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
- "Who Needs Allergy Testing and How to Get It Done" *(PIR, 2006)*

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)*
- AAP Section on Allergy & Immunology—provider & parent resources
- Treatment of Allergic Rhinitis *(American Family Physician, 2015)*
- Update on Allergic Rhinitis *(PIR, 2005)*
- **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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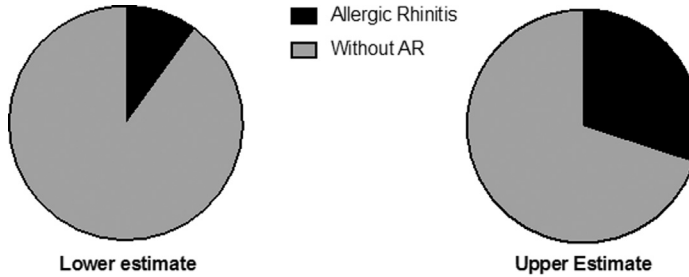

Fig. 1. AR prevalence estimate range worldwide in developed countries.

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.

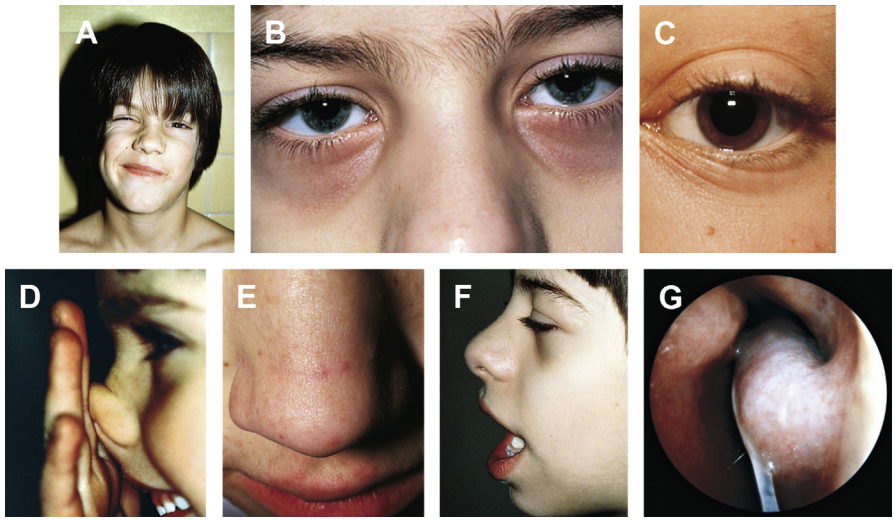

Fig. 2. The pathophysiology of AR results in typical examination findings illustrated here. See text for full descriptions. (*A*) Facial grimacing or twitching. This is related to nasal itching. (*B*) Allergic shiners. (*C*) Dennie-Morgan lines. (*D*) The allergic salute. (*E*) Nasal creasing related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

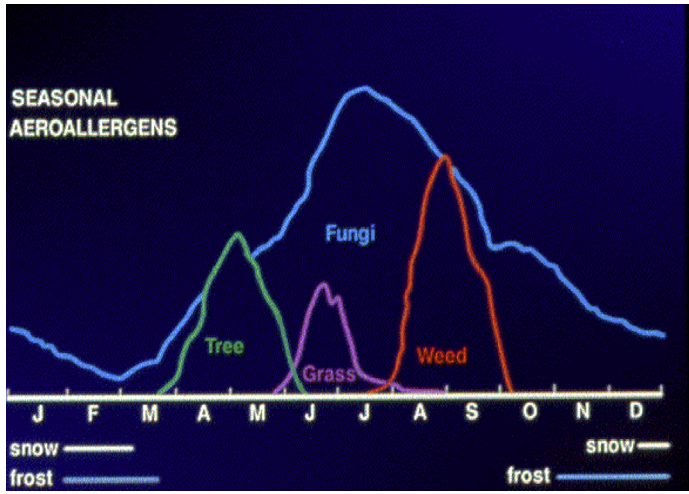

Fig. 3. Representative seasonal aeroallergen counts for Ann Arbor, MI. (*Courtesy of* WR. Solomon, MD, Ann Arbor, MI.)

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

CONSULTATION WITH THE SPECIALIST

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Who Needs Allergy Testing and How to Get It Done

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Objectives

After completing this article, readers should be able to:

1. Understand the indications for immunoglobulin E allergy testing in patients who have allergic disorders.
2. Discuss advantages and disadvantages of different allergy tests.
3. Recognize factors that can influence allergy test results.

Case Studies

Patient 1

A 15-year-old girl whom you have been following since birth is rushed to the local emergency department (ED) following dinner at the family's favorite restaurant. During the meal, she developed facial flushing, acute urticaria, vomiting, and diarrhea. In the ED, she is given epinephrine and diphenhydramine, and the symptoms resolve. At a follow-up visit the next day in your office, the girl's mother informs you that her daughter had eaten cashew-crusted tuna with a serving of fresh fruit, including mango, papaya, and kiwi.

Patient 2

A 4-year-old boy is playing outside and is stung by an unidentified insect. He runs inside crying, and his mother cleans the sting site on his hand. Over the next 2 hours, the hand and distal forearm become red, swollen, and pruritic. His mother takes him to a local ED. He is given diphenhydramine and parenteral corticosteroids and is observed for several hours. Several days later, the ED calls the mother to report that a honeybee venom allergy test performed in the ED is positive at a level of 2.3 kU/L.

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Allergies and Allergy Testing

Immunologic reactions traditionally are classified by using the Gell and Coombs system (Table 1). This simple scheme is useful for learning and thinking about different mechanisms of immunopathology, although a medical condition in an individual patient might involve more than one of the mechanisms. Reactions involving immunoglobulin (Ig)E-mediated immediate hypersensitivity are called type I. Cytotoxic reactions that are Ig-mediated are called type II. Mechanisms involving immune complexes are type III, and type IV reactions are delayed hypersensitivity reactions mediated by T cells. Antigen-specific tests are available clinically for investigation of type I and type IV immunopathology.

The classic allergy testing methods of skin testing and serum-specific IgE measurement merely test for the presence of allergen-specific IgE, the primary mediator of Gell and Coombs type I reactions. Allergen-specific IgE is either detectable (a "positive" allergy test) or not (a "negative" allergy test).

In clinical practice, the role of allergy testing is not always clear because the term "allergy" has multiple meanings for patients, parents, and health-care personnel. A small child might inform school authorities that he is "allergic" to broccoli, meaning

Table 1. The Gell and Coombs Classification of Immunologic Mechanisms

Class	Descriptive Term	Mechanism	Clinical Example
Type I	Immediate hypersensitivity	IgE	Anaphylaxis
Type II	Cytotoxic	Cell-bound IgG or IgM	Hemolytic anemia
Type III	Immune complex	IgG or IgM	Vasculitis
Type IV	Delayed hypersensitivity	T lymphocytes	Contact dermatitis

Ig=immunoglobulin
Adapted from Coombs PR, Gell PG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR, ed. *Clinical Aspects of Immunology.* Oxford, England: Oxford University Press; 1968:575–596.

that he doesn't like the taste. To a lay person, "allergy" might indicate some sort of adverse reaction, such as bloating and abdominal pain due to lactose intolerance but inappropriately called "milk allergy." In either case, IgE allergy testing would not be helpful. Even in medical circles, the term "allergies" might be synonymous with "seasonal allergic rhinitis." The European Academy of Allergology and Clinical Immunology (EAACI) defines allergy as "a hypersensitivity reaction initiated by immunologic mechanisms." This broad definition might encompass any of the Gell and Coombs mechanisms. The EAACI defines hypersensitivity as a state that causes objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by healthy individuals. Such definitions are precise and academically useful, but not practical. Thus, a discussion of allergy testing requires precise definitions.

Understanding Allergy Testing

Certain diseases may be associated with IgE-meditated sensitization to allergens. The classic "diseases of immediate hypersensitivity" include atopic dermatitis, asthma, and chronic rhinosinusitis. These three components of the "atopic march" tend to occur together in individuals and in families. IgE also can play a role in some cases of anaphylaxis and urticaria, in certain gastrointestinal disorders, and in a few other well-characterized conditions. In each of these disorders, there is an "allergic" and a "nonallergic" form. IgE allergy testing reveals clinically relevant allergen-specific IgE sensitization in some individuals and no evidence of specific IgE in others. Clinical history alone does not allow discernment between the allergic and nonallergic forms of the conditions, although the history can identify potential triggers warranting investigation. Even in a symptomatic individual, a positive test result does not necessarily have cause-and-effect clinical relevance.

The presence of allergen-specific IgE-mediated sensitization is not a disease state. IgE is a tissue-bound immunoglobulin class. It normally is present in the serum in nanogram amounts, in an equilibrium with that bound to mast cells, basophils, and other cells. In an otherwise healthy person, selective IgE deficiency (an undetectable total IgE concentration) is very rare. Thus, skin testing or specific IgE immunoassay can identify IgE-mediated allergen sensitization in about 15% of healthy, "wheeze-free, sneeze-free" individuals tested. Under these circumstances, the test result is not false-positive. Rather, the test result is not clinically relevant at the time. In long-term follow-up, such individuals are at greater risk of developing disease symptoms than are individuals who have negative test results.

For some other conditions (such as celiac disease) that are associated with exogenous substances (such as wheat gluten), "allergy" is blamed, but the mechanism does not involve IgE. In such situations, allergy testing is not indicated.

Patch testing is the time-honored method for identifying antigens in patients who have contact dermatitis and certain other conditions that involve Gell and Coombs type IV mechanisms. Contact dermatitis sometimes is called "contact allergy," and the antigens that trigger contact dermatitis sometimes are called "allergens." Patch testing traditionally has been the purview of dermatologists, but an increasing number of allergist-immunologists have training in contact dermatitis and patch testing.

In other situations, there are so-called "allergy tests" for mechanisms other than IgE-mediated immediate hypersensitivity. These tests are either "unproved" (should only be used in the context of a peer-reviewed clinical investigation) or "disproved" (should not be used at all).

Failure to recognize the previously noted concepts has resulted in a complex modern mythology surrounding allergy and allergy testing. In some cases, there are expectations that allergy testing should identify sensitization to smoke and perfumes (respiratory irritants) for a person who has chronic rhinitis or asthma or that IgE allergy testing can identify sensitization to contact antigens such

as nickel or poison ivy for a patient who has rashes. Sometimes, legitimate IgE allergy testing is ordered inappropriately for diseases that have not been shown to be caused by IgE-related mechanisms, such as behavior disorders or multiple sclerosis.

The fundamental purpose for allergy testing is to determine whether a patient presenting to a clinician for evaluation and management of a "disease of immediate hypersensitivity" has demonstrable allergen-specific IgE. Allergy testing also is used in prescribing specific allergen avoidance and immunotherapy ("allergy shots") and in epidemiologic studies of IgE-mediated sensitization. Allergy testing conducted outside the context of a careful clinical evaluation can produce misleading results.

Who to Test and Why?

The decision to obtain allergy testing comes after the clinician has performed a history and physical examination and considered the differential diagnosis. If there is a clinical scenario consistent with an IgE-mediated disease (Table 2) and if symptoms have been severe or persistent, allergy testing may be indicated, not to diagnose disease, but to assess for trigger factors. Indiscriminate testing can provide misleading results, particularly when testing is ordered without a clinical history or for clinical situations in which testing is not indicated. For example, it is inappropriate to rely on allergy testing to diagnose new-onset asthma in a wheezing toddler. A few coincidentally positive allergy test results might delay the diagnosis of foreign body aspiration. Allergy testing only identifies allergen-specific sensitization; it does not diagnose asthma. Thus, although allergy testing is indicated as part of the evaluation of asthma, it is not useful in the *differential diagnosis* of asthma. For a child who has moderate persistent asthma, allergy testing could uncover inhalant allergy that, when treated, can improve the clinical course of the asthma.

Table 2. Diseases of Immunoglobulin E–mediated Sensitization

Classic "atopic" diseases

- Asthma
- Chronic eosinophilic rhinosinusitis, chronic otitis media
- Atopic dermatitis

Other conditions (some cases)

- Allergic conjunctivitis
- Eosinophilic gastroenteritis
- Anaphylaxis (including insect stings, food, drugs)
- Urticaria–angioedema
- Other types of adverse drug reactions
- Other types of adverse food reactions

Interpreting results of testing always takes into account the clinical scenario. A positive test result does not diagnose disease (such as asthma), and a negative test result does not refute disease. The physician who has interviewed and examined the patient must determine the clinical relevance of each test result (whether positive or negative). For example, the positive test for honeybee venom in the patient described in Case 2, who experienced a large, local reaction to a sting from an unidentified insect, has entirely different clinical significance than would the same result in another individual who has had systemic anaphylaxis following a bee sting.

One aspect of the mythology of allergy testing is the belief that infants and very small children cannot have clinically relevant allergy and cannot undergo allergy testing. Although IgE-mediated sensitization is uncommon in infants, it does occur in both ingested (food allergy) and inhalant (dust mite or animal dander) varieties, with disease expressed in the airways, the skin, or the gastrointestinal system. Pollen allergy is less common in infants and very young children because generally repeated exposure in multiple seasons is required to develop an IgE response. If an infant has a disease that can be associated with IgE-meditated allergic sensitization, allergy testing can be performed.

Who Should Order Allergy Testing?

Allergy testing is fundamentally a subspecialty procedure because of the level of complexity in medical decision making (Table 3). The American Board of Allergy and Immunology, a conjoint board of the American Board of Pediatrics and the American Board of Internal Medicine, certifies individuals in allergy-immunology upon completion of an examination following a 2- to 3-year fellowship in an accredited training program. Candidates for the examination also must be certified in pediatrics or internal medicine. In practice, most allergists see patients of all ages because allergy often is a "family affair."

Conceptually, any physician who has time to take a detailed history and the diligence to learn practical aspects of the matters listed in Table 3 could incorporate IgE allergy testing into routine practice. However, the cost of stocking extracts and keeping office personnel trained makes skin testing impractical in most general pediatric offices. Specific IgE immunoassay is an alternative, but not all laboratories report consistent results. That being said, when assistance is

Table 3. Ordering and Interpreting Allergy Tests

Cognitive aspects

- General and specific knowledge of aerobiology
- Specific local botanical knowledge
- Correlation between seasonal symptoms and aeroallergen prevalence
- Foods, food allergens, food chemistry
- Fungal, indoor, and other allergens
- Crossreactivity
- Testing methods; how to evaluate laboratory performance

Practical aspects

- Deciding whether testing is indicated
- Selecting test items from a panel of several hundred available tests
- Interpreting test results, whether positive or negative
- Acting on test results appropriately

not needed with the differential diagnosis and the allergens that need to be tested are clinically clear, the most practical approach is to send blood to a laboratory that uses a reliable method of measuring allergen-specific IgE.

Nuts and Bolts of Allergy Testing

Allergen Selection

Hundreds of allergen extracts are available for testing; selecting items for testing a given individual is part of the art of medicine. Development of allergic sensitization is a function of genetic factors, exposure, and time. Because sensitization to seasonal inhalants such as pollens generally requires exposure over multiple seasons, children younger than 3 to 4 years of age are more likely to be sensitized to perennial allergens such as foods and indoor inhalants. Appropriate testing also requires knowledge about local environmental flora so the tests ordered are clinically relevant. Testing to pollens of trees, grasses, and weeds that do not grow in the area where the patient lives will not help explain the patient's symptoms. Testing with a preset "panel" of allergens is not appropriate in infants and young children.

Types of Allergy Testing

In practice, the various types of legitimate IgE allergy testing can be classified as skin testing (in vivo) or specific IgE immunoassay (in vitro). The latter method was once called the radioallergosorbent test (RAST). Radioactive isotopes no longer are used, making the term RAST obsolete. Other methods for detecting allergen-specific IgE are primarily for research.

SKIN TESTING. Skin testing is the time-honored technique for detecting specific IgE sensitization. In skilled hands, it is fast, accurate, and precise. It provides immediate results and is more sensitive and less expensive than specific IgE immunoassays. There are epicutaneous and intradermal methods, each of which has advantages and disadvantages.

When performed properly, the epicutaneous methods are not particularly painful and, thus, are tolerated better by children. Two techniques called "prick" or "puncture" are in wide use. In general, a small drop of extract is placed on the skin, and a testing device is used to disrupt the superficial epidermal layers, allowing a small amount of the extract to enter. The wheal and flare of a positive test result, which occurs within a few minutes of test application, is obvious to patient and parents. The epicutaneous tests have sufficient sensitivity for the detection of allergy in children when potent extracts are used. The primary disadvantages of prick or puncture testing are that the numerous devices for testing have different performance characteristics and successful testing requires trained, experienced personnel.

Intradermal (ID) test methods are substantially more tedious and painful than the epicutaneous methods. In ID testing, extract is drawn into a syringe fitted with a small needle and injected into the superficial dermis, forming a small bleb. In children, ID testing usually is performed when low-potency extracts (such as venoms or drugs) are tested. ID testing is the gold standard for venoms and drugs. If clinical suspicion of sensitization for a particular allergen is high, but an epicutaneous test result is negative, some clinicians retest with an ID test using a dilute extract. This approach to testing increases sensitivity. However, the extract concentrations used for ID testing can produce irritant reactions in some individuals. ID testing also has a greater risk of provoking a systemic anaphylactic reaction than does epicutaneous testing.

CONFOUNDING FACTORS IN SKIN TESTING. In dermographism, physical trauma to the skin leads to a wheal and flare reaction, producing a false-positive test result. Certain epicutaneous methods can produce reliable results in dermographic individuals. Irritant false-positive responses are rare in epicutaneous testing, but in ID testing, concentrated extracts (stronger than 1:1,000 w/v) can yield false-positive irritant responses.

A larger variety of factors can produce false-negative results. Recent use of histamine-1 receptor antihistamines or related compounds (such as selective serotonin reuptake inhibi-

tors, tricyclic antidepressants, and phenothiazine) can be detected by history and by use of positive control substances such as histamine. Histamine-2 receptor antihistamines affect skin testing minimally; current recommendations suggest withholding them on the day of testing. The acute use of oral or topical steroids does not affect skin tests substantially, but use for more than 1 week could inhibit mast cell degranulation and might affect test results.

Medications commonly used in allergic diseases that do not affect skin tests significantly include beta-agonists, antileukotrienes, inhaled or intranasal steroids, and cromolyn. Patients should not be told to stop these before skin testing.

In allergy practice, skin testing is more sensitive and less expensive than immunoassay and provides immediately available results.

Although the skin of infants and small children is less reactive than that of children and adults, skin testing usually is possible when clinically indicated.

A potential cause of false-negative results is failure to introduce an adequate amount of allergen into the epidermis. In allergy practices that conduct periodic proficiency assessments of testing personnel, improper skin testing technique should not be a common cause of false-negative results. Other factors that could influence skin test results include certain chronic diseases (renal failure, neuropathies, and malignancies) associated with decreased skin reactivity, body location for skin test placement (the back is more reactive than the forearms), and poor extract quality. Certain food extracts tend to degrade quickly, and for some such as apple, testing with fresh fruit is preferable to testing with an extract.

SPECIFIC IgE IMMUNOASSAYS. Modern methods for detecting allergen-specific IgE in the serum are immunoassays that report quantitative results related to the World Health Organization IgE standards. A typical test report may state that short ragweed was positive at a level of 3.2 kU/L. Some methods also report semiquantitative class results that are not particularly useful. As in the case of skin testing, the available assays differ in their performance characteristics, as do the laboratories that test. Perusal of the results of the quarterly proficiency testing survey conducted by the College of American Pathologists documents these differential performance characteristics and demonstrates that individual laboratories vary in their ability to report consistent results with the same assay method.

When serum IgE immunoassays and epicutaneous skin testing are performed under optimal conditions, the results generally agree. The sensitivity of immunoassay compared with skin testing is between 80% and 100%, depending on the allergens studied and the test methods used. In allergy practice, skin testing is more sensitive and less expensive and provides immediately available results. Also, properly performed epicutaneous skin testing is less painful than phlebotomy, making it usually preferable to blood testing. In less than optimal conditions, such as the necessity for sending blood to a laboratory whose test performance is unknown or performing skin testing with an unqualified tester, allergy testing should be deferred.

Specific IgE immunoassays are indicated in several situations in allergy-immunology practice: 1) the inability to stop an antihistaminelike medication; 2) the inability to stop a medication (such as a beta blocker) that is a relative contraindication to skin testing; 3) a clinical history suggestive of great risk of a systemic reaction to skin testing; 4) lack of an adequate amount of healthy skin, as in severe atopic dermatitis; and 5) testing with some substances that are not available commercially for skin testing (eg, natural rubber latex), which necessitates the use of specific IgE measurement.

QUANTITATIVE TESTING. The fundamental question to be answered by immunoassay is whether allergen-specific IgE antibody is detectable. In carefully defined patient populations, high levels of allergen-specific IgE antibody are more likely to be associated with clinical symptoms than are low levels. The levels that provide 95% positive predictive value vary with allergen, patient age, and disease. This correlation has been investigated carefully in children who have atopic dermatitis, in whom the finding of high levels of food-specific IgE antibody obviates the need for traditional food challenges.

ALLERGY TESTING FOR FOODS. The general principles of allergy testing already described apply to patients who are suspected of having food allergy. The folklore and myths

associated with IgE and various types of "adverse food reactions" warrant special attention because "food allergy" is not a diagnosis. The clinical approach is as stated previously, including obtaining a history, performing a physical examination, and formulating a differential diagnosis. If a disease associated with food allergy, such as atopic dermatitis or eosinophilic gastroenteritis, is diagnosed, food allergy testing can be undertaken to identify specific triggers. However, particularly in atopic dermatitis, food-specific IgE may be present in patients who have no clinical symptoms from food ingestion, and inappropriate dietary restrictions can affect normal growth and development. Thus, the gold standard for assessing the relevance of a positive or negative allergy test result for patients who are suspected of having adverse food reactions remains a double-blind, placebo-controlled food challenge (DBPCFC), which is safest to perform in a medical setting and generally is not performed if the adverse reaction has been severe anaphylaxis. Because DBPCFCs are labor-intensive, open challenges are used more commonly in office settings.

OTHER TESTS USED IN CLINICAL ALLERGY. Allergen nasal provocation testing and allergen bronchial challenge are counterparts to the DBPCFC used in food allergy. The patient inhales large amounts of allergen into the nose or the lungs in an attempt to establish relevance of a positive allergy test result. Both of these tests primarily are research tools.

Discussion

Patient 1

Because the episode happened during a meal, a cause-and-effect relationship between the foods she ate and the subsequent reaction can be postulated. The fundamental question, however, relates to the nature of the reaction. The reported symptoms have some features of anaphylaxis, and the time course is consistent with that of IgE-mediated allergy. Thus, allergy testing is indicated. However, a telephone call to the restaurant to get specific details of the ingredients used revealed that some other customers who ate tuna that night had similar, but less severe, symptoms. This additional information suggests that the reaction may have been scombroid fish poisoning and lessens the likelihood of (although it does not exclude) anaphylaxis. In such a situation, skin prick testing to tuna, cashews, mango, papaya, and kiwi might be useful to reassure the patient, parents, and physician. All of this patient's skin test results were negative with good controls, and she subsequently tolerated open oral challenges to each of the foods in question. The diagnosis was probable scombroid fish poisoning.

Patient 2

The honeybee venom allergy test result is positive (the assay's lower limit of detection is less than 0.10 kU/L), and the mother is asking whether her son will need allergy shots, like his uncle. This is an example of an inappropriate use of allergy testing that has resulted in the identification of an individual who has made IgE antibody to honeybee venom, but who has not had a systemic reaction. Such individuals remain at risk for "large local" reactions in the future, but are not at substantially greater risk for anaphylaxis than is the general population. Thus, venom immunotherapy is not indicated, and the test should not have been ordered in the first place.

Summary

Allergy testing helps to determine whether IgE is playing a role in the pathogenesis of a disease of immediate hypersensitivity. History alone does not distinguish allergic from nonallergic individuals reliably. In some cases, such as mild intermittent asthma or rhinitis, distinguishing between allergic and nonallergic patients may not be important clinically. However, for patients who have persistent or acute severe symptoms, testing is indicated. Identification of allergens can allow the patient to institute appropriate avoidance measures, especially with allergy to dust mites, foods, and animals. Knowledge of pollen sensitization can predict seasonal exacerbations so therapy can be increased during these times. Finally, allergy testing can be used to initiate allergen-specific immunotherapy, a treatment that has provided substantial, proven benefit to patients for almost 100 years.

Suggested Reading

Dykewicz MS. Rhinitis and sinusitis. *J Allergy Clin Immunol.* 2003;111(suppl):S520–529

Gruchalla RS. Drug allergy. *J Allergy Clin Immunol.* 2003;111(suppl):S548-S559

Lemanske RF Jr, Busse WW. Asthma. *J Allergy Clin Immunol.* 2003;111(suppl):S502-S519

Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2003;111(suppl):S540–S547

Allergic Rhinitis Quiz

1. Up to **14-40** (variable depending on reference)percent 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).

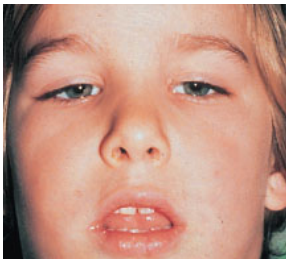
4. Place the following **antihistamines** in the correct categories below:
1st generation H1 blockers:
diphenhydramine (Benadryl), cyproheptadine (Periactin), hydroxyzine (Atarax)
2nd generation H1 blockers:
fexofenadine (Allegra), loratadine (Claritin), azelastine (Astelin), cetirizine (Zyrtec)

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 names Veramyst and Flonase Sensimist) are FDA approved down to age 2 years. Since we do not have these on formulary, many 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)	RAST *(older)* 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).