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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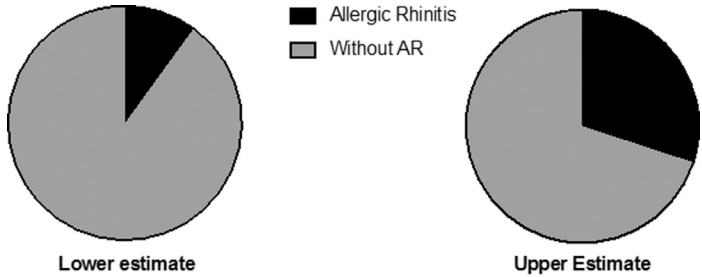

Fig. 1. AR prevalence estimate range worldwide in developed countries.

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.

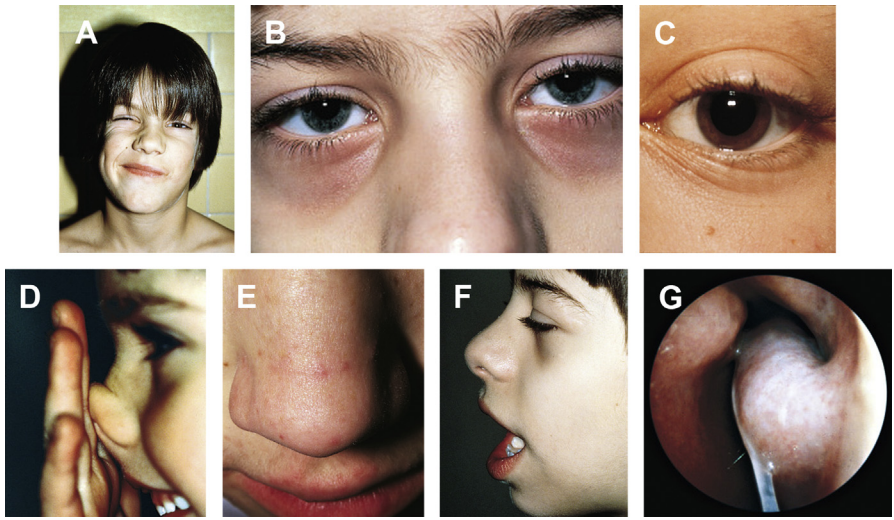

Fig. 2. The pathophysiology of AR results in typical examination findings illustrated here. See text for full descriptions. (*A*) Facial grimacing or twitching. This is related to nasal itching. (*B*) Allergic shiners. (*C*) Dennie-Morgan lines. (*D*) The allergic salute. (*E*) Nasal creasing related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

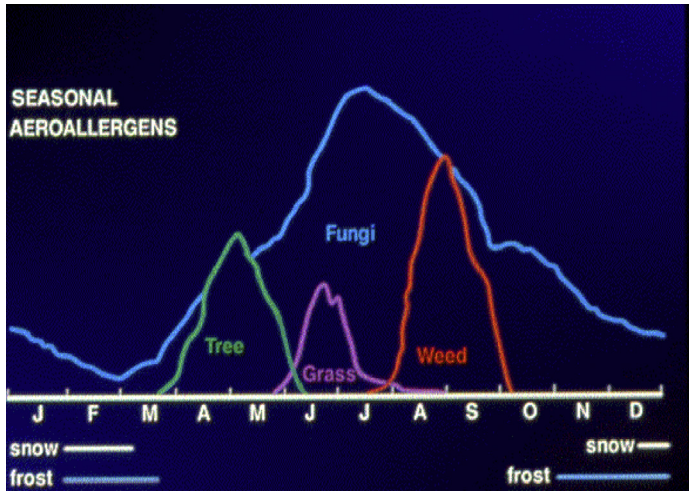

Fig. 3. Representative seasonal aeroallergen counts for Ann Arbor, MI. (*Courtesy of* WR. Solomon, MD, Ann Arbor, MI.)

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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