain raw fruits/vegetables
- ▶ Prevalence- 5-17% and up to 50% of the pollen allergic patients
- ▶ Occurs due to cross reactivity between aeroallergens inhaled and cross reactive heat labile food proteins of plant origin
- ▶ Antigens are heat labile, patients usually can tolerate the cooked version of the causative fruit/vegetable



Alcohol induced Rhinitis

- ▶ Alcohol induced rhinitis is more common in women than men
 - ▶ Characterized by nasal congestion
 - ▶ Most common with red wine ingestion
 - ▶ Direct alcohol consumption has been associated with a trend toward developing SPT positivity and with increased serum total IgE levels



Section III Definition and differential diagnosis

III.C.9 pg. 125 Non-allergic Rhinitis with Eosinophilia Syndrome (NARES)

- ▶ Syndrome with symptoms consistent with perennial allergic rhinitis, but negative atopic testing and eosinophilia present on nasal cytology
- ▶ Patients have congestion, rhinorrhea, sneezing, pruritis, and anosmia
- ▶ On nasal smear often have 10-25% eosinophilia
- ▶ Pro-inflammatory cytokines are elevated in this disease (tryptase, ECP, Th2 cytokines)
- ▶ May be associated with aspirin exacerbated respiratory disease and obstructive sleep apnea
- ▶ Treatment is typically with intranasal corticosteroids, and may also utilized topical antihistamine sprays



Section III Definition and differential diagnosis

III.C.10 pg. 126 Vasomotor rhinitis (non-allergic rhinopathy)

- ▶ Most common type of non-allergic rhinitis
- ▶ “Rhinopathy” is used to distinguish the fact that this is not an inflammatory condition
- ▶ Primary symptom is rhinorrhea, but may be associated nasal congestion, post nasal drainage, throat clearing, cough, Eustachian tube dysfunction, sneezing, hyposmia, facial pain and pressure
- ▶ Typically elicited by defined triggers, such as cold air, climate changes (ie, temperature, humidity, barometric pressure), strong smells, tobacco smoke, changes in sexual hormone levels, environmental pollutants, physical exercise, and alcohol
- ▶ Thought to be due to neurosensory abnormalities
- ▶ Typical treatment is intranasal anticholinergics such as ipratropium bromide



Section III Definition and differential diagnosis

III.C.11 pg. 126 Age-related Rhinitis (ie Elderly Rhinitis)

- ▶ Multiple age-related changes in the nasal passages
- ▶ Rhinorrhea is a common complaint in the elderly
 - ▶ More than 70% of elderly patients report clear rhinorrhea
 - ▶ Thought to be due to an imbalance of sympathetic and parasympathetic tone, leading to increased parasympathetic tone and secretion
- ▶ Age related congestion
 - ▶ Decreased water content leads to thicker mucus
 - ▶ Loss of cartilage elasticity and nasal tip support
 - ▶ Decreased mucociliary clearance in the elderly
 - ▶ Loss of nasal cycle in the elderly

Section III Definition and differential diagnosis

III.C.11 pg. 126 Age-related rhinitis (ie elderly rhinitis)

- ▶ Allergic rhinitis in the elderly
 - ▶ Rate of allergic rhinitis does not decrease in the elderly
 - ▶ Likely underdiagnosed in the elderly and should be considered as a possibility



Section III Definition and differential diagnosis

III.C.12. pg. 127 Empty nose syndrome and atrophic rhinitis

- ▶ Empty nose syndrome
 - ▶ Impaired nasal airflow sensation usually as a result of tissue loss from turbinate surgery
 - ▶ Symptoms- nasal dryness, mild crusting, paradoxical nasal congestion
 - ▶ Differential diagnosis- atrophic rhinitis, sarcoidosis
 - ▶ Pathophysiology- turbinate resection, loss of nasal mucosa and airflow sensing thermoreceptors (TRPM8), nerve damage and aberrations in neurosensory system
 - ▶ Diagnosis- H&P, PE, cotton test
 - ▶ Treatment- Moisturizing agents, saline irrigations, surgery with submucosal expansion of the internal nasal mucosa



Atrophic rhinitis

- ▶ Inflammation and atrophy of the nasal and paranasal mucosa
- ▶ Symptoms- thick, adherent nasal crusting, congestion, foul odor, atrophy of the nasal structures, hyposmia, saddle nose deformity, septal perforation
- ▶ Diagnosis- PE, nasal biopsy, nasal cultures
- ▶ Pathophysiology- mucosal injury as a result of from prolonged microvascular or ischemic injury
 - ▶ Primary atrophic rhinitis- associated with *Klebsiella Ozaenae*
 - ▶ Secondary atrophic rhinitis- direct injury from trauma, irradiation, surgery, bacterial infection, granulomatous disease



Comparison of empty nose syndrome and atrophic rhinitis

	Empty nose syndrome	Atrophic rhinitis
Cause	Iatrogenic removal of turbinate tissue Not associated with bacterial infection	Chronic inflammatory process associated with bacterial infection that progresses to resorption of turbinate tissue
Crusting	Minor or no crusting	Heavy crusting
Cause of congestion	Loss of nasal mucosa and turbinate tissue	Crusting and subsequent loss of nasal structures
Bacteria	No association	Primary- <i>Klebsiella ozaenae</i> Secondary- <i>Staphylococcus aureus</i> , <i>Proteus mirabilis</i> , <i>Escherichia coli</i>

Section III Definition and differential diagnosis

III.C.13. pg. 128 Autoimmune, granulomatous, and vasculitis rhinitis

- ▶ Granulomatosis with polyangiitis
 - ▶ Idiopathic disease with necrotizing and granulomatous inflammation of the upper and lower airways (85%), glomerulonephritis (75%), and systemic vasculitis
 - ▶ Nasal symptoms- obstruction, rhinorrhea, epistaxis, crusting, pain, anosmia, cacosmia
 - ▶ Nasal endoscopy findings- Erythematous friable mucosa, crusting, granulation tissue, septal perforation and loss of nasal structures
 - ▶ Diagnosis- biopsy, positive c-ANCA
 - ▶ Treatment- prednisone, cyclophosphamide, methotrexate
 - ▶ Rituximab, anti-CD20 monoclonal antibody may be effective therapy in refractory or relapsing c-ANCA vasculitis



Eosinophilic granulomatous with polyangiitis (Churg Strauss Syndrome)

- ▶ Small-sized vessel vasculitis, prevalence 1.3 cases per 100,000
- ▶ Symptoms- rhinitis, nasal polyps, anosmia/hyposmia, asthma
- ▶ Diagnosis- Asthma, peripheral blood eosinophil count > 10%, pulmonary manifestation, positive p-ANCA
- ▶ Treatment- steroids, immunosuppressants, anti-IL-5 therapy



Sarcoid

- ▶ Chronic multisystem disorder characterized by bilateral hilar adenopathy, pulmonary infiltration, ocular and skin lesions
- ▶ Nasal symptoms- congestion, epistaxis, nasal pain, epiphora, anosmia
- ▶ Physical findings- friable edematous nasal mucosa, submucosal yellow nodules, septal perforation, saddle nose deformity
- ▶ Diagnosis- clinical findings, biopsy (non-caseating granulomas)
- ▶ Treatment- steroids, chloroquine, immunosuppressants, lung transplantation, biologics



Systemic lupus erythematosus

- ▶ Autoimmune disorder that can affect any body system
- ▶ Predominately affects women (10:1)
- ▶ Incidence 5.6 per 100,000 people
- ▶ Skin of nose and nasal vestibule can be involved in the skin rashes
- ▶ Mucosal lesions are seen in 9-18% of cases
- ▶ Diagnosis- history and physical, laboratory tests (ANA, anti-double-stranded DNA)
- ▶ Treatment- corticosteroids, immunomodulators, immunosuppressants



Section III Definition and differential diagnosis

III.C.14 pg. 129 Rhinosinusitis

- ▶ Rhinosinusitis includes diagnoses of acute rhinosinusitis, recurrent acute and chronic
 - ▶ Symptoms- nasal obstruction, congestion, facial pain/pressure, nasal discharge, anosmia/hyposmia for varying durations of time
- ▶ Allergic rhinitis- may share several overlapping symptoms mainly rhinorrhea and nasal congestion with the various subtypes of rhinosinusitis
 - ▶ Typically not associated with purulent or unilateral nasal drainage
 - ▶ Facial pain atypical for AR
 - ▶ Duration variable often with seasonal or exposure-related fluctuations



Rhinosinusitis

- ▶ Acute rhinosinusitis- Sudden onset of sinonasal inflammation lasting < 4 weeks
- ▶ Recurrent acute rhinosinusitis- at least 4 episodes of ARS per year with disease-free intervals between episodes
- ▶ Chronic rhinosinusitis with and without polyps- Inflammatory condition lasting more than 12 weeks with at least 2 symptoms of nasal obstruction/congestion, mucopurulent nasal drainage, facial pressure/pain, anosmia/hyposmia. In addition patients must have objective evidence of sinonasal inflammation on either endoscopy or on CT scan of sinuses



Section IV Pathophysiology and mechanism of allergic rhinitis

IV.A.1. pg. 130 Systemic mechanism and manifestation

- ▶ Immune response leading to AR is often a systemic phenomenon
- ▶ Manifestations of systemic atopy in AR
 - ▶ Cutaneous reaction elicited by skin testing
 - ▶ Atopic march- temporal relationship between AR and atopic dermatitis, food allergy and allergic asthma
- ▶ Immunologic process underlying IgE-mediated AR involves activation of the adaptive immune system
 - ▶ Th1 profile responsible for defense against intracellular pathogens
 - ▶ Th2 profile responsible for IgE-mediated eosinophilic inflammation of allergy



Steps for initiation of Th2-predominant response

1. Exposure of nasal mucosa to inhalant allergens
2. Epithelial cells secrete inflammatory mediators (cytokines, chemokines, eicosanoids, endopeptidases), thymic stromal lymphopoietin²⁷⁶
3. Allergens engulfed by dendritic cells and presented to naïve T helper cells on MHC II molecules²⁷⁴
4. Th2 differentiation occurs
5. Production of IL-4, IL-5, IL-13 which promote IgE-mediated eosinophilic inflammation and allergy
6. Differentiation of B cells into IgE secreting plasma cells
7. B-cells produce IgE under the influence of Th2 effectors cells and IL-4 or IL-13
8. IgE antibodies bind high-affinity receptors on the surface of mast cells and basophils²⁸⁰
9. Crosslinking of IgE- degranulation, release of histamine causing the classic symptoms of AR



Section IV. Pathophysiology and mechanisms of allergic rhinitis

IV.A.2. pg. 131 IgE-IgE receptor cascade

- ▶ IgE plays a central role in AR
- ▶ IgE plasma is short lived, IgE receptor bound (mast cells, basophils) via high affinity receptor $Fc\epsilon RI$ - remains attached for weeks/months
- ▶ IgE bound to receptor cross-links antigen
 - ▶ Release of preformed inflammatory mediators from mast cells/basophils resulting in clinical manifestations of allergic disease



IgE-IgE receptor cascade

- ▶ Local IgE is produced in the nasal mucosa of patients with AR²⁸²⁻²⁸⁴
- ▶ Local IgE upregulates Fc ϵ RI expression on mast cells²⁸³⁻²⁸⁵
- ▶ Augmented expression of Fc ϵ RI allows for increased binding of IgE-antigen complexes
 - ▶ Enhances mast cell sensitivity
 - ▶ Leads to increased production of immunomodulating cytokines/chemical mediators
- ▶ Form positive feedback amplification loop involving the IgE-IgE receptor cascade perpetuating ongoing inflammation

Section IV. Pathophysiology and mechanisms of allergic rhinitis

IV.A.3. pg. 131 Local IgE production and local allergic rhinitis (LAR)

- ▶ LAR- regional inflammatory condition defined by local symptoms and sIgE-mediated inflammation without evidence of systemic hypersensitivity
- ▶ Negative allergy skin test or in vitro test does NOT exclude regional IgE-mediated sensitivity (LAR)
- ▶ LAR- affects more than 47% of children and adults previously thought to have non-allergic rhinitis
- ▶ Diagnosis- positive NPT and/or detection of sIgE and/or basophil activation test in the absence of systemic atopy



Local allergic rhinitis

- ▶ Flow cytometry studies in nasal secretions of patients with LAR
 - ▶ Th2 inflammatory response with increased eosinophils, basophils, mast cells, CD3+, CD4+ T cells
- ▶ Local sIgE is produced from the respiratory airway mucosa
- ▶ Cellular studies confirmed the expression of gene transcripts and mRNA for the heavy-chain of IgE in nasal mucosal B-cells
- ▶ Rate of local IgE production is sufficient to saturate IgE receptors on local mast cells

Section IV. Pathophysiology and mechanisms of allergic rhinitis

IV.B. pg. 132 Non-IgE mediated inflammation in allergic rhinitis

- ▶ The innate immune response appears to contribute to the pathogenesis of AR
- ▶ Nasal epithelium is the first structure to encounter inhaled allergens
 - ▶ Proteolytic activity of allergen disrupts epithelial barrier allowing allergen penetration and chronic inflammation
 - ▶ Nasal epithelium expresses toll-like receptors
 - ▶ Allergen activates toll like receptors leading to production of various mediators which propagate the local inflammatory response
 - ▶ In allergic disease the nasal epithelium seems to be in a permanently activated state

Non-IgE mediated inflammation in allergic rhinitis

- ▶ Innate lymphoid cells- key players in pathogenesis of Th2-type disease such as AR, CRSwNP, asthma
- ▶ ILCs do not express antigen specific T-cell receptors but can react to “danger signals” by producing cytokines that direct immune response
- ▶ Airway epithelial cells release cytokines which activate ILC2s that then produce cytokines IL-5 and IL-13
- ▶ Allergen challenge in AR subjects induce an increasing number of peripheral serum ILC2s



Section IV. Pathophysiology and mechanisms of allergic rhinitis

IV.C. pg. 132 Unified airway concept

- ▶ The upper and lower airways are linked forming a united airway system
 - ▶ Inflammation in one part of the airway influences the other part
- ▶ The mucosa is similar of the upper and lower airways- pseudostratified epithelium with ciliated columnar cells
- ▶ Both AR and asthma support a Th2 endotype
 - ▶ Production of IL-4, IL-5, IL-13, IL-25, IL-31, IL-33, basophils, eosinophils, mast cells
 - ▶ Type 2 profile associated with good response to corticosteroid treatment



Unified Airway Concept

- ▶ Sinonasal inflammation influences the lower airways
 - ▶ Pulmonary aspiration of nasal contents, nasobronchial reflex, uptake of inflammatory mediators in the systemic circulation
 - ▶ Mouth breathing independently associated with asthma morbidity³⁴⁶
 - ▶ Reduced filtration and air conditioning functions of the nose may lead to increased exposure of the lower airways to allergens
 - ▶ Small molecules such as molds and cat dander- higher risk for asthma
 - ▶ Larger molecules such as tree/grass pollen- primarily associated with upper airways symptoms



Unified airway concept

- ▶ Nasal-bronchial crosstalk in allergic airway disease
 - ▶ Segmental bronchial or nasal provocation can induce allergic inflammation in both the nasal and bronchial mucosa
- ▶ Systemic allergic response is characterized by increased expression of adhesions molecule on nasal and bronchial endothelium facilitating migration of inflammatory cells into the tissue
- ▶ Same mechanisms behind AR may be important in airway inflammation throughout the respiratory tract



Section IV Pathophysiology and mechanisms of allergic rhinitis

IV.D. pg. 133 Cellular inflammatory infiltrates

- ▶ Pathophysiology of AR orchestrates a type 2 immune response³⁵⁶
- ▶ Both innate and effector mechanisms play essential roles during the development of allergic disease
 - ▶ Effector Th2 cells produce IL-4, IL-5, IL-9, IL-13
 - ▶ TSLP, IL-25, IL-31, IL-33 contribute the Th2 response
- ▶ Cytokines lead to the production of sIgE, eosinophilia, mucus, tissue migration of Th2 cells and eosinophils, regulation of tight junctions, epithelial barrier integrity
- ▶ Dendritic cells are increased in number in AR and have close contact with epithelial cells and ILCs and control T-cell and B-cell activation and differentiation
 - ▶ Elimination of dendritic cells has been shown to suppress development of AR



Cellular inflammatory infiltrates

- ▶ B-cells and plasma cells are capable of producing IgE in nasal tissue in AR patients
- ▶ Within the nasal epithelium of allergic individuals increased numbers of major basic protein-positive and EG2+ eosinophils are found during pollen season
- ▶ Mast cells are found within the epithelium and submucosal layer
- ▶ Basophils within the lamina propria are increased within 1 hour of allergen provocation
- ▶ Degranulation of mast cells and basophils occurs during the early and late phases of type I reactions

Section IV Pathophysiology and mechanisms of allergic rhinitis

IV.E. pg. 134 Cytokine network and soluble mediators

- ▶ Type 2 cytokines regulate the allergic inflammatory cascade
 - ▶ Produced by Th2 cells, mast cells, eosinophils, epithelial cells, type 2 ILCs
 - ▶ IL-4, IL-5, IL-6, IL-13- increase presence of eosinophils, mast cells, upregulated IgE production
 - ▶ IL-5- key role in modulating eosinophil maturation, differentiation and survival
 - ▶ Upregulate the production of other cytokines and chemokines from epithelial cells and fibroblasts leading to influx of inflammatory cells
 - ▶ Elevated levels of TARC, CCL17, MDC, CCL22, eotaxin, RANTES, MCP-1, MIP-1 α



Cytokine network and soluble mediators

► Airway mast cells

- Important source of type 2 cytokines, proinflammatory cytokines, chemokines, TSLP
- Crucial role in mast cell-induced local IgE synthesis by B cells and upregulation of FcεRI
- Production of TNF- α by mast cells in concert with IL-4 and IL-13 enhances production of TARC, TSLP and eotaxin from epithelial cells
- Chemokines tryptase and chymase upregulate RANTES and GM-CSF production from epithelial cells

Cytokine network and soluble mediators

- ▶ Nasal epithelial cells
 - ▶ Release IL-1, IL-6, IL-8, IL-25, IL-33, TSLP, TNF- α
 - ▶ Aid migration and activation of eosinophils, basophils, and Th2 cells
 - ▶ Crucial role in the regulation of allergic inflammatory cascade
- ▶ Eosinophils
 - ▶ Major source of MIF, NGF
 - ▶ Express 5-lipoxygenase, LTC4S, CysLT₁, CysLT₂ receptors which play a role in the arachidonic acid pathway
- ▶ Th17 cells- unique subpopulation of CD4+ T cells
 - ▶ Produce IL-17A, IL-17F, IL-22, TNF- α , IL-21
 - ▶ IL-17 thought to play a role in AR and found to be increased in nasal mucosa of patients with dust mite allergy

Summary cytokine network and soluble mediators

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



Section IV. Pathophysiology and mechanisms of allergic rhinitis

IV.F. pg. 135 Histologic and epithelial changes

- ▶ Epithelial remodeling is a key feature in CRS and asthma but less defined in AR
- ▶ Limited studies have found no significant increase in basement membrane thickness, subepithelial fibrosis, goblet cell hypertrophy, or blood vessel volume and surface density
- ▶ Epithelial inflammatory response over remodeling is a key feature of AR
 - ▶ Leads to mucosal edema, autonomic neural stimulation, increased mucosal secretions
 - ▶ Manifests as nasal obstruction, pruritis, sneezing, rhinorrhea



Histologic and epithelial changes

- ▶ Penetration of the epithelial barrier leads to allergen sensitization and local/systemic inflammatory response
 - ▶ Barrier comprised of mucus and epithelial cells linked by apical junctional complexes
 - ▶ Mechanical or infective insults to the epithelium or defective epithelium leads to barrier breach and allergen penetration
 - ▶ Allergens can induce junctional dysfunction and penetration of the epithelial barrier by allergens
 - ▶ Proteolytic allergens directly disrupt the apical junctional complex
 - ▶ APC activation and ensuing Th2 response induces further leakiness of the apical junctional complex
- ▶ Corticosteroids may reverse the barrier impairment



Section IV Pathophysiology and mechanisms of allergic rhinitis

IV.G. pg. 136 Microbiome

- ▶ Human microbiome comprises the complex community of microorganisms that resides and interacts with the human body
- ▶ Changes in the microbiome may influence the development of AR
- ▶ Disruption of the gastrointestinal bacteria is thought to alter mucosal immunological tolerance
- ▶ Development of allergy symptoms in children associated with
 - ▶ Overall lower microbial diversity
 - ▶ Increased prevalence of *Bacteroides*, *Bifidobacterium adolescentis*
 - ▶ Lower counts of *Akkermansia muciniphilia*, *Faecalibacterium*, *Clostridium*



Microbiome

- ▶ Systematic review by Melli et al compared intestinal microbiota of allergic patients and healthy controls
 - ▶ 21 studies noted an association between the intestinal microbiota and allergic disease
 - ▶ 4 Studies had specific outcomes related to AR or sensitization
 - ▶ Most of the studies linking microbiome to the development of atopic disease were varied and difficult to interpret

1. Penders et al found presence of *Clostridium difficile* at 1 month associated with increased risk for allergic sensitization until the age 2 years
2. Adlerberth et al noted increase ratio of gram-negative to gram-positive bacteria at 1 year of age to be associated with IgE levels > 100 kU/L at 1.5 years of age
3. Bisgaard et al found lower bacterial diversity was associated to higher risk of allergic sensitization and AR
4. Johansson et al reported lower frequency of colonization with *Lactobacilli* and *Bifidobacterium bifidum* in allergic children



Section V. Epidemiology of allergic rhinitis

V.A. pg. 136 Prevalence of allergic rhinitis in adults

- ▶ Population studies show an increase in AR in adults in recent decades
- ▶ Lifetime prevalence of allergic rhinitis in the United States can be estimated between 11% (physician reported) and 33% (self reported)
- ▶ In Europe, prevalence of AR in adults likely ranges between 10% and 41%
- ▶ Surveys involving patient self-reporting AR show 1/3 population reported “sneezing and/or nasal symptoms in the absence of cold or flu” with about 24% reporting seasonal symptoms and 10% reporting year-round symptoms



Prevalence of allergic rhinitis in adults

- ▶ National Health and Nutrition Examination Survey 2005-2006 presented population figures in which 2/3rds of the patients were over 20 years of age
 - ▶ Physician diagnosed hay fever 11.3%
 - ▶ Reliance of physician diagnosed AR is likely to considerably underestimate the actual prevalence of AR since patients self diagnose and self treat
- ▶ Swiss Study of Air Pollution and Lung Disease in Adults
 - ▶ Prevalence of self reported nasal allergies in adults was 17.9% and the prevalence of current symptoms was 14.2%
 - ▶ Prevalence estimates lower if a positive SPT was included (11.2% for current hay fever and at least 1 positive SPT)



Section V. Epidemiology of allergic rhinitis

V.B. pg. 137 Incidence and prevalence of allergic rhinitis in children

- ▶ Cincinnati Childhood Allergen and Air Pollution Study- 9% of 12 month-old children with a parental history of respiratory allergy fulfilled the criteria for AR
- ▶ In Pollution and Asthma Risk: an infant study birth cohort 9.1% of 18-month old children had AR-like symptoms with strong association with atopy and sensitization to inhalant allergens
 - ▶ 23.7% had rhinoconjunctivitis
- ▶ In 29,662 US children the incidence of physician-diagnosed AR⁴⁶⁷
 - ▶ 1% first year of life
 - ▶ 3.6-4.5% from 1-5 years of life
 - ▶ Highest incidence between 2-3 years of age
- ▶ In 1,314 German children, incidence of SAR was 3-4% per year from 3-7 years of age



Incidence and prevalence of allergic rhinitis in children

- ▶ Longitudinal studies show that AR often occurs first in childhood and increases in prevalence with increasing age
- ▶ The International Study of Asthma and Allergies in Childhood
 - ▶ Estimated prevalence of allergic disease in 2 different age groups 6-7 years and 13-14 years surveyed 1999-2004 through a multicenter global survey
 - ▶ 6-7 year old age group- current rhinoconjunctivitis 8.3%
 - ▶ Slightly higher in boys than girls
 - ▶ 13-14 year age group- current rhinoconjunctivitis 15.1%
 - ▶ Slightly higher in girls than boys
- ▶ Meta-analysis of all studies performed according to the ISAAC-protocol (1,430,329 Children age 0-18 years) found the overall prevalence of AR 12.66%



Section V. Epidemiology of allergic rhinitis

V.C. pg. 138 Geographic variation of allergic rhinitis

- ▶ Prevalence of AR shows marked geographic variation
- ▶ Studies suggest increased sensitivities rates in urban settings and colder climates
 - ▶ Li et al theorized urban dwellers have indoor activities compared to rural counterparts leading to increased exposure to perennial allergens (HDM).
 - ▶ Exposure to urban pollution may be associated with increased risk for developing AR in children
- ▶ Role of latitude in PAR- prevalence of persistent AR is higher in both Northern Europe and Northern China compared to their southern counterparts
 - ▶ Allergenic plant species may have a propensity to grow in certain geographic locations
 - ▶ Colder climates shorten growing season



Section VI. Risk factors for allergic rhinitis

VI.A. pg. 138 Genetics

- ▶ One of the strongest risk factors is the presence of disease in first-degree family member
- ▶ Twin studies show high concordance rates for AR in monozygotic twins compared to dizygotic twins
- ▶ Estimated heritability of AR suggested as high as 70-80%
- ▶ Many genes and several variants are believed to contribute to AR
- ▶ Strong association between genes involved in T-cell activation (LRRC32) and innate immunity (TLRs)



Single-nucleotide polymorphisms associated with AR

- ▶ Genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) associated with AR
- ▶ 5 GWASs on AR have been published as of 9/2016
 - ▶ SNPs in leucine-rich repeat-containing protein 32 (LRRC32) have been strongly associated with AR in 3 of the GWAs
 - ▶ LRRC32- regulated T-cell proliferation, cytokine secretion, TCF- β activation
- ▶ Toll like receptors play a crucial role in immune regulation and SNPs in different TLRs play a crucial role in immune regulation and SNPs in different TLRs have been associated with AR GWAs (TLR1, TLR6, TLR10)



Gene-environment interactions and epigenetic effects

- ▶ Epigenetics- change in gene expression caused by methylation with preservation of the underlying DNA sequence
 - ▶ Possible link between genetic and environmental factors
- ▶ DNA methylation in children is strongly influenced by well-known risk factors for allergic diseases such as maternal smoking during pregnancy and air pollution
- ▶ Small scale studies link methylation profiles to AR



Section VI Risk factors for allergic rhinitis

VI.B. pg. 139 Inhalant allergens (in utero and early childhood exposure)

- ▶ AR is characterized by a loss of immunological and clinical tolerance toward a specific allergen.
- ▶ Involves production of sIgE, hallmark of allergy and its production defines sensitization
- ▶ If a subject is never exposed to an allergen, sensitization to that allergen cannot occur
- ▶ Without sensitization allergy cannot exist



Mites

- ▶ 6 studies on the topic of early mite exposure and the development of AR
 - ▶ Most failed to demonstrate an association between early exposure to mites and the development of AR Studies are conflicting and additional research is needed
- ▶ Marinho et al. reported that early exposure to HDM is not a protective factor for current AR
- ▶ Kim et al. proposed exposure to spider mites as a risk factor for AR
- ▶ Pets may be a relevant source of mites



Mites

Aggregate Grade of Evidence: C

Level 2b: 5 studies

Level 3b: 1 study

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; 95% CI, 0.7–1.1).
					Der f 1 In dust sample at 1 year	No association with AR at 7 years (OR 0.9; 95% 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 study	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; 95% 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; 95% CI, 0.6–1.3).
Kullig et al. ⁴⁶³	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; 95% CI, 1.2–1.5).

Pollens

Only 2 studies addressed impact of early pollen exposure on AR

Aggregate Grade of Evidence: C

Level 2b: 1 study

Level 3b 1 study

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 ^b
Erbas et al. ⁴⁸¹	2013	2b	Prospective birth cohort	620 children (6–7 years old) from MACS RCT (with at least 1 first-degree family member with a history of eczema, asthma, hay fever, severe food allergy)	Pollen exposure ^a during infancy (at 3–6 months)	Risk factor for hay fever (OR 1.1; 95% CI, 1.01–1.3)
Kihström 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 with allergic rhinoconjunctivitis (OR 1.0; 95% CI, 0.6–1.8)
					High-dose exposure to birch pollen at 1 year	No association with allergic rhinoconjunctivitis (OR 1.3; 95% CI, 0.8–2.2)

Animal dander

- ▶ Studies evaluating the association between early exposure to animal dander and subsequent development of AR are conflicting
- ▶ Studies are divided according to three findings
 1. Positive studies reporting a protective effect on AR development
 2. Negative studies showing the early exposure to pets represents a risk factor for AR
 3. Neutral studies reporting that early exposure to animal dander is not associated with AR
- ▶ Evidence based guidelines regarding having pets at home cannot be established



Fungal allergens

- ▶ Most studies demonstrate evidence that early exposure to fungal allergens represents a risk factor for AR development
- ▶ 3 studies demonstrated that early exposure to fungal allergens is not associated with AR
- ▶ Aggregate Grade of Evidence: C
- ▶ Level 2b: 3 studies
- ▶ Level 3 b: 10 studies



Section VI Risk factors for allergic rhinitis

VI.C. pg. 141 Food allergens (in utero and early childhood exposure)

- ▶ Maternal food antigen avoidance
 - ▶ Does not appear to have a beneficial effect on AR development
 - ▶ May be associated with a higher risk of preterm birth and a possible adverse effect on mean birth weight
 - ▶ No data supports maternal diet as a contributing factor for the development of food allergy and AR
- ▶ Delayed introduction of solids past 4-6 months of age was not associated with decreased odds for AR, asthma or food sensitization
- ▶ Presence of food allergy during childhood may increase the risk factor for AR



Food allergens

Aggregate Grade of Evidence: A

Level 1b: 3 studies

Level 2a: 1 study

Level 2b: 1 study

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
Zelger 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 years.	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 cow's milk; 2. Daily ingestion of egg and cow's 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.
Faith-Magnusson et al. ⁵⁷¹	1987	1b	RCT	1. Strictly cow's milk-free 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.
Alduraywish 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.
Zutavem 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.

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



Section VI Risk factors for allergic rhinitis

VI.D. pg. 146 Pollution and AR

- ▶ Most studies looking at the relationship between pollution and AR primarily focus on particulate matter $< 10\mu\text{m}$, particulate matter $< 2.5\mu\text{m}$, nitrogen dioxide, sulfur dioxide, carbon monoxide and ozone
- ▶ Pollutants may potentiate atopy through multiple mechanisms
 - ▶ Injury to the nasal epithelium
 - ▶ May damage nasal mucosa and impair mucociliary allowing for enhanced access of inhaled allergens to cells of the immune system
 - ▶ Altering the immune response
 - ▶ Increasing the allergenicity of certain antigens
 - ▶ Diesel fuel exhaust is able to carry allergens potentially increasing the spread of allergens or the duration of their exposure



Pollution

- ▶ 3 prospective cohort studies found no significant correlation between air pollutants and development of AR
- ▶ Several international case control and cross-sectional studies have varied results
 - ▶ Anderson et al evaluated effect of PM₁₀ on the development of rhinoconjunctivitis in 322,529 children across 51 countries
 - ▶ No between-country association of rhinitis with modeled pollution levels
 - ▶ Within countries- weakly positive associations between PM₁₀ levels and rhinoconjunctivitis symptoms in 6-7 year olds and diagnosed hay fever in 13-14 year olds
 - ▶ Some pediatric studies identified positive correlation between increased exposure to various pollutants and an increased diagnosis of AR during childhood



Pollution

- ▶ Studies show varied results regarding the relationship of pollution and AR
- ▶ Relationship between pollution exposure and development of AR is currently unclear
- ▶ Aggregate Grade of Evidence: C
- ▶ Level 2b: 3 studies
- ▶ Level 3b: 2 studies
- ▶ Level 4: 9 studies



Section VI Risk factors for allergic rhinitis

VI.E. pg. 147 Tobacco Smoke

- ▶ Tobacco smoke exposure causes direct surface damage of the nasal mucosa
 - ▶ Epigenetic changes via histone acetylation and DNA methylation
 - ▶ Immunosuppressive effect on allergic disease by suppressing eosinophil trafficking and Th2 cytokine/chemokine responses
- ▶ Most studies evaluation AR and tobacco found no correlation between active or passive tobacco smoke and AR. Some studies suggest tobacco may have a protective effect against the development of AR
- ▶ Tobacco smoke has a positive association with the development of non-allergic/chronic rhinitis
- ▶ Tobacco smoke does not appear to influence the efficacy of AR treatment



Tobacco smoke

Aggregate Grade of Evidence: C

Level 2a: 1 study

Level 2b: 5 studies

Level 3a: 1 study

Evidence for the effect of active and passive tobacco smoke exposure on the development of allergic rhinitis

Year	LOE	Study design	Active vs passive smoke exposure	Study groups	Clinical endpoint	Conclusion
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.
2010	2b	Prospective cohort study	Passive	1. Environmental tobacco smoke exposure; 2. No exposure	Diagnosis of AR by age 3 years	Environmental tobacco exposure has no effect on the development of AR by age 3 years.
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.
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.
1997	2b	Prospective cohort study	Active	1. Lifetime nonsmokers; 2. Ex-smokers (>1 month); 3. Current smokers	Chronic rhinitis, SAR, or perceived nasal hyperresponsiveness	No association between smoking and seasonal AR. Significant association between chronic rhinitis and current smoking.
1994	2b	Prospective cohort study	Passive	1. Maternal smoking; 2. No smoking in the first year	Physician diagnosed AR at age 6 years	No significant association between maternal smoking and physician diagnosed AR.
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.

tis: LOE = level of evidence: PAR = perennial allergic rhinitis: SAR = seasonal allergic rhinitis: SR = systematic review.



Section VI Risk factors for allergic rhinitis

VI.F. pg. 149 Socioeconomic factors

- ▶ Lifetime prevalence of hay fever was historically elevated in patients of high social economic status (SES) compared to low
- ▶ Positive association between hay fever and high social class was reported in Britain between 1958-1970
- ▶ In Western world before 1970 high SES was a risk factor for AR, but among children in the same regions after 1990 low SES, particularly early in life, seemed to be a risk factor



Socioeconomic factors

- ▶ Currently there is conflicting evidence regarding the association between SES and AR
 - ▶ Most studies show an association between high SES and the diagnosis of AR
- ▶ Overall SES is likely a proxy for various exposures
 - ▶ Number of siblings, viral infections, exposure to tobacco smoke, housing conditions and location, allergen exposures, dietary factors, nutrition including breastfeeding and general diet
- ▶ Aggregate Grade of Evidence: C
 - ▶ Level 2b: 4 studies
 - ▶ Level 4: 6 studies



Section VI Risk factors for allergic rhinitis

VI.G.1 pg. 152 Protective factors against allergic rhinitis- breastfeeding

- ▶ Breast milk is an immunologically complex solution, containing multiple compounds that support infant growth and facilitate the infant immune response
- ▶ Breastfeeding is associated with several beneficial effects on mother and child health and therefore has been recommended for all infants



Breastfeeding

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
Lodge et al. ⁶²⁴	2015	3a	SR	Association between breastfeeding and AR	Development of AR	Nonsignificant protective effect overall. Protective benefit for children under 5 years old, but not over 5 years old.
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.

Breastfeeding

- ▶ Aggregate Grade of Evidence: C (Level 3a: 2 studies)
- ▶ 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 has 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.



Section VI Risk factors for allergic rhinitis

VI.G.2. pg. 152 Childhood exposure to pets

- ▶ Early pet exposure may induce immune tolerance and thus reduce the chance of development of allergic disease
 - ▶ Systemic review of 62 studies- most showed early exposure to dog antigen was protective for sensitization against aeroallergens
 - ▶ Cross-sectional studies reported inconsistent associations between cat or dog exposure and sensitization and development of atopic diseases later in life
- ▶ There is no clear evidence that pet avoidance in childhood prevents the development of AR or sensitization to aeroallergens later in life
 - ▶ In a pooled analysis of 11 European birth cohorts any furred pet ownership during the first 2 years was associated with lower risk of sensitization to aeroallergens, but not decreased prevalence of AR later in childhood



Childhood exposure to pets

- ▶ Overall, pet allergens are ubiquitous
- ▶ There is no evidence that pet avoidance in childhood prevents the development of AR or sensitization of aeroallergens later in life
- ▶ Alternatively, early exposure to pets may induce immune tolerance and thus reduce the chance of development of allergic disease
- ▶ 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



Section VI Risk factors for allergic rhinitis

VI.G.3. pg. 153 Hygiene

- ▶ Hygiene hypothesis- exposure to frequent infections in large families is a protective factor in the development of AR⁶¹⁸
- ▶ Hygiene hypothesis has evolved toward a more contemporary “biodiversity hypothesis”
 - ▶ Potential protective effect related to the colonization of mucus membranes and the skin with diverse environmental microflora



Section VI Risk factors for allergic rhinitis

VI.G.3. pg. 153 Hygiene

- ▶ Siblings- Higher number of siblings is associated with decreased atopy
 - ▶ Metanalysis of 53 studies, 38 studies showed that higher number of siblings was associated with decreased atopy
- ▶ Farming- Risk of sensitization was 40% lower among subjects who had lived on a farm during the first year of life
 - ▶ The protective farm effect seems to be stronger when exposed to farm animals and stables and greatest with highest exposure occurring early in life
- ▶ Bacterial endotoxins- Exposure to bacterial endotoxins in infancy may have a protective effect



Hygiene- microbial diversity

- ▶ Changes in lifestyle, urbanization, diet, and 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 disease between rural and urban areas
- ▶ Urbanization reduces microbial diversity
- ▶ Skin microbiota may be associated with protection from atopy
- ▶ Probiotics- meta-analysis of 29 randomized controlled studies show no significant association of probiotics supplementation with sensitization or allergic rhinitis



Hygiene

- ▶ Hygiene is important to prevent infections
 - ▶ 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 allergic disease
- ▶ Aggregate Grade of Evidence: B
 - ▶ Level 2a: 2 studies
 - ▶ Level 2b: 10 studies
 - ▶ Level 3a: 2 studies
 - ▶ Level 3b: 1 studies



Section VII. Disease burden

VII.A.1 pg. 157 Effect of quality of life

- ▶ AR patients suffer from significantly decreased quality of life due to impact on both physical and mental health
- ▶ The most commonly used general QOL instruments in AR literature
 - ▶ Short form 12, Short form 36, Rhinoconjunctivitis quality of life questionnaire
- ▶ Extranasal symptoms, particularly ocular symptoms have a significant impact on QOL and should not be ignored in the evaluation and management of AR



Individual burden- effect of quality of life

- ▶ Successful treatment of AR with topical nasal corticosteroids, antihistamines or AIT leads to improvement in symptoms and QOL
- ▶ RCT examined monotherapy vs polytherapy and showed the combination of mometasone with either levocetirizine or Montelukast led to greater symptom control and QOL improvement than mometasone alone
- ▶ RCT of acupuncture vs medical therapy showed improvement in QOL in both groups but degree of improvement larger in the acupuncture group
- ▶ Allergy immunotherapy RCT show improvement in QOL measures in treatment arm compared to placebo arm



Individual burden- effect on quality of life

- ▶ Aggregate Grade of Evidence: B
- ▶ 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 further specified in Section IX.
- ▶ Cost: Management strategies for AR are associated with variable levels of cost and are further specified in Section IX.
- ▶ Benefit-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.



Section VII. Disease burden

VII.A.2. pg. 157 Effect on sleep

- ▶ AR negatively impacts sleep and the successful treatment of AR reduces sleep disturbance
- ▶ AR has been associated with worse sleep fragmentation and snoring
- ▶ Studies demonstrate that AR patients have improvements in sleep quality and daytime sleepiness, in addition to sinonasal symptoms and QOL after treatment with nasal corticosteroids or a combination of corticosteroids and montelukast



Effect on sleep and OSA

- ▶ Treatment of AR has been suggested to improve CPAP compliance in patients with OSA
- ▶ AR patients have worse PSG parameters and sleep disturbance when their symptoms are present or during peak allergen season
- ▶ In children, level 2 and 3 studies suggest AR is associated with sleep disturbance in the form of increased risk of snoring, sleep disordered breathing, and OSA
- ▶ AR has been suggested to be a risk factor for deterioration of OSA QOL after adenotonsillectomy



Effect on sleep

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefits: 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.
- ▶ Costs: Management strategies for AR are associated with variable levels of cost and are further specified in Section IX.
- ▶ Benefits-Harm Assessment: The benefits of treating patients with AR for symptoms of sleep disturbance may outweigh risks of treatment
- ▶ Value Judgement: Successful control of AR symptoms leads to improvement in sleep.
- ▶ Policy Level: Recommend treatment in AR to decrease sleep disturbance.
- ▶ Intervention: AR patients may be offered various management strategies to improve sleep.



Section VII. Disease burden

VII.B. pg. 164 Societal burden

- ▶ AR ranks 5th among chronic conditions in the United States
- ▶ AR is the most common chronic disorder in the pediatric population
- ▶ Estimated annual direct costs of AR is \$2-5 billion
 - ▶ Direct costs include physician appointments, medication, lab tests, immunotherapy
 - ▶ Hidden direct costs include treatment of comorbid conditions that occur at an increased incidence in patients with AR
 - ▶ More than 50% of the direct costs come from prescription medication
- ▶ Indirect costs make up the majority of the burden of AR
 - ▶ Indirect costs include absenteeism, presenteeism, impaired productivity



Societal burden

- ▶ In US AR results in 3.5 million lost workdays, 2 million lost school days annually
- ▶ In a survey of 8,000 U.S. employees, 55% reported AR symptoms for an average of 52.5 days/year, missing 3.6 days of work/year because of AR and reported being unproductive 2.3 hours per workday when symptomatic
- ▶ Blanc et al. reported more than 1/3rd of AR patients with reduced workplace performance



Societal burden

- ▶ Health impairments associated with AR may effect sleep, result in daytime sleepiness, impair cognition and memory, may effect the learning process and impact school/work performances
- ▶ AR poses a substantial societal burden to individuals and society
- ▶ AR can reduce productivity and QOL and can contribute to comorbid conditions resulting in a significant impact to the overall health system



Section VIII. Evaluation and diagnosis

VIII.A. pg. 165 Clinical examination- History

- ▶ History taking includes the type of symptoms experienced, timing/duration of symptoms, frequency of symptoms, environmental exposures triggering symptoms, medications or other measures used to relieve or exacerbate symptoms
 - ▶ Patients with suspected AR present with multiple complaints with 96% presenting with 2 or more symptoms
 - ▶ Rhinorrhea, sneezing, sniffing, hyposmia/anosmia, nasal obstruction, and itchy nose rank highest for diagnostic utility among symptoms of AR
- ▶ In clinical practice the diagnosis of allergic rhinitis is often made by history alone



History

- ▶ Classic symptoms of allergic rhinitis- Nasal congestion or obstruction, nasal pruritis, clear rhinorrhea, sneezing
- ▶ Associated symptoms of allergic rhinitis- anosmia/hyposmia, post nasal drip, ocular pruritis, erythema, tearing, oral or pharyngeal pruritis, sore throat, wheezing, cough, sleep disordered breathing, aural congestion
- ▶ PMH- elicit comorbid condition such as asthma, OSA
- ▶ Family history of atopic disorders
- ▶ Social history- pets, work exposures, home environment



Section VIII. Evaluation and diagnosis

VIII.A. pg. 166 Physical exam

- ▶ Physical signs- mouth breathing, transverse supratip crease, periorbital edema, allergic shiners
- ▶ Examination of the ear- retraction of the tympanic membrane, transudative fluid
- ▶ Examination of the nose- inferior turbinate hypertrophy, congested/ edematous nasal mucosa, purplish/bluish nasal mucosa, clear rhinorrhea
- ▶ Examination of the eyes- conjunctival erythema and/or chemosis
- ▶ Physical examination alone is a poorly predictive and more variable when compared to history taking in the diagnosis of AR



Evaluation and diagnosis

- ▶ Aggregate Grade of Evidence: D
- ▶ Benefits: Improve accuracy of diagnosis, avoid unnecessary referrals, testing, or treatment. Possible improved diagnosis of AR with physical examination findings, evaluation/exclusion of alternative diagnosis.
- ▶ 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 in appropriate treatment if physical exam used in isolation
- ▶ Value Judgement: Making a presumptive diagnosis of AR on history is reasonable and would not delay treatment initiation. Confirmation with diagnostic testing is required for progression to ALT, 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.



Section VIII Evaluation and diagnosis

VIII.B. pg. 166 Nasal endoscopy

- ▶ Nasal endoscopy is an option for evaluation of suspected AR
- ▶ Endoscopic findings with AR inconsistent, however, endoscopy may aid in the identification or exclusion of other possible causes of symptoms such as nasal polyps, or CRS
- ▶ May aid diagnosis of central compartment atopic disease (CCAD)-centrally-located inflammation involving the middle/superior turbinate or superior nasal septum
 - ▶ Brunner et al evaluated patients with CRSwNP vs isolated polypoid change of middle turbinate
 - ▶ Higher prevalence of AR in patients with middle turbinate polypoid change (83% vs 34%) supporting CCAD as a unique atopic condition



Nasal endoscopy

- ▶ Aggregate Grade of Evidence: D
- ▶ 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.



Section VIII Evaluation and diagnosis

VIII.C. pg. 167 Radiology

- ▶ Routine radiographic imaging is not recommended for diagnosis of AR
- ▶ May be used to rule in/out other conditions (rhinosinusitis)
- ▶ Concerns regarding unnecessary exposure to ionizing radiation, with the risk for future cancer development, preclude recommendation for routine use



Radiology

- ▶ 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.



Section VIII Evaluation and diagnosis

VIII.D pg. 168 Use of Validated Survey Instruments

▶ **Validated Surveys**

- ▶ Offer structured way to expose important historical elements
- ▶ Particularly helpful when testing or imaging unavailable
- ▶ May be useful to determine effectiveness of therapy



Use of validated survey

- ▶ Aggregate Grade of Evidence: A
- ▶ 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
- ▶ Cost: No financial burden to patients. Some fees associated with validated tests used for clinical research
- ▶ Balance of benefit and harm: Preponderance of benefit over harm
- ▶ 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.



Section VIII Evaluation and diagnosis

VIII.E.1 pg. 170 Skin prick testing

- ▶ Useful to Confirm Diagnosis of AR
- ▶ Useful to Direct AIT
- ▶ Crosslinks IgE on cutaneous Mast cells resulting in release of Mediators (histamine et al) which causes wheal and flare within 15-20 minutes
- ▶ Rare reports of anaphylaxis; no fatalities
- ▶ Contraindications: severe asthma, uncontrolled CV disease, beta-blocker use, pregnancy
- ▶ Sensitivity and Specificity around 80%



Skin prick testing

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Supports diagnosis and directs pharmacological therapy while possibly avoiding unnecessary or ineffective treatment; guides avoidance; directs AIT
- ▶ Harm: Adverse events from testing including discomfort, pruritus, erythema, worsening of asthma symptoms, and anaphylaxis, inaccurate test results, and misinterpreted test results.
- ▶ Cost: Low
- ▶ Balance of benefit and harm: 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.



Section VIII Evaluation and diagnosis

VIII.E.2. pg. 173 Skin intradermal testing

- ▶ Diagnosis of AR
- ▶ Primary Testing Modality or Secondary following SPT
- ▶ Determining Starting Point for AIT
- ▶ Vial Test
- ▶ Evaluation of Sensitivity to other substances
 - ▶ local anesthetics, neuromuscular blockers, antibiotics, contrast media
 - ▶ foods
 - ▶ use for suspected food or chemical allergies not recommended in routine practice



Skin intradermal testing

- ▶ Technique: 0.02mL injected with short bevel needle to produce 4 mm wheal and expanding to 5 mm by hydrostatic force
- ▶ Positive control: Histamine
- ▶ Negative control: Phenolated saline and glycerin
- ▶ Observe 10 minutes
- ▶ Positive result at least 7 mm (2mm wider than glycerin control)
- ▶ Technically more demanding than Skin Prick Testing
- ▶ Difficult to perform in young children
- ▶ Adverse events rare (5 fatalities between 1945-1987)



Skin intradermal testing

- ▶ Aggregate Grade of Evidence: B
- ▶ 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
- ▶ Balance of benefit and harm: 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 sensitively 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 IT as a stand-alone diagnostic test for individual with suspected AR. Option for using IT 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: IT may be used to determine specific airborne allergen sensitization for individuals suspected of having AR.



Section VIII. Evaluation and diagnosis

VIII.E.3. pg. 177 Blended Skin Testing Techniques

- ▶ Uses Both SPT and IDT to establish endpoint
- ▶ Modified Quantitative Testing (MQT)
- ▶ AIT based on MQT shown successful
- ▶ Advantage
 - ▶ Less time consuming
 - ▶ Qualitative and Quantitative data
- ▶ Disadvantage: Additional risk and time involved in placing intradermal portion of test
- ▶ More Cost effective than IDT and In Vitro testing
 - ▶ If AR 20% prevalence in population



Blended skin testing technique

- ▶ Aggregate Grade of Evidence: D
- ▶ Benefit: Ability to establish an endpoint in less time than IDT.
- ▶ Harm: The additional risks, including systemic or anaphylactic reactions, of intradermal test; additional time and discomfort.
- ▶ Cost: Similar to intradermal testing.
- ▶ Balance of benefit and harm: Benefit outweighs harm.
- ▶ Value Judgement: 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.



Section VIII. Evaluation and diagnosis

VIII.E.4. pg. 177 Issues that affect the performance or interpretation of skin tests

- ▶ Medications
 - ▶ Antihistamines (H1 and H2 blockers)
 - ▶ Including topically administered antihistamines
 - ▶ Tricyclic Antidepressants (e.g. Doxepin)
 - ▶ Omalizumab
 - ▶ Leukotriene receptor antagonists do not appear to interfere
 - ▶ Topical Steroids have been shown to suppress wheal and flare
 - ▶ Note Systemic have not been shown to reduce responses on skin test
 - ▶ Intranasal or Inhaled steroids - No studies examining effect on skin test results
 - ▶ Appropriate Positive control (Histamine) helps to mitigate risk of false-negative result from medications



Issues affecting performance or interpretation of skin testing

- ▶ Skin Conditions
 - ▶ Dermatitis
 - ▶ Physical Trauma
 - ▶ Skin color
- ▶ Dermatographism - may have exaggerated responses
- ▶ Due to lack of published studies on this topic, an Aggregate Grade of Evidence and evidenced based recommendations cannot be made.



Section VIII. Evaluation and diagnosis

VIII.F.1. pg. 182 Serum total IgE (tIgE)

- ▶ Total IgE is frequently increased in AR
- ▶ Modest clinical utility
- ▶ Literature presents divergent studies that fail to find consistent role or value for tIgE in AR management
- ▶ Ratio between allergen-specific and tIgE may be useful in predicting AIT effectiveness



Serum total IgE

- ▶ Aggregate Grade of Evidence: C
- ▶ Benefit: Possibility to suspect allergy in a wide screening
- ▶ Harm: Low level does not excuse allergy
- ▶ Cost: Moderate 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



Section VIII. Evaluation and diagnosis

VIII.F.2. pg. 185 Serum antigen-specific IgE (sIgE)

- ▶ RAST introduced in 1967
- ▶ Process:
 - ▶ Allergens are bound to a substrate
 - ▶ sIgE from patient's serum binds to specific allergens
 - ▶ non-human anti-IgE tagged with marker is added
 - ▶ Analyzer reads the intensity of the tags
 - ▶ Intensity of the reaction is proportional to the amount of sIgE in the patient's serum
- ▶ Benefits:
 - ▶ Highest Safety Profile
 - ▶ Not limited by certain medical conditions or skin conditions



Serum-antigen specific IgE

- ▶ Similarities and Differences between skins testing and sIgE
 - ▶ Skin testing allows immediate feedback and visible results resulting in patient preference
 - ▶ Neither skin or sIgE testing can definitively predict the severity of sensitivity to aeroallergen
 - ▶ Cross-reacting allergens and poly-sensitizations can confound both leading to false positive results
 - ▶ sIgE use more extensively quality-controlled allergens and defined human serum controls



Serum antigen-specific IgE

- ▶ Multiallergen screens: sIgE provides option to rule in or out allergy as driving factor behind symptoms without subjecting patients to time and cost of full testing battery
- ▶ Levels of sIgE correlate with severity of AR symptoms and may help in selection of candidates for AIT because more severely symptomatic patients have been shown to respond better to AIT
- ▶ In situations with polysensitized patients, sIgE levels can help discriminate the most relevant allergen and guide AIT



Serum antigen-specific IgE

- ▶ Sensitivity 67-96%
- ▶ Specificity 80-100%
- ▶ Correlates with NPT and SPT in diagnosis for AR
- ▶ In many ways, equivalent to SPT
- ▶ Acceptable alternative to skin testing
- ▶ Safe in patients who are not candidates for skin testing



Serum antigen-specific IgE

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Confirms sensitization in support of AR diagnosis and directs appropriate therapy while possibly avoiding unnecessary/ineffective treatment; guides avoidance measures; directs AIT
- ▶ Harm: Discomfort from blood draw, inaccurate test results, false-positive results, and misinterpreted test results
- ▶ Cost: Moderate cost of testing
- ▶ Balance of benefit and harm: Preponderance of benefit over harm
- ▶ Value Judgments: Patients can benefit from identification of their specific sensitivities. Safe and effective alternative patients who cannot undergo skin testing
- ▶ Policy level: Recommendation
- ▶ Recommendation Intervention: Serum sIgE sting may be used in the evaluation of AR. Using standardized allergens and rigorous proficiency testing on the part of lab may improve accuracy.



Section VIII. Evaluation and diagnosis

VIII.F.3 pg. 186 Correlation between skin and in vitro testing

- ▶ Modern Skin Prick Testing (SPT) can be up to 25% more sensitive than sIgE (Average pooled sensitivity is 85%, which is slightly higher than serum IgE testing).
- ▶ SPT generally costs about one half as much as sIgE
- ▶ SPT test measurements are directly observable within 20 minutes (much faster than lab reports)
- ▶ SPT is accurate and combined with a detailed clinical history can confirm the diagnosis of allergic rhinitis
- ▶ Sensitivity and specificity depends on allergen tested, quality of reagents, methodologies employed and technician expertise and patient demographics



Correlation between skin and in-vitro testing

- ▶ In vitro testing:
 - ▶ Avoids the need to withhold medications that can affect skin testing
 - ▶ Allows for testing of individuals with dermatographism or other widespread skin disorders
 - ▶ The cutoff for positive tests affects both sensitivity and specificity
 - ▶ Immunocap was superior to SPT in measuring Dust mite sensitivity in Korean populations > 50 years old for House Dust Mites
 - ▶ Safe (no risk of anaphylaxis)



Correlation between skin and in-vitro testing

- ▶ Skin testing and sIgE serology portend unique biologic functions. The two tests are not fully interchangeable
- ▶ Serum IgE testing measures circulating IgE that may or may not represent downstream allergic responses
- ▶ SPT and IDT measure end organ pathological mechanisms associated with sIgE bound to the surface of mast cells
- ▶ SPT is often chosen as a first line diagnostic instrument based on accuracy, convenience, cost and promptness of results
- ▶ IDT has a higher sensitivity than SPT but lower specificity for all allergens tested
- ▶ IDT is a second line test that can be ordered to determine reactivity if clinical suspicion is high



Correlation between skin and in-vitro testing

Aggregate Grade of Evidence: B

References: 1. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. *J. Allergy Clin Immunol.* 1999;103:773-779. 2. Centers for Medicare and Medicaid Services. Clinical laboratory Fee Schedule. <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/>. 3. Nevis IF, Binkley K, Kabali C. Diagnostic accuracy of skin-prick testing for allergic rhinitis: a systematic review and meta-analysis. *Allergy Asthma Clin Immunol.* 2016;12:20. 4. Tversky JR, Chelladurai Y, McGready J, Hamilton RG. Performance and pain tolerability of current diagnostic allergy skin prick test devices. *J Allergy Clin Immunol Pract.* 2015;3:888-893. 5. Choi IS, Koh YI, Koh JS, Lee MG. Sensitivity of the skin prick test and specificity of the serum-specific IgE test for airway responsiveness to house dust mites in asthma. *J Asthma.* 2005;42: 197-202. 6. Jung YG, Cho HJ, Park GY, et al. Comparison of the skin-prick test and Phadia ImmunoCAP as tools to diagnose house-dust mite allergy. *Am J Rhinol Allergy.* 2010;24:226-229. Nelson HS, Oppenheimer J, Buchmeier A, Kordash TR, Freshwater LL. An Assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to Timothy grass. *J Allergy Clin Immunol.* 1996;97:1193-1201.



Section VIII. Evaluation and diagnosis

VIII. F.4. pg. 190 Nasal specific IgE

- ▶ Many patients with allergic rhinitis have local allergic phenomenon (LAR) in the nasal mucosa with
 - ▶ slgE in the nasal mucosa
 - ▶ Class switching and antibody production in the nasal mucosa
- ▶ Some patients with a clinical history of AR have negative SPT and/or slgE testing
 - ▶ Given diagnosis of idiopathic rhinitis, vasomotor rhinitis or Non allergic rhinitis



Nasal specific IgE

- ▶ Many of these patients have local allergic phenomenon or LAR.
- ▶ LAR may affect > 45% of patients otherwise categorized as NAR
- ▶ LAR may be present in up to 25% of patients referred to allergic clinics with suspected AR
- ▶ LAR can be seasonal or perennial
- ▶ Low rate of conversion of LAR to AR
- ▶ The incidence of LAR in Elderly patients with rhinitis has been reported as high as 21%



Nasal specific IgE

- ▶ The diagnosis of LAR is confirmed by positive response to NPT and evidence of sIgE in the nasal secretions
- ▶ The local production of nasal mast cells, eosinophils and sIgE rapidly increases after allergen specific stimulation in the nasal mucosa
- ▶ Different methods of identifying nasal sIgE have been reported but no gold standard has been agreed on
- ▶ Normative data for nasal sIgE levels and their clinical correlations have yet to be agreed upon

Nasal specific IgE

- ▶ Aggregate Grade of Evidence: C
- ▶ Value judgment: Standards for abnormal levels of nasal IgE have not been established nor correlated with clinical outcomes
- ▶ Policy level: Option
- ▶ References: 1. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol.* 1979;122:2218-2225. 2. Takhar P, Smurthwaite L, Coker HA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol.* 2005;174:5024-5032. 3. Rondon C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol.* 2012;129:1460-1467. 4. Rondon C, Campo P, Zambonino MA, et al. Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *J Allergy Clin Immunol.* 2014; 188:1026-1031. 5. Rondon C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy.* 2012;67:1282-1288. 6. Rondon C, Dona I, Lopez S, et al. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy.* 2008;63:1352-1358. 7. Bozek A, Ignasiak B, Kasperska-Zajac A, Sciarski W, Grzanka A, Jarzab J. Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol.* 2015;114:199-202. 8. Rondon C, Fernandez J, Lopez S, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol.* 2009;124:1005-1011. e1.



Section VIII. Evaluation and diagnosis

VIII.F.5. pg. 193 Basophil activation test (BAT)

- ▶ An ex vivo peripheral blood test shown to be useful in the diagnosis of allergy to food and drugs and hypersensitivity syndromes
- ▶ Useful when first line tests are discordant with clinical history
- ▶ Useful for monitoring of allergen immunotherapy
- ▶ BAT is useful in defining the allergen responsible for LAR in patients with high false negative results using first line tests
- ▶ The basophil sensitivity or eliciting concentration (EC-50) can be used to monitor the treatment affect of AIT and anti-IgE therapy



Basophil activation test

- ▶ Small scale trials performed evaluating utility and reliability of BAT testing for
 - ▶ Specific allergens related to the AR symptoms
 - ▶ Monitoring therapy
- ▶ Methodology was heterogeneous between trials
- ▶ BAT is rarely required but has been shown to be comparable with traditional allergen testing methods



Basophil activation test

- ▶ 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 SPT 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.



Basophil activation test, cont.

- ▶ 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 ALT. Many small-scale studies have been completed.
- ▶ There is scope for meta-analysis and for larger trials to
- ▶ be completed.

e: 8



Section VIII. Evaluation and diagnosis

VIII. F.6. pg. 193 Component resolved diagnosis

- ▶ Used to define allergen sensitization of a patient at the individual protein level
- ▶ Allows identification of the potential disease eliciting molecules
- ▶ Can improve diagnostic accuracy
- ▶ Distinguish cross reactivity phenomenon from co-sensitization
- ▶ Resolve low risk markers from high risk markers of disease activity
- ▶ Improve the indication and selection of suitable antigens for AIT



Component resolved diagnosis

- ▶ Demonstrated to be cost effective in some scenarios
- ▶ Certain patterns of sensitization may identify patients with higher risk of adverse reaction during AIT
- ▶ All in vitro testing should be evaluated along side the clinical history (sensitization doesn't always equal clinical responsiveness)



Component resolved diagnosis

- ▶ Measured using a fluorescence enzyme immunoassay
- ▶ Singleplex and multiplex platforms are available
- ▶ Sensitivity of the multiplex platform is lower than that of the singleplex platform
- ▶ Multiplex platforms with 112 allergens are available



Component resolved diagnosis

- ▶ Can better define the sensitization to inhalant allergens in patients that are:
 - ▶ Polysensitized
 - ▶ Have unclear symptoms and/or sensitization patterns
 - ▶ Not responding to treatment
 - ▶ Remains a 3rd level approach (not a screening method)

Evidence Grading is not available.

References: 1. Sastre J. Molecular diagnosis in allergy. Clin Exp Allergy. 2010;40:1442-1460. 2. Canonica GW, Ansotegui IJ, Pawankar R, et al. A WAO-ARIA-GA-LEN consensus document on molecular-based allergy diagnostics. World Allergy Organ J. 2013;6:17. 3. Sastre J, Sastre-Ibanez M. Molecular diagnosis and immunotherapy. Curr Opin Allergy Clin Immunol. 2016;16:565-570. 4. Sastre J. Molecular diagnosis and immunotherapy. Curr Opin Allergy Clin Immunol. 2013;13:646-650. 5. Sastre J, Rodriguez F, Campo P, Laffond E, Marin A, Alonso MD. Adverse reactions to immunotherapy are associated with different patterns of sensitization to grass allergens. Allergy. 2015;70:598-600.



Section VIII. Evaluation and diagnosis

VIII.G. pg. 196 Sensitization vs. clinical allergy

- ▶ IgE mediated sensitization is a risk factor for rhinitis
- ▶ The strength of this association is not constant
- ▶ Patients are diagnosed as being sensitized based on a positive SPT (> 3 mm wheal) or a positive specific serum IgE (> 0.35)
- ▶ Both tests can be positive in the absence of symptoms
- ▶ Neither positive SPT nor IgE can confirm the expression of rhinitis upon allergen exposure
- ▶ Clear distinction has to be made between sensitization and clinical allergic disease
- ▶ Quantification of blood or skin tests using sIgE titer and SPT wheal size increases the specificity of the allergy tests with regards to the presence and severity of allergic rhinitis



Sensitization vs. clinical allergy

- ▶ Whole allergen extract vs individual allergenic molecules
 - ▶ Positive test to whole allergen extract may reflect sensitization to a cross reactive components.
 - ▶ Measuring sensitization to individual allergen molecules (CRD) may be more informative than standard tests using whole extracts.
 - ▶ Distinct patterns of IgE responses to different families are associated with different clinical symptoms.
 - ▶ The risk of allergic disease increases with increasing sensitizations to individual allergenic proteins.
 - ▶ Age of onset of sensitization is crucially important.



Sensitization vs. clinical allergy

- ▶ Disaggregating atopic disease
 - ▶ Atopic sensitization is an umbrella term for several different atopic vulnerabilities which differ in their association with rhinitis and asthma.
- ▶ Beyond IgE
 - ▶ A decreasing ratio of grass allergenic specific IgG/IgE antibodies is associated with increasing risk of symptomatic SAR.
 - ▶ The IgG/IgE ratio may help distinguish between benign sensitization and pathologic sensitization.
 - ▶ Measurement of allergenic specific IgG cannot as yet be recommended in a routine clinical practice.
 - ▶ References: 1. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in a 5-year old children: a population-based birth cohort study. *Allergy*. 2007;62:385-393. 2. Carroll WD, Lenney W, Child F, et al. Asthma severity and atopy: how clear is the relationship? *Arch Dis Child*. 2006;91:405-409. 3. Dreborg S, Frew A. Position paper: allergen standardization and skin tests. *Allergy*. 1993;48:49-82. 4. Roberts G, Ollert M, Aalberse R, et al. A new framework for the interpretation of IgE sensitization tests. *Allergy*. 2016;71:1540-1551. 5. Marinho S, Simpson A, Soderstrom L, Woodcock A, Ahlstedt S, Custovic A. Quantification of atopy and the probability of rhinitis in preschool children: a population-based birth cohort study. *Allergy*. 2007;62:1379-1386. 6. Treudler R, Simon JC. Overview of component resolved diagnostics. *Curr Allergy Asthma Rep*. 2013;13:110-117. 7. Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Gronlund H. The recombinant allergen-based concept of component-resolved diagnostics and immunotherapy. *Clin Exp Allergy*. 1999;29:896-904. 8. Simpson A, Lazic N, Belgrave DC, et al. Patterns of IgE responses to multiple allergen components and clinical symptoms at age 11 years. *J Allergy Clin Immunol*. 2015;136:1224-1231. 9. Posa D, Perna S, Resch Y, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol*. 2017;139:541-549.e8. 10. Custovic A, Sonntag HJ, Buchan IE, Belgrave D, Simpson A, Prospero MC. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol*. 2015;136:1645-1652.e8. 11. Lazic N, Roberts G, Custovic A, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy*. 2013;68:764-770. 12. Holt PG, Strickland D, Bosco A, et al. Distinguishing benign from pathologic TH2 immunity in atopic children. *J Allergy Clin Immunol*. 2016;137:379-387.



Section VIII Evaluation and diagnosis- sensitization vs clinical allergy

VIII.G pg. 197 Disaggregating atopic sensitization

- ▶ Atopic Sensitization" is not a single phenotype, but an umbrella term for several different atopic vulnerabilities
- ▶ 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.



Section VIII Evaluation and diagnosis- sensitization vs clinical allergy

VIII.G pg. 197 Beyond IgE

- ▶ Data suggest the decreasing ratio of allergen- specific IgG/IgE antibodies is associated with increasing risk of symptomatic SAR
- ▶ IgG/IgE ratio may help distinguish between “benign” sensitization (sensitization with no symptoms) and “pathologic” sensitization
- ▶ But measurement of allergen- specific IgG cannot as yet be recommended in a routine clinical practice



Section VIII Evaluation and diagnosis- allergen challenge testing

VIII.H.1. pg. 198 Allergen challenge chambers (ACCs)

- ▶ Environmental exposure chambers (EECs) - 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.
- ▶ Limited number of EECs world- wide.
- ▶ Currently 15 allergen challenge chamber (ACC) facilities around the globe
- ▶ Contributed to our understanding of the pathophysiology of allergic diseases
- ▶ Allergen exposure exacerbates atopic dermatitis
- ▶ Pollen allergen fragments impact AR symptoms
- ▶ Used in clinical drug development to study pharmacological properties of new drugs during phase II trials, such as dose-finding, onset of action, and duration of action



Section VIII Evaluation and Diagnosis

VIII. H.2. pg. 198 Local Allergen Challenge Tests

- ▶ Challenging the target organs of respiratory allergy (ie, 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
- ▶ NPT nasal provocation test designed for AR
- ▶ CPT conjunctival provocation test for rhino-conjunctivitis or AR alone



Nasal Challenge

- ▶ To reproduce the response of the upper airway upon nasal exposure to allergens
- ▶ Allergens administered by various devices, including syringes, nose droppers, micropipettes, nasal sprays, or impregnated disks, all with limitations or pitfalls
- ▶ Results 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
- ▶ Contraindications to NPT are acute bacterial or viral rhinosinusitis, exacerbation of AR, history of anaphylaxis to allergens, severe general diseases, and pregnancy
- ▶ Standardized technique for NPT is not yet available



Nasal Challenge

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
Krzych-Falta 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.
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.
Jang & Kim ¹⁰⁸⁴	2015	2b	Open controlled	HDM 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.
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.

HDM = house dust mite; LOE = level of evidence; NPT = nasal provocation test; SPT = skin-prick test; TNSS = Total Nasal Symptom Score.

Nasal Challenge

- ▶ A pivotal role for NPT is in the diagnosis of occupational rhinitis and LAR- Local Allergic Rhinitis
- ▶ EAACI's position is, 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 —the gold standard



Nasal Challenge in LAR

- ▶ Absence of sIgE in serum and in the skin requires that IgE is found locally or that they are revealed by a positive NPT
- ▶ Inability to currently measure locally-present IgE makes NPT of critical importance
- ▶ Aggregate Grade of Evidence for NPT: C -Level 2b: 4 studies
- ▶ Evidence grade based on the studies listed in Table VIII.H.2



Section VIII Evaluation and diagnosis

VIII.H.1. pg. 198 Allergen challenge chambers

- ▶ Allergen challenge chambers study the affects on subjects of controlled exposures of allergens, particulate or gaseous air pollutants, chemicals or climate conditions.
- ▶ Contributed to our understanding of pathophysiology of allergic diseases
 - ▶ Allergen exposure exacerbates atopic dermatitis
 - ▶ Impact of Pollen exposure on AR symptoms
 - ▶ Importance of the epithelial barrier integrity for induction of local and systemic inflammatory responses



Allergen challenge chambers

- ▶ Intensively used to study pharmacological properties of new drugs in phase II trials
 - ▶ Dose finding, onset of action and duration of action
 - ▶ Randomized placebo controlled trials have tested efficacy of drugs (antihistamines, topical steroids, novel anti-inflammatory compounds or probiotics)
 - ▶ Better signal to noise ratio
 - ▶ Repeatability of symptoms during intra-individual testing
 - ▶ Not approved for phase III studies
 - ▶ Evaluation during natural exposure is still mandatory



Section VIII. Evaluation and diagnosis

VIII.H.2. pg. 198 Local allergen challenge tests

- ▶ Challenges the target organs of respiratory allergy with a suspected allergen
- ▶ Can demonstrate clinical reactivity when initial allergy tests are inconclusive
- ▶ Nasal challenge: reproduce the response of the upper airway upon nasal exposure to allergens
- ▶ Several devices can be used to administer the allergen
- ▶ Results can be assessed by several measures (TNSS, rhinomanometry, peak inspiratory flow, nasal NO concentration, inflammatory markers)



Local allergen challenge test

- ▶ A standardized technique for NPT in diagnosis of AR is not available
- ▶ The use of NPT in diagnosis of AR is likely to decrease because of emerging tools such as CRD and BAT
- ▶ Occupational rhinitis can only be diagnosed by NPT with the suspected agents (the Gold standard)



Local allergen challenge test

- ▶ Conjunctival provocation test (CPT) may be used in patients with rhinoconjunctivitis or AR alone
- ▶ Instill 20-30 microliters of an allergen solution into the inferior external quadrant of the ocular conjunctiva
- ▶ Use diluent in the contralateral eye as a control
- ▶ The response is simple to evaluate
- ▶ The Sensitivity and specificity was high in mite allergy patients
- ▶ Grade B evidence for the capacity to individuate the allergen trigger



Local allergen challenge test

- ▶ Aggregate grade of evidence for Nasal Provocation testing: C (Due to the variation in NPT technique and outcome measures, a reliable evidence grade for NPT is difficult to determine)
- ▶ References: 1. Werfel T, Heratizadeh A, Niebuhr M, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol*. 2015;136:96-103.e9. 2. Badorrek P, Dick M, Emmert L, et al. Pollen starch granules in bronchial inflammation. *Ann Allergy Asthma Immunol*. 2012;109:208-214.e6. 3. Ahuja SK, Manoharan MS, Harper NL, et al. Preservation of epithelial cell barrier function and muted inflammation in resistance to allergic rhinoconjunctivitis from house dust mite challenge. *J Allergy Clin Immunol*. 2017;189:844-854. 4. Horak F, Jager S, Nirnberger G, et al. Pharmacodynamic dose finding of dimetindene in a sustained release formulation. *Arzneimittelforschung*. 1993;43:1193-1195. 5. Horak FF, Jager S, Nirnberger G, et al. Dose-related control allergic rhinitis symptoms by a H1-receptor antagonist. Finding the proper doses of dimethindene maleate in patients with allergic rhinitis. *Int Arch Allergy Immunol*. 1994;103:298-302. 6. Day JH, Briscoe MP, Ratz JD, Ellis AK, Yao R, Danzig M. Onset of action of loratadine/montelukast in seasonal allergic rhinitis subjects exposed to ragweed pollen in the Environmental Exposure Unit. *Allergy Asthma Proc*. 2009;30:270-276. 7. Day JH, Briscoe MP, Rafeiro E, Hewlett D Jr, Chapman D, Kramer B. Randomized double-blind comparison of cetirizine and fexofenadine after pollen challenge in the Environmental Exposure Unit: duration of effect in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2004;24:59-68. 8. Badorrek P, Dick M, Schauerte A, et al. A combination of cetirizine and pseudoephedrine has therapeutic benefits when compared to single drug treatment in allergic rhinitis. *Int J Clin Pharmacol Ther*. 2009;47:71-77. 9. Krug N, Hohlfeld JM, Geldmacher H, et al. Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. *Allergy*. 2005;60:354-359. 10. Bareille P, Murdoch RD, Denyer J, et al. The effects of a TRPV1 antagonist, SB-705498, in the treatment of seasonal allergic rhinitis. *Int J Clin Pharmacol Ther*. 2013;51:576-584. 11. Xiao JZ, Kondo S, Yanagisawa N, et al. Clinical efficacy of probiotic *Bifidobacterium longum* for the treatment of symptoms of Japanese cedar pollen allergy in subjects evaluated in an environmental exposure unit. *Allergol Int*. 2007;56:67-75. 12. Dordal MT, Lluch-Bernal M, Sanchez MC, et al.; SEAIAC Rhinoconjunctivitis Committee. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Invest Allergol Clin Immunol*. 2011;21:1-12. 13. Malm L, Gerth van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. *Rhinology*. 2000;38:1-6. 14. Cassel A, Khayath N, de Blay F. How in vitro assays contribute to allergy diagnosis. *Curr Allergy Asthma Rep*. 2016;16:82. 15. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy*. 2015;70:1393-1405. 16. Moscato G, Vandenplas O, Gerth Van Wijk R, et al. Occupational rhinitis. *Allergy*. 2008;63:969-980. 17. Riechelmann H, Eppe B, Gropper G. Comparison of conjunctival and nasal provocation test in allergic rhinitis to house dust mite. *Int Arch Allergy Immunol*. 2003;130:51-59. 18. Agache I, Bilo M, Braunstahl GJ, et al. In vivo diagnosis of allergic diseases—allergen provocation tests. *Allergy*. 2015;70:355-365. 19. Bertel F, Mortemousque B, Sicard H, Andre C. Conjunctival provocation test with *Dermatophagoides pteronyssinus* in the diagnosis of allergic conjunctivitis from house mites. *J Fr Ophtalmol*. 2001;24:581-589. 20. Fauquet JL, Jedrzejczak-Czechowicz M, Rondon C, et al. Conjunctival allergen provocation tests: guidelines for daily practice. *Allergy*. 2017;72:43-54.

Section VIII. Evaluation and diagnosis

VIII.I. Pg. 200 Nasal cytology and histology

- ▶ Evaluates the health of the nasal mucosa by recognizing and counting cell types and their morphology
- ▶ In AR the predominant cell type is Eosinophils, followed by mast cells and basophils
- ▶ The nasal cytology (NC) in polyallergic patients shows a more intense inflammatory response than in monoallergic patients
- ▶ NC demonstrates seasonal changes
- ▶ NC is 1 method of diagnosing NAR and has been used to differentiate between variants in experiments



Nasal cytology and histology

- ▶ Nasal histology assessed by biopsies
 - ▶ The only technique to study tissues and cells in patients for many decades
 - ▶ Doesn't allow for sequential sampling (nasal cytology does)
 - ▶ Mucosa cellular compartment unchanged after allergen challenge (but the secretions have increased inflammatory cells)
 - ▶ Requires more expertise to obtain than nasal cytology

Nasal cytology and histology

- ▶ Aggregate grade of evidence for nasal cytology is C
- ▶ Aggregate grade of evidence for nasal histology is B
- ▶ References: 1. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. Nasal cytology: practical aspects and clinical relevance. Clin Exp Allergy. 2016;46:785-792. 2. Canakcioglu S, tahamiler R, Saritzali G, et al. Evaluation of nasal cytology in subjects with chronic rhinitis: a 7-year study. Am J Otolaryngol. 2009;30:312-317. 3. Gelardi m, Incorvaia C, Passalacqua G, Quanranta N, Frati F. The classification of allergic rhinitis and its cytological correlate. Allergy. 2011;66:1624-1625. 4 Gelardi M, Peroni DG, Incorvaia C, et al. Seasonal changes in nasal cytology in mite-allergic patients. J Inflamm Res. 2014;7:39-44, 5. Gelardi M, Quaranta N, Passalacqua G. When sneezing indicatesthe cell type. Int Forum Allergy Rhinol. 2018;3:393-398. 6. Lim MC, Taylor RM, Naclerio RM. The histology of allergi rhinitis and its comparison to cellular changes in nasal lavage. Am J Respir Crit Care Med. 1995;151:136-144. 7. Howarth PH, Persson CG, Meltzer EO, Jacobson MR, Durham SR, Silkoff PE. Objective monitoring of nasal airway inflammation in rhinitis. J Allergy Clin Immunol. 2005;115:S414-S441.



IX. Management

- ▶ IX.A. Allergen avoidance
- ▶ IX.B. Pharmacotherapy
- ▶ IX.C. Surgical treatment
- ▶ IX.D. Allergen immunotherapy



Section IX Management

IX.A pg 200 Allergen Avoidance

- ▶ House Dust Mite
- ▶ Cockroach
- ▶ Pets
- ▶ Other (Occupational, Environmental)



IX.A. Allergen avoidance

- ▶ IX.A.1. House dust mite 200
- ▶ IX.A.2. Cockroach 201
- ▶ IX.A.3. Pets 206
- ▶ IX.A.4. Other (pollen, occupational) 207



Section IX Management

IX.A.1 pg 200 House Dust Mites (HDM)

- ▶ One of the most common triggers of allergic rhinitis
- ▶ Physical techniques
 - ▶ Heating, ventilation, freezing, barrier methods, air filtration, vacuuming, ionizers
 - ▶ Studies suggest reduction in HDM antigen concentration
 - ▶ Associated clinical benefit has *not* been reliably demonstrated
- ▶ Chemical techniques
 - ▶ Acaricides
 - ▶ Cochrane review found acaricides to be the most effective as single measure or in combination to



HDM Avoidance

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Reduced concentration of environmental HDM antigens with potential improvement in symptom scores and QOL
- ▶ Harm: None
- ▶ Cost: Low to moderate, although cost effectiveness has not been evaluated
- ▶ Benefit outweighs harm
- ▶ Value Judgments: The use of acaricides and environmental control programs in reducing HDM concentration is promising; high quality studies are needed to evaluate clinical outcomes
- ▶ Policy Level: Option
- ▶ Intervention: Concomitant use of acaricides and environmental control measures are options



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 decrease HDM and improve symptoms.
Ghazala et al. ¹¹²⁰	2004	1b	Randomized crossover 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 p 1 and Der f 1 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 QOL scores.
Brehler & 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 & Choi ¹¹²²	1999	2b	Open RCT	1. Adults and children with atopy and multimodality environmental control; 2. Adults and children with atopy and verbal advice on allergen avoidance	Change in HDM load, daily rhinitis symptom scores	Multimodality 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; 2. Children with atopy without acaricide	Daily rhinitis and asthma symptom scores, medication use, twice-weekly PEF	Acaricide is associated with decreased mean symptom scores.

Continued

TABLE IX.A.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kneist 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, tlgE, slgE, serum and nasal eosinophils, guanine exposure	Acaricide associated with improvement in all outcome measures except for mite-specific IgE.
Antonicelli et al. ¹¹²⁵	1991	2b	Randomized crossover 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 crossover 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.

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

HDM Avoidance

Section IX Management

IX.A.2. pg. 201 Cockroach

- ▶ Allergen concentrations high in multi-occupant dwellings in densely populated inner city areas; also warmer, rural regions
- ▶ Allergen: Bla g 1, Gla g2
- ▶ Interventions
 - ▶ Education-based: instructions on house cleaning, sealing cracks/crevices
 - ▶ Physical methods: insecticides, bait traps
 - ▶ Combination
- ▶ Most effective treatment to eliminate infestation and reduce allergen load: professional pest control
- ▶ Bait traps with labor and monitoring were less expensive than multiple commercial applications of insecticide sprays to baseboards and cracks



Cockroach Avoidance

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Reduction in cockroach count, but Bl a g 1 and Bl a g 2 often above acceptable levels for clinical benefits. No studies include AR as clinical endpoint
- ▶ Harm: none
- ▶ Cost: Moderate
- ▶ Balance of benefit and harm
- ▶ Value Judgments: Control of cockroach populations is important to controlling allergen levels
- ▶ Policy level: Option
- ▶ Intervention: Physical and educational 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 (eg, 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 and 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 months. 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.
Arbes et al. ¹¹³⁵	2004	1b	RCT with crossover of control group	1. Intervention: education; insecticide bait placement; professional cleaning; 2. Control: no intervention for months 0–6; insecticide bait placement at months 6 and 9	No direct clinical endpoints, Bla g 1 and 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.
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 healthcare services	Intervention group: Reduced levels of CR allergen in bedroom were strongly correlated with decreased asthma-related morbidity.
McConnell et al. ¹¹³⁶	2003	1b	RCT	1. Professional cleaning and insecticide bait traps; 2. Professional cleaning and 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.

Continued

TABLE IX.A.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
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% to 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.
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 and 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 and Bla g 2 CR allergen. No significant difference: active vs placebo.
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% to 93% over 8 months; mean allergen concentrations still above threshold of asthma morbidity.

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

Cockroach Avoidance

Section IX Management

IX.A.3. pg. 206 Pets

- ▶ Allergen: Fel d 1, Can f 1
- ▶ Pet removal is a commonly cited strategy *without* high-quality outcomes evaluation
 - ▶ Patient compliance – 4%
- ▶ Avoidance and environmental control strategies
 - ▶ HEPA filter – no significant effect identified
 - ▶ Pet bathing – must be completed at least 2x/wk to maintain antigen reduction
 - ▶ “Hypoallergenic breeds” – similar Can f 1 level to other species



Pet Avoidance and Environmental Controls

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Decreased environmental antigen exposure with possible reduction in nasal symptoms and secondary prevention of asthma
- ▶ Harm: Emotional distress (pet removal); Financial and time costs for possible ineffective intervention
- ▶ Cost: Low to Moderate
- ▶ Balance of benefit and harm
- ▶ Value Judgments: Only a single, multimodality RCT has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity
- ▶ Policy level: Option
- ▶ Intervention: Pet avoidance and EC strategies, particularly multimodality EC among patients with diagnosed Fel d 1 sensitivity, are an option for the treatment of AR related to pets



Pet Avoidance and Environmental Controls

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.
Björnsdóttir et al. ¹¹⁴⁷	2003	2b ^a	RCT	Cat-allergic patients: 1. EC; 2. Unchanged environment	Environmental (settled dust) Fel d 1 levels, nasal inspiratory flow, nasal symptoms	Multimodality EC is associated with decreased allergen concentration and significant improvements in nasal inspiratory flow and patient symptoms.

^aFollow-up <80% prevents 1b.

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

Section IX Management

IX.A.4. pg. 207 Pollen, Occupational Allergen Avoidance

- ▶ Most recommended strategies for **pollen avoidance** are based on expert consensus and clinical experience
- ▶ Limiting residential exposure during periods of high pollination
 - ▶ Avoiding extensive outdoor exercise during peak pollen levels
 - ▶ Air conditioning during high pollination season
 - ▶ Dust/pollen filters
 - ▶ Removing clothing and hair washing before bed
 - ▶ Use of wrap-around eye glasses / active nasal filters
- ▶ Avoidance of exposures to **occupational allergens**
- ▶ Engineering controls
 - ▶ Physical changes to the work area or process that effectively minimize a worker's exposure to hazards
 - ▶ Substitution of hazardous chemical with nonhazardous or less hazardous alternative
 - ▶ Isolation of the hazardous chemical
 - ▶ Efficient ventilation to reduce exposure
- ▶ Administrative controls
 - ▶ Employee education
 - ▶ Personal protective equipment



Pollen, Occupational Allergen Avoidance

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Decreased allergen exposure with possible reduction in symptoms and need for allergy medication, along with improved QOL
- ▶ Harm: Financial and time costs for potentially ineffective intervention
- ▶ Cost: Low, but dependent on strategy
- ▶ Balance of benefit to harm
- ▶ Value Judgments: Limited number of studies show clinical effects of investigated environmental control measures. Recommendations primarily based on expert opinion
- ▶ Policy level: Option
- ▶ Intervention: Pollen and occupational allergen avoidance by environmental control strategies are an option for AR treatment; clinical effectiveness has not been definitively demonstrated.



Pollen, Occupational Allergen Avoidance

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.

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

IX.B. Pharmacotherapy

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Section IX Management

IX.B.1. pg. 208 Antihistamines

- ▶ Block the proinflammatory effects of histamine by binding the histamine H₁ receptor
- ▶ Agents classified by generation
 - ▶ First generation – lipophilic, cross blood-brain barrier, produce sedation, fatigue, impaired concentration, impaired memory, antimuscarinic effects, cardiac effects
 - ▶ Second generation – lipophobic, limited side effects, highly specific for H₁ receptor
- ▶ Metabolized by cytochrome P450 CYP3A4 system
- ▶ Many RCTs establishing efficacy



Section IX.B.1. – Oral H₁ Antihistamines

- ▶ Aggregate Grade of Evidence: A
- ▶ Benefit: Reduced nasal itching, sneezing, rhinorrhea, nasal obstruction
- ▶ Harm: Mild drowsiness, fatigue, headache, nausea, dry mouth
- ▶ Cost: Direct costs low (\$2 /day); indirect costs lower for newer agents
- ▶ Risk Assessment: Benefits outweigh harm for newer-generation agents
- ▶ Value Judgments: Due to the CNS side effects of the first-generation oral agents, their use is not recommended for typical AR
- ▶ Policy level: Strong recommendation for newer agents
- ▶ Intervention: Prescribing newer-generation oral agents for patients with AR should be considered early in treatment



Section IX.B.1. – Oral H₂ Antihistamines

- ▶ Role in mediating nasal symptoms is controversial
- ▶ Few small studies with varied results
- ▶ May improve nasal airway resistance in patients refractory to H₁ antagonists alone
- ▶ No data comparing H₂ receptor antagonism efficacy to common first-line therapy



Section IX.B.1. – Oral H₂ Antihistamines

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Decreased objective nasal resistance, improved symptom control in 1 study when used in combination with H₁ antagonists
- ▶ Harm: Drug-drug interaction (P450 inhibition, inhibited gastric secretion and absorption)
- ▶ Cost: Increased cost with H₂ antagonist
- ▶ Risk Assessment: Unclear benefit and possible harm
- ▶ Value Judgments: No studies evaluating efficacy of H₂ antihistamines in context of topical nasal corticosteroids
- ▶ Policy level: No recommendation
- ▶ Intervention: Addition of an oral H₂ antagonist to an oral H₁ antagonist may improve symptom control in AR, though evidence is not strong



Section IX.B.1. – Intranasal Antihistamines

- ▶ Topical application of newer generation H₁ antagonists
- ▶ Two agents currently available (azelastine and olopatadine)
- ▶ Superior to placebo for symptom relief in numerous studies
- ▶ Comparable or better than oral H₁ antagonists in several studies
- ▶ No additional benefit from combination therapy with oral H₁ antagonists
- ▶ Variable results when compared to INCS
 - ▶ Generally equivalent
 - ▶ More rapid onset of action for intranasal antihistamines
- ▶ No reported serious adverse effects
- ▶ Minor adverse effects include adverse taste, somnolence, headache and epistaxis



Section IX.B.1.– Intranasal Antihistamines

- ▶ Aggregate Grade of Evidence: A
- ▶ Benefit: Rapid onset, improve QOL, more effective for nasal congestion than oral antihistamines, more effective for ocular symptoms than INCS
- ▶ Harm: Patient tolerance due to adverse taste
- ▶ Cost: Low-to-moderate
- ▶ Risk Assessment: Preponderance of benefit over harm
- ▶ 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-line or second-line therapy in the treatment of AR



Section IX Management

IX.B.2. pg. 217 Corticosteroids

- ▶ Reduces local histamine and eosinophil levels, and decreases vascular permeability during late phase response to allergen challenge
- ▶ Reduces priming response to consecutive allergen challenge
- ▶ Generally effective at improving symptoms of AR
- ▶ Numerous systemic adverse effects have led to replacement by topical intranasal preparations



Section IX.B.2. – Oral Corticosteroids

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Attenuate symptoms of AR
- ▶ Harm: Adverse effects on hypothalamic-pituitary axis, growth and musculoskeletal system, ocular system, gastrointestinal system, hypertension, glycemic control, mental/emotional state, and others
- ▶ Cost: Low
- ▶ Risk Assessment: Risks outweigh benefits when compared to similar symptom improvement with use of INCS
- ▶ Value Judgments: In the presence of effective symptom control using INCS, the risk of adverse effects from oral corticosteroids outweigh the benefit
- ▶ Policy level: Recommendation against
- ▶ Intervention: Although not recommended for routine use in AR, oral corticosteroids may be considered in patients with severe nasal obstruction to facilitate penetration of intranasal agents



Section IX.B.2.– Injectable Corticosteroids

- ▶ Most commonly intramuscular injection of corticosteroids
 - ▶ Generally effective at improving symptoms of AR
 - ▶ Comparable to other agents in limited studies
- ▶ Intratubinate injection of corticosteroid was superior to placebo in single RCT
- ▶ Concern for significant systemic adverse effects including adrenal suppression and osteoporosis



Section IX.B.2.– Injectable Corticosteroids

- ▶ Aggregate Grade of Evidence: B
- ▶ Benefit: Improve symptoms of AR
- ▶ Harm: Adverse effects on hypothalamic-pituitary axis, growth and musculoskeletal system, ocular system, gastrointestinal system, hypertension, glycemic control, mental/emotional state, and others
- ▶ Cost: Low
- ▶ Risk Assessment: Risks outweigh benefits in routine management of AR
- ▶ Value Judgments: Injectable corticosteroids are effective for symptom relief, but the risk of significant adverse effects and the availability of effective alternatives precludes recommendation for routine use
- ▶ Policy level: Recommendation against
- ▶ Intervention: None



Section IX.B.2.– Intranasal Corticosteroids

- ▶ Effective in reducing and managing nasal and ocular symptoms of AR
- ▶ First-line therapy
- ▶ Multiple RCTs in adults and children
 - ▶ Superior to placebo
 - ▶ Superior to oral H₁ antihistamines and LTRAs
- ▶ Available as aqueous and non-aqueous preparations
- ▶ Continuous daily use is superior to other dosing strategies
 - ▶ Prophylactic use recommended
 - ▶ As-needed use may be superior to placebo
- ▶ Systematic reviews have shown limited potential for ocular adverse effects or hypothalamic-pituitary axis suppression



Section IX.B.2.– Intranasal Corticosteroids

- ▶ Aggregate Grade of Evidence: A
- ▶ Benefit: INCS is effective in reducing nasal and ocular symptoms of AR, with superior efficacy compared to oral antihistamines and LRTAs
- ▶ Harm: Local adverse effects, epistaxis, possible negative effect on short-term growth in children though long-term effects are unclear
- ▶ Cost: Low
- ▶ Risk Assessment: Preponderance of benefit over harm
- ▶ Value Judgments: None
- ▶ Policy level: Strong recommendation
- ▶ 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



Section IX Management

IX.B.3. pg. 227-229 Oral Decongestants

- ▶ Oral decongestants act on adrenergic receptors to cause vasoconstriction and can reduce symptoms of nasal congestion in patients with AR
- ▶ Pseudoephedrine has been shown to have beneficial effects in patients with AR
 - ▶ Phenylephrine has not been shown to benefit patients with AR
 - ▶ Availability of pseudoephedrine in US is limited to behind the counter pharmacies
- ▶ Use is tempered by side effect profile including insomnia, anxiety, tremors, palpitations, and elevated blood pressure
 - ▶ Use should be cautioned in patients with known cerebrovascular disease, coronary artery disease, hypertension, and hyperthyroidism
 - ▶ Effective in children but should be limited to age > 2 years old



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. Phenylpropanolamine; 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 10 mg (n = 109); 2. Phenylephrine 20 mg (n = 108); 3. Phenylephrine 30 mg (n = 107); 4. Phenylephrine 40 mg (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.

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

Section IX Management

IX.B.3. pg. 227 Oral Decongestants

- ▶ Aggregate Grade of Evidence: B
- ▶ 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: Patient's other comorbidities and age should be considered before use.
- ▶ 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.



Section IX Management

IX.B.3. Nasal Decongestants

- ▶ Xylometazoline and oxymetazoline are alpha-adrenergic stimulators and result in vasoconstriction and reduction in nasal mucosa thickness
- ▶ Side effects include nasal stinging, burning, dryness, bleeding and ulceration
- ▶ Long term use is limited by risk of rhinitis medicamentosa
 - ▶ Studies differ on when rebound effects start but typically limit use to 3 days



TABLE IX.B.3.b. 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 furoate.
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 oxymetazoline; 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; nPIF = nasal peak inspiratory flow; RCT = randomized controlled trial; TID = 3 times daily.



Section IX Management

IX.B.3. Nasal Decongestants

- ▶ Aggregate Grade of Evidence: 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



Section IX Management

IX.B.4. pg. 229 232 Leukotriene Receptor Antagonists

- ▶ Monteleukast is FDA approved for seasonal AR in patients >2 years age and for perennial AR in patients >6 months age
- ▶ Effective in treatment of all symptoms of AR in multitude of studies above placebo
- ▶ However, AAOHNS has recommended against **mono**therapy with monteleukast in patients with AR without asthma when other medications are available and tolerated by patient
 - ▶ Monotherapy shown to be inferior to intranasal corticosteroids
 - ▶ Therapy is more expensive compared to alternatives



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 levocetirizine 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 levocetirizine improved symptoms following artificial allergen exposures. Levocetirizine was more effective than montelukast.
Jiang ¹³⁴⁸	2006	1b	RCT	1. Zafirlukast; 2. Loratadine; 3. Loratadine + pseudoephedrine	Symptoms, acoustic rhinometry, rhinomanometry	All treatment groups had a significant reduction of pretreatment symptoms. Zafirlukast was superior at reduction of nasal congestion. There were no differences in acoustic rhinometry and rhinomanometry between the 3 treatment groups.
Mucha et al. ¹³²¹	2006	1b	RCT	1. Montelukast; 2. Pseudoephedrine	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.

Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
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. ¹³⁴⁶	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.

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

Section IX Management Leukotriene Receptor Antagonists



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Section IX Management

IX.B.4. Leukotriene Receptor Antagonists

- ▶ Aggregate Grade of Evidence: A
- ▶ 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



Section IX Management

IX.B.4. Leukotriene Receptor Antagonists

- ▶ 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: Evidence is lacking to recommend LTRAs as first-line 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 INCSs are contraindicated.



Section IX Management

IX.B.5. pg. 232- 234 Cromolyn

- ▶ Cromolyn or disodium cromogylcate (DSCG) is a mast cell stabilizer and prevents histamine release and is best used preemptively prior to exposure to allergens
- ▶ Excellent safety profile and approved for ages > 2 years
- ▶ However, half life short and frequent dosing of 3-6 times a day limits its usefulness
- ▶ May be used in patients with known triggers prior to exposure
- ▶ However, lower effectiveness in monotherapy compared to intranasal corticosteroids



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 2.6 mg 6 times per day (n = 29); 2. Flunisolide 25 µg BID (n = 38)	Nasal symptoms	Flunisolide performed better than DSCG.
Craig et al. ¹³⁷³	1977	1b	DBRCT	SAR (n = 39): 1. DSCG 5.2 mg 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 2.5 mg 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 10 mg 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 10 mg QID; 2. Placebo	Nasal symptoms	No difference between DSCG and placebo.
Cohan et al. ¹³⁶⁰	1976	1b	DBRCT, crossover	PAR, 16–37 years old: 1. DSCG 4%, 6 times per day; 2. Placebo	Symptom score, medication use	DSCG performed better than placebo.
Knight et al. ¹³⁷⁷	1976	1b	DBRCT	SAR: 1. DSCG 10 mg 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 200 µg QD (n = 41); 2. Levocabastine 200 µg BID (n = 40); 3. DSCG 5.6 mg QID (n = 42)	Symptom scores, nPIF	MF performed best.
Fisher ¹³⁶²	1994	2b	RCT, blinded, no placebo	SAR, 6–15 years old: 1. DSCG 31.2 mg, 6 times per day (n = 26); 2. Budesonide BID, 400 µg/day (n = 30)	Nasal symptoms	Budesonide performed better than DSCG.
Bousquet et al. ¹³⁶³	1993	2b	DBRCT, no placebo	SAR: 1. FP 200 µg QD (n = 110); 2. DSCG 5.2 mg QID (n = 108)	Nasal/ocular symptoms, medication use	FP better in all except nasal discharge. No difference in medication use.

Continued

TABLE IX.B.5. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Welsh et al. ¹³⁶⁴	1987	2b	RCT, blinded	1. BDP 2 sprays BID, 336 µg/day; 2. Flunisolide 2 sprays BID, 200 µg/day; 3. DSCG 1 spray QID, 41.6 mg/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 200 µg BID (n = 22); 2. DSCG 5.2 mg, 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, 400 µg/day (n = 47); 2. DSCG 2.6 mg, 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 50 µg QID; 2. DSCG 10 mg QID	Nasal symptoms	BDP performed better than DSCG.
Wilson & Walker ¹³⁶⁸	1976	2b	RCT, no placebo	SAR, adults: 1. DSCG 10 mg QID (n = 10); 2. BV 100 µg BID (n = 10)	Nasal symptoms	BV performed better than DSCG.
Frankland & Walker ¹³⁶⁹	1975	2b	DBRCT, no placebo	SAR, adults: 1. DSCG 80 µg, 6 times per day (n = 14); 2. BV 100 µg BID (n = 18)	Nasal symptoms, nPIF	BV performed better than DSCG for symptoms. The 2 medications performed the same for nPIF.

BDP = beclomethasone dipropionate; BID = 2 times daily; BV = betamethasone valerate; DBRCT = double-blind randomized controlled trial; DSCG = disodium cromoglycate; FP = fluticasone propionate; LOE = level of evidence; MF = mometasone furoate; nPIF = nasal peak inspiratory flow; PAR = perennial allergic rhinitis; QD = once daily; QID = 4 times daily; RCT = randomized controlled trial; SAR = seasonal allergic rhinitis.

Section IX Management

IX.B.5. pg. 232- 234 Cromolyn

Section IX Management

IX.B.5 Cromolyn

- ▶ Aggregate Grade of Evidence: A
- ▶ 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



Section IX Management

IX.B.6. pg. 234-236 Intranasal Anticholinergics

- ▶ Ipratropium bromide (IPB) controls watery rhinorrhea in adults and children
- ▶ Short half life and can be used up to 6 times a day
- ▶ Side effects include nasal dryness, epistaxis, and irritation
- ▶ Systemic anticholinergic effects have not been observed in patients taking therapeutic dosing but patients should be cautioned of overuse
- ▶ Only treats rhinorrhea symptoms in AR and improving evidence on its combined use with intranasal corticosteroids



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 (42 µg) TID + BDP 82 µg BID (n = 109); 2. IPB 0.03%, 2 sprays (42 µg) TID (n = 222); 3. BDP 82 µg 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% (42 µg) TID + terfenadine 60 mg PO BID; 2. Placebo + terfenadine	Nasal symptoms	Control of rhinorrhea and sneezing better in IPB + terfenadine. No differences in nasal congestion.
Kaiser et al. ¹³⁷⁹	1998	1b	DBRCT	PAR, adults: 1. IPB 0.03% (42 µg) TID; 2. IPB 0.06% (84 µg) TID; 3. Placebo	Nasal symptoms	High-dose and low-dose IPB resulted in significant reduction of nasal hypersecretion vs 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 80 µg 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 21 µg (n = 48) or 42 µg (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 80 µg 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 80 µg 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 20 µg QID; 2. Placebo	Nasal symptoms	IPB had a significant effect on rhinorrhea. No effect on other 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 (42 µg) 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 (42 µg), 2 sprays BID (n = 75); 2. BDP (n = 71)	Nasal symptoms, QOL	Equally effective in controlling rhinorrhea and improving QOL. BDP more effective in controlling sneezing.
Kaiser et al. ¹³⁹⁰	1995	2b	Prospective	PAR, 18–75 years old (n = 219): First 6 months: 0.06% IPB TID (84 µg); 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.

BDP = beclomethasone dipropionate; DBRCT = double-blind randomized controlled trial; IPB = ipratropium bromide; LOE = level of evidence; NAR = non-allergic rhinitis; PAR = perennial allergic rhinitis; QID = 4 times daily; QOL = quality of life; RCT = randomized controlled trial; SAR = seasonal allergic rhinitis; TID = 3 times daily; BID = 2 times daily.

Section IX Management

IX.B.6. pg. 234-236 Intranasal Anticholinergics

Section IX Management

IX.B.6. Intranasal Anticholinergics

- ▶ Aggregate Grade of Evidence: B
- ▶ 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 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.



Section IX Management

IX.B.7. Biologics

- ▶ No biologic is currently FDA approved for the treatment of AR
- ▶ Omalizumab is an anti-IgE antibody that has been studied in the treatment of AR both as a monotherapy and in combination with AIT
 - ▶ RCTs and systematic review of RCTs demonstrates improvement of AR symptoms, use of rescue medication and QOL
 - ▶ Combination with AIT is superior to anti-IgE alone; also reduces anaphylaxis risk of AIT
- ▶ Extremely high cost of approximately \$18,000 USD per year and lack of FDA approval limits normal use



Section IX Management

IX.B.7. Biologics

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 al. ¹³⁹³	2001	1b	RCT	1. Omalizumab; 2. Placebo	Symptom score, rescue medication, QOL	Dose-finding trial, 300-mg 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.

AR = allergic rhinitis; LOE = level of evidence; PAR = perennial allergic rhinitis; QOL = quality of life; RCT = randomized controlled trial; SR = systematic review.

Section IX Management

IX.B.7. Biologics

- ▶ Aggregate Grade of Evidence: A
- ▶ 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. (\$18,000 USD per year)
- ▶ 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.



Section IX Management

IX.B.7. Biologics

- ▶ Value Judgments: 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 AIT for highly sensitive polyallergic rhinitis patients with increased risk of anaphylaxis



Section IX Management

IX.B.8. pg. 237 - 239 Nasal saline

- ▶ Frequently utilized in the treatment of AR
- ▶ Regimens vary:
 - ▶ Hypertonic saline
 - ▶ Isotonic (normal) saline
 - ▶ Seawater
 - ▶ Buffered vs non-buffered
 - ▶ Varying volumes (300 μ L to 500mL)



Evidence

► 5 Adult RCTs

- Hypertonic saline vs no irrigations [Garavello et al and Rogkakou et al]
 - Hypertonic saline improved nasal symptoms, increased quality of life, and decreased oral antihistamine use
- Non-buffered isotonic saline vs buffered with mild alkalinity (pH 7.2-7.4) vs buffered with alkalinity (pH 8.2-8.4) [Chusakul et al]
 - Nasal symptoms were only improved with buffered saline with mild alkalinity
- Hypertonic saline vs isotonic saline [Ural et al]
 - Isotonic saline improved mucociliary clearance time
- Dead sea saline spray vs triamcinolone spray vs placebo saline spray [Cordray et al]
 - Significant improvement: Triamcinolone > Dead Sea saline > placebo saline



Evidence

- ▶ 6 Pediatric RCTs
 - ▶ Hypertonic saline vs no irrigations [Garavello et al]
 - ▶ Hypertonic saline improved nasal symptoms, increased quality of life, and decreased oral antihistamine use
 - ▶ Hypertonic saline vs isotonic saline [Marchisio et al, Satdhabudha and Poachanukoon]
 - ▶ Improvement in nasal symptom scores: Hypertonic saline > isotonic saline
 - ▶ Steroid spray + saline [Li et al, Chen et al]
 - ▶ Additive effect with either sprays or irrigations

Conclusions

Grade of Evidence:

A

- Level 1a: 1 study
- Level 1b: 11 studies

Benefit/Harm

Benefit

- Reduced nasal symptom scores
- improved QOL
- improved mucociliary clearance
- well tolerated with excellent safety profile.

Harm

- Intranasal irritation
- Headaches
- ear pain

Value/Intervention

Nasal saline should be used as an adjunct to other pharmacologic treatments for AR

- Adults: Isotonic solutions may be more beneficial
- Children: Hypertonic solutions may be more beneficial.

Section IX Management

IX.B.9. pg. 239 - 242 Probiotics

- ▶ Relationship between microbiome and development of atopy is complex and incompletely understood
 - ▶ Manipulation of the microbiome via probiotic administration could theoretically lead to clinical improvement of allergic disease
- ▶ Immunomodulatory effects on atopic disease via gut associated lymphoid tissue
 - ▶ Stimulation of dendritic cells induces:
 - ▶ Th1 responses via IL-12 and IFN- γ
 - ▶ Upregulation of Treg cells via IL-10 and TGF- β
 - ▶ Suppression of Th2 pathways through downregulation of IL-4, sIgE, IgG1, and IgA



Evidence

- ▶ Timing of probiotic administration
 - ▶ Meta-analysis of 17 studies: probiotics in pregnancy and early infancy were associated with decreased incidence of eczema but not asthma or rhinosinusitis in early childhood
- ▶ Guvenc et al
 - ▶ Systematic review and meta-analysis 22 studies
 - ▶ 17 demonstrated clinical benefit of probiotics, with improvement in TNSS, TOSS, total QOL, nasal QOL, and ocular QOL
- ▶ Overall data suggests beneficial effect for probiotics
 - ▶ Limited by heterogeneity of age and diagnosis, interventions (dose, delivery, strains, etc), and outcomes



Conclusions

Grade of Evidence:

A

- Level 1a: 2 studies
- Level 1b: 26 studies

Benefit/Harm

Benefit

- Improved nasal/ocular symptoms or QOL in most studies
- Possible improvement in immunologic parameters (Th1:Th2 ratio)

Harm

- Low

Value/Intervention

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.

Consider adjuvant use of probiotics for patients with symptomatic SAR and PAR.



Section IX Management

IX.B.10. pg. 242-250 Combination Therapy

Oral antihistamine and oral decongestant

- ▶ Oral antihistamine + oral decongestant more effective in controlling AR symptoms compared to:
 - ▶ INCS
 - ▶ oral antihistamines alone
 - ▶ oral decongestants alone
 - ▶ placebo
- ▶ ARIA 2010 guidelines recommend against routine treatment of AR with combination therapy despite efficacy
 - ▶ Significant risk of adverse events (HTN, urinary retention, birth defects, etc)
 - ▶ Propensity of interactions with other medicines
 - ▶ Recommend limiting utilization as rescue medication during symptom exacerbations



Conclusions

Grade of Evidence:

A

- Level 1a: 0 studies
- Level 1b: 21 studies

Benefit/Harm

Benefit

- Improved control of nasal congestion

Harm

- Can cause significant adverse effects
 - HTN, CV disease, BPH
- Not to be used age < 4 or pregnant patients

Value/Intervention

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.

Recommend against chronic use given the significant side effect profile of oral decongestants.



Oral antihistamine and intranasal corticosteroid

- ▶ Oral antihistamine + INCS provides no added benefit
 - ▶ Wilson et al. Combo therapy not better than antihistamine + placebo OR antihistamine + anti-leukotriene
 - ▶ Barnes et al, Ratner et al, & Di Lorenzo et al. Combo therapy not better than single modality INCS
- ▶ Systematic review and meta-analysis [Feng et al.]
 - ▶ Combination > oral antihistamine alone
 - ▶ Combination not better than INCS alone
- ▶ 2010 ARIA guidelines
 - ▶ Do not recommend addition of oral antihistamine to effective INCS



Conclusions

Grade of Evidence:

B

- Level 1a: 0 studies
- Level 1b: 5 studies

Benefit/Harm

Benefit

- Reduction of nasal congestion with combination of oral antihistamines and INCS compared to oral antihistamines alone.

Harm

- Antihistamine side effects
 - Sedating (less with 2nd gen)
- INCS side effects
 - Nasal dryness
 - Epistaxis
 - Nasal burning
 - Possible growth suppression in peds

Value/Intervention

Combination therapy of oral antihistamine and INCS can be helpful when managing the symptoms of nasal congestion.

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.



Oral antihistamine and LTRA

- ▶ Combination therapy generally improved symptoms and QOL compared to placebo
- ▶ Combination therapy vs oral antihistamine alone vs LTRA alone
 - ▶ Less clear, conflicting results
 - ▶ Systematic review [Wilson et al]: combo therapy improved patient symptoms compared to either agent as monotherapy, however no differences in QOL
- ▶ Combination therapy < INCS
 - ▶ Combination therapy might be option for patients where INCS is not tolerated or contraindicated
- ▶ Adverse events
 - ▶ Headache (4.5%)
 - ▶ Fatigue (1.2%)
 - ▶ Pharyngolaryngeal pain (1.2%)



Conclusions

Grade of Evidence:

A

- Level 1a: 1 studies
- Level 1b: 11 studies
- Level 2b: 1 study

Benefit/Harm

Benefit

- Inconsistent evidence that combination LTRA and oral antihistamine were superior 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.

Value/Intervention

Combination therapy of LTRA and oral antihistamines does not result in consistently improved AR symptoms compared to either agent alone.

The addition of an LTRA may have a role in management of comorbid asthma.

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.



Intranasal corticosteroid and intranasal antihistamine

- ▶ Combination therapy > INCS alone OR intranasal antihistamine alone OR placebo
 - ▶ 10 RCTs, 2 observational studies
- ▶ Currently available commercially
 - ▶ Azelastine hydrochloride + fluticasone propionate (AzeFlu; trade name Dymista)
- ▶ Also beneficial in children. Superior to placebo
- ▶ Serious adverse effects not reported

Conclusions

Grade of Evidence:

A

- Level 1a: 0 studies
- Level 1b: 9 studies
- Level 2b: 1 study
- Level 2c: 2 studies

Benefit/Harm

Benefit

- Rapid onset, more effective for relief of multiple symptoms than either INCS or intranasal antihistamine alone.

Harm

- Patient intolerance, especially due to taste.

Value/Intervention

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

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.



Section IX Management

IX.B.11. pg. 250-253 Nontraditional and Alternative Therapies

Acupuncture

- ▶ The aim of acupuncture is to stimulate acupuncture points (acupoints) with needles to recover equilibrium. Excellent safety profile with only minor side effects reported
- ▶ Grade of evidence
 - ▶ B (Level 1a: 2 studies; level 2b: 13 studies)
- ▶ Benefit
 - ▶ Unclear, as 1 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 ongoing treatment to maintain any benefit gained.
- ▶ Value/Intervention:
 - ▶ In patients who wish to avoid medications, acupuncture may be suggested as possible therapeutic adjunct.



Honey

- ▶ 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
- ▶ Grade of evidence
 - ▶ B (Level 1b: 2 studies; level 2b: 1 study)
- ▶ 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 prediabetics and diabetics would likely need to be avoided
- ▶ Value/Intervention:
 - ▶ Studies are inconclusive and heterogeneous.



Herbal therapies

- ▶ 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
- ▶ 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.
- ▶ Value/Intervention:
 - ▶ The authors determined that there is a lack of sufficient evidence to recommend the use of herbal supplements in AR.



Section IX Management

IX.C. Surgical treatment

- ▶ Surgery for AR is primarily aimed at reducing nasal obstruction and/or rhinorrhea, with the contributing structures being the nasal septum and turbinates
- ▶ Septoplasty
 - ▶ Nasal septum is not a major contributor to allergic disease because it does not experience the extent of dynamic change the turbinate tissue does
 - ▶ Paucity of literature
- ▶ Inferior turbinate reduction
 - ▶ Most beneficial treatment for nasal obstruction in AR refractory to medical therapy
 - ▶ Direct removal (bony resection, microdebrider) vs tissue damage/remodeling (cautery, radiofrequency, laser, coblation). All have been shown to have good results
- ▶ Vidian neurectomy
 - ▶ Primarily to address non-allergic rhinitis by damaging the parasympathetic innervation



Conclusions

Grade of Evidence:

C

- Level 1a: 1 study
- Level 1b: 1 study
- Level 2b: 1 study
- Level 3b: 4 studies
- Level 4: 5 studies

Benefit/Harm

Benefit

- Improved postoperative symptoms and nasal airway.

Harm

- Possible septal perforation
- Empty nose syndrome
- Nasal dryness
- Mucosal damage
- Epistaxis

Value/Intervention

Properly selected patients can experience an improved nasal airway with judicious surgical 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

IX.D. Allergen immunotherapy

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Section IX Management

IX.C pg. 253 Surgical Treatment

- ▶ Goal: reducing nasal obstruction and/or rhinorrhea
- ▶ Major Targets: nasal septum and turbinates
- ▶ Options
 - ▶ Septoplasty
 - ▶ Inferior turbinate reduction
 - ▶ Middle turbinate contouring
 - ▶ Vidian neurectomy
 - ▶ Posterior nasal nerve section



Section IX Management

IX.C Surgical Treatment

- ▶ Karatzanis et al.
 - ▶ Subjective improvement in patients undergoing septoplasty was higher in those without allergic rhinitis (AR) than those with it
 - ▶ Recommend cautious approach to the management of nasal septal deviation in AR
- ▶ Kim et al.
 - ▶ AR patients undergoing septoplasty with turbinoplasty felt more relief of nasal obstruction than those undergoing turbinoplasty alone

Section IX Management

IX.C Surgical Treatment

- ▶ Inferior turbinate reduction is the most beneficial treatment for nasal obstruction in AR refractory to medical therapy
- ▶ 3 primary components:
 - ▶ Mucosal covering
 - ▶ Submucosal layer (containing the capacitance vessels)
 - ▶ Bony center
- ▶ Submucosal tissue can be reduced through
 - ▶ Direct removal (eg. submucous bony resection or microdebrider submucosal resection)
 - ▶ Energy applied to damage tissue with subsequent remodeling (eg. cautery, radiofrequency, laser, Coblation).



Section IX Management

IX.C Surgical Treatment

- ▶ Mori et al. – Patients underwent submucous bony resection over a 5-year follow-up period and found a significant improvement in symptoms and nasal allergen responses
- ▶ Caffier et al. – Found statistically significant improvements in rhinomanometry and nasal obstruction, rhinorrhea, sneezing, and nasal pruritus in 40 patients with AR undergoing diode laser turbinoplasty. Improvement in nasal obstruction was sustained at 2 years.
- ▶ Lin et al. – 101 AR patients after radiofrequency ablation turbinoplasty with 6-month and 5-year response rates of 77.3% and 60.5%, respectively, and statistically significant improvement was achieved in nasal obstruction, rhinorrhea, sneezing, itchy nose, and itchy eyes



Section IX Management

IX.C Surgical Treatment

- ▶ Tan et al. – 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
- ▶ Posterior nasal nerve section may also be considered for recalcitrant rhinorrhea; avoids the dry eye complications of vidian neurectomy.



Section IX Management

IX.C Surgical Treatment

- ▶ Aggregate Grade of Evidence: C
- ▶ Conclusion: 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



Section IX Management

IX.D pg. 255 Allergen Immunotherapy

- ▶ Allergen immunotherapy (AIT) involves scheduled administration of allergen extracts at effective doses with the goal of instituting a sustained immunologic change



Section IX Management

IX.D.1. pg. 255 Allergen extract units, potency, and standardization

- ▶ Multiple sources of **variance** in allergen extracts
 - ▶ Biologic variability in the raw material, and proteins can vary in antigenicity and composition
 - ▶ Relative amounts of allergenic proteins may vary
 - ▶ Impurities in source material
 - ▶ Variation occurs in the collection and processing of the raw material; manufacturers using different techniques including filtration, extraction, sterilization, and preservation



Section IX Management

IX.D.1. Allergen extract units, potency, and standardization

- ▶ Nonstandardized allergen extracts
 - ▶ Most allergen extracts available in the United States are nonstandardized.
 - ▶ **Weight/volume** – ratio of grams of dry raw material to milliliters of extract solvent.
 - ▶ Commonly this is 1/20 wt/vol, which means that for every 1 g of raw material (pollen for example) there is 20 mL of extract solvent.
 - ▶ Does not provide direct information about the amount of allergenic proteins in the allergen extract nor its biologic activity.
 - ▶ **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.



Section IX Management

IX.D.1. Allergen extract units, potency, and standardization

- ▶ Standardized allergen extracts
 - ▶ In the United States, 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 for Biologics Evaluation and Research (CBER).
 - ▶ Government's standard is referenced to the reactivity in highly allergic individuals, creating a standard of biologic activity.
 - ▶ **Major allergen** – specific protein epitope that more than 50% of individuals allergic to that species react
 - ▶ Amount of major allergen is sometimes listed in μ g/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**



Section IX Management

IX.D.2. pg. 256 Modified Allergen Extracts

- ▶ 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
- ▶ Aim: enhance immunogenicity while decreasing risk of adverse reactions



Section IX Management

IX.D.2 Modified Allergen Extracts

- ▶ Recombinant-derived allergens
 - ▶ Produced by cloning of native allergen proteins with use of recombinant DNA technology
 - ▶ Aggregate Grade of Evidence for Timothy grass and Birch: B
 - ▶ Recombinant allergens for birch and Timothy grass demonstrate safety and efficacy
- ▶ Peptide constructs
 - ▶ Synthetic peptides are linear fragments of amino acids that correspond to T-cell epitopes
 - ▶ Lack the secondary and tertiary structure that activate IgE receptors, but can induce immunologic tolerance by targeting allergen-specific T-cells
 - ▶ Aggregate Grade of Evidence for Cat and ragweed: B
 - ▶ Aggregate Grade of Evidence for birch: indeterminate



Section IX Management

IX.D.2 Modified Allergen Extracts

- ▶ Allergoids and polymerized allergens
 - ▶ Allergoids are chemically modified allergens which were developed for improved immunotherapy protocols via accelerated dosing and decreased side effects.
 - ▶ Aggregate Grade of Evidence for ragweed and Grass: B
 - ▶ Aggregate Grade of Evidence for HDM: indeterminate
 - ▶ Approved in Europe but none has received FDA approval
- ▶ Adjuvant constructs
 - ▶ The addition of molecules (adjuvants) to the native allergen has been attempted to improve desensitization protocols.
 - ▶ Aggregate Grade of Evidence for ragweed and grass: B
 - ▶ Aggregate Grade of Evidence for HDM: indeterminate



Section IX Management

IX.D.2 Modified Allergen Extracts

- ▶ The studies of adjuvant-modified extracts demonstrate potential for improved immunotherapy protocols
- ▶ 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



Section IX.C. Surgical Treatment

IX.D.3 pg. 261 Subcutaneous Immunotherapy

Alcohol induced Rhinitis

- ▶ Alcohol induced rhinitis is more common in women than men
 - ▶ Characterized by nasal congestion
 - ▶ Most common with red wine ingestion
 - ▶ Direct alcohol consumption has been associated with a trend toward developing SPT positivity¹⁷¹ and with increased serum total IgE levels¹⁷²



Section IX.C. Management

IX.D.3 Subcutaneous Immunotherapy (SCIT)

► SCIT

- Effective in allergic rhinitis, asthma, hymenoptera venom, and selected patient with atopic dermatitis
- Contraindications to SCIT: uncontrolled asthma, active autoimmune disorders, malignancies, pregnancy (initiation of SCIT contraindicated in pregnancy).
- Dosing: benefits of SCIT dependent on administering a sufficient maintenance dose, for 3-4 years. Standard and accelerated regimens are used in practice.
- Safety: 2 fatalities per 28.9 million injections; 1.9% experience systemic reactions



TABLE IX.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, effectiveness, safety, Symptoms, medication use, QOL	Rhinitis or rhinoconjunctivitis: 1. Symptoms (n = 1734): Strength of evidence high for SCIT. 2. Medication use (n = 564): Strength of evidence moderate for SCIT. 3. 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	1. Symptoms (n = 659 active, 525 placebo): SMD -0.65, $p < 0.00001$ favoring SCIT. 2. Medication use (n = 621 active, 483 placebo): SMD -0.55, $p < 0.00001$ favoring SCIT. 3. 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 ($p = 0.004$) and 37% vs placebo.
Klimek et al. ¹⁶⁰⁶	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 and Phl p 5 15.75 µg	Symptom-medication score	Symptom-medication score reduced for grass and birch pollen seasons: 1st year 21% (NS), 2nd year 19.4% ($p = 0.0385$).
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% ($p < 0.01$).
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 $\geq 2/10$ in symptoms: active 65%, placebo 35% ($p = 0.024$).

LOE — level of evidence; NS — not significant; PAR — perennial allergic rhinitis; QOL — quality of life; RDBPCT — randomized double-blind placebo-controlled trial; RQLQ — Rhinoconjunctivitis Quality of Life Questionnaire; SAR — seasonal allergic rhinitis; SCIT — subcutaneous immunotherapy; SMD — standardized mean difference.

- Systematic reviews and selected RDBPCT's demonstrate SCIT effective in improving symptoms & QOL, as well as decreasing need for medication



Section IX.C. Management

IX.D.4 pg. 266 Sublingual Immunotherapy (SLIT)

- ▶ Efficacy in adults high with longer treatment (12 months), in children strong evidence the grass pollen SLIT reduces symptoms of allergic rhinitis.
- ▶ Dust mite SLIT is more effective than any single pharmacotherapy, pollen SLIT is almost as effective as INCS and more effective than other pharmacotherapies.
- ▶ In comparison to SCIT, few direct head to head studies; evidence the SCIT is more effective than SLIT is weak.
- ▶ Safety: 1 anaphylaxis per 100 million doses
- ▶ U.S.: epinephrine auto injector must be prescribed for those on SLIT tablets.



Section IX.C. Management

IX.D.4 pg. 266 Sublingual Immunotherapy (SLIT)

TABLE IX.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 ^a
Di Bona et al. ¹⁶¹⁵	2015	1a	Meta-analysis of RCTs	SLIT grass pollen tablets vs placebo for SAR	Symptom and medication score	Small improvement in symptom and medication scores vs placebo: (SMD -0.28 ; 95% CI, -0.37 to -0.19 ; $p < 0.001$) and (SMD -0.24 ; 95% CI, -0.31 to -0.17 ; $p < 0.001$). Adverse events: 7/2259 SLIT patients were given epinephrine.
Leatherman et al. ¹⁶⁰²	2015	1a	Systematic review of RCTs for SLIT doses	SLIT for AR vs 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 ^b	Clinical impact: 5-grass pollen tablet > INCS > Timothy grass pollen tablet > montelukast > antihistamines
Makatsori et al. ¹⁶⁹³	2014	1a	Systematic review of RCTs	SLIT vs placebo	Drop-out rates in SLIT and placebo groups	No tendency for a skewed dropout ratio between SLIT and placebo groups. Confirms trial results are unbiased and SLIT appears to be safe.
Lin et al. ¹⁶⁹⁴	2013	1a	Systematic review of RCTs	Aqueous SLIT vs placebo for SAR (and asthma)	Symptom and medication scores	Moderate evidence aqueous SLIT reduces symptoms and medication use in AR/ARC.
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.
Di Bona et al. ¹⁶⁹⁶	2011	1a	Meta-analysis of RDBPCTs	Grass pollen SLIT vs placebo for SAR (and asthma)	Symptom and medication scores	SLIT vs placebo: Reduction in symptoms (SMD -0.32) and medication use (SMD -0.33). No epinephrine use.
Radulovic et al. ¹⁶⁹⁵	2011	1a	Meta-analysis of RDBPCTs	SLIT vs placebo for AR	Symptom and medication scores	SLIT vs placebo: Reduction in symptoms (SMD -0.49) and medication use (SMD -0.32). 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% to 4% systemic AE with in-season 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 offspring. 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 offspring.

Continued

Section IX.C. Management

IX.D.4 pg. 266 Sublingual Immunotherapy (SLIT)

TABLE IX.D.4-1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion ^a
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 and 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 and medication scores	Insufficient evidence that AIT in any form has a positive effect on AR in children.
SLIT vs SCIT						
Chelladurai et al. ¹⁶⁹⁷	2013	1a	Systematic review of RCT	SCIT vs SLIT (and vs placebo) in AR	Symptom and medication scores	Low grade evidence favors SCIT over SLIT for AR symptom and medication reduction. Moderate evidence for nasal and 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 and 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. Grass pollen SLIT drops vs placebo. Grass pollen SCIT vs placebo.	Symptom and medication scores	Symptom and medication scores with SCIT, SLIT tablets and drops all reduced vs. placebo, except for symptom score with SLIT drops.
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 and Ellis ¹⁷⁰¹	2014	2a	Systematic review of RCTs and indirect comparison	Timothy 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 and indirect comparison	SCIT and aqueous SLIT vs placebo, SCIT vs SLIT in AR	Symptom and medication scores	Trend favoring SCIT over SLIT for AR symptom and medication score reduction. No conclusive results.
SLIT vs SCIT: children only						
Kim et al. ¹⁶⁷²	2013	2a	Systematic review of RCTs and indirect comparison	Children with SAR (asthma): Aqueous SLIT vs SCIT vs placebo for SAR (and asthma)	Symptom and 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	SLIT vs placebo in children with asthma/ARC	Symptom and medication scores	Not enough evidence because of poor quality of the studies.

^aOnly outcomes with statistically significance are mentioned here.

^bClinical impact score = season-long nasal or total symptom scores: $100 \times (\text{scorePlacebo} - \text{scoreActive})/\text{scorePlacebo}$.

AE = adverse event; AIT = allergen immunotherapy; AR = allergic rhinitis; ARC = allergic rhinoconjunctivitis; CI = confidence interval; HDM = house dust mite; INCS = intranasal corticosteroid; LOE = level of evidence; PAR = perennial allergic rhinitis; RCT = randomized controlled trial; RDBPCT = randomized double-blind placebo-controlled trial; SAR = seasonal allergic rhinitis; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SMD = standardized mean difference.

Sublingual Immunotherapy

- ▶ Aggregate Grade of Evidence: A
- ▶ 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.
- ▶ 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.
- ▶ Balance of benefit and harm: Benefit of treatment over placebo is small, but tangible. SLIT benefit is demonstrated beyond the improvement seen with rescue medications. 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 biallergic 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.



Section IX.C. Management

IC.D.5 pg. 270 Transcutaneous/epicutaneous immunotherapy

- ▶ IX.D.5 Transcutaneous/epicutaneous immunotherapy (pg 270)
 - ▶ Non-invasive form of AIT that consists of application of allergens to the skin
 - ▶ Epidermis is rich in antigen presenting cells while being less vascularized, potentially reducing risk of systemic reaction
 - ▶ Variety of techniques have been used:
 - ▶ Scarification or scratch
 - ▶ Tape stripping
 - ▶ Microneedle arrays
 - ▶ Sweat accumulation through the application of a patch



Section IX.C. Management

Transcutaneous/epicutaneous immunotherapy

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.

Section IX.C. Management

Transcutaneous/epicutaneous immunotherapy

- ▶ Transcutaneous/epicutaneous Immunotherapy
 - ▶ Aggregate Grade of Evidence: B
 - ▶ Benefit: Limited and variable improvement in symptoms, medication use, and allergen provocation tests in patients with AR and conjunctivitis
 - ▶ Harm: Systemic reactions in ~15% of patients
 - ▶ Costs: Unknown
 - ▶ Benefits-Harm Assessment: Limited and inconsistent data on benefit of treatment, while there is concern of adverse effects
 - ▶ Value: Further research needed. Could represent alternative form of IT
 - ▶ Policy: Recommend against
 - ▶ Intervention: May have future clinical application, but given known risks and uncertain benefit this is not presently recommended.



Section IX.C. Management

IC.D.6 pg. 273 Intralymphatic immunotherapy (ILIT)

- ▶ IX.D.6 Intralymphatic immunotherapy (ILIT) (pg 273)
 - ▶ Novel method where allergen is injected directly into lymph nodes
 - ▶ Major advantages – marked reduction in duration of IT and amount of allergen given, which confers a lower risk of adverse allergic side effects
 - ▶ Injection is given under ultrasound guidance to the inguinal lymph nodes
 - ▶ Trials have shown that a reduction in AR symptoms can be achieved with just 3 doses at dosing interval of 1 month, whereas SCIT may take 70 doses over a 5-year period



Section IX.C. Management

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-pollen-induced or grass-pollen-induced AR (n = 36): 1. Aluminum hydroxide adsorbed, depot birch-pollen 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.

Section IX.C. Management

TABLE IX.D.6. Evidence for the use of intralymphatic immunotherapy in the treatment of allergic rhinitis

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 1000 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.

AR = allergic rhinitis; Ig = immunoglobulin; ILIT = intralymphatic immunotherapy; LOE = level of evidence; MAT = modular antigen transporter; QOL = quality of life; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SPT = skin-prick test; SQ-U = standardized quality units; VAS = visual analogue scale.

Section IX.C. Management

- ▶ Intralymphatic immunotherapy (ILIT)
 - ▶ Aggregate Grade of Evidence: B
 - ▶ Benefit: Reduced treatment period, number of injections, and dose of allergen. Decreased risk of adverse events
 - ▶ Harm: Risk of anaphylaxis
 - ▶ Costs: May be associated with reduced costs. Application requires training.
 - ▶ Benefits-Harm Assessment: Balance of benefit over harm
 - ▶ Value: Appears efficacious and burden on healthcare system may be lower
 - ▶ Policy: Option, pending additional studies.
 - ▶ Intervention: Research is promising, but further studies are needed before translation into routine clinical practice



Section IX.C. Management

IX.D.7 pg. 275 Alternative forms of immunotherapy

- ▶ IX.D.7 Alternative forms of immunotherapy (pg 275)
 - ▶ Non-injectable, alternative immunotherapies involve the topical absorption of allergen extracts via oral/gastrointestinal, nasal, or inhalation exposures.
 - ▶ These forms of AIT represent alternate treatment options and are mostly of historical significance.
 - ▶ While these forms of therapy were investigated to alleviate comfort and resource utilization associated with SCIT, the adoption of SLIT has largely replaced interest in these methods



Section IX.C. Management

- ▶ Summary of data
 - ▶ Double-blind, placebo controlled RCTs have evaluated oral/gastrointestinal immunotherapy
 - ▶ No significant decline in symptoms, reduction in medication utilization, or improvements in provocation testing; however, these were associated with gastrointestinal side effects
 - ▶ Oral mucosal immunotherapy (OMIT)
 - ▶ Pilot study – decreased side effects and higher adherence as compared to SLIT. Improvement in QOL measurements and significant rise in IgG4 over the first 6 months. Further study is needed. May be an emerging alternative to SCIT and SLIT.
 - ▶ Nasal immunotherapy
 - ▶ Effective treatment of pollen and HDM sensitivity, however high rates of adverse reactions that limit patient compliance



Section IX.C. Management

IX.D.8 pg. 275 Combination omalizumab and SCIT

- ▶ IX.D.8 Combination omalizumab and SCIT (pg 275)
 - ▶ Each intervention targets different mechanism in allergic cascade
 - ▶ AIT desensitizes body's response by altering Th1/Th2 balance and induction of T-cell anergy.
 - ▶ Omalizumab indiscriminately targets the humoral effector of allergic inflammation by using a humanized monoclonal antibody to block unbound IgE
 - ▶ Two benefits of combination therapy have been described:
 - ▶ Decreased incidence of AIT-associated systemic reactions
 - ▶ Improved control of AR symptoms



Section IX.C. Management

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 a}	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 a}	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.
Rolnick-Werninghaus et al. ^{1401 b}	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 b}	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 b}	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.

^aImmune Tolerance Network Group.

^bOmalizumab Rhinitis Study Group.

AIT = allergen immunotherapy; AR = allergic rhinitis; Ig = immunoglobulin; IgE-FAB = IgE-facilitated allergen binding; IT = immunotherapy; LOE = level of evidence; RCT = randomized controlled trial; RIT = rush immunotherapy; SAR = seasonal allergic rhinitis; sIgE = antigen-specific IgE.



Section IX.C. Management

- ▶ Combination omalizumab and SCIT
 - ▶ Aggregate Grade of Evidence: B
 - ▶ Benefit: Improved safety of accelerated cluster and rush AIT protocols
 - ▶ Harm: Financial cost and anaphylaxis
 - ▶ Costs: Moderate to high
 - ▶ Benefits-Harm Assessment: Preponderance of benefit over harm
 - ▶ Value: Improves safety of AIT. Cost and risks of reactions must be considered. Individualized approach to patient management is important. Not all patients who benefit from AIT will need combination approach.
 - ▶ Policy: Option. Of note, omalizumab is not currently FDA approved for AR.
 - ▶ Intervention: Option for carefully selected patients. At present this should not be part of routine clinical practice.



X. Associated conditions

- ▶ X.A. Asthma 277
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X.A. Asthma

- ▶ X.A.1. Asthma definition 277
- ▶ X.A.2. Asthma association with allergic and non-allergic rhinitis 277
- ▶ X.A.3. Allergic rhinitis as a risk factor for asthma 278
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Section X Associated Conditions

X.A-X.B. pg. 277-287 Asthma, Rhinosinusitis

- ▶ 10-40% of patients with AR have comorbid asthma.
- ▶ AR and NAR are risk factors for developing asthma.
- ▶ In adulthood, development of asthma is often independent of allergy, whereas in childhood, it is frequently associated with allergy.
- ▶ Pharmacotherapy for treatment of AR with coexistent asthma improves subjective and objective severity of asthma.
- ▶ Biologic therapy and immunotherapy provide additional improvement for patients with AR and asthma that is not controlled
- ▶ AR regarded as a disease-modifying factor for rhinosinusitis
- ▶ Increased incidence of ARS with AR, although relationship not causative with no studies showing whether treatment of AR decreases ARS. Unknown association between AR and RARS.
- ▶ No controlled studies examining the role of AR in development of CRSsNP including treatment of AR altering disease course in CRSsNP.
- ▶ Despite overlapping pathophysiologic features, there is no clear association between AR and CRSwNP



Key References: AR and Asthma

▶ Ohta et al., 2011

- ▶ Study design: case series, LOE 3b
- ▶ Study group: Asthmatic patients (n = 26,680)
- ▶ Clinical endpoint: rhinitis and asthma
- ▶ Conclusion: Rhinitis is common in asthma and impairs asthma control.

▶ Baena-Cagnani et al., 2003

- ▶ Study design: DBRCT, LOE 1b
- ▶ Study groups: AR and Asthma (N=924)
 - ▶ 1. Desloratadine 5mg
 - ▶ 2. Montelukast 10mg
 - ▶ 3. Placebo
- ▶ Clinical endpoint: TASS, FEV1, β -agonist medication use
- ▶ Conclusion: Desloratadine vs. placebo: reduction in mean TASS, improvement in FEV1, reduction in β -agonist medication use. Desloratadine vs. montelukast showed no difference.

▶ Lohia et al, 2013

- ▶ Study design: SR and meta-analysis, LOE 1a
- ▶ Study groups: 18 RCTs (n = 2162)
 - ▶ 1. INCS spray vs placebo
 - ▶ 2. INCS spray plus oral inhaled CS vs oral inhaled CS alone
 - ▶ Nasal inhaled CS vs. placebo
- ▶ Clinical endpoint: asthma symptoms, rescue medication use, FEV1, PEF, PC₂₀, QOL
- ▶ Conclusion: INCS improved FEV1, PC₂₀, asthma symptom scores and rescue medication use. No asthma outcome changes with INCS plus oral inhaled vs oral inhaled CS alone. Nasal inhaled CS improved PEF.

▶ Erekosmia et al, 2014

- ▶ Study design: SR, LOE 1a
- ▶ Study groups: 61 RCTs
 - ▶ 1. SCT vs. placebo
 - ▶ 2. SCT vs. pharmacotherapy
- ▶ Clinical endpoint: asthma and AR symptoms, medication use; safety of SCIT
- ▶ Conclusion: Symptoms reduced with SCT, medication use reduced with SCIT; adverse reactions mild

X.B. Rhinosinusitis

- ▶ Allergic rhinitis and acute rhinosinusitis 286
- ▶ Allergic rhinitis and recurrent acute rhinosinusitis 287
- ▶ Allergic rhinitis and chronic rhinosinusitis without nasal polyposis 287
- ▶ Allergic rhinitis and chronic rhinosinusitis with nasal polyposis 287



Key References: AR and Rhinosinusitis

▶ Rantala et al., 2013

- ▶ Study design: Cross-sectional, LOE 2a
- ▶ Study groups: atopic and nonatopic adults aged 21-63 (n = 1008)
- ▶ Clinical endpoint: upper and lower respiratory tract infections
- ▶ Conclusions: individuals with atopic disease had higher risk of developing URTI, including rhinosinusitis

▶ Winson et al., 2014

- ▶ Study design: SR, LOE 3a
- ▶ Study Groups: CRSsNP with or without allergy, CRSwNP with or without allergy
- ▶ Clinical endpoint: association between CRSsNP, CRSwNP and allergy
- ▶ Conclusion: conflicting evidence with no clear association between CRSsNP and allergy or CRSwNP and allergy



Aggregate grade of evidence

- ▶ AR is a risk factor for asthma (**Grade C**)
- ▶ Pharmacotherapy for AR (antihistamines, INCS, LTRAs) improves subjective and objective severity of asthma in patients with coexistent AR (**Grade A**)
- ▶ Added benefit for omalizumab as therapy for patients with AR and asthma that is uncontrolled despite maximal conventional interventions (**Grade B**)
- ▶ AIT has demonstrated benefit in concomitant AR and asthma (**Grade A**)
- ▶ AR has a moderate association with ARS (**Grade C**)
- ▶ The preponderance of evidence does not support an association between AR and RARS, CRSsNP and CRSwNP (**Grade D**)



Section X Associated Conditions

X.C. pg. 290 Conjunctivitis

- ▶ Despite limitations in study design (lack of phenotype description and objective evidence of allergic sensitization), there is a substantial body of evidence supporting allergic conjunctivitis (AC) as a frequently occurring comorbidity of allergic rhinitis (AR), particularly in children.
- ▶ Evidence shows that AR may have a 35-74% incidence of AC, and that patients with AC may have AR in up to 97% of cases.
- ▶ Recommendation: AR patients should be assessed for ocular symptoms with consideration given to providing treatment specifically targeting relief of ocular symptoms.
- ▶ Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3a: 2 studies; Level 3b: 3 studies; Table X.C)



X.C. Conjunctivitis

- ▶ An aggregate level of evidence was produced for each topic guidelines from the American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM)
- ▶ A recommendation using the AAP SCQIM guidelines was then produced



Section X Associated Conditions

X.D. pg. 290 Atopic Dermatitis

- ▶ Atopic dermatitis (AD) is a chronic and/or relapsing skin disorder characterized by pruritus, scratching, and eczematous lesions.
- ▶ 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.”
- ▶ 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 (e.g. lack of phenotype description and objective evidence of allergic sensitization).



X.D. Atopic Dermatitis

- ▶ Longitudinal studies show that AD improves/resolves with age.
- ▶ Increasing severity is associated with increased risk of developing AR with 15-61% prevalence of AR in patients with AD.
- ▶ One study showed a 2-fold increase in incidence of AR in patients with AD (60.8%) versus those without AD (31%).
- ▶ No recommendations suggested. Section is informational only.
- ▶ Aggregate Grade of Evidence: C (Level 2b: 4 studies; Level 3b: 15 studies; Level 4: 1 study; Table X.D)



Section X Associated Conditions

X.E. pg. 291 Food Allergy and Pollen-Food Allergy Syndrome (PFAS)

- ▶ Pathophysiology: IgE specific for certain pollen cross reacts with highly homologous proteins in certain fruits, vegetables, nuts, or spices.
 - ▶ Most common example in Western populations is birch pollen and apples.
- ▶ Manifests as oral itching, stinging pain, angioedema, and rarely systemic symptoms.
- ▶ Oral allergy syndrome (OAS) is a subtype of PFAS that affects only oral mucosa.
- ▶ 5-8% of people with pollen allergy will develop food allergy and PFAS.
- ▶ As many as 70% of patients with birch allergy will manifest PFAS.
- ▶ Estimated rate of systemic reaction to pollen-food allergy is 10%; anaphylaxis carries a 1.7-10% risk.



X.E. Food Allergy and Pollen-Food Allergy Syndrome (PFAS)

- ▶ Diagnosis
 - ▶ Detailed history guided by understanding of patient's underlying pollen allergy and knowing foods with highly homologous proteins.
 - ▶ Gold standard diagnostic test is double-blind food challenge.
 - ▶ Difficult to perform successfully due to bias inherent to appearance, texture, and taste of food.
 - ▶ Other tests include skin prick, serum IgE, oral food challenge



X.E. Food Allergy and Pollen-Food Allergy Syndrome (PFAS)

► Treatment

- Remove offending food agent.
- Counsel patient on systemic and anaphylactic symptoms and provide epipen if there is a history of these symptoms.
- One study showed that cooked foods (denatures proteins) may prevent reactions.
- Astemizole (anti-histamine) showed clinically significant reduction in symptoms severity compared to placebo when ingesting offending foods, but was removed from the market secondary to QT prolongation.
- Immunotherapy: mixed results on effects on PFAS. Recommendations against use solely for improvement of food-related symptoms, but patients receiving IT for pollen allergies should be counseled on the possible but unsubstantiated benefits of increased food tolerance.



X.E. Food Allergy and Pollen-Food Allergy Syndrome (PFAS)

- ▶ 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-reactivity¹⁹²⁸

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

Section X Associated Conditions

X.F. pg. 294 Adenoid Hypertrophy (AH)

- ▶ Adenoid enlargement usually begins in infancy and continues through the first 5-6 years of life, with involution occurring during puberty.
- ▶ AH and AR may present with similar symptoms (nasal obstruction, rhinorrhea, etc)
- ▶ Recruitment for studies focusing on the association between AR and AH is of importance:
 - ▶ Studies recruiting patients with AR and looking for incidence of AH show a statistically significant association.
 - ▶ Studies recruiting based on nasal symptoms and identifying AH followed by allergy testing reveal no such association, and some have shown an inverse correlation between adenoid size and allergen sensitization.
- ▶ Children with both AR and AH may have an increased incidence of mold sensitivity compared to children with AR alone



X.F. Adenoid Hypertrophy (AH)

- ▶ Immunologic evidence of allergy in adenoid tissue is limited in the literature.
- ▶ Treatment studies also limited, but do suggest:
 - ▶ Adenoidectomy for AH improves symptoms regardless of AR diagnosis.
 - ▶ Intranasal corticosteroids (INCS) do relieve nasal symptoms of AH independent of allergy, based on systematic reviews, but the literature is limited in explaining the mechanism.
- ▶ One explanation of the discrepancy in AH/AR association may be that AH presents earlier in childhood than pediatric AR. One study found an association between AH and AR in children aged 8-14 ($p=0.0043$) but not age 1-7 ($p=0.34$).
- ▶ Aggregate Grade of Evidence: C (Level 4: 11 studies; Table X.F).



X.G. Otologic conditions

- ▶ Eustachian tube dysfunction 298
- ▶ Otitis media 298
- ▶ Inner ear disease 300



Section X Associated Conditions

X.G. pg. 298 Otologic Conditions

- ▶ Eustachian tube dysfunction (ETD)
 - ▶ ET opens into the nasopharynx and is in direct communication with the upper airway.
 - ▶ Inflammation of nasal mucosa may involve the torus tubarius or mucosa of the ET, which results in negative pressure as middle ear gases are resorbed.
 - ▶ Frequent sniffing in the setting of nasal obstruction may transmit negative pressure to the middle ear.
 - ▶ High-level evidence has shown that nasal challenge with histamine or relevant aeroallergens in patients with AR results in transient ETD.
 - ▶ Literature supports a direct causal role for AR in some cases of ETD.
- ▶ 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)



X.G. Otologic Conditions

- ▶ Otitis media (OM)
 - ▶ Role of allergy in otitis media has not been clearly demonstrated and more research is needed.
 - ▶ Allergy has historically been considered a major factor in OM development but this has been called into question as research quality has improved.
 - ▶ Current literature is discordant and ranges from no association to near universal link between AR and OM.
 - ▶ Variability is likely due to selection bias, differences in allergy testing, and difficulty in identifying an appropriate control group.
 - ▶ High-level evidence has shown no benefit in use of traditional AR treatments (INCS, oral antihistamines and decongestants) in treatment OM and OM CPG regularly recommend against their routine use.
- ▶ Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3b: 3 studies; Level 4: 11 studies; Table X.G-2).



X.G. Otologic Conditions

- ▶ Inner ear disease
 - ▶ 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.
 - ▶ Overall, the evidence supporting a connection between type 1 IgE- mediated hypersensitivity and Meniere’s disease is of low grade, with substantial defects in study design.
- ▶ Aggregate Grade of Evidence: C (Level 3b: 4 studies; Level 4: 4 studies; Table X.G-3).



Section Inner Ear Disease

X.H. pg. 300 Cough

- ▶ Cough is often considered a co-morbidity of AR
- ▶ Potential etiologies include
 - ▶ Rhinobronchial reflex
 - ▶ Post-nasal drip
 - ▶ Diffuse inflammation and activation of eosinophils
- ▶ AR and asthma frequently co-exist, which may also contribute to cough



X.H. Cough

Passali, et al 2011

There is an increased frequency of rhinobronchial syndrome with allergic disease, namely AR.

Cough was a symptom in 96% of patients.

Lin, et al 2016

Cough was reported to be the most frequent reason to seek a medical visit in asthmatics.

Nasal symptoms were reported to be the most frequent reason to seek a medical visit in AR and CRS patients.

Chakir, et al 2000

Non non-asthmatic AR patients, bronchial mucosa had increased levels of:

- Lymphocyte numbers
- Eosinophil recruitment
- IL-5 expression

Aggregate level of evidence: C



Section Inner Ear Disease

X.I. pg. 301 Laryngeal Disease

- ▶ The potential relationship between AR and laryngeal disease has largely focused on laryngopharyngeal reflux (LPR)
- ▶ Vocal cord dysfunction may also be associated with AR
- ▶ Several studies have reported higher Voice Handicap Index scores in AR patients compared to controls
- ▶ Characterization of a causative relationship between AR and laryngeal disease has been elusive



X.I. Laryngeal Disease

Koc, et al 2014

In a case-control study, patients with AR had a higher prevalence of dysphonia and mean Voice Handicap Index scores, compared to controls

Turley, et al 2011

In this case-control study, AR patients with worse rhinitis symptoms had:

- Worse voice-related quality of life
- More severe chronic laryngeal symptoms

Simberg, et al 2007

- Patients with more AR had more several vocal symptoms than controls
- AR patients who underwent allergy immunotherapy for > 2 years had fewer vocal symptoms

Aggregate level of evidence: C



Section Inner Ear Disease

X.J. pg. 305 Eosinophilic esophagitis (EoE)

- ▶ Eosinophilic esophagitis (EoE) symptoms include dysphagia, heartburn and vomiting
- ▶ Affected mucosa demonstrates infiltration with eosinophils
- ▶ Among both pediatric and adult patients with EoE, it has been shown that 50-75% have co-morbid AR
- ▶ The evidence for a relationship between environmental allergies and EoE pathogenesis is not clear



X.J. Eosinophilic Esophagitis

Wang, et al 2007

Seasonal peaks of EoE diagnoses tend to be in the spring and summer

- This mirrors seasonal fluctuations in AR
- Additionally, the least intense EoE disease tended to be diagnosed in the winter

Moawad, et al 2010

EoE diagnosis trends may mirror seasonal grass pollen counts

- Highest percentage of patients diagnosed in the summer (33%)
- Lowest percentage diagnosed in the winter (16%)

Ramirez, et al 2013

This describes a case of EoE resolution in a pediatric patient with AR after dust mite immunotherapy

- Confirmed on esophageal biopsies

Aggregate level of evidence: C



Section Inner Ear Disease

X.K. pg. 305 Sleep Disturbance and Obstructive Sleep Apnea

- ▶ Nasal obstruction due to AR has been well described to cause sleep disruption
- ▶ Nasal obstruction is present in 90% of AR patients
- ▶ The severity of AR symptoms have been shown to negatively affect the duration of sleep, frequency of daytime somnolence and sleep latency
- ▶ It has been hypothesized that the effect of AR on sleep is multifactorial and likely includes upper airway resistance, as well as hormonal and biochemical effects



X.K. Sleep Disturbance and Obstructive Sleep Apnea

Yamanda, et al 2012

In AR patients, regular use of intranasal mometasone improved:

- Nasal symptoms
- Overall quality of life
- Sleep quality

Leger, et al 2006

Patients with AR had some degree of impairment in all aspects of sleep quality

- Patients with severe AR had worsened sleep quality than patients with mild AR

Shedden 2005

In AR patients:

- >80% of patients with nasal congestion as part of their symptoms had nighttime symptoms
- The most frequent symptoms were difficulty falling asleep or nighttime awakening

Aggregate level of evidence: B



XI. Knowledge gaps and research opportunities

- ▶ XI.A. Epidemiology and risk factors 308
- ▶ XI.B. Evaluation and diagnosis 312
- ▶ XI.C. Management 313
- ▶ XI.D. Associated conditions 313



Section XI Knowledge gaps and research opportunities

XI.A. pg. 308 Epidemiology

- ▶ Improved understanding and evaluation of:
 - ▶ Incidence, prevalence and phenotypes worldwide.
 - ▶ variation by geographic region, patient age, and sex.
 - ▶ climate change effect on the pattern and degree of allergen exposure.



Section XI Knowledge gaps and research opportunities

XI.A. pg. 308 Risk Factors

- ▶ Further understanding and investigation of:
 - ▶ gene alterations and potential functional characterization.
 - ▶ epigenetic mechanisms of gene-environment interactions and disease development.
 - ▶ pollutants and tobacco smoke in the development and severity symptoms.
 - ▶ potential environmental exposures as risk factors and protective factors.
 - ▶ risk factor reduction and its effect on the pattern and degree of allergen exposure.



Section XI Knowledge gaps and research opportunities

XI.B. pg. 312 Evaluation and Diagnosis

- ▶ Improved characterization and study of:
 - ▶ newer testing techniques (ie, nasal sIgE, BAT) in larger populations → standardization and incorporation into mainstream clinical practice.
 - ▶ IDT and single-dilution intradermal testing.
 - ▶ role of single intradermal testing after a negative prick test.
 - ▶ standardization and interpretation of testing for LAR.
 - ▶ further defining the clinical utility of testing.
 - ▶ clinical uses for CRD in patient management.
 - ▶ allergen units in antigen standardization.



Section XI Knowledge gaps and research opportunities

XI.C. pg. 313 Management

- ▶ Improved understanding and study of:
 - ▶ impact of EC strategies on AR symptom control and rescue medication use, (l,e, cockroach, pet, and pollen allergens).
 - ▶ polyallergic AR patients and appropriate AIT regimens.
 - ▶ ILIT for possible routine clinical application.
 - ▶ comparative efficacy/effectiveness of SLIT vs SCIT and other treatments
 - ▶ AIT with multiple allergens.
 - ▶ cost effective management for optimal AR control and the use of multimodality therapy.



Section XI Knowledge gaps and research opportunities

XI.D. pg. 313 Associated Conditions

- ▶ Association between AR and other conditions is weak / conflicting.
- ▶ Need better definition of relationship between AR and rhinosinusitis, otitis media with effusion, cough, laryngeal disease, and eosinophilic esophagitis.
- ▶ Further delineate the role that AR treatment in potential improvement of associated conditions.



Section XII. Manuscript Conclusion

XII. pg. 313 Conclusion

Purpose and Aims

- ▶ Synthesis of best external evidence
- ▶ Include multiple aspects of Allergic Rhinitis
- ▶ Apply consistent methodology

Results

- ▶ Assign evidence grades when possible
- ▶ Provide recommendations where appropriate
 - ▶ Diagnosis and differential diagnosis
 - ▶ Management strategies
- ▶ Reference for the current evidence in Allergic Rhinitis

Future Directions

- ▶ Identification of knowledge gaps
- ▶ Identification of research opportunities

