NCC Pediatrics Continuity Clinic Curriculum: **Allergic Rhinitis**

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)*
- AAP Section on Allergy & Immunology—provider & parent resources
- "Treatment of Allergic Rhinitis" *(American Family Physician, 2015)*
- "Allergic Rhinitis" *(PIR, 2023)*
- **Resources for Patients/Parents:**
    - Patient Handout Allergic Rhinitis
    - www.acaai.org – American College of Allergy, Asthma & Immunology
    - www.healthychildren.org – articles about allergies under "Health Issues"

Allergic Rhinitis in Children and Adolescents

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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**).

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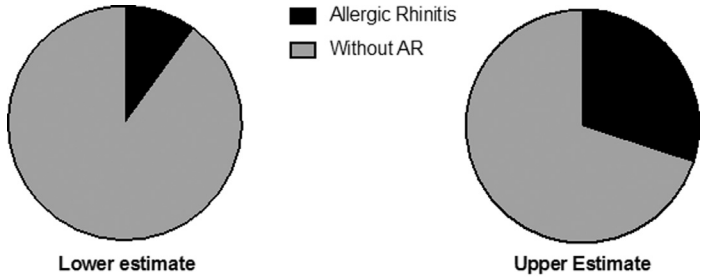

Fig. 1. AR prevalence estimate range worldwide in developed countries.

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.

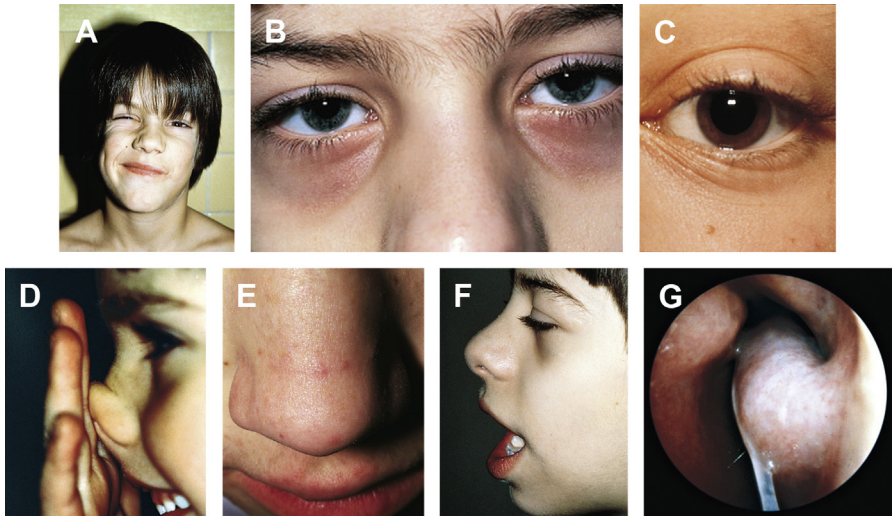

Fig. 2. The pathophysiology of AR results in typical examination findings illustrated here. See text for full descriptions. (*A*) Facial grimacing or twitching. This is related to nasal itching. (*B*) Allergic shiners. (*C*) Dennie-Morgan lines. (*D*) The allergic salute. (*E*) Nasal creasing related 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.

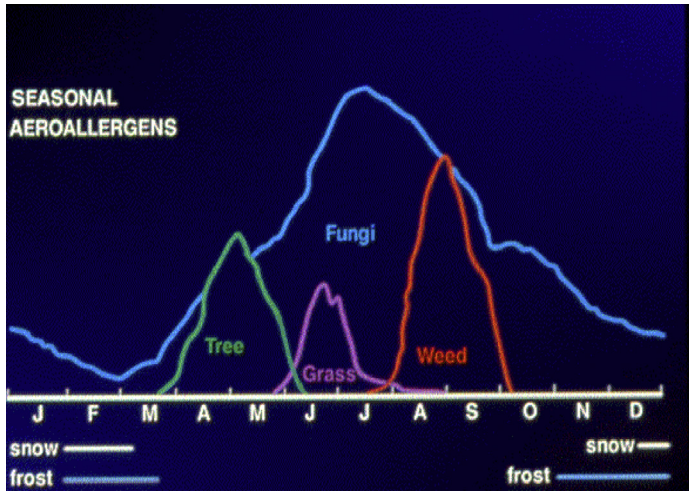

Fig. 3. Representative seasonal aeroallergen counts for Ann Arbor, MI. (*Courtesy of* WR. Solomon, MD, Ann Arbor, MI.)

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.

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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

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

Recent Updates of Immunotherapy for Allergic Rhinitis in Children

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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*

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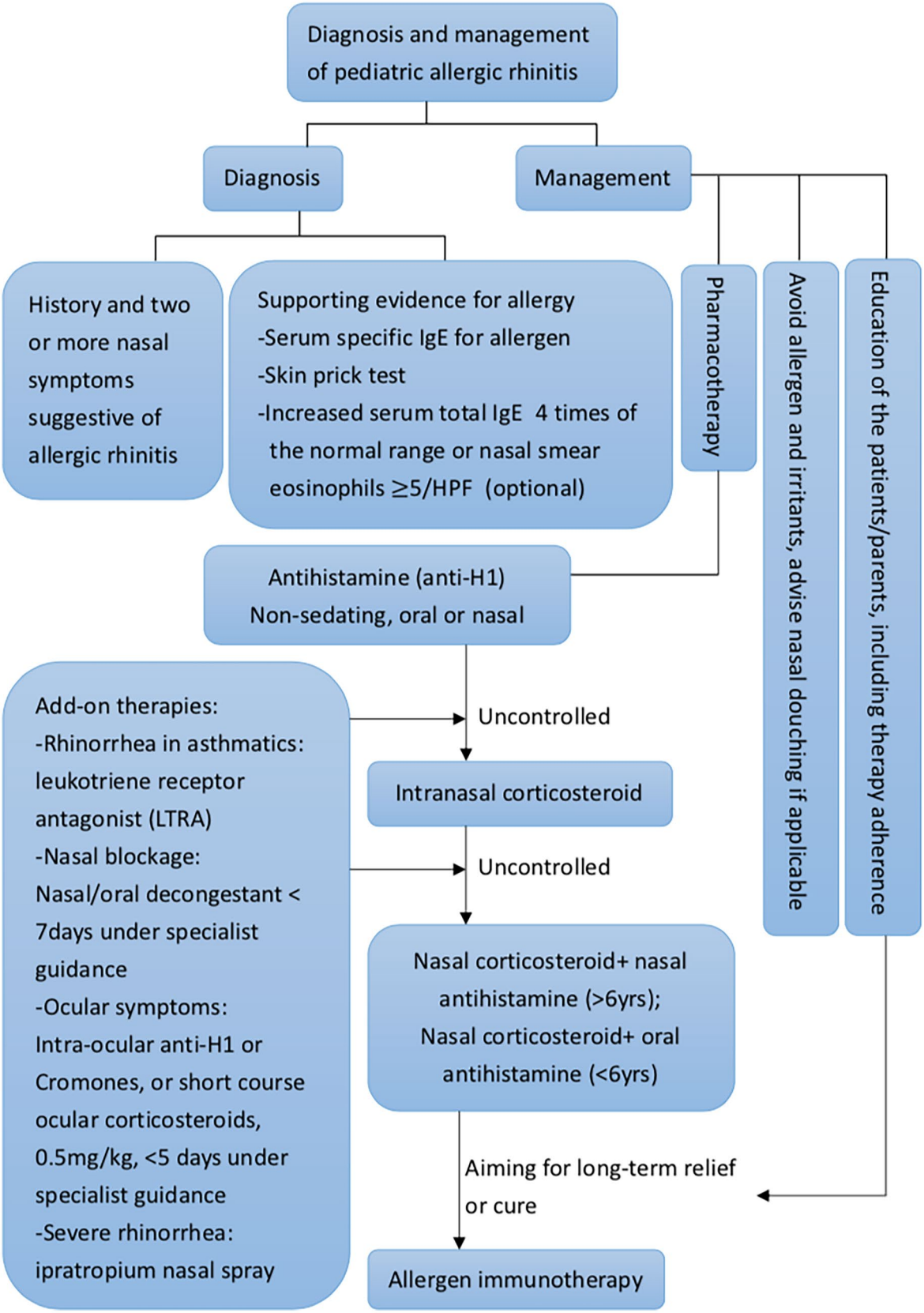

Fig. 1 Pediatric allergic rhinitis diagnosis and management algorithm. HPF, high power field; IgE, immunoglobulin E

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.

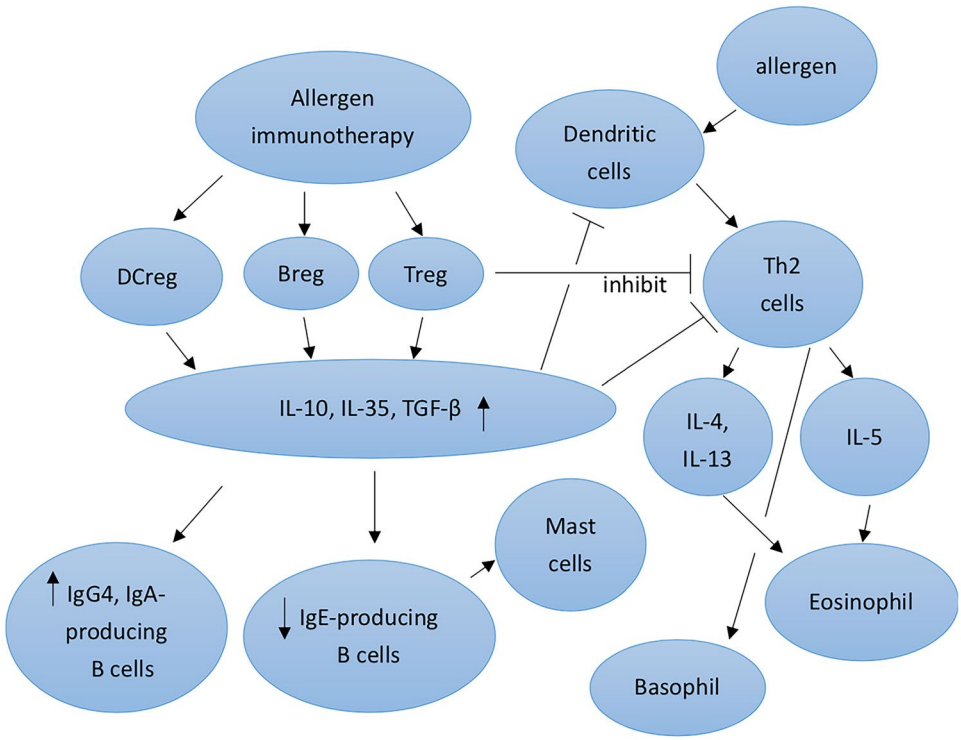

Fig. 2 Mechanism of allergen immunotherapy

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.

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•• Of major importance

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Allergic Rhinitis Quiz

1. Up to _____ percent children have allergic rhinitis.

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

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

3. Name **3 co-morbidities** of allergic rhinitis:

4. Place the following **antihistamines** in the correct categories below: diphenhydramine (Benadryl), fexofenadine (Allegra), cyproheptadine (Periactin), loratadine (Claritin), hydroxyzine (Atarax), azelastine (Astelin), cetirizine (Zyrtec)

   1st generation H1 blockers:

   2nd generation H1 blockers:

   What advantage do 2nd generation H1 blockers have over 1st generation H1 blockers?

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.

6. List **4 indications** for "allergy testing".

   What do these conditions have in common?

   What are the clinical implications of a positive allergy test?

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?

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?

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 were 2 years old?

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

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?

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?**

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

	_____	_____
Types		
Speed		
Price		
Sensitivity		
Confounds		
Setting		

Ask Your Neighborhood Allergist: Which allergy tests, if any, would you perform in Stu?

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

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

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 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 w/ addition of 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

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