Allergic Rhinitis

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Allergic rhinitis is the most common of all allergic disorders, affecting over 20 million people in the USA. Because it is not life-threatening and its symptoms may not be incapacitating, allergic rhinitis may be ignored by the pediatrician. Yet this frequent illness causes significant morbidity which results in the expenditure of many millions of dollars in health care and the loss of millions of school and working days. The symptoms may be episodic or perennial; when symptoms recur annually during certain months, the syndrome is called seasonal allergic rhinitis, and when symptoms occur throughout the year, the syndrome is called perennial allergic rhinitis. Typically, seasonal allergic rhinitis does not develop until after the patient has been sensitized by two or more pollen seasons. Seasonal allergic rhinitis is frequently referred to as "hay fever" or "summer cold". These descriptive terms are misleading and should be discarded because fever is not a symptom associated with allergic rhinitis, and hay or the common cold virus are not incriminated in the etiology of this syndrome.

The prevalence of allergic rhinitis in the general population is considered to be about 10 per cent, with the peak incidence in the post-adolescent teenage child. Broder et al in the study of a well-defined population in Tecumseh, Michigan, found the prevalence of allergic rhinitis to increase from less than 1 per cent in infancy to 15 to 16 per cent after adolescence.

The term allergy was introduced by a pediatrician, Clemens von Pirquet, in 1906 to designate the host's altered reactivity to an antigen; the end result could be helpful or harmful to the host. The term allergy as commonly used in contemporary clinical practice indicates an adverse reaction. In this context, allergic rhinitis is best defined as the adverse pathophysiologic response of the nose and adjacent organs which results from the interaction of allergen with antibody in a host sensitized by prior exposure to that allergen.

Symptoms and Signs

Initial symptoms in seasonal allergic rhinitis progress from frequent sneezing and nasal pruritus to rhinorrhea and finally to nasal obstruction. These symptoms vary considerably from season to season and may also differ markedly at various times of night and day. Patients not only have nasal pruritus but also itching of the eyes, throat and ears. Many children constantly rub the nose with the hand or arm in an effort to relieve the nasal itch and perhaps to improve the nasal obstruction. Other children may press the palm of the hand upward against the nose in an "allergic salute", which often leads to the development of a transverse nasal crease. The patient with nasal obstruction will be a constant mouth breather and snoring will be a prominent nighttime symptom. Patients may report generalized malaise, irritability, and fatigue; these symptoms are often difficult to differentiate from the side effects of antihistamines frequently used for symptomatic therapy. The pattern of symptoms frequently distinguishes seasonal from perennial allergic rhinitis, especially in areas with obvious seasonal climatic changes.

With development of the allergic reaction, clear nasal secretions will be evident and the nasal mucous membranes will become edematous without much erythema. The mucosa appear boggy and blue-gray. The turbinates may appear to be congested and swollen. If nasal obstruction is present, it may be necessary to shrink the mucosa with a vasoconstrictor in order to document the absence of nasal polyps, which are relatively uncommon in allergic rhinitis, occurring in less than 0.5 per cent of patients. Patients, particularly children, with allergic rhinitis and significant nasal obstruction and venous congestion, may also demonstrate edema and darkening of the tissues beneath the eyes, the so-called "allergic shiners". The conjunctiva may also demonstrate a lymphoid follicular pattern with a cobblestone appearance.

Etiology

The development of allergic rhinitis requires two conditions: atopic familial predisposition to develop allergy, and exposure of the sensitized patient to the allergen. Inhalants are the principal allergens responsible for allergic rhinitis. These microscopic airborne particles include pollens, mold spores, animal danders, and environmental dust, either house or occupational. Seasonal allergic rhinitis is primarily induced by pollens from the germination of nonflowering vegetation. In the temperate climates, the most important are tree pollens in the spring, grass pollens in the late spring and early summer, and ragweed pollens in the late summer and early fall. In warm climates, mold spores may be airborne year round, but in climates in which snow and freezing occur in the winter months, airborne mold spores are present intermittently during the spring, summer, and fall until there is significant frost. In patients with perennial allergic rhinitis, mold spores may be a significant inhalant allergen indoors along with epidermal animal danders and house dust. The principal allergen in house dust has not been identified but may be attributed in part to the house dust mite, dermatophagoides. Food allergens are less important in the etiology of allergic rhinitis, but cannot be ignored, especially in young children.

Despite several extensive retrospective family and twin studies, there is no agreement as to the hereditary pattern in allergic diseases. Most investigators believe that several genetic loci are involved in the expression of allergic disease and that inheritance is multifactorial. Recent immunologic studies have isolated some of these genetic influences. Animal studies have shown that synthesis of specific antibodies to well characterized antigens is controlled in part by immune response (Ir) genes which are linked to the major tissue histocompatibility locus (HLA). The studies by Levine and co-workers have suggested that ragweed allergic rhinitis and immune responses to purified ragweed antigen E were linked to a particular HLA haplotype in successive generations of allergic families. Marsh et al reported a significant correlation between haploptype HL-A7 and increased IgE antibodies, to a low molecular-weight purified ragweeed antigen (Ra5) in a group of patients with allergic rhinitis who were sensitive to this small portion of the ragweed allergen.

Immunopathophysiology

Allergic rhiitis, along with allergic asthma and allergic urticaria, is described immunologically as an immediate hypersensitivity syndrome and is mediated in large part by immunoglobulin E (IgE) antibodies. The properties of IgE compared with the other serum and secretory immunoglobulins are shown in Table 1. IgE is normally present in minute quantities

compared with the serum immunoglobulins IgG, IgA and IgM. The IgE antibodies are synthesized after allergen challenge largely by plasma cells that are located in lymphoid tissues adjacent to mucosal membranes. These IgE antibodies passively sensitize the membranes of tissue mast cells and circulating blood basophils. The exact nature of the binding of IgE to mast cell and basophil cell membranes is not known, but it involves the Fc portion of the IgE molecule and an appropriate receptor in the cell surface. The combination of allergen and its specific IgE antibody results in a sequence of energy-dependent enzyme reactions with alteration of the mast cell membrane. This initiates the release and synthesis of the specific pharmacologic mediators of the IgE immediate hypersensitivity reaction. These mediators include histamine, the slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor (ECF-A), platele aggregation factor (PAF), and other kinins and vasoactive substances that cause the increased vascular permeability, local edema, and increased eosinophil-laden secretions seen in patients with allergic rhinitis.

Table 1. *Properties of Human Serum and Secretory Immunoglobulins*

	IgG	IgA	S-IgA	IgM	IgD	IgE
Adult serum concentration (mg/mL)	10	2	-	1.5	0.03	0.0002
Antibody activity	+	+	+	+	?	+
Neutralization (viral, toxin)	+	±	+	+	-	-
Anaphylactic (histamine release)	±	-	-	-	-	+
Blocking antibody	+	±?	±?	-	-	-
Maternal-fetal transfer	+	-	-	-	-	-
Present in secretions	±	+	++	-	-	+
Fix to mast cells (homocytotropic)	-	-	-	-	-	+
Classic complement activation	+	-	-	+	-	-
Alternate complement pathway	+	+	+	+	-	+

Histologic examination of the nasal mucosa will demonstrate distended goblet cells in the presence of enlarged, congested mucous glands. The tissues are infiltrated with eosinophils and with lymphoid cells that have a paucity of neutrophils. The intracellular spaces are enlarged, and the basement membrane is thickened. Mast cells are also present in the mucosal tissues, but the significance of their relative numbers has not been defined.

Using airway resistance studies and quantitative pollen challenges, Connell has shown that a larger dose of allergen was required to increase resistance in the nasal mucosa that had remained unchallenged than was required to obtain the same effect after a week of daily exposures. He also demonstrated that, in patients sensitized to several pollens, repeated challenges with one allergen conditioned the nasal mucosa to react to lower dose of the second allergen than would have been needed if given singly. This priming phenomenon could well account for the persistence of symptoms experienced by many patients toward the end of the pollen season, in spite of decreased exposure to allergen. It is also thought that this priming effect favors an increase in responsiveness to nonspecific stimuli such as changes in humidity and temperature.

Laboratory Studies

A variety of laboratory studies are useful to the clinician in establishing a diagnosis of allergic disease and in providing a guide to specific therapy. Several of these tests are enumerated in Table 2.

Table 2. *Laboratory Studies Helpful in Diagnosis of Allergic Disease*

- Nonspecific Studies
  - Eosinophils
    - Blood (> 600 eosinophils per mm^3)
    - Secretions (nasal, sputum, conjunctival)
  - Total serum IgE (age-related)
- Specific Antigen-Antibody Studies
  - In vivo (provocative) tests
    - Skin tests (20 min wheal and flare)
      - Scratch
      - Prick
      - Intracutaneous
    - Nasal inhalation challenge
    - Bronchial inhalation challenge
  - In vitro serum tests
    - RAST (radioallergosorbent)

The nasal secretions of patients with allergic rhinitis usually contain increased numbers of eosinophils. It is difficult to quantify nasal eosinophilia accurately. Greater than 3 per cent eosinophils seen on a nasal smear is considered to be an increase. Eosinophilia may not be present in patients who have not been exposed to specific allergens recently or in patients with a superimposed infection. Steroids can significantly reduce eosinophilia but antihistamine therapy has no significant effect on nasal eosinophils. Documentation of nasal eosinophilia is a simple, inexpensive procedure that can be performed easily in an office setting.

In certain patients it may be helpful to confirm the clinical impression of allergic rhinitis with documentation of specific IgE antibodies by in vivo skin testing or in vitro serum radioallergosorbent (RAST) testingt. Skin testing with the suspected allergens is mandatory in all patients prior to initiation of immunotherapy. Clinicians should be selective in the use of allergens for skin testing and should employ only common allergens of potential clinical importance in their patients. To avoid false-negative skin tests, antihistamines should be withheld for 24 to 48 hours before skin tests are performed. Prick skin testing may be more reliable than intradermal skin testing; the specifics of such testing are outlined in standard allergy textbooks. Food skin testing should be reserved for patients who present diagnostic problems, with intermittent or perennial symptomatology. The major problems with skin testing, especially for food allergens, have been the lack of potency, stability, and purity of the allergen solution. The crude, undefined composition of allergens often produces false-positive reactions secondary to an irritating effect on the skin. Great care must be used in interpreting the results of food skin testing because there is often a discrepancy between the production of clinical symptoms after ingestion of the food and positive skin reactions to foods.

As mentioned earlier, the in vitro RAST for assessing the presence of serum IgE antibodies to various allergens has recently been employed as a diagnostic aid in allergic rhinitis. For certain allergens, RAST has been shown to be as reliable as skin tests; it is also more specific, although less sensitive, than skin tests. At present, skin testing is felt to be a more useful tool than RAST for the diagnosis of allergic disease. It is generally accepted that skin testing is less expensive, more sensitive, and technically easier to perform. Furthermore, there is a wider range of antigens available for skin testing, and the results may be interpreted immediately. RAST is indicated in the management of the allergic patient with generalized dermatitis and in the young infant in whom skin tests would be difficult to perform. Table 3 summarizes the relative advantages of RAST and skin tests in diagnosing allergic conditions.

Table 3. *Relative Advantages of RAST Test and Skin Test in Diagnosis of Allergic Conditions*

Skin Test	RAST Test
Less expensive	No patient risk
More sensitive	Specific and quantitative
More antigens available	Not affected by drugs
Results available promptly	Antigen stability
Technically easier	Patient convenience
May detect non-IgE mediated	Useful (dermatographism, widespread dermatitis)
Good correlation with history and RAST tests	Good correlation with history and skin tests.

Because of the recent observations that IgE antibodies may be present in nasal secretions but not evident by skin testing or the presence of serum IgE antibodies, a nasal provocation test occasionally may be useful in assessing a patient with a negative skin test who is suspected of reacting to a particular allergen.

The in vitro cytotoxic leukocyte test for foods and other allergens has been advocated by some, but its usefulness as a laboratory test has not been confirmed in controlled studies by other investigators. Also, recent studies have employed the use of leukocyte inhibition factors and lymphocyte transformation to investigate the possible role of food allergy in patients with symptoms of allergic rhinitis but these tests have not yet been documented to be clinically relevant.

Differential Diagnosis

Children who present with rhinorrhea and nasal obstruction may have symptoms not only because of allergy, but also as the result of infections, foreign bodies, structural changes, pregnancy, drug reactions, neoplasms, or other nonallergic causes. The common cold virus is the most frequent cause of upper respiratory infection (URI), and at the outset a viral URI, with its symptoms of clear, watery rhinorrhea and sneezing, resembles allergic rhinitis. Redness of the nasal mucosa is characteristic of a URI and usually distinguishes it from allergic rhinitis. Nasal infections can be superimposed on allergic rhinitis.

Table 4. *Comparison of Allergic and Nonallergic Rhinitis*

	Allergic	Nonallergic ENR	Nonallergic Vasomotor
Usual onset	Child	Child	Adult
Family history of allergy	Usual	Coincidental	Coincidental
Collateral allergy	Common	Unusual	Unusual
Symptoms			
Sneezing	Frequent	Occasional	Occasional
Itching	Common	Unusual	Unusual
Rhinorrhea	Profuse	Profuse	Profuse
Congestion	Moderate	Moderate to marked	Moderate to marked
Physical examination			
Edema			
Secretions	Moderate to marked	Moderate	Moderate
Nasal eosinophilia	Watery	Watery	Mucoid to watery
Allergic evaluation	Common	Common	Occasional
Skin tests			
IgE antibodies			
Therapeutic response	Positive	Coincidental	Coincidental
Antihistamines	Positive	Coincidental	Coincidental
Decongestants			
Corticosteroids			
Cromolyn	Good	Fair	Poor to fair
Immunotherapy	Fair	Fair	Poor to fair
	Good	Good	Poor to fair
	Fair	Unknown	Poor
	Good	None	None

ENR = eosinophilic nonallergic rhinitis.

The above conditions can usually be differentiated from allergic rhinitis, but the separation of perennial allergic from perennial nonallergic rhinitis is often difficult. Nonallergic rhinitis can be classified as either eosinophilic nonallergic rhinitis (ENR) or vasomotor rhinits (Table 4). ENR may occur in children, but is more common in adults. It stimulates the perennial type of allergic rhinitis, but no immunologic etiology can be implicated. In this disorder, the edematous mucous membranes are often pale and eosinophilia is always present, but the usual methods of detecting a specific allergen and its mediating antibodies fail to establish a specific cause. Vasomotor rhinitis is a nonallergic form of persistent nasal disease usually seen in older children and adults, which also is manifested by watery rhinorrhea and nasal obstruction. The patient reports over-responsiveness of the nose to minimal changes in air temperature, odors, and often to change in the position of the head. These patients appear to have unusual awareness of symptoms and their complaints are disproportionate to the magnitude of their symptoms. It is important to delineate patients with ENR and vasomotor rhinitis from patients with allergic diseasebecause of their different responses to therapy. Immunotherapy is not to be used in patients with nonallergic disease,

and drug therapy with antihistamine decongestants control symptoms inconsistently. Recent evidence suggests that ENR, unlike vasomotor rhinitis, may improve significantly with either topical or systemic corticosteroids (unpublished data by authors).

Therapy

Successful therapy of allergic rhinitis involves three primary considerations: identification and avoidance of the specific allergens, pharmacologic management, and immunotherapy.

Identification and Avoidance. Complete avoidance of causative allergens is the best therapy for allergic disease because without exposure to allergens the allergic reaction will not take place. Elimination of exposure to an animal dander by elimination of the animal from the household, or elimination of a food allergen from the diet, may provide complete or partial relief of symptoms. Measures to control house dust, especially in the bedroom, can be effective treatment for certain patients. These measures include providing rubberized or plastic airtight enclosures for mattresses and box springs, the use of synthetic bedding fabrics, and the removal of stuffed toys, stuffed furniture, heavy drapery, and dust catchers, such as book shelves and record cabinets, from the bedroom. Electrostatic precipitrons can be installed in central forced-air heating and cooling systems, and these can substantially reduce not only house dust but pollens and other airborne particles. Because single-room electrostatic precipitron units are less effective and may generate irritating ozone, they are not recommended.

Pharmacologic Management. If the patient cannot completely avoid the allergen, symptoms can be controlled with drugs in many cases. Antihistamines are preferred for treating mild to moderate allergic rhinitis. Several groups of antihistamines differ in chemical structure and in action. Since the effectiveness of one group may diminish after several months or years of use, an antihistamine of another group may then be efficacious clinically. Therefore, the clinician should become familiar with the use of one or more antihistamines in each of the listed groupings (Table 5). When nasal obstruction by secretions is a prominent symptom, an alpha-adrenergic decongestant, such as phenylephrine, phenylpropanolamine, or pseudoephedrine, should be used individually or in combination with an antihistamine. Topical nasal alpha-adrenergic vasoconstrictors usually provide prompt symptomatic relief but should not be used for more than several days. After 7 to 10 days of using a topical decongestant many patients develop so-called rebound vasodilatation and, at times, habituation. It is necessary to discontinue nose drops in order to relieve this "rhinitis medicamentosa".

If symptoms cannot be controlled with antihistamines, decongestants, and avoidance of allergens, several clinicians have suggested corticosteroid therapy. In children, the risk-benefit ratio of treating even severe allergic rhinitis with oral or parenteral corticosteroids is sufficiently high to contraindicate their use. However, several topical corticosteroids, especially for short-term seasonal use, might prove to be useful in the future. Beclomethasone, a poorly absorbed and rapidly metabolized topical corticosteroid, is currently enjoying considerable popularity in Europe for the treatment of allergic rhinitis without severe or systemic side effects. Cromolyn sodium, which inhibits the release of mediators from mast cells, is another topical aerosol pharmacologic agent that is available in Europe but not yet available for the treatment of allergic rhinitis in the USA. Although European investigators

have found the drug to be effective in 75 per cent of patients treated, such high efficacy has not been reported in a recent study of patients with allergic rhinitis in the USA.

Table 5. *Oral Antihistamines*

	Trade Name	Oral Preparations	Dose (per 24h)	Max Sin Dos mg
Ehylendiamines				
Tripelennamine hydrochloride	Pyribenzamine	Tables, 25 and 50 mg; delayed action, 50 and 100 mg	5 mg/kg	50
Tripelennamine citrate	Pyribenzamine	Elixir, 37.5 mg/5 mL		50
Ethanolamines				
Diphenhydramine hydrochloride	Benadryl	Capsules, 25 and 50 mg; elixir 12.5 mg/5 mL	5 mg/kg	50
Carbinoxamine maleate	Clistin	Tablets, 4 mg Timed release tablets, 8 and 12 mg Elixir, 4 mg/5 mL	0.4 mg/kg	4
Alkylamines				
Chlorpheniramine maleate	Chlor-Trimeton Teldrin	Tablets, 4 mg Timed release tables, 8 and 12 mg	0.35 mg/kg	4
Brompheniramine maleate	Dimetane	Tablets, 4 mg Timed release tablets 8 and 12 mg	0.5 mg/kg	4
Triprolidine hydrochloride	Actidil	Tablets, 2.5 mg Syrup, 12.5 mg/5 mL	0.2 mg/kg	2.5
Piperazines				
Cyclizine hydrochloride	Marezine	Tablets 50 mg	3 mg/kg	50
Piperidines				
Cyproheptadine hydrochloride	Periactin	Tablets 4 mg Syrup, 2 mg/5 mL	0.25 mg/kg	4
Azatadine maleate	Optimine	Tablets, 1 mg	0.1 mg/kg 2 div doses	2
Phenothiazines				
Promethazine hydrochloride	Phenergan	Tablets, 12.5, 25, and 50 mg Syrup, 6.25 and 25 mg/5 m	0.5 mg/kg	50
Methdilazine	Tacaryl	Tablets, chewable, 3.6 mg Tablets, 8 mg Syrup, 5 mg/5 mL	0.3 mg/kg	8

Immunotherapy. If symptomatic drug therapy and avoidance cannot adequately control symptoms or if drugs inadvertently provoke significant side effects, immunotherapy (hyposensitization) with allergen solutions may be indicated. The specifics of this therapy are discussed in greater detail in one of several allergy texts. Before proceeding with immunotherapy, the physician should institute a comprehensive investigation of the causative factors, and the patient's history of symptoms should be closely correlated with the presence of specific IgE antibodies, determined preferably by skin test results or by an in vitro RAST. In several double-blind studies, immunotherapy or hyposensitization injections with solutions

of pollen have been shown to be effective in reducing the symptoms of allergic rhinitis. Immunotherapy may be expected to provide significant clinical improvement in 80 to 90 per cent of patients with pollen-induced allergic rhinitis. If improvement is not obtained after a 2 year trial of immunotherapy, the patients should be reevaluated and discontinuation of immunotherapy should be considered. Duration of immunotherapy injections in patients who achieve clinical benefits depends on the patient's overall clinical response. In the presence of clinical improvement, patients should be given the opportunity to stop the immunotherapy after approximately 5 years of injections. It has been claimed that immunotherapy in children for seasonal allergic rhinitis may reduce their chances of developing pollen-induced asthma but this report is open to question and has never been confirmed.

The mechanism by which immunotherapy promotes clinical improvement has not been precisely delineated. Laboratory evidence has shown that immunotherapy results in the development of IgG blocking antibodies, a decrease in specific IgE antibodies, and a reduction in leukocyte histamine release. Immunotherapy has also been shown to modulate T cell function by inducing the generation of antigen-specific T suppressor lymphocytes. The clinical correlation of these studies with efficacy of immunotherapy may in the future provide the clinician with means to better manage the patient with allergic rhinitis.