NCC Pediatrics Continuity Clinic Curriculum:
Allergic Rhinitis
Faculty Guide

Goals & Objectives:

- Know the H&P that distinguishes allergic rhinitis (AR) from other causes of nasal congestion.
- Know the most effective therapies for AR and common side effects.
- Name the most common comorbidities of AR.
- Know indications for allergy testing and how it is performed.

Pre-Meeting Preparation:

Please read the following enclosures:

- "Allergic Rhinitis In Children and Adolescents" *(Pediatric Clinics of North America, 2019)*
- Selected Charts from Pediatrics in Review
- "Recent Updates in Allergy Immunotherapy for Allergic Rhinitis in Children"*(Current Otorhinolaryngology Reports, 2023)*

Conference Agenda:

- *Review* Allergic Rhinitis Quiz
- Complete Allergic Rhinitis Cases
- Board Review Q&A

Extra-Credit:

- "Allergic Rhinitis in Childhood and the New EUFOREA Algorithm" *(Frontiers in Allergy, 2021)*
- "Current and Future Directions in Pediatric Allergic Rhinitis" (*J Allergy Clin Immunol: In Practice, 2013)*
- "Stuffy Nose" *(PIR,2015)*
- "Rhinitis in Children less than 6 years old. . ." *(Asia Pac Allergy, 2011)*
- "Testing for Allergy" *(PIR, 2000)*
- "Does allergen immunotherapy for allergic rhinitis prevent asthma?" *(AAAI, vol 129, 2022)*
- "Who Needs Allergy Testing and How to Get It Done" *(PIR, 2013)*
- "New progress in pediatric allergic rhinitis" *(Frontiers in Immunology, 2024)*
- "Treatment of Allergic Rhinitis" *(American Family Physician, 2015)*
- "Allergic Rhinitis" *(PIR, 2023)*
- **Resources for Patients/Parents:**
    - Patient Handout Allergic Rhinitis
    - What Parent Should Know About Allergic Rhinitis -- JAMAPeds
    - www.acaai.org – American College of Allergy, Asthma & Immunology
    - www.healthychildren.org – articles about allergies under "Health Issues"
    - Instructions for INCS Administration

Allergic Rhinitis in Children and Adolescents

Charles Frank Schuler IV, MD*, Jenny Maribel Montejo, MD

KEYWORDS

• Allergic rhinitis • Immunotherapy • Allergic rhinoconjunctivitis • Allergy
• Prevention of allergic sensitization

KEY POINTS

- Allergic rhinitis is a common disorder that frequently occurs in children and adolescents and carries a high burden of disease.
- Allergic rhinitis can be classified according to severity and timing of symptoms.
- There are several seasonal and perennial triggers of allergic rhinitis, including airborne pollens, molds, dust mites, and animals.
- Avoidance, medications, and immunotherapy may play a role in treating allergic rhinitis.
- Immunotherapy in allergic rhinitis can prevent development of further allergic sensitizations and asthma.

INTRODUCTION

Definition

Allergic rhinitis (AR) is defined as a chronic, waxing/waning, immunoglobulin E (IgE) -based inflammation in the nasopharynx that occurs in response to typically innocuous environmental proteins.[1] Typical symptoms include nasal congestion, rhinorrhea (anterior and/or posterior), sneezing, and itching.[1] When ocular symptoms are included, the disease may be called allergic rhinoconjunctivitis (ARC). This article focuses primarily on AR but will include comments on ARC where relevant.

Epidemiology

AR is a common disease. Typical incidence reports are between 10% and 30% of children and adults in the United States and other developed nations.[2,3] Surveys that specifically use physician-diagnosed AR report rates of approximately 13% in children.[4] Most individuals develop AR symptoms before 20 years of age, with nearly half of such patients becoming symptomatic by age 6 years[5] (**Fig. 1**).

Disclosure Statement: The authors have nothing to disclose.
Division of Allergy and Clinical Immunology, University of Michigan, Domino's Farms, 24 Frank Lloyd Wright Drive, PO Box 442, Suite H-2100, Ann Arbor, MI 48105, USA
* Corresponding author.
E-mail address: schulerc@med.umich.edu

Pediatr Clin N Am 66 (2019) 981–993
https://doi.org/10.1016/j.pcl.2019.06.004
pediatric.theclinics.com

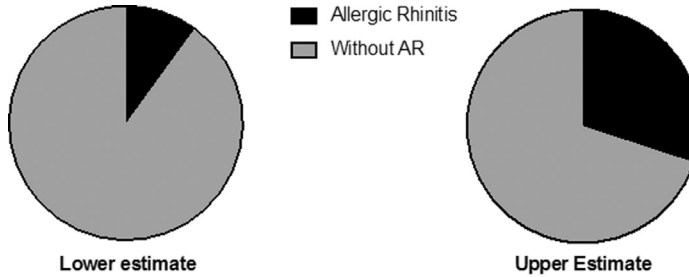


Fig. 1. AR prevalence estimate range worldwide in developed countries.

Indeed, in school-aged children aged 6 to 7, prevalence globally has been reported greater than 8.5%.[6] In adolescents aged 13 to 14, prevalence globally has been reported greater than 14%.[6] Thus, although many patients may develop symptoms at older ages, this is indeed a disease of childhood that can present early in development.

Burden of disease

Furthermore, AR may carry a heavy burden of disease. Symptoms include fatigue, attention, learning, and memory deficits, and even depression.[4,7–9] Nasal obstruction resulting from AR has been shown to contribute to sleep-disordered breathing and can be particularly disruptive of continuous positive airway pressure adherence in patients with obstructive sleep apnea.[10,11] Furthermore, patients with AR may experience a 2-fold increase in medication costs and nearly a 2-fold increase in physician visits.[12] Overall, adolescents with AR and ARC have worse quality of life, which is associated with more nasal symptoms and nasal obstruction as well as reductions in daily functioning and sleep.[13] In addition, there is some evidence that allergic diseases may be more common in patients with attention-deficit/hyperactivity disorder (ADHD), including AR.[14] Treatment of AR is relevant to treatment of ADHD, because treatment of AR reduces ADHD symptom scores.[15]

In addition, AR is consistently associated with asthma. In one population, 38% of patients with AR had asthma, and about 78% of patients with asthma had AR.[16] The additional disease burden of asthma can contribute significantly to patients' difficulty with AR. The authors discuss further how this process might be interrupted using immunotherapy (IT) in later discussion.

Numerous risk factors have been found to predispose to AR. These risk factors include a family history of allergic diseases, male sex, birth during the pollen season, firstborn status, early-life antibiotic use, maternal smoking, indoor allergen exposure, elevated serum IgE levels (>100 IU/mL) before age 6, and any presence of allergen-specific IgE.[17,18]

Diagnostic Considerations

A typical history of AR includes symptoms of sneezing, rhinorrhea, nasal obstruction, and nasal itching. Other common symptoms include cough, postnasal drip, irritability, and fatigue. Some patients also describe palate and inner ear itching. ARC may include ocular symptoms, such as ocular itching, tearing, and burning. Younger children may exhibit different symptoms, such as snorting or sniffing, throat clearing, and cough. To scratch an itchy palate, children may make a clicking sound as they move the tongue against the palate to relieve this pruritic sensation.[19–21] Symptoms may be present year-round or seasonally, depending on the timing of allergen exposures.

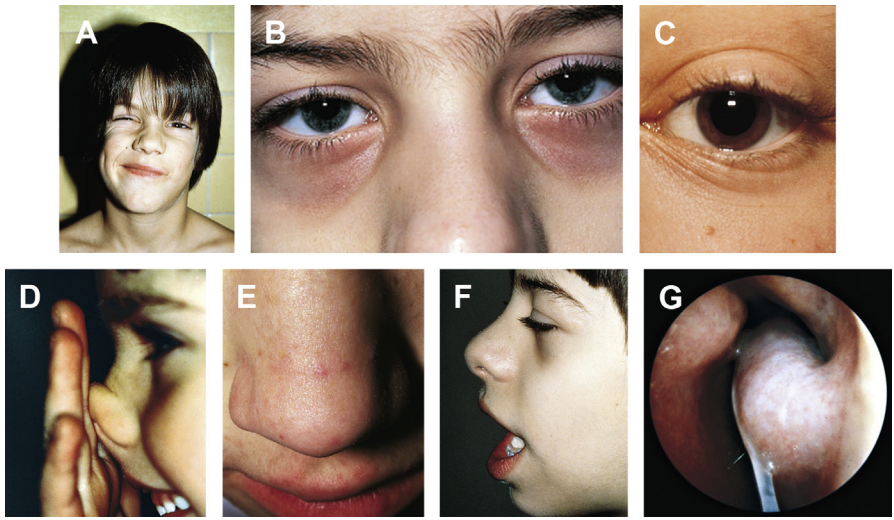


Fig. 2. The pathophysiology of AR results in typical examination findings illustrated here. See text for full descriptions. (*A*) Facial grimacing or twitching. This is related to nasal itching. (*B*) Allergic shiners. (*C*) Dennie-Morgan lines. (*D*) The allergic salute. (*E*) Nasal creasing related to the allergic salute. (*F*) Allergic facies. (*G*) Typical nasal mucosa. (*From* Chong H, Green T, Larkin A. Allergy and Immunology. In: Zitelli, B., McIntire, S. and Nowalk, A. (2018). Zitelli and Davis' Atlas of Pediatric Physical Diagnosis. Philadelphia: Elsevier, pp.108-109; with permission.)

Patients may be able to identify triggers, such as pet exposure, or a specific time of year when symptoms worsen, and it can be helpful to elicit these history points to guide avoidance measures (discussed later).

a. Typical examination findings include the following (**Fig. 2**)[19]:
   i. Allergic shiners: These occur because of infraorbital edema from venodilation related to blood vessel changes in the context of allergic inflammation.
   ii. Dennie-Morgan lines: These consist of increased folds or lines below the lower eyelid and are more common in patients with AR. The pathophysiology is not precisely understood. These lines do not always denote AR and can be more common in some ethnic groups without an increase in AR.
   iii. Allergic salute: This is a behavior related to nasal itching and rhinorrhea consisting of repeated rubbing of the nose. This repeated pushing the tip of the nose up with the hand leads to a transverse nasal crease.
   iv. Allergic facies: Typical allergic facies consist of a high arched palate, mouth breathing, and dental malocclusion. This is generally seen in children with early-onset AR.
   v. Nasal mucosa: With anterior rhinoscopy, the nasal mucosa may appear pale and blue colored with turbinate edema. This may be accompanied by visible clear rhinorrhea (anterior or posterior in oropharynx).
   vi. Cobblestoning: The posterior oropharynx may develop hyperplastic lymphoid tissue leading to a "cobblestone" appearance of the mucosa.
   vii. The tympanic membranes may also be abnormal, either with retraction or with serous fluid accumulation. This is related to nasal mucosal swelling and eustachian tube dysfunction.[22]
b. Specific IgE testing

Once the diagnosis of AR is suggested by the history and examination, determining specific IgE positivity may be helpful to confirm the diagnosis. Determination of specific IgE is indicated when it is necessary to establish an allergic cause for the patient's symptoms, to confirm or exclude specific allergic causes for a patient's symptoms, or to determine specific allergen sensitivity to guide avoidance measures or IT.[19] Skin testing to specific antigens can be done safely in the allergy office and provides results within 20 minutes with good sensitivity and specificity. Specific blood IgE testing has similar sensitivity to skin testing when considering patients with nasal allergic reactions upon allergen challenge testing.[19] The authors generally prefer skin testing in children because of the rapid results (20 minutes), lack of need for blood and laboratory-associated processing time, and ability to perform counseling in the same visit as testing based on real-time results. Anecdotally, patients and families appreciate this real-time diagnostic approach.

Allergic Rhinitis Classification

Once the diagnosis of AR is made, the disease can be classified according to whether it is intermittent or persistent as well as based on severity.[23] Intermittent AR is defined as having symptoms present for less than 4 weeks and for less than 4 days per week. Persistent AR occurs when symptoms are present for greater than 4 weeks and greater than 4 days per week.

Severity of disease can be classified according to the following:

a. Mild: Does not meet definition of moderate/severe
b. Moderate/severe: Meets one or more of the following criteria:
    i. Sleep disturbance
    ii. Impairment of school/work performance
    iii. Impairment of daily activities, leisure, or sports involvement
    iv. Troublesome symptoms

In practice, AR is often divided into seasonal and perennial subtypes as well, because this tends to relate to the allergic sensitizations specific to the patient.[1,19] Persistent or perennial symptoms tend to be more common than isolated seasonal symptoms, although a mixed picture, with persistent symptoms coupled with seasonal exacerbations, is quite common.[24] Many patients will lose awareness of the disability associated with AR if chronic symptoms are present. Children are particularly vulnerable to ignoring severe symptoms when present for prolonged periods. Lack of symptom awareness can have a profoundly detrimental effect on school/examination performance and contributes to the burden of disease described previously.[25–27]

Triggers

Triggers of AR are divided according to their temporal pattern during the year, as either perennial or seasonal triggers. Perennial triggers include items present in the home year round, such as mold, dust mites, or animals (particularly cats and dogs). Some patients also have perennial symptoms from an occupational exposure.[28] Thus, a thorough environmental history can be helpful in identifying potential control or avoidance measures that might improve perennial symptom control. Typical history might include visible mold presence in the home, presence of animals, bedding and other dust mite exposures, occupation, and hobbies. This information can be useful in guiding avoidance measures, detailed in later discussion.

Seasonal triggers include various pollens and molds. The typical pollens involved are tree, grass, and weed species that pollinate via wind-based pollen distribution.

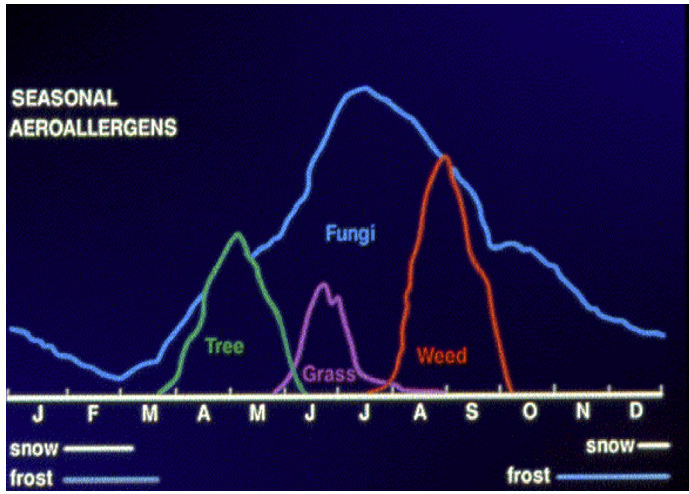


Fig. 3. Representative seasonal aeroallergen counts for Ann Arbor, MI. (*Courtesy of* WR. Solomon, MD, Ann Arbor, MI.)

A representative pollen count is displayed (Fig. 3) based on data historically collected in the authors' local area by Dr Bill Solomon. Correlating symptoms with pollen counts can give insight into the cause of a patient's seasonal symptoms. Insect-pollinated plants are not as commonly implicated in AR disease pathogenesis because of the lack of diffuse airborne pollen dispersal in these plants' life cycles. Some colloquial names for seasonal allergies identify times of the year with an event. However, physicians should be aware that the name may not identify the actual culprit pollinating species. For example, one colloquial name for AR is rose fever. This name correctly identifies that symptoms occur in early summer when rose blooming occurs. However, the rhinitis symptoms associated with the name is actually from pollinating grasses. Another classic example is the term hay fever. This term notes symptoms that occur during the fall hay harvest. However, the actual culprit allergens are more likely mold growing on the hay or weed pollens disseminated during the fall that contribute to rhinitis.

Therapy

Therapy for AR can be conceptualized as a 3-pronged approach. This approach includes avoidance, medications, and IT. Each aspect of therapy is discussed in detail. Special focus is given to the prevention of the development of other allergic sensitizations and asthma with IT in this section.

a. Avoidance: Success in avoidance of a culprit allergen is best measured by measuring the reduction in symptoms and medication use rather than a change in allergen concentration.[29] Each type of specific allergen is dealt with in later discussion.
   i. Dust mite: Dust mite feces are a major allergenic source in house dust, and the principal food of dust mites is human skin.[30,31] Major reservoirs of dust mite include mattresses, bedding, and upholstery. In general, a combination of multiple measures has been found to be most effective in mitigating symptoms from dust mite exposure. Typically, this includes dust mite covers for bedding, humidity control (between 35% and 50%) of the ambient air in the home, HEPA

vacuuming of carpet, and acaricides.[32] Using only a single measure to attempt to mitigate dust mite exposure does not seem to be effective. For example, using mite-proof bedding alone may not be sufficient for dust mite control.[32] In practice, patients and families may have difficulty implementing a full dust mite regimen, and physicians should be aware that partial implementation may not lead to dramatic symptom improvement.

ii. Animals: Total animal avoidance is thought to be the most effective way to improve symptoms.[19] Anecdotally, it is the opinion of the authors that it can be very hard for patients and families to remove animals from the home; if total home avoidance is to be accomplished, it must often be done prospectively rather than after an animal has joined a family. If the animal must remain in the house, the combination of a HEPA filter, mattress/pillow covers, and animal removal from the bedroom has been shown to reduce airborne antigen but not clinical symptoms in asthma; the effect on AR is less clear.[33] This underlines the difficulty of mitigating the continued presence of a pet. Furthermore, in counseling patients about possible new pets, hypoallergenic pets are not thought to actually exist, as even animals engineered to not produce a major allergen will still produce other allergens from the species, which can still elicit symptoms.[34] There is observational evidence that living with an animal during the first year of life may reduce the risk of developing sensitization to cat or dog in the future.[35,36] This suggests that avoiding animal purchases before a member of the household develops AR will not prevent allergy, but actually quite the opposite.

iii. Pollen: Avoidance of pollens during the season is very difficult because of their airborne ubiquity. Suggested measures include keeping windows closed, staying indoors on high-pollen days if highly allergic, avoiding drying clothing outside, and showering before bed to reduce carrying pollens through the night.[19]

iv. Mold: Avoidance measures for mold primarily focus on reducing indoor exposure. Suggested measures include reducing moisture sources, removing contaminated items from the home, applying diluted bleach to molds growing in the home on nonporous surfaces, wearing face masks for exposure to soil, leaves, compost, increasing air circulation, and cleaning air conditioning units regularly.[19]

b. Medications: Numerous medications have been developed to treat AR. These medications generally treat only symptoms and do not address the underlying allergic inflammation. Nevertheless, medical management of AR can be quite effective at mitigating the negative effects of the disease.

i. Nasal irrigation: Nasal saline irrigation, typically performed once daily, has shown benefit in AR. The practice led to improved symptoms and nasal peak flows in pediatric patients in one randomized placebo-controlled study.[37] Nasal irrigation may also serve as an adjunctive therapy that could decrease the need for nasal steroid dosing, because it improved symptoms and mucociliary clearance in children also on nasal steroids in a separate study.[38]

ii. Antihistamines: Oral antihistamines are used in AR to target the H1 receptor. This can effectively reduce symptoms of rhinorrhea, sneezing, and nasal itching.[39] First-generation H1 antihistamines, such as diphenhydramine, tend to cross the blood-brain barrier and induce sedation partly via an anticholinergic action.[40] Cumulative use over the lifetime has previously been associated with risk of dementia based on this anticholinergic property set.[41] Second-generation oral antihistamines, such as fexofenadine or cetirizine, appear to

have similar effectiveness as first-generation H1 antihistamines without evidence of the same risk profile because of the lack of brain penetration.[42] Fexofenadine and cetirizine are approved for children older than 6 months old and are an important tool in the AR armamentarium in children.

iii. Intranasal steroids: Intranasal steroids (NS) demonstrate excellent evidence toward anti-inflammatory properties that reduce rhinorrhea, itching, sneezing, and nasal obstruction or congestion.[43,44] Some limited evidence exists to suggest that NS reduce ocular symptoms of ARC as well, such as tearing, redness, itching, and swelling.[45] Overall, NS are thought to be the most effective single pharmaceutical in AR.[46] Mometasone, fluticasone, and triamcinolone nasal sprays are approved for children older than 2 years old. Adherence in small children especially can be troublesome. The authors find that choosing NS varieties with minimal volume and scent seems to help children tolerate these drugs.

iv. Intranasal antihistamines: Intranasal antihistamines also work on the H1 receptor and show similar effects to oral antihistamines; in fact, they may significantly reduce symptoms.[46] They are thought to achieve higher drug levels in nasal tissues and thus have a true anti-inflammatory effect, such as mast cell stabilization, not present with oral antihistamines.[47] Azelastine nasal spray is approved for children older than 5 years old. Adherence is an issue in children, because side effects may include bitter taste and sedation.[48] The bitter taste in particular can make it difficult for small children to tolerate the medication.

v. Leukotriene modifiers: Leukotrienes are inflammatory mediators related to AR pathogenesis. Leukotriene modifiers block the cysteinyl leukotriene receptor. Montelukast is approved in the United States for children 6 months and older and is effective at relieving AR symptoms; it also has a good safety profile.[49] Because montelukast is approved for both asthma and AR in children, it is often a good choice in patients with both diseases.[49] Physicians should be aware of the postmarketing data suggesting that montelukast may be detrimental in mood and be related to suicidality. However, the association is weak and thought to be very rare, and with proper counseling and monitoring, the use of the drug need not be limited.[50,51]

c. Immunotherapy: IT involves giving patients extracts containing allergens to which they produce specific IgE in order to induce immune changes and a desensitized state. Various formulations have been tried, but the most widely used at this time are subcutaneous injections and sublingual applications. Only these two are discussed in this section.

i. Subcutaneous immunotherapy: Subcutaneous immunotherapy (or "SCIT," often pronounced "skit") consists of injecting a patient with diluted extracts of the allergens that are thought to exacerbate the patient's AR. Very dilute extracts are used to start, and these are gradually escalated to higher concentrations, usually on a weekly schedule that requires several months of regular adherence. Once the highest concentration is achieved, this is called "maintenance," and the interval between injects can be lengthened. SCIT directly affects the immune system and changes the response to allergen. The details of this process are listed in **Table 1**. There is some disagreement surrounding whether multiple allergens should be combined or whether only a single relevant allergen should be administered at 1 time; this discussion is beyond the scope of this article.

1. Indications: Current guidelines suggest considering SCIT in AR when patients have evidence of elevated levels of specific IgE to clinically relevant allergens. The applicability to a particular patient should include

Table 1
Immunologic changes associated with subcutaneous immunotherapy and sublingual immunotherapy

Decrease in humoral and cellular response to allergens	IgE levels to allergen initially increase and then decrease over time Allergen-specific IgG1, IgG4, and IgA increase with time (although this does not predict effectiveness of IT) Decreased allergen-related eosinophil, basophil, and mast cell infiltration
Decreased end-organ response to allergen	Includes skin, conjunctiva, nasal mucosa, bronchi Blunted mucosal priming in response to allergen Decrease in bronchial histamine sensitivity
Increasing tolerance of allergen	Increase in regulatory T-cell number and production of interleukin-10 and transforming growth factor-B Waning of T-helper 2 (Th2) response and transition to Th1 response to allergen

SLIT is less well studied but thus far shows similar effects.
Data form Cox, L., et al., *Allergen immunotherapy: a practice parameter third update.* J Allergy Clin Immunol, 2011. **127**(1 Suppl): p. S1-55.

consideration of patient preference, adherence issues, other medication needs, response to avoidance measures, medication adverse effects, and the possibility of preventing allergic asthma in patients with AR (see later discussion).[52]

2. Effectiveness: Multiple double-blind, placebo-controlled, randomized clinical trials show effectiveness for SCIT for AR, and effectiveness of 3 to 5 years of therapy is the best studied.[53] SCIT is effective at ameliorating ocular symptoms as well.[54] Efficacy has been confirmed for pollens, fungi, animal allergens, dust mites, and cockroaches.[52] Improvements typically occur across multiple measurement domains, including symptoms, medication scores, organ challenges, immunologic changes, and quality of life.[52]

ii. Sublingual immunotherapy: Sublingual immunotherapy (or "SLIT") has also been studied in AR. SLIT involves the sublingual application of diluted allergen extracts thought to exacerbate a patient's AR with a similar buildup schedule to SCIT. The mechanism of action is thought to be similar to SCIT (see later discussion). SLIT is less relevant for pediatric patients because of a current lack of available products for children. A Timothy grass pollen extract is approved down to 5 years old. A 5-grass extract is approved down to 10 years old. Dust mite and ragweed extracts are approved only starting at age 18.

1. Indications: SLIT has similar indications to SCIT, although this is less well defined. SLIT can be particularly appropriate for patients who wish to avoid injections. Each product is only approved for single use, not in a combined fashion as SCIT may be used.[55]
2. Effectiveness: Timothy and combined 5-grass tablets have shown improvement in symptom and medication scores in the first year of treatment.[55] Dust mite and ragweed extracts are not approved for patients less than 18 years old. No direct studies between SCIT and SLIT have been done to date.

iii. Avoidance of asthma development with SCIT, avoidance of other sensitizations: SCIT has shown an ability to reduce the risk of asthma development and reduce the risk of developing additional IgE sensitizations. Studies of SLIT have also

begun to show this effect. This has implications for interrupting the progression of atopic disease, and IT is one of only a few interventions shown to have this effect on the atopic march. Particularly in children, IT should be considered early in the treatment of AR due to the potentially preventative effects detailed in later discussion.

1. Asthma development: Multiple studies have shown a reduction in asthma development associated with SCIT and SLIT. In 1 study, 3 years of pollen-based SCIT in children with AR reduced the risk of asthma development 2 years after stopping SCIT; this effect persisted at a 10-year follow-up (7 years after stopping SCIT) with an odds ratio of no asthma of 4.6.[56,57] Coseasonal grass SLIT administered for 3 years reduced asthma development versus controls in children aged 5 to 14 years.[58] This has been borne out in a multinational double-blind placebo-controlled setting out to 5 years.[59] Similar effects have been shown using dust mite SLIT, which reduced asthma development and new allergic sensitization in children as well up to 15 years later.[60–63]
2. Further sensitization:
   a. Twelve years after stopping grass SCIT, treated children had a lower rate of new sensitization development versus controls (58% vs 100%).[64]
   b. House dust mite SCIT in children monosensitized to dust mite also reduced the rate of new sensitization to other allergens up to 6 years later.[65–67]
   c. Among all monosensitized AR patients, one retrospective trial of greater than 8000 patients showed a decrease in new sensitization over 7 years in SCIT-treated patients.[68]
   d. Some studies have not shown a difference between SLIT and placebo with respect to new sensitizations with house dust mite SLIT.[69]

SUMMARY

Overall, AR is an allergic disease characterized by nasal symptoms, and when accompanied by ocular symptoms, is called ARC. The disease is common, may start early in life, and is associated with a high burden of disease that can particularly impair the functioning of children in school and other domains of life. Identifying seasonal and perennial triggers can be helpful, and the first step of treating the patient is avoidance. Medications are very helpful for treating symptoms and mitigating the disease burden but do not usually affect the underlying inflammation. IT not only has been shown to improve AR but also may prevent additional allergic sensitizations and asthma development.

REFERENCES

1. Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. Ann Allergy Asthma Immunol 2017;119(6):489–511.e41.
2. Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. Allergy Asthma Proc 2001;22(4):185–9.
3. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010;126(4):778–783 e6.
4. Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. Allergy Asthma Proc 2012;33(Suppl 1):S113–41.

5. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009; 124(3 Suppl):S43–70.
6. Mallol J, Crane J, von Mutius E, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) phase three: a global synthesis. Allergol Immunopathol (Madr) 2013;41(2):73–85.
7. Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. Immunol Allergy Clin North Am 2016;36(2):235–48.
8. Muliol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. J Investig Allergol Clin Immunol 2008;18(6):415–9.
9. Colas C, Galera H, Añibarro B, et al. Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). Clin Exp Allergy 2012;42(7):1080–7.
10. Georgalas C. The role of the nose in snoring and obstructive sleep apnoea: an update. Eur Arch Otorhinolaryngol 2011;268(9):1365–73.
11. Koinis-Mitchell D, Craig T, Esteban CA, et al. Sleep and allergic disease: a summary of the literature and future directions for research. J Allergy Clin Immunol 2012;130(6):1275–81.
12. Nathan RA. The burden of allergic rhinitis. Allergy Asthma Proc 2007;28(1):3–9.
13. Blaiss MS, Hammerby E, Robinson S, et al. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: a literature review. Ann Allergy Asthma Immunol 2018;121(1):43–52.e3.
14. Miyazaki C, Koyama M, Ota E, et al. Allergic diseases in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis. BMC Psychiatry 2017;17(1):120.
15. Yang MT, Chen CC, Lee WT, et al. Attention-deficit/hyperactivity disorder-related symptoms improved with allergic rhinitis treatment in children. Am J Rhinol Allergy 2016;30(3):209–14.
16. Casale TB, Dykewicz MS. Clinical implications of the allergic rhinitis-asthma link. Am J Med Sci 2004;327(3):127–38.
17. Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study–an international population-based cohort study. J Allergy Clin Immunol 2011; 128(4):816–823 e5.
18. Saulyte J, Regueira C, Montes-Martínez A, et al. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. PLoS Med 2014; 11(3):e1001611.
19. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1–84.
20. Ng ML, Warlow RS, Chrishanthan N, et al. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (I). Clin Exp Allergy 2000;30(9):1314–31.
21. Ng ML, Warlow RS, Chrishanthan N, et al. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (II). Clin Exp Allergy 2000;30(10):1417–22.
22. Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. J Allergy Clin Immunol 1997;99(2):S787–97.
23. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(5 Suppl):S147–334.

24. Mullarkey MF, Hill JS, Webb DR. Allergic and nonallergic rhinitis: their characterization with attention to the meaning of nasal eosinophilia. J Allergy Clin Immunol 1980;65(2):122–6.
25. Kremer B, den Hartog HM, Jolles J. Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. Clin Exp Allergy 2002;32(9):1310–5.
26. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. Ann Allergy Asthma Immunol 2000;84(4):403–10.
27. Walker S, Khan-Wasti S, Fletcher M, et al. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J Allergy Clin Immunol 2007;120(2):381–7.
28. Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. Clin Exp Allergy 2000;30(11):1519–34.
29. Platts-Mills TA, Thomas WR, Aalberse RC, et al. Dust mite allergens and asthma: report of a second international workshop. J Allergy Clin Immunol 1992;89(5):1046–60.
30. Park GM, Lee SM, Lee IY, et al. Localization of a major allergen, Der p 2, in the gut and faecal pellets of Dermatophagoides pteronyssinus. Clin Exp Allergy 2000;30(9):1293–7.
31. Pollart S, Chapman MD, Platts-Mills TA. House dust mite and dust control. Clin Rev Allergy 1988;6(1):23–33.
32. Sheikh A, Hurwitz B, Nurmatov U, et al. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database Syst Rev 2010;(7):CD001563.
33. Wood RA, Johnson EF, Van Natta ML, et al. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158(1):115–20.
34. Portnoy J, Kennedy K, Sublett J, et al. Environmental assessment and exposure control: a practice parameter–furry animals. Ann Allergy Asthma Immunol 2012;108(4):223.e1-15.
35. Mandhane PJ, Sears MR, Poulton R, et al. Cats and dogs and the risk of atopy in childhood and adulthood. J Allergy Clin Immunol 2009;124(4):745–750 e4.
36. Wegienka G, Johnson CC, Havstad S, et al. Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. Clin Exp Allergy 2011;41(7):979–86.
37. Wang YH, Yang CP, Ku MS, et al. Efficacy of nasal irrigation in the treatment of acute sinusitis in children. Int J Pediatr Otorhinolaryngol 2009;73(12):1696–701.
38. Li H, Sha Q, Zuo K, et al. Nasal saline irrigation facilitates control of allergic rhinitis by topical steroid in children. ORL J Otorhinolaryngol Relat Spec 2009;71(1):50–5.
39. Simons FE. Advances in H1-antihistamines. N Engl J Med 2004;351(21):2203–17.
40. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy 2010;65(4):459–66.
41. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med 2015;175(3):401–7.
42. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. Drugs 2005;65(3):341–84.
43. Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. Clin Exp Allergy 2011;41(2):160–70.

44. Penagos M, Compalati E, Tarantini F, et al. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy 2008;63(10):1280–91.
45. Bielory L, Chun Y, Bielory BP, et al. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. Allergy 2011; 66(5):686–93.
46. Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. Ann Allergy Asthma Immunol 2010;104(1):13–29.
47. Pipkorn P, Costantini C, Reynolds C, et al. The effects of the nasal antihistamines olopatadine and azelastine in nasal allergen provocation. Ann Allergy Asthma Immunol 2008;101(1):82–9.
48. Lumry W, Prenner B, Corren J, et al. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol 2007; 99(3):267–72.
49. Nayak A. A review of montelukast in the treatment of asthma and allergic rhinitis. Expert Opin Pharmacother 2004;5(3):679–86.
50. Philip G, Hustad C, Noonan G, et al. Reports of suicidality in clinical trials of montelukast. J Allergy Clin Immunol 2009;124(4):691–6.e6.
51. Holbrook JT, Harik-Khan R. Montelukast and emotional well-being as a marker for depression: results from 3 randomized, double-masked clinical trials. J Allergy Clin Immunol 2008;122(4):828–9.
52. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1 Suppl):S1–55.
53. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. Clin Ther 2000;22(3):342–50.
54. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N Engl J Med 1965;273(13):675–9.
55. Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol 2017;118(3):276–282 e2.
56. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62(8):943–8.
57. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109(2):251–6.
58. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114(4):851–7.
59. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2018;141(2):529–38.e13.
60. Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 2003;33(2):206–10.
61. Marogna M, Spadolini I, Massolo A, et al. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. Allergy 2004;59(11):1205–10.

62. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol 2008;101(2):206–11.
63. Marogna M, Spadolini I, Massolo A, et al. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. J Allergy Clin Immunol 2010;126(5):969–75.
64. Eng PA, Borer-Reinhold M, Heijnen IA, et al. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61(2):198–201.
65. Des Roches A, Paradis L, Menardo JL, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99(4):450–3.
66. Pajno GB, Barberio G, De Luca F, et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31(9):1392–7.
67. Inal A, Altintas DU, Yilmaz M, et al. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007;17(2):85–91.
68. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31(8):1295–302.
69. Lim JH, Kim JY, Han DH, et al. Sublingual immunotherapy (SLIT) for house dust mites does not prevent new allergen sensitization and bronchial hyperresponsiveness in allergic rhinitis children. PLoS One 2017;12(8):e0182295.

Table 1. **Differential Diagnosis of Rhinitis in Pediatric Patients**

Diagnosis	Clinical Presentation
Allergic Rhinitis	Sneezing, rhinorrhea, nasal congestion, pruritus (nasal, ocular, palate, throat), watery eyes, postnasal drip with cough.
Cough-variant Asthma	Nocturnal cough; no history of wheezing; responsive to bronchodilator therapy.
Infectious Rhinitis	*Acute viral rhinitis:* Rhinorrhea, congestion, fever. *Chronic infectious rhinosinusitis:* Mucopurulent nasal discharge, postnasal drip with cough, olfactory disturbance.
Foreign Body	Unilateral nasal obstruction and purulent nasal discharge.
Adenoid Hypertrophy	Bilateral nasal obstruction, nasal discharge, and mouth breathing (often severe and unresponsive to therapy).
Structural (deviated septum, nasal turbinate)	Nasal blockage, rhinorrhea, postnasal drip.
Vasomotor Rhinitis	Profuse rhinorrhea, nasal obstruction; symptoms often occur when going from a warm home to frigid outdoor temperatures.
Immune Deficiencies	Recurring upper respiratory tract infections.
Choanal Atresia	Chronic mouth breathing and recurrent infections.
Food-induced (gustatory) Rhinitis	Copious watery rhinorrhea immediately after ingestion of food.
Food Allergy	Nasal, laryngeal, or pulmonary reactions accompanied by gastrointestinal, dermatologic, or systemic manifestations.
Rhinitis Medicamentosa	Nasal congestion and hypertrophy or nasal mucosa (resulting from overuse of topical decongestants).

Table 2. **Management of Allergic Rhinitis: Assessing Pharmacologic Agents**

Agent	Sneezing	Itching	Congestion	Rhinorrhea	Eye Symptoms
Oral antihistamine	++	++	+/−	++	++
Nasal antihistamine	+	+	+/−	+	−
Intranasal corticosteroid	++	++	++	++	+
Oral decongestant	−	−	+	−	−
Intranasal decongestant	−	−	++	−	−
Intranasal mast cell stabilizer	+	+	+	+	−
Topical anticholinergic	−	−	−	++	−

− provides no benefit, +/− provides little or minimal benefits, + provides modest benefit, ++ provides substantial benefit. This table represents a consensus of the Task Force's opinion.

Table. Differential Diagnosis of Rhinitis

Most Common

- Allergic rhinitis
- Viral upper respiratory tract infection
- Sinusitis

Less Common

- Vasomotor rhinitis
- Rhinitis medicamentosa
- Cystic fibrosis
- Nasal polyps
- Cocaine use
- Gustatory rhinitis
- Nonallergic rhinitis with eosinophilia syndrome
- Choanal atresia

Table 3. Recommended and Commonly Used Medications for Allergic Rhinitis and Allergic Rhinoconjunctivitis

CLASS	NAME	BRAND NAME	DOSE	MECHANISM	ONSET OF ACTION	MAJOR REPORTED ADVERSE EFFECTS
Second-generation OAH	Cetirizine	Zyrtec	6 mo–2 y: 2.5 mg qd,[a] 2–5 y: 5 mg qd, >6 y: 10 mg qd	Bind H1 receptor to downregulate activity, shifting the active form of the H1 receptor to the inactive form, reducing histamine release in the respiratory system, blood vessels, and gastrointestinal system	60 min	Drowsiness, headache
	Levocetirizine	Xyzal	6–11 y: 2.5 mg qd, >12 y: 5 mg qd		45 min	Drowsiness
	Loratadine	Claritin	2–5 y: 5 mg qd, >6 y: 10 mg qd		60–75 min	Headache
	Desloratadine	Clarinex	6 mo–1 y: 1 mg,[a] 1–5 y: 1.25 mg, 6–11 y: 2.5 mg, >12 y: 5 mg qd		30–90 min	Drowsiness, headache, diarrhea
	Fexofenadine	Allegra	6 mo–2 y: 15 mg BID,[a] 2–11 y: 30 mg BID, >12 y: 180 mg qd		60 min	Headache
INCS	Fluticasone propionate	Flonase	4–11 y: 1–2 spray[b] qd, >12 y: 1–2 spray[b] qd	Bind glucocorticoid receptors to decrease allergic inflammation and inhibit release of inflammatory cytokines	2–12 h	Unpleasant aftertaste, epistaxis, nasal dryness and mucosal irritation, may affect short-term growth velocity, rare septal perforation
	Fluticasone furoate	Sensimist	2–11 y: 1 spray[b] qd, >12 y: 2 spray[b] qd–BID		8 h	
	Mometasone	Nasonex	2–11y: 1 spray[b] qd, >12 y: 2 spray[b] qd		2.5 h	
	Triamcinolone acetonide	Nasacort	2–6 y: 1 spray[b] qd, 6–11 y: 1–2 spray[b] qd, >12 y: 2 spray[b] qd		8–10 h	
	Budesonide	Rhinocort	6–11 y: 1–2 spray[b] qd, >12 y: 2 spray[b] qd		3–8 h	
INAH	Azelastine	Astelin, Astepro	6 mo–6 y: 0.1%,[c] 1 spray[b] BID, 6–12 y: 0.1 or 0.15% 1 spray[b] BID, >12 y: 0.1 or 0.15% 1–2 sprays[b] BID	Bind local H1 receptor to downregulate activity, inhibiting release of histamine and other allergic mediators, reduces hyperactivity of the airways	15–30 min	Bitter taste, headache
	Olopatadines	Patanase	6–11 y: 1 spray[b] BID, >12 y: 2 sprays[b] BID		15–30 min	Bitter taste
INCS + INAH	Fluticasone/azelastine[c]	Dymista	>6 y: 1 spray[b] BID	Combination of above mechanisms	5 min	Bitter taste, headache
Mast cell stabilizer	Intranasal cromolyn	Nasalcrom	1–2 sprays[b] TID-QID	Mast cell stabilizer	1–7 min	Burning sensation in nose, nasal irritation
Anticholinergic	Intranasal ipratropium	Atrovent	2 sprays[b] BID-TID	Inhibits nasal seromucous glands	15 min	Nasal dryness and epistaxis, headache
Ocular	Ketotifen	Zaditor	>3 y: 1 drop[d] BID	H1 receptor antagonist and mast cell stabilizer	5–15 min	Eye irritation or pain
	Olapaditine	Pataday	>2 y: 0.1%, 1 drop[d] BID, 0.2% and 0.7% 1 drop[d] qd		5–15 min	Headache, eye irritation
	Azelastine[c]	Optivar	>3 y: 1 drop[d] BID		3 min	Headache, transient ocular burning
	Epinastine	Elestat	>2 y: 1 drop[d] BID		3–5 min	Headache, eye irritation

BID=twice daily, INAH=intranasal antihistamine, INCS=intranasal corticosteroid, OAH=oral antihistamine, qd=every day, QID=4 times a day, TID=3 times daily.

[a]Limited data available; use OAHs with caution in patients younger than 2 years.

[b]Spray per nostril.

[c]Requires a prescription.

[d]Drop per eye.

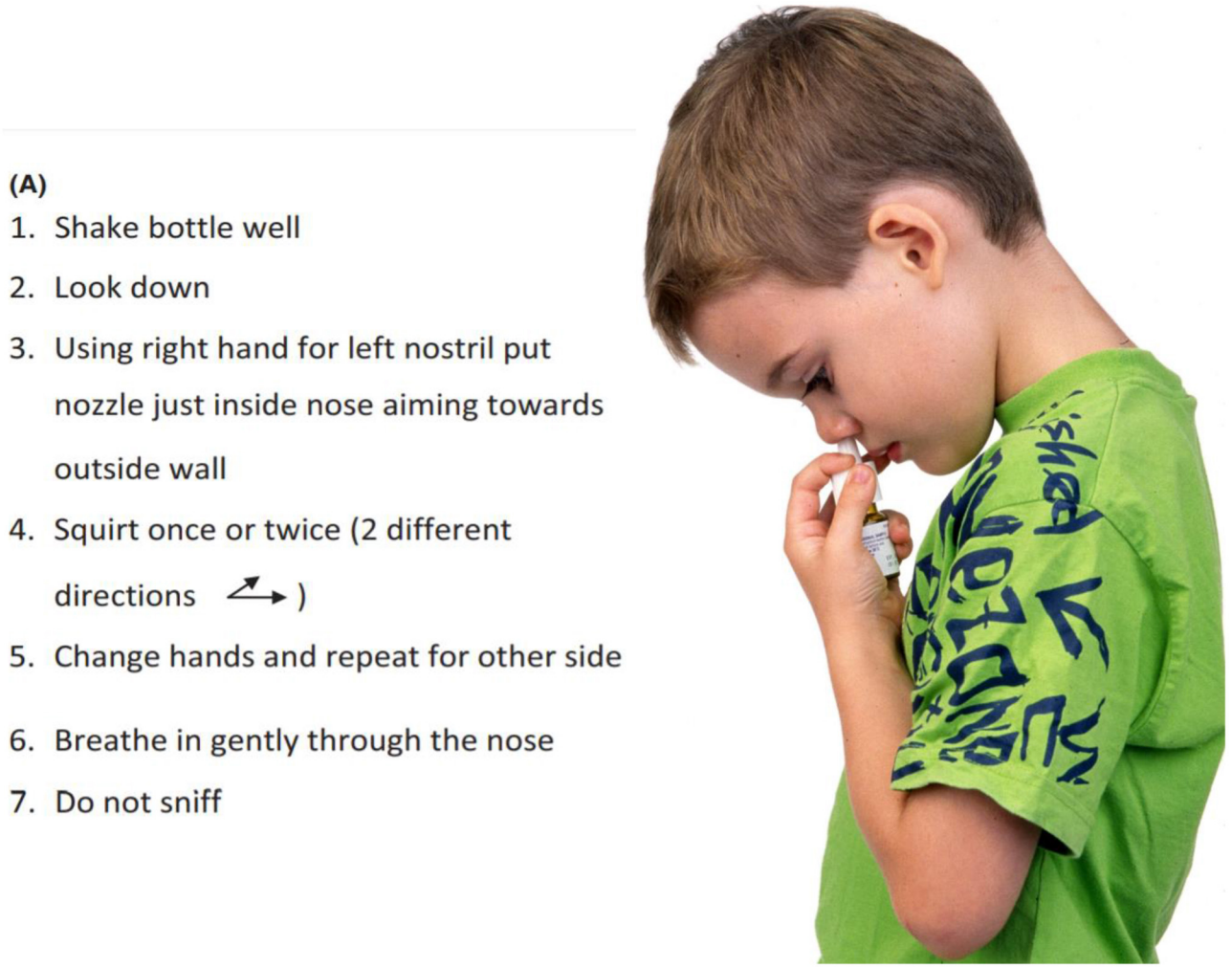


FIGURE 6 | How to use a nasal spray. It is necessary to put the spray onto the lateral walls of the nose, not the septum. It should not be sniffed back hard into the nose but should be moved slowly by mucociliary clearance over the nasal mucosa where the corticosteroid can enter epithelial cells to exert its effects. From Scadding et al. (12), with permission.

Current Otorhinolaryngology Reports (2023) 11:37–43
https://doi.org/10.1007/s40136-023-00440-x

PEDIATRIC OTOLARYNGOLOGY: CHALLENGES IN PEDIATRIC OTOLARYNGOLOGY (W-C HSU, SECTION EDITOR)

Recent Updates of Immunotherapy for Allergic Rhinitis in Children

Chih-Feng Lin[1] · Yi-Tsen Lin[1,2] · Chun-Kang Liao[1] · Te-Huei Yeh[1,2]

Accepted: 19 December 2022 / Published online: 27 January 2023

Abstract

Purpose of Review Allergen immunotherapy (AIT) is a novel treatment approach with disease-modifying and preventative benefits that are not shared with other strategies for treating allergic illnesses. It has been demonstrated to be safe and effective in children. This review provides the most recent information on AIT in children as well as any pertinent updates.

Recent Findings Although there is not a standard way to begin AIT, there are clear indications for AIT. Each case needs to be evaluated on its own by weighing the pros and downsides. AIT has been proven to significantly improve symptoms and quality of life in children with allergic illness, reduce medication use, stop the development of new allergen sensitizations, and stop the progression of allergic rhinitis to asthma. Novel approaches are under investigation to overcome some known AIT disadvantages.

Summary This review provides a thorough summary of the most recent research and updates on AIT in children.

Keywords Allergic rhinitis · Allergen immunotherapy · Children · Atopy · Treatment

Introduction

Around the world, reports of allergy disorders as allergic rhinitis, asthma, and atopic dermatitis have increased and are highly prevalent [1–4]. There are 10 to 30% of adults and up to 40% of children impacted, according to epidemiologic research [3]. Pharmacotherapy, allergy immunotherapy, and education about allergen-specific avoidance precautions are possible treatment options for these illnesses [5••, 6]. To achieve a more comprehensive approach, common clinical diagnosis and management algorithm was summarized as Fig. 1. Pharmacotherapy is usually the first step of the management for pediatric patients with allergic rhinitis. However, advantages and disadvantages exist between different treatment options. We listed the pros and cons of current treatment modalities in Table 1.

For individuals with these cross-linked allergy disorders, allergen immunotherapy (AIT), which has been used as a treatment for allergic disease for more than a century, has been shown to be safe, efficient, and potentially disease-modifying. Patients with moderate to severe allergic rhinitis who do not react well to medical treatment are candidates for AIT. The hazards and benefits of each case should be carefully weighed. The use of fewer medication, a considerable improvement in symptoms and quality of life, the prevention of the emergence of new allergen sensitizations, and the prohibition of progression of allergic rhinitis to asthma are all advantages of AIT in children with allergic illness. Severe systemic allergic reactions are a rare but possible risk of AIT.

Mechanism

AIT normalizes allergen-specific T and B cells, controls IgE and IgG production, and modifies mast cells, basophil activation thresholds, and dendritic cell phenotypes through general processes of immunological tolerance to allergens. To decrease type 2 immune responses and allergic inflammation, the major objectives are to retain regulatory T cells (Tregs), regulatory B cells (Bregs), and several other regulatory cells [7•].

This article is part of the Topical Collection on *PEDIATRIC OTOLARYNGOLOGY: Challenges in Pediatric Otolaryngology*

✉ Te-Huei Yeh
tehueiyeh@ntu.edu.tw

[1] Department of Otolaryngology, National Taiwan University Hospital, No. 7, ChungShan S. Rd., Zhongzheng Dist., Taipei City 100225, Taiwan

[2] Department of Otolaryngology, College of Medicine, National Taiwan University, Taipei, Taiwan

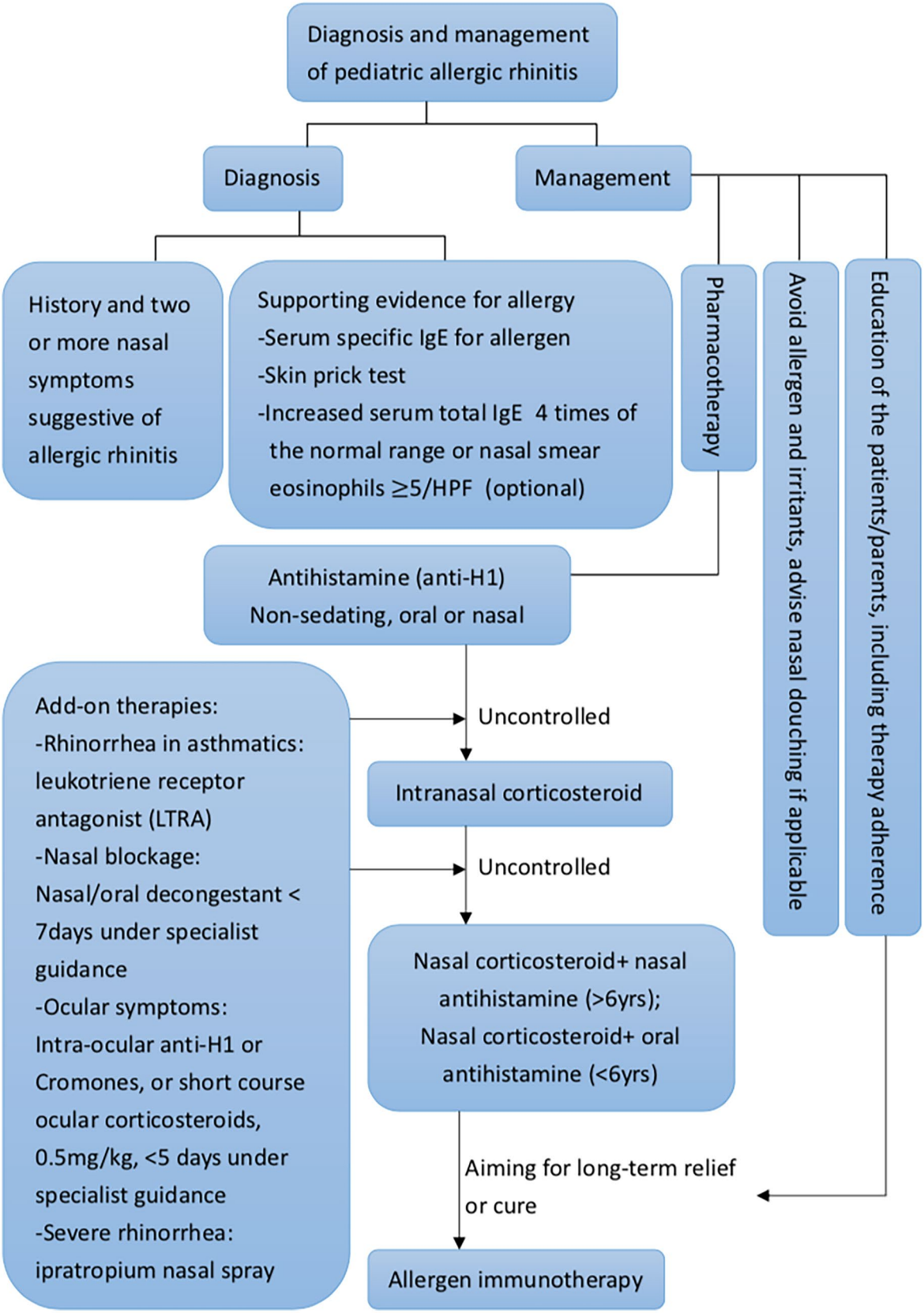


Fig. 1 Pediatric allergic rhinitis diagnosis and management algorithm. HPF, high power field; IgE, immunoglobulin E

Table 1 Pros and cons on treatment modalities for pediatric allergic rhinitis (AR)

Medication	Pros	Cons
Oral H1 antihistamines	Non-sedating antihistamine as the first-line treatment and well tolerable	Mild fatigue, headache, nausea, dry mouth, poor drug adherence
Intranasal antihistamines	First or second-line treatment, effective for ocular symptoms	Concerns for patient tolerance, especially with regard to taste
Intranasal corticosteroids	First or second-line treatment All nasal symptoms relief as well as ocular symptoms	Nasal irritation, epistaxis, slow onset, some negative effects on short-term growth in children, but it is unclear for long term
Oral decongestant	For short-term relief of nasal obstruction	Insomnia, loss of appetite, irritability, palpitations, and increased blood pressure. Risk of toxicity in young children
Topical decongestant	For short-term nasal decongestion	Chronic use may carry the risk of rhinitis medicamentosa. Rebound congestion
Leukotriene receptor antagonist	For AR combined asthma symptoms relief	Little effect as monotherapy for AR Cost
Cromones	As alternative for patient cannot tolerate intranasal corticosteroid	Nasal irritation, slow onset, frequent dosing needed
Ipratropium nasal spray	Adjunct to intranasal corticosteroid for the uncontrolled rhinorrhea	Nasal irritation, headache, pharyngitis, epistaxis, nasal dryness, over-dosing
Nasal saline douching	Adjunct to pharmacotherapy Effective in discharge removal	Practice and education needed, intranasal irritation, headaches, and ear pain
Combination: intranasal antihistamine and corticosteroid	Rapid onset, effective when monotherapy fail to control symptoms. Used as second-line therapy	Patient intolerance, especially due to taste Cost

The regulation of antigen-specific immune cells, including T and B cells, was assumed to be AIT's main mechanism of action since it operates in an antigen-specific manner. Innate lymphoid cells, monocytes/macrophages, natural killer cells, and dendritic cells are examples of non-antigen-specific immune cells that may be modulated by AIT, according to recent research. The amelioration of symptoms following AIT may also be attributed to these effects [7•]. Possible mechanism of allergen immunotherapy was illustrated as Fig. 2.

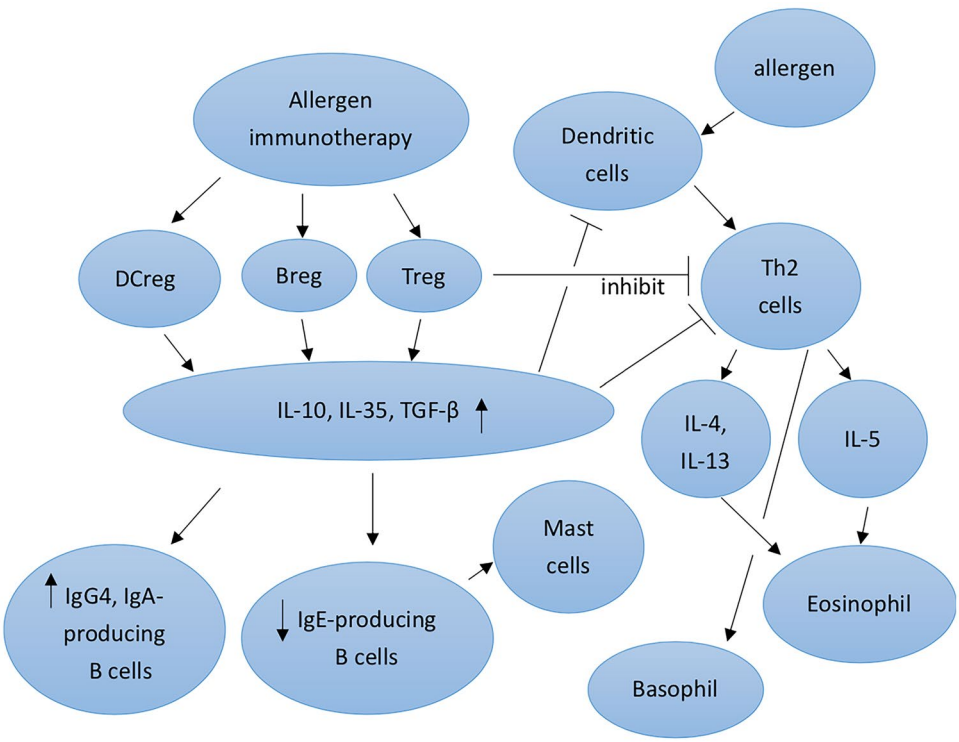


Fig. 2 Mechanism of allergen immunotherapy

Indications

Patients who exhibit allergen-specific IgE antibodies as determined by serum specific IgE laboratory testing or skin prick testing and have allergic rhinitis with or without conjunctivitis, allergen-induced asthma, or stinging insect hypersensitivity should consider AIT [8, 9]. Children with allergic rhinitis frequently acquire asthma over time since the two diseases are closely related. However, there are still a lot of unanswered questions regarding whether allergen immunotherapy for allergic rhinitis can prevent asthma. These questions concern the age groups, how to prepare allergens, how to administer AIT, and how long to treat patients [10].

Contraindications

Communication difficulties and a few medical illnesses are contraindications to AIT. A rare but potential risk of AIT is the development of severe systemic allergic reactions [11, 12]. Patients chosen for AIT should be able to verbally and physically express to the medical care team any discomforts and symptoms that might point to an adverse reaction. Starting AIT with children under the age of 5 is a topic of some discussion. Although there is a benefit to starting AIT before the age of 5 years old due to the preventative effect of AIT on the development of new aeroallergen sensitizations and the progressive march to asthma, each case to start AIT should be carefully assessed by evaluating the severity of disease and benefits/risks ratios. Because there is a higher risk of systemic reactions to AIT injections in individuals with uncontrolled labile asthma, allergen immunotherapy is not advised for these patients. According to survey studies, people with uncontrolled and/or labile asthma were more likely to die from AIT; hence, asthma control must be attained before beginning immunotherapy [13]. Medical diseases that make it more difficult for the patient to overcome the systemic allergic reaction or the subsequent treatment are also relative contraindications for AIT. Heart disease, significantly reduced lung function, and ailments needing beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) are among these medical disorders. These comorbidities are present in children even if they are less common than in adults.

Route for Administration

AIT can be given sublingually or subcutaneously, and new delivery methods including intra- and epicutaneous are continuously being researched. AIT attempts to alter innate and adaptive immunologic responses to induce allergen tolerance. Induction of diverse functional regulatory cells, such as regulatory T cells (Tregs), follicular T cells (Tfr), B cells (Bregs), dendritic cells (DCregs), innate lymphoid cells (IL-10 + ILCs), and natural killer cells, is the primary mechanism of AIT for controlling type 2 inflammatory cells.

For AIT, subcutaneous delivery (SCIT) was the usual route of administration. The typical SCIT regimen for allergen extracts involves dose titration by once-weekly injection, followed by maintenance dose injections at intervals of 4 to 8 weeks, continuing for at least 3 to 5 years. By using cluster or rush protocols to help the patients reach maintenance, the build-up period can be cut short [14]. These accelerated AIT offer patients quicker relief from allergy symptoms while maintaining comparable safety to standard regimens. However, compared to typical timetables, these protocols require more time commitment initially, but they ultimately save time and money in the long term. In order to reduce the frequency of systemic allergic reactions during accelerated AIT, premedication, which typically only requires an H1 antihistamine 1 h before the treatment, is advised. In appropriately selected patients, the risk for severe systemic reactions during accelerated AIT is low, but life-threatening reactions can occur.

Sublingual immunotherapy (SLIT) tablets serve as another allergen immunotherapy option for clinicians. Nowadays, there are five SLIT tablets that have been licensed for the treatment of allergic rhinoconjunctivitis in North America. These tablets are directed against home dust mites, ragweed, Timothy grass, and other allergens. On the other hand, the FDA has not yet approved any SLIT drops products. In SLIT, allergens are often given daily under the tongue. Large, double-blind, placebo-controlled trials involving both patients who were monosensitized and those who were polysensitized found that SLIT tablets consistently demonstrated therapeutic efficacy [15]. Patients who are allergic to pollen during their individual pollen seasons have showed success with treatment with house dust mite SLIT tablets [15]. Efficacy studies of SLIT drops demonstrate substantial heterogeneity of treatment effect, in contrast to SLIT tablets [15, 16]. Although data are limited, studies that compared the efficacy of SLIT tablets versus pharmacotherapy generally indicated that SLIT tablets had a greater benefit than pharmacotherapy when compared with placebo, particularly for perennial allergic rhinoconjunctivitis. When compared with subcutaneous immunotherapy, the results showed that SLIT tablets were superior to subcutaneous immunotherapy in terms of safety but somewhat less superior in terms of efficacy [15]. Additionally, there is no build-up phase necessary with SLIT, and it may be done securely and successfully at home. An intricate immunological network that includes the mouth mucosa and local lymph nodes is a necessary requirement for SLIT [17]. The efficient dosing range of allergy management is another obvious distinction between SCIT and SLIT. For many allergens, SCIT employs a small effective dose range of 5 to 25 μg

of allergen per injection, but SLIT needs at least 50 to 100 times more allergen than SCIT to be equally effective [18].

Direct injection of allergens into the lymphatic system is known as intra-lymphatic immunotherapy (ILIT). By reducing the number of treatment applications and the length of the therapy, attaining good compliance and quick symptom relief, and demonstrating safety, ILIT tend to increase the efficiency of AIT. Only three low allergen dosage injections into the inguinal lymph nodes under ultrasound guidance, spaced 1 month apart, are needed for ILIT. When compared to SCIT, the cumulative allergen dose can be reduced 1000-fold [19, 20]. The demand for experienced professionals for injection under ultrasound guidance, which may make this procedure less practical, is the drawback of ILIT.

A unique therapy being researched right now is epicutaneous immunotherapy(EPIT). EPIT involves applying allergens to the skin and antigen-presenting cells in the superficial layers of the skin repeatedly. Electronic spreading, ablative fractional laser, and microneedle arrays are examples of epidermal allergen powder delivery technologies [21]. In contrast to mast cells or the vasculature, epidermal Langerhans cells are the focus of EPIT, which can lessen both local and systemic side effects [22]. The following benefits have been noted for EPIT: (1) a high safety profile due to the application of the allergen into the non-vascularized epidermis and subsequent delivery of the allergen to the less-vascularized dermis, (2) increased patient convenience due to the non-invasive (needle-free) and self-administrable application method, likely improving compliance, (3) absence of additional potential irritant constituents (e.g., alum, preservatives), and (4) less expensive. Regarding patients with AR and indoor allergen sensitivity, further information is required.

Local nasal immunotherapy(LNIT) appears to be only beneficial on rhinitis symptoms, according to considerable research conducted over the past 40 years. Local nasal LNIT, however, is not well accepted by patients due to its difficulties in use and local adverse effects that must be prevented using topical nasal premedication [23]. LNIT is not advised for clinical use at this time.

Efficacy

It has been demonstrated that pediatric immunotherapy is both efficient and well tolerated. By reducing symptoms and medication use, SCIT and SLIT have been shown in numerous clinical trials to be helpful for allergic rhinitis and asthma. One study in children aged 5 to 10 years found that both SCIT and SLIT significantly reduced the overall score for rhinitis and asthma symptoms, the overall medical score, and skin reactivity to house dust mites when compared to pharmacotherapy [24]. Another study from 2017 showed that patients with AR who received AIT for 3 years had a considerably lower probability of developing asthma [25]. The impact persisted for up to 2 years after the end of treatment, but it was unable to draw any meaningful conclusions about whether it would last for longer. According to several studies, there might be a lower prevalence of allergy in children born to mothers who underwent AIT during pregnancy. AIT's effectiveness is influenced by the allergen dose and length of treatment. The clinical findings revealed a significant amount of heterogenicity and responsiveness in people. The personal dose was associated to the immunological response, and the length of the treatment was related to long-term recovery after stopping it. Current practice advises doctors to stop AIT if there is no clinical response after 18 to 24 months because there are no reliable diagnostic methods or markers for identifying responder patients [26]. Each country's extracts vary in terms of their strength, allergen dosage, allergen combinations, and adjuvants.

Safety

Although AIT is regarded as a safe treatment, it can have unfavorable side effects, including local, large local reactions (LLRs), systemic reactions, and, in rare instances, anaphylaxis. Within 30 min following injection, the majority of the severe systemic reactions will manifest. Severe systemic reactions like anaphylaxis must be promptly identified by the medical care team which is also necessary while administering injections for AIT. Because SLIT has fewer systemic adverse effects than SCIT and no fatalities have been documented, it offers a higher safety profile [27]. One prospective study that looked at the safety of AIT in children under the age of 5 reported that out of 6689 injections in 239 individuals, there was just one systemic reaction. The authors came to the conclusion that AIT is a safe treatment for children under the age of 5 [28]. AIT frequently has side effects that are localized. In a survey study of 249 individuals receiving AIT, 71% of the participants said their AIT caused a local reaction. In 96% of patients who reported local reactions, it was indicated that the local reactions would not induce them to cease AIT. Individual local reactions may not necessarily portend future systemic or local reactions [29].

Duration of AIT

Many randomized controlled trials show long-term efficacy in improving clinical and immunological change following SCIT and SLIT. When AIT was used for less than 3 years, allergy symptoms typically returned 1 year after treatment

ended. In a thorough 5-year prospective controlled trial comparing 3- and 5-year HDM SCIT, it was discovered that after 3 years, both groups had significantly lower rhinitis severity scores, asthma severity scores, and visual analog scales. Additionally, both groups continued to receive the treatment benefit after 5 years [30]. For long-term clinical benefit, SCIT and SLIT should both be at least 3 years long. Numerous factors, including the inconvenience of repeated injection visits, unfavorable side effects, and expense, which are the main causes of cessation, have an impact on AIT adherence [27].

Particular Considerations

AIT has a number of drawbacks, including the prolonged duration of therapy necessary to attain better efficacy, high cost, systemic allergic reactions, and the lack of a biomarker for identifying treatment responders. To address the issues related to AIT, supplementary medicines, vaccination adjuvants, and innovative vaccine technologies are currently being researched. All are not in the same developmental stage. For instance, allergoids have not yet received US FDA approval in the USA despite being used in clinical trials in Europe. Since the effects of using biologics to minimize the systemic reaction have been minimal, the expense is not justified. In Europe, modified recombinant proteins and peptides are being developed, but thus far, their level of efficacy has been disappointing [31•]. Before being prepared for future usage or regulatory approval, all require additional research.

COVID-19 Pandemic Attack

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and AR is not a risk factor for severe disease. There is currently no immunologic or clinical proof of an interaction between AIT and SARS-CoV-2. Patients who have been diagnosed as confirmed COVID-19-positive cases should stop receiving AIT, and those who have recovered from COVID-19 and are asymptomatic can resume receiving AIT as planned. With SLIT, patients can self-treat at home rather than traveling to or staying at an allergy hospital or clinic. Regarding patients who receive AIT and contract COVID-19 infection, more information is required.

Conclusion

In practice, allergen-specific immunotherapy has been advised for the treatment of severe AR patients who do not respond to standard medication therapies. In order to reduce type 2 inflammation, AIT produces allergic immunological tolerance by increasing many regulatory cells. AIT has been demonstrated to be helpful in easing allergic symptoms, decreasing the need for medicine, lowering allergen reactivity, enhancing quality of life, and preventing the onset of asthma. However, the drawbacks of conventional SCIT include the need for many injections and clinic visits, a high cost, and systemic allergic reactions. In terms of safety, SLIT tablets outperformed SCIT, although with a little lower benefit in terms of efficacy. AIT can be administered through a variety of methods, which offers options and enhances patient compliance and safety. To increase the efficacy of AIT even more, new approaches, adjuvants, adjunctive therapies, biologicals, and novel technologies are being investigated.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Arrais M, Lulua O, Quifica F, Rosado-Pinto J, Gama JMR, Brito M, et al. Sensitisation to aeroallergens in relation to asthma and other allergic diseases in Angolan children: a cross-sectional study. Allergol Immunopathol (Madr). 2020;48(3):281–9. https://doi.org/10.1016/j.aller.2019.10.005. Epub 2020/02/10. PubMed PMID: 32035729.
2. Christiansen ES, Kjaer HF, Eller E, Bindslev-Jensen C, Host A, Mortz CG, et al. The prevalence of atopic diseases and the patterns of sensitization in adolescence. Pediatr Allergy Immunol. 2016;27(8):847–53. https://doi.org/10.1111/pai.12650. Epub 2016/09/04. PubMed PMID: 27591739.
3. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, et al. Japanese guidelines for allergic rhinitis 2020. Allergol Int. 2020;69(3):331–45. https://doi.org/10.1016/j.alit.2020.04.001. Epub 2020/06/01. PubMed PMID: 32473790.
4. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8(3):483–91. https://doi.org/10.1183/09031936.95.08030483. Epub 1995/03/01. PubMed PMID: 7789502.
5. •• Bousquet J, Pfaar O, Togias A, Schunemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy. 2019;74(11):2087–102. https://doi.org/10.1111/all.13805. **The report reviews care pathways for the administration of AIT using evidence-based criteria and may maximize its impact on allergic diseases.**
6. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, et al. International consensus statement on allergy and rhinology:

allergic rhinitis. Int Forum Allergy Rhinol. 2018;8(2):108–352. https://doi.org/10.1002/alr.22073. Epub 2018/02/14. PubMed PMID: 29438602; PubMed Central PMCID: PMCPMC7286723.

7.• Boonpiyathad T, Lao-Araya M, Chiewchalermsri C, Sangkanjanavanich S, Morita H. Allergic rhinitis: what do we know about allergen-specific immunotherapy? Front Allergy. 2021;2:747323. https://doi.org/10.3389/falgy.2021.747323. Epub 2022/04/08. PubMed PMID: 35387059; PubMed Central PMCID: PMCPMC8974870. **This review presents an updated overview of AIT, and summarized adjunctive therapies, vaccine adjuvants, and novel vaccine technologies studied to overcome the problems associated with AIT.**

8. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55. https://doi.org/10.1016/j.jaci.2010.09.034. Epub 2010/12/03. PubMed PMID: 21122901.

9. Cox L, Esch RE, Corbett M, Hankin C, Nelson M, Plunkett G. Allergen immunotherapy practice in the United States: guidelines, measures, and outcomes. Ann Allergy Asthma Immunol. 2011;107(4):289–99. https://doi.org/10.1016/j.anai.2011.06.018. Epub 2011/10/04. PubMed PMID: 21962088.

10. Arshad SH. Does allergen immunotherapy for allergic rhinitis prevent asthma? Ann Allergy Asthma Immunol. 2022. https://doi.org/10.1016/j.anai.2022.04.028. Epub 2022/05/03. PubMed PMID: 35500864.

11. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: is a modification needed? J Allergy Clin Immunol Pract. 2017;5(1):58-62.e5. https://doi.org/10.1016/j.jaip.2016.11.009. Epub 2017/01/10. PubMed PMID: 28065342.

12. Passalacqua G, Nowak-Wegrzyn A, Canonica GW. Local side effects of sublingual and oral immunotherapy. J Allergy Clin Immunol Pract. 2017;5(1):13–21. https://doi.org/10.1016/j.jaip.2016.06.020. Epub 2016/08/17. PubMed PMID: 27527548.

13. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee AAoAA, Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. J Allergy Clin Immunol. 2004;113(6):1129–36. https://doi.org/10.1016/j.jaci.2004.02.006. Epub 2004/06/23. PubMed PMID: 15208595.

14. Jutel M, Kosowska A, Smolinska S. Allergen immunotherapy: past, present, and future. Allergy Asthma Immunol Res. 2016;8(3):191–7. https://doi.org/10.4168/aair.2016.8.3.191. PubMed PMID: 26922928; PubMed Central PMCID: PMCPMC4773206.

15. DuBuske L. Efficacy and safety of sublingual allergen immunotherapy. Allergy Asthma Proc. 2022;43(4):272–80. https://doi.org/10.2500/aap.2022.43.220036. Epub 2022/07/13. PubMed PMID: 35818141.

16. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2014;133(3):751–8. https://doi.org/10.1016/j.jaci.2013.10.041. Epub 2013/12/18. PubMed PMID: 24332263.

17. Passalacqua G, Compalati E, Canonica GW. Sublingual immunotherapy: clinical indications in the WAO-SLIT Position Paper. World Allergy Organ J. 2010;3(7):216–9. https://doi.org/10.1097/WOX.0b013e3181e8d19c. Epub 2010/07/01. PubMed PMID: 23282652; PubMed Central PMCID: PMCPMC3651141.

18. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy. 2012;67(3):302–11. https://doi.org/10.1111/j.1398-9995.2011.02761.x. Epub 2011/12/14. PubMed PMID: 22150126.

19. Senti G, Freiburghaus AU, Larenas-Linnemann D, Hoffmann HJ, Patterson AM, Klimek L, et al. Intralymphatic immunotherapy: update and unmet needs. Int Arch Allergy Immunol. 2019;178(2):141–9. https://doi.org/10.1159/000493647. Epub 2018/11/06. PubMed PMID: 30391954.

20. von Moos S, Kundig TM, Senti G. Novel administration routes for allergen-specific immunotherapy: a review of intralymphatic and epicutaneous allergen-specific immunotherapy. Immunol Allergy Clin North Am. 2011;31(2):391–406. https://doi.org/10.1016/j.iac.2011.02.012. Epub 2011/05/03. PubMed PMID: 21530827.

21. Wang Y, Kong Y, Wu MX. Innovative systems to deliver allergen powder for epicutaneous immunotherapy. Front Immunol. 2021;12:647954. https://doi.org/10.3389/fimmu.2021.647954. Epub 2021/04/13. PubMed PMID: 33841430; PubMed Central PMCID: PMCPMC8033039.

22. Scheurer S, Toda M. Epicutaneous immunotherapy. Allergol Immunopathol (Madr). 2017;45(Suppl 1):25–9. https://doi.org/10.1016/j.aller.2017.09.007. Epub 2017/11/08. PubMed PMID: 29108765.

23. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clin Exp Allergy. 2011;41(9):1177–200. https://doi.org/10.1111/j.1365-2222.2011.03794.x. Epub 2011/08/19. PubMed PMID: 21848757.

24. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy. 2010;40(6):922–32. https://doi.org/10.1111/j.1365-2222.2009.03448.x. Epub 2010/01/27. PubMed PMID: 20100188.

25. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. Pediatr Allergy Immunol. 2017;28(1):18–29. https://doi.org/10.1111/pai.12661. Epub 2016/09/23. PubMed PMID: 27653623.

26. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E, et al. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61(Suppl 82):1–20. https://doi.org/10.1111/j.1398-9995.2006.01219_1.x. Epub 2006/08/26. PubMed PMID: 16930249.

27. Tankersley M, Han JK, Nolte H. Clinical aspects of sublingual immunotherapy tablets and drops. Ann Allergy Asthma Immunol. 2020;124(6):573–82. https://doi.org/10.1016/j.anai.2019.12.025. Epub 2020/01/11. PubMed PMID: 31923544.

28. Perez NR, Moreno MDJA. Safety of immunotherapy and skin tests with allergens in children younger than five years. Rev Alerg Mex. 2006;53(2):47–51 Epub 2006/08/04. PubMed PMID: 16884027.

29. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. Ann Allergy Asthma Immunol. 2008;101(1):96–100. https://doi.org/10.1016/S1081-1206(10)60841-1. Epub 2008/08/07. PubMed PMID: 18681091.

30. Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol. 2011;127(1):57–63. https://doi.org/10.1016/j.jaci.2010.10.025. Epub 2011/01/08. PubMed PMID: 21211641.

31.• Nelson HS. Future directions in allergen immunotherapy. Allergy Asthma Proc. 2022;43(4):356–62. https://doi.org/10.2500/aap.2022.43.210098. **This review listed several approaches that seem to have the best chance of becoming available in the next few years of AIT.**

Allergic Rhinitis Quiz

1. Up to **14-40** percent (variable depending on reference) of children have allergic rhinitis.

2. Match the finding with the **cause of rhinitis**:

1) Rhinorrhea, congestion and fever **E**	A) Rhinitis Medicamentosa
2) Chronic mouth-breathing, nasal obstruction/discharge, unresponsive to therapy **D**	B) Allergic Rhinitis
3) Sneezing, nasal congestion, nasal/ocular pruritis **B**	C) Nasal Foreign Body
4) Overuse of topical decongestants **A**	D) Adenoid Hypertrophy
5) Unilateral purulent nasal discharge **C**	E) Acute Viral Rhinitis

3. Name **3 co-morbidities** of allergic rhinitis:
Asthma, sinusitis, OM, snoring/disrupted sleep, impaired school performance, emotional/ behavioral disturbances, craniofacial anomalies (palatal arch, incr facial length, flat mid-face).

4. Place the following **antihistamines** in the correct categories below:

1st generation H1 blockers:
diphenhydramine (Benadryl), cyproheptadine (Periactin), hydroxyzine (Atarax)
2nd generation H1 blockers:
fexofenadine (Allegra), loratadine (Claritin), azelastine (Astelin), cetirizine (Zyrtec)

What advantage do 2nd generation H1 blockers have over 1st generation H1 blockers?
2nd generation H1 blockers have little to no sedation effect.

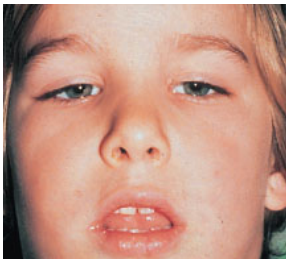
5. All of the following statements below are true except:
   A. Children who have one aspect of atopy (AR, eczema or asthma) have two-times the risk of developing a second atopic condition.*
   B. AR typically begins in childhood and improves in older adults.
   C. 50% of children with chronic otitis media with effusion also have AR.
   D. Inhaled nasal corticosteroids are the first-line treatment for AR.

* They have three-times the risk.

6. List **4 indications** for "allergy testing".
Asthma, chronic rhinosinusitis, chronic otitis media, atopic dermatitis *(see Table 2 for more)*

What do these conditions have in common?
All are diseases of IgE-mediated sensitization (Gell and Coombs Type I reactions).

What are the clinical implications of a positive allergy test?
Results can be used to prescribe specific allergen avoidance and/or immunotherapy.



Allergic Rhinitis *Mega*-Case

Stu Stuffy is a 4 year old boy who presents for his 3rd visit in the last 3 months for nasal congestion. His mother reports that he has had nasal congestion “all the time” since they moved to the D.C. area from California 6 months ago and she thinks he needs antibiotics. At prior visits he was diagnosed with viral upper respiratory infections.

His mother admits that he has 1 to 2 days/week where his symptoms seem to be improving, then his symptoms will return. Stu’s main complaint today is "I can't breathe out of my nose". He has not had any recent fever, vomiting, diarrhea or rash. He occasionally has episodes of non-productive cough, especially upon waking in the morning, and has been more "tired-appearing" over the last 6 months.

What is your differential diagnosis for his persistent nasal congestion? What additional history will you obtain?

Differential diagnosis: Allergic rhinitis, infectious rhinitis/sinusitis, nasal foreign body, anatomical abnormalities, Rhinitis medicamentosa

Additional history desired: PMHx (especially atopy history), Family Hx of atopy, Social Hx (pets, secondhand smoke exposure, home environment), Medication Hx (using nasal decongestants?), Allergy Hx

Mrs. Stuffy reports that Stu has a history of eczema as an infant that occasionally required 1% topical hydrocortisone, but he has not had any flares recently. He is not taking any medications and does not have any known allergies. Mrs. Stuffy reports that she had asthma as a child. There is no additional family history of atopy and Stu is an only child.

On social history you find out that Mrs. Stuffy used to smoke cigarettes around Stu when he was younger, but quit 2 years ago. They live in a single-level carpeted home and have central air-conditioning/heating, but they have not been using it recently because of the beautiful D.C. Spring weather. They have an indoor cat, “Furball”, at home that sleeps in Stu's bed at night, but have had him for 3 years.

What signs on physical exam would suggest AR over other diagnoses?

"Allergic shiners" (dark circles under eyes), "Allergic salute" (upward rubbing of nose with open palm), “Allergic gape” (continuous open-mouth breathing), Dennie-Morgan lines (extra skin folds on lower eyelids); cobble-stoning of posterior pharynx; pale/blue nasal mucosa; boggy nasal turbinates; conjunctival edema, hyperemia, or tearing.

** Note that absence of these PE findings does not exclude allergic rhinitis as a diagnosis.*

During your encounter you note that Stu is frequently wiping his nose with the palm of his hand. On your exam you find that he has darkening of his lower eyelids, a single linear crease on his nasal bridge, cobble-stoning of his posterior pharynx, pale blue nasal mucosa and boggy nasal turbinates on exam. The remainder of his exam is unremarkable.

What is your suspected diagnosis and what will be your treatment plan? Would your plan change if Stu was 2 years old?
Allergic rhinitis

Treatment Plan:

- Inhaled nasal steroids like Nasonex (Mometasone) or Flonase (Fluticasone) are first line therapies for AR and have been shown to provide the greatest relief of symptoms.
- Could also consider using a 2nd generation oral or nasal antihistamine as needed for symptoms or as a daily scheduled medication.
- Nasal decongestants are *not* recommended as a regular medication due to potential rebound effect and decreased efficacy compared to inhaled nasal steroids and PO antihistamines.
- Leukotriene agonists have *decreased efficacy* compared to inhaled nasal steroids and antihistamines, but can be used as an adjunct to therapy, especially if the patient has asthma.
- For children under 4 years old treatment options are more limited. Nasonex and fluticasone furoate (brand name Flonase Sensimist is FDA approved down to age 2 years. Since we do not have it on formulary, some providers will prescribe regular Flonase to younger children after a discussion of risks and benefits with parents.

Mrs. Stuffy is concerned about the potential systemic effects of inhaled nasal steroids**. What are the main side effects of inhaled nasal steroids?**

- Nasal steroids have *not* been shown to permanently adversely affect linear growth when used alone and no additional suppression of the hypothalamic-pituitary axis has been shown when both inhaled and intranasal corticosteroids are used.
- The most common side effect of inhaled nasal steroids is nasal mucosal thinning and nose-bleeds, which can be avoided by administering the medication pointing towards the ear instead of the nasal septum.

You have 5 more minutes left in your encounter to discuss allergen abatement measures.
What tips will you give Stu's mother to help decrease his exposure to common allergens?
BONUS: What are the three most common indoor/perennial allergens?

- Common perennial allergens: dust mites, pet dander, cockroach spores, mold spores
- Remove pets in the bedroom at night
- Decrease dust mite exposure by...
    - Limit the number of stuffed animals in the bed and wash them regularly
    - Wash bed linens in hot water weekly
    - Use hypoallergenic covers on mattresses and pillows
    - Vacuum carpets weekly, or get rid of carpeting
    - Consider buying a dehumidifier for the home -- dust mites like humid conditions
- Keep air conditioner on during the Spring/Fall to limit pollen/aero-antigen exposure
- Clean areas prone to mold with a bleach solution.

** Improvement should be seen within weeks of allergen removal*

One month later, Stu returns for follow-up. Mrs. Stuffy reports that she has been giving Stu Zyrtec and Flonase daily, but he is still having some symptoms. She has taken most of your allergen avoidance recommendations, except for kicking Furball out of Stu's bed since the cat helps Stu go to sleep. Mrs. Stuffy asks whether you can test Stu so she will know "for sure" that he is allergic to Furball. **What is your response?**

Because of his chronic rhinosinusitis, you could consider referring Stu to Allergy-Immunology to test for **allergen-specific IgE mediated sensitization** (e.g. cats, in addition to common perennial allergens). Explain to mom that allergy-testing does not diagnose a specific disease, but assesses for trigger factors when performed for clinically-relevant exposures.

What are the 2 most common methods of allergy testing and how do they compare?

	Skin Testing	**Serum Testing**
Types	Epicutaneous (prick & puncture) Intradermal (for low-potency extracts)	ImmunoCAP (CAP-RAST)
Speed	Fast: results in 15-20min	Requires lab processing
Price	Less expensive	More expensive
Sensitivity	More sensitive- measures allergen-specific IgE bound to mast cells in skin	Less sensitive- measures allergen-specific IgE in serum
Confounds	Dermatographism (false-pos) Recent use of H1/H2 blockers, steroids Infants < 2yrs (false-neg) Chronic disease (false-neg) Extensive atopic derm (false neg)	Available assays differ in their performance characteristics. Can be performed in infants and young children.
Setting	Requires trained, experienced personnel	Can be done in Gen Peds office, but requires expertise to interpret.

Allergic Rhinitis Board Review

1. In early May, a 12-year-old girl comes to your office with symptoms of rhinitis, congestion, and fatigue most mornings, but says she is well by midday. The symptoms have been occurring for the past 3 weeks, which coincides with the start of tree pollen season. An oral antihistamine and intranasal steroid are being used appropriately and have provided incomplete benefit. She wants to do something now that can improve her symptoms for this season.

Of the following, your BEST option is to:
A. begin allergy immunotherapy
B. begin antileukotriene monotherapy
C. change her intranasal steroid
D. change her oral antihistamine
E. recommend she close her bedroom windows

The girl described in the vignette clearly has seasonal allergic rhinitis. The mainstays of treatment are allergen avoidance, antihistamines, intranasal steroids, and allergen immunotherapy. Oral antileukotriene therapy is another treatment modality and its efficacy is similar to that of oral antihistamines.

The most appropriate intervention for this patient at this time is to close her bedroom windows, which will provide immediate effective therapy. Her morning symptoms probably are due to pollination of most trees late at night. In this child, efforts to reduce the pollen entering her bedroom may be helpful, although, other children who have allergies may require more extensive efforts to provide environmental control measures in their home. She improves by midday because of lessening allergen exposure.

Allergy immunotherapy can also be of benefit, but it may take up to 2 years to produce symptomatic relief. Some patients improve dramatically in as few as 6 months, but that is not typical. Changing the patient's therapy to antileukotriene monotherapy would not be of particular benefit because antileukotriene therapy has similar efficacy to antihistamines. Therefore, it is unlikely that this one medication could replace the oral antihistamine *and* the intranasal steroid. The child may benefit from the addition of antileukotriene therapy, but then she would be receiving 3 medications. Changing her oral antihistamine or intranasal steroid is unlikely to cause a dramatic difference. Clearly some patients respond better to one therapy than another, but it is unlikely for a child to have a significant improvement with a change in antihistamine or intranasal steroid.

2. A 5-year-old girl presents with rhinitis, congestion, and sneezing of several months' duration. Antihistamine therapy has been somewhat helpful, but the girl still has symptoms. You have recommended removing the stuffed animals from her bed and closing the bedroom windows. There are no animals in the home, but some relatives do have pets.

Of the following, the BEST next step is to:
A. add an intranasal steroid to her regimen
B. begin antileukotriene therapy
C. change the type of antihistamine
D. not allow the child to visit her relatives
E. order immediate-type skin testing

The girl described in the vignette has classic allergic rhinitis. The mainstay for therapy is avoidance of the allergen, followed by medication and possibly allergen immunotherapy. Oral antihistamines, intranasal steroids, and antileukotriene medications are helpful medications to treat allergic rhinitis.

Because the child has been having symptoms for several months, despite routine environmental controls to eliminate pets, dust mites, and pollens as triggers, it is unlikely that any one allergen is triggering all of the symptoms. The most appropriate next step is to order immediate-type skin testing to identify the allergen trigger.

Adding an intranasal steroid or antileukotriene therapy would treat the symptoms without identifying the trigger. Changing the type of antihistamine may be somewhat effective, but it is unlikely to solve the problem because the trigger remains unknown. Not allowing the child to visit relatives may be appropriate if there is a known trigger in the relative's environment and the child was visiting them regularly, but such a step may create a burden for the family.

3. You have just assisted in the delivery of a 38-week gestational age male infant who was born via cesarean section to a 25-year-old woman. As you are completing the infant's initial physical examination, the father mentions that he and his wife have allergic rhinitis and asthma. He asks whether his son is at increased risk for allergies and how they can reduce the boy's chance for developing such allergic disorders.

Of the following, the MOST appropriate next step is to
A. explain that because both parents have asthma, breastfeeding will not reduce the risk of eczema
B. explain that breastfeeding or formula choices do not matter now because the mother did not restrict her diet during pregnancy
C. measure the cord blood immunoglobulin E concentration to help establish the newborn's risk for atopic disorders
D. recommend exclusive breastfeeding for 4mo with addition of a hypoallergenic formula if needed
E. start the newborn on a cow milk formula for the first month, then switch to strict breastfeeding if he develops eczema

PREP 2009 Answer: The incidence of atopy (allergic rhinitis, asthma, eczema) has increased significantly over the past few decades. The ability to intervene and either delay or prevent atopic disease in infants born to atopic parents has been the subject of numerous studies. Application of these studies to the population as a whole is difficult because the specific interventions and endpoints for each study often differ. However, one aspect that is agreed on is that atopy risk for infants increases significantly when both parents have a history of atopy (30% to 60%) compared with a history for just one parent (20% to 40%) or neither parent (10% to 15%).

Prior to delivery, two prevention strategies have been studied: maternal diet restriction and supplementation with probiotics. Currently, no evidence supports maternal dietary restriction to common allergenic foods. Some studies have supported administration of probiotics (eg, *Lactobacillus rhamnosus*) to the mother 2 to 4 weeks before delivery and to the infant for 6 months after birth. One study demonstrated a reduction in eczema at 2 years but no reduction in asthma, immunoglobulin (Ig) E concentrations, or allergen sensitization. Further, the dose and type of probiotic has differed in various investigations, making generalized recommendations difficult.

Even if both parents have atopy, as described in the vignette, breastfeeding or formula choices may affect atopy outcomes for the infant. In "high-risk" newborns (ie, both parents have atopy or one parent and one sibling have atopy), the American Academy of Pediatrics Committee on Nutrition recommends exclusive breastfeeding for at least 4 months, with supplementation of a hypoallergenic formula if needed. Although it is difficult to compare studies because the duration of breastfeeding and atopic outcome (ie, eczema, allergic rhinitis, asthma) differ, breastfeeding for at least 3 months reduces the risk for eczema. The protective benefit becomes more complex when controlling for the specific maternal atopic condition. For "high-risk" infants born to women who choose not to breastfeed, most studies and experts support starting

an extensively hydrolyzed formula. Starting a cow or soy milk formula, compared with an extensively hydrolyzed formula, increases the risk for early eczema. Or note, interventions resulting in decreased atopy early in life may not predict later atopic outcomes.

Cord IgE concentrations can be used to assess a newborn's risk for atopy, but its measurement currently is not recommended as a routine screening tool. Furthermore, because both parents in the vignette have a history of atopy, the child already is considered "high risk." The ability to predict atopy based on cord IgE concentrations also depends on the cutoff value used. In one study, 80% of newborns whose cord IgE concentrations were greater than 0.9 kU/L subsequently developed atopy by 5 years of age, but the specific IgE value did not correlate with atopy severity.

4. You are evaluating a 14-year-old girl for seasonal allergic rhinitis. Despite a regimen of multiple allergy medications, she continues to have significant sneezing, rhinorrhea, and nasal congestion. You decide to evaluate for possible allergic triggers and discuss the advantages and disadvantages of allergy skin testing and blood testing.

Of the following, a TRUE statement regarding allergy skin and blood testing is that
A. infants younger than 1 year of age cannot undergo skin testing
B. patients may experience anaphylaxis during aeroallergen or food skin testing
C. patients need to fast prior to blood allergy testing
D. patients need to stop their antihistamines prior to blood allergy testing
E. the negative predictive value of aeroallergen skin testing is poor

Two primary diagnostic tools are used to determine the role of indoor and outdoor aeroallergens as triggers for allergic rhinitis or allergic asthma: skin testing and blood testing. Aeroallergen skin testing involves the application of specific allergens (eg, oak, Bermuda grass, cat, ragweed) on the skin, typically using a prick or puncture method. Although sometimes uncomfortable for infants and toddlers, allergy skin testing is tolerated extremely well by most children and adolescents and can be performed at any age. The advantages of skin testing are that a broad array of allergens can be tested, testing materials are inexpensive, and results are immediately evident to the patient. One disadvantage is that patients must stop their antihistamine medication(s) 1 week prior to skin testing. Also, although most patients tolerate the local pruritus experienced at "positive" skin test sites, those who are very sensitive (eg, severe food anaphylaxis) may experience a systemic reaction with even a simple skin test. For patients who have a history of severe anaphylaxis to a specific allergen, allergists may choose to perform serum (Ig) E testing instead of skin testing because blood testing does not have a risk for anaphylaxis.

In the past, serum IgE testing employed primarily the radioallergosorbent test (RAST) method. Because of the significant variability in results between laboratories, RAST has been replaced in most institutions with the more sensitive and reproducible CAP-system fluorescein enzyme immunoassay. This system uses a cellulose matrix system. The advantage of serum IgE testing is that it is not affected by medications (ie, patients do not need to stop an antihistamine). Patients do not need to fast prior to either allergy skin or blood testing.

While ongoing studies are comparing the sensitivity and specificity of skin testing compared with the CAP system fluorescein enzyme immunoassay, skin testing is regarded as more sensitive and specific. Finally, although skin testing is considered "inexpensive," most general pediatricians find the cost of an allergy consultation with skin testing to be more expensive than a routine battery of serum IgE tests for aeroallergens or food. The availability and clinical application of serum IgE testing continues to expand, but clinicians who do not seek allergy consultation should be comfortable with interpretation and application of test results for a specific clinical scenario (eg, a wheat IgE of 10 kU/L in a patient who has atopic dermatitis has little to no clinical significance).