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

Goals & Objectives:

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

Pre-Meeting Preparation:

Please read the following enclosures:

- "Update on Allergic Rhinitis" *(PIR 2005)*
- "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:

- "Testing for Allergy" *(PIR, 2000)*
- AAP Section on Allergy & Immunology—provider & parent resources
- "Treatment of Allergic Rhinitis" *(American Family Physician, 2010)*
- **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"

Update on Allergic Rhinitis

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Author Disclosure
Dr Mahr is a consultant, a member of the Speaker's Bureau, and a research participant with Aventis, AstraZeneca, GlaxoSmithKline, Merck, Pfizer, Inspire, Genentech, Alcon, Schering, and Novartis.
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Objectives

After completing this article, readers should be able to:

1. Recognize the various signs and symptoms of allergic rhinitis (AR) in children.
2. Understand the impact of AR on pediatric patients.
3. Discuss the treatment of AR in children.
4. Describe the systemic effects of antihistamines in infants and young children.
5. Understand the roles of topical and oral corticosteroids in the treatment of AR.

Introduction

Allergic rhinitis (AR) is the most common chronic disease in children, affecting up to 40%. However, the disease frequently is overlooked and undertreated because it often is mistaken for recurrent upper respiratory tract infections in children who cannot adequately communicate the impact of their symptoms. AR generally is not considered to be a life-threatening disease, yet it is one of the major reasons for visits to pediatricians.

Definitions

In 1998, the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology defined rhinitis as "inflammation of the membrane lining the nose, characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose and/or postnasal drainage." AR is a hypersensitivity reaction to specific allergens occurring in sensitized patients that is mediated by immunoglobulin (Ig)E antibodies and results in inflammation. Traditionally, AR is classified as seasonal or perennial and as either mild, moderate, or severe. Mild AR involves no sleep interruption, no impairment of daily activities, and no troublesome symptoms. Moderate-to-severe AR involves one or more of those factors. A newer classification system specifies that AR be characterized as intermittent or persistent. Intermittent disease involves symptoms for fewer than 4 days per week or for a duration of fewer than 4 weeks. Persistent disease involves symptoms that occur more than 4 days per week and are present for longer than 4 weeks (Bousquet, 2001).

Epidemiology

Because approximately 50 million Americans have AR, almost all primary care physicians encounter the disease. In one study, 42% of children were diagnosed as having AR by the age of 6 years. The prevalence of AR has increased dramatically in the past 30 years. Children who have one component of atopy (allergic rhinitis, asthma, eczema) have a threefold greater risk of developing a second component (Wright, 1994).

The financial impact is significant. In 1996, the overall direct costs of treating AR exceeded $3 billion, with an additional $4 billion spent to treat related comorbidities triggered or exacerbated by the disease. Not surprisingly, indirect costs are lowest when AR is treated adequately.

Clinical Impact

Signs and Symptoms

Patients who have AR may experience a variety of signs and symptoms. Parents usually report mouth breathing, snoring, or a nasal voice in affected children. Other symptoms

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typically include paroxysmal sneezing, nasal itching, sniffing, snorting, nose blowing, congestion or postnasal drainage, and occasionally coughing. Additional symptoms include itchiness of the eyes, throat, and palate. Although it may be easy to dismiss the disease symptoms as trivial, patients often experience headaches, fatigue, impaired concentration, reduced productivity, loss of sleep, and decreased emotional well-being and social functioning. AR typically begins in childhood, persists throughout adolescence and early adulthood, and tends to improve in older adults.

On physical examination, nasal obstruction often can be seen, with pale to bluish nasal mucosa, enlarged or boggy turbinates, clear nasal secretions, and pharyngeal cobblestoning. Because some affected children do not have these classic findings, negative examination findings do not eliminate AR. Other characteristic signs of AR in children include allergic shiners (darkening of the lower eyelids due to nasal congestion and suborbital edema) and the allergic crease (transverse skin line below the bridge of the nose) that is caused by constant rubbing upwards from the palm of the hand ("allergic salute"). Due to the chronic nasal airway obstruction, some children have chronic mouth breathing, which also can lead to craniofacial abnormalities and orthodontic disturbances, such as palatal arching, increased facial length, and a flattened mid-face.

Effects on Quality of Life

AR impairs school performance, and its symptoms interfere with daily life. Schoolchildren who have AR often suffer from both its emotional and behavioral effects. Sedation, irritability, fatigue, and sleeplessness can affect both attentiveness and concentration during school. These place an additional burden on a child's ability to learn and function in school. It has been shown that children whose allergies are untreated exhibit greater impairment of short-term memory and knowledge acquisition and application compared with children who do not have allergies.

A teenager's ability to function in school also has been shown to be impaired by AR. A survey of adolescents ages 12 to 17 years demonstrated the impact of seasonal AR on quality of life (Juniper, 1994). The teenagers complained about the lack of a good night's sleep, difficulty concentrating when doing school work, feeling tired and worn out, accomplishing less, interference with outdoor activities, irritability, and generally not feeling well. Overall, these youth generally believed that the disease significantly impaired their quality of life.

Risk Factors

Several risk factors have been noted for the diagnosis of AR by the age of 6 years. These include asthma, maternal smoking (one or more packs per day) in the child's first postnatal year, parental allergies, and a mother who has asthma. It has been shown recently that the most important factor associated with AR in 6- to 7-year-old children is a family history of rhinitis, personal history of asthma or eczema, and exposure to house dust mites.

Whether exposure to pets during early childhood protects against the development of allergic disease later in life is controversial. Indoor pets can contribute to allergic disease in someone who is known to be allergic to them, but investigators recently have found that exposure to two or more dogs or cats in the first postnatal year is associated with a significantly lower risk of developing atopy by age 6 or 7 years (Holsche, 2002).

Sinusitis often is underdiagnosed in children and can be a complication of allergic rhinitis. Allergic rhinitis also is one of the risk factors associated with otitis media.

Comorbidities

Children who have AR often have coexisting conditions related to their upper and lower airways. Some studies have found that nearly one third of children who have AR also have asthma. Other studies suggest that poorly controlled rhinitis symptoms exacerbate coexisting asthma. Sinusitis often is underdiagnosed in children and can be a complication of AR. Some studies have found that persons who have allergies are more susceptible to viral infections and that the increased mucus and nasal congestion associated with viral infections may expose the patient to the development of sinusitis. AR also is one of the risk factors associated with otitis media. Investigators have reported that about 20% of children who have AR have otitis media with effusion (OME), and 50% of children who have chronic OME have AR. Children who have allergies can become mouth breathers and snore, making them susceptible to disrupted sleep. Some data

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).

suggest an association between allergies and snoring, explaining an increased frequency of obstructive sleep apnea syndrome in children who have allergies.

Diagnosis

Differential Diagnosis

The differential diagnosis for chronic rhinitis in pediatric patients includes allergies, sinusitis, infectious rhinitis, structural abnormalities, and a foreign body. AR often is misdiagnosed as infectious rhinitis, which is very common in the younger child (Table 1).

Diagnostic Tools

Although the nasal smear for eosinophils is suggestive but not pathognomonic for AR, in the correct setting, it is helpful. Nasal eosinophilia can be defined by a nasal smear showing an eosinophil count of greater than 4% in children. Eosinophils increase in nasal secretions of patients who have seasonal AR during the pollen season and correlate significantly with the signs and symptoms of AR. Nasal eosinophilia helps distinguish AR from viral infections and nonallergic rhinitis. Nasal secretions can be taken from both nostrils. The specimen may be obtained by swabbing the area with a thin wire swab or by having the patient blow his or her nose on wax paper. Hansel stain is used.

Evidence of hypersensitivity to a specific allergen usually is necessary to confirm a suspected diagnosis of AR. Techniques used for measuring specific IgE include in vitro assays such as radioallergosorbent testing or skin-prick testing with suspected allergens. The testing can be extremely useful in identifying the allergens that are causing the child's AR, and specific allergen avoidance can be recommended.

Management

Management of AR is important to prevent both the symptoms and potential complications of the disease, such as sinusitis, otitis, and sleep disturbance. Options for treatment include allergen avoidance, pharmacotherapy, and immunotherapy. In addition, there is a role for prevention of comorbid diseases.

Allergen Avoidance

Allergy avoidance is the first recommendation for the patient who has AR. Although it may be easy to recommend avoiding pets or pollen, such avoidance is extremely difficult for many patients. A more realistic goal is to decrease allergen exposure as much as possible, keeping in mind that many patients are allergic to multiple allergens. Strategies include staying inside during high pollen times (5 AM to 10 AM), keeping air-conditioning on during spring and fall pollen seasons, and avoiding drying clothes outside during high pollen

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.
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times. To avoid molds, strategies include decreasing humidity in the home, using a dehumidifier, and keeping obvious areas of mold clean with a bleach solution. Patients also should avoid conditions in which mold may be elevated, such as in barns, on hayrides, and outdoors during harvesting.

The ideal solution for pets is to remove them from the home, although this often is not feasible or easy to accomplish. An alternative is to remove pets from the bedroom at night and during the day. Reservoirs for pet dander and allergen also should be avoided, such as pillows and heavy upholstered furniture.

For dust mites, total avoidance is difficult if not impossible. Therefore, strategies to decrease exposure should be used, such as bed and pillow coverings and hypoallergenic pillows and comforters. Feather and down pillows and comforters should be avoided because they may increase dust mite exposure. Clothing should be washed in hot water to denature any remaining mite allergen. The relative humidity of the house should be decreased to prevent dust mite growth. Recent studies have suggested that avoidance alone may not be sufficient to treat AR, especially when the allergen is dust mites. It also has been well documented that passive exposure to cigarette smoke, which is not a true allergen, can exacerbate symptoms for patients who have AR or asthma.

Pharmacotherapy

Pharmacologic options for treating AR include antihistamines (oral and intranasal), oral leukotriene receptor antagonists (LTRA), and intranasal corticosteroids (INS). Treatment guidelines for AR support the use of INS as first-line therapy. INS are approved for use in patients as young as 2 years of age. The onset of INS action has been shown to be within 12 hours, and in some studies, INS have been shown to work when used as needed. Oral antihistamines and LTRA improve symptoms of AR when compared with placebo. Decongestants work by vasoconstriction. Because of specific adverse effects of both oral and topical forms, decongestants should be used only intermittently for break-through symptoms of nasal congestion.

Comparisons between INS and oral antihistamines have shown that INS provide superior efficacy for most AR symptoms. When ocular symptoms occur, oral antihistamines may provide slightly greater efficacy than INS, but several recent studies have shown a similar improvement in ocular symptoms when either INS or an oral antihistamine are used for treatment. INS show greater symptom improvement when compared with LTRA (Table 2).

Sedation often is a problem with first-generation antihistamines and can lead to reduced school and cognitive performance. This effect can be avoided by the use of second-generation antihistamines that have low or no sedation effects. With INS use, parents often raise the concern of potential growth suppression. Several studies of INS have shown no effect on growth over 1 year of treatment in pediatric patients. Other concerns include the use of INS with concomitant therapy for asthma, such as inhaled steroids. One recent study has shown that the use of INS in addition to inhaled asthma therapy does not cause any increase in hypothalamic-pituitary-axis adverse effects.

Allergy Immunotherapy

Allergy immunotherapy (IT) should be considered as adjunctive therapy for children whose disease is significant. IT has been shown to decrease symptoms of AR when administered appropriately. The exact mechanisms of action of IT remain uncertain. Recent studies have suggested that IT induces the production of Treg cells (T-regulatory) and interleukin-10, which are anti-

inflammatory, thereby downregulating allergic inflammation. Other mechanisms include prevention of the seasonal rise in specific IgE that occurs during exposure and potentially the production of blocking antibodies (IgG).

Disease Prevention

Treatment of AR improves a patient's quality of life and has been shown to decrease asthma-related emergency department visits and potentially to reduce the development of asthma in pediatric patients. One recent study has shown that treatment of grass pollen or dust mite allergies with an oral antihistamine in children younger than age 2 years reduced the subsequent development of asthma compared with a placebo group. Another study showed that children whose AR was due to grass or birch pollen and who were treated with IT were less likely to develop subsequent asthma (Moller, 2002). Those who were treated with placebo were 2.5 times more likely to develop asthma compared with those treated with allergy IT. These data suggest that treatment of AR also may modify and potentially prevent asthma.

Conclusion

Symptomatic relief and improved quality of life can be achieved for most patients who have AR by avoiding the inciting allergen and using pharmacotherapy appropriately. For those who do not respond to medical management, further evaluation by an allergy specialist and consideration for allergy IT may be beneficial.

Suggested Reading

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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 _____ percent children have allergic rhinitis.

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

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

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

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

   1st generation H1 blockers:

   2nd generation H1 blockers:

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

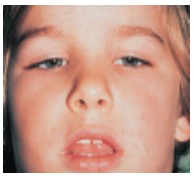
5. All of the following statements below are true except:
   - A. Children who have one aspect of atopy (AR, eczema or asthma) have two-times the risk of developing a second atopic condition.
   - B. AR typically begins in childhood and improves in older adults.
   - C. 50% of children with chronic otitis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

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

   What do these conditions have in common?

   What are the clinical implications of a positive allergy test?

This is Stu Stuffy



Allergic Rhinitis *Mega*-Case

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

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

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

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

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

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

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

What is your suspected diagnosis and what will be your treatment plan?

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

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

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

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

	_____	_____
Types		
Speed		
Price		
Sensitivity		
Confounds		
Setting		

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

Allergic Rhinitis Board Review

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

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

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

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

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

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

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

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