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Allergies and Allergy Therapy—Part I

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Editor's Note—*The field of allergy has its roots in the science of immunology, which was initially described as the body's host defenses against foreign objects. The allergic reaction (type I immediate hypersensitivity) is simply a host response, through IgE mediated mechanisms, to common environmental stimuli. These reactions vary from unpleasant itching, sneezing, or wheezing, to life-threatening anaphylactic shock. While the term allergy actually has a very specific pathophysiologic meaning, common vernacular has led to a connotation representing a simple adverse reaction, and for others, allergy means any Gel and Coomb reaction, type 1 through type IV. It is often difficult for patients, and even health care professionals to make this distinction. Adverse reactions, which are nonimmunologically mediated, may not be effectively treated with standard allergy therapies, especially as target-specific therapies evolve. Therefore, it is becoming increasingly important for health care providers to possess a thorough understanding of the features and mechanisms of the immune response in order to offer the most effective diagnosis and treatment.*

The spectrum of allergic disease is extremely broad and includes a number of organ systems. Respiratory manifestations are most commonly encountered clinically, and include allergic rhinitis and asthma. Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a much less common immunologically induced inflammatory lung disease. This disorder, however, is non-IgE mediated and will not be discussed in detail. Generally closely associated with rhinitis and asthma is allergic conjunctivitis. Several cutaneous manifestations, including atopic dermatitis and acute urticaria, are also quite common. Much less common, but potentially life threatening, is angioedema and anaphylaxis. Finally, the broad category of GI manifestations also causes considerable distress, particularly in the case of food allergies.

Agents that elicit an immune-mediated response include various inhaled allergens, such as pollens, molds, grasses, dusts, mites, low molecular weight chemicals, and drugs. Contact agents include plants, latex, low molecular weight chemicals, and drugs. Foods are capable of eliciting any manifestation of the allergic response. Likewise, insect stings, particularly hymenoptera, may elicit anything from local tissue response to anaphylaxis. Environmental agents inciting an IgE-mediated response have characteristic physical quantities. They are generally ubiquitous and relatively small molecular weight proteins. Very small agents require interaction with a hapten, which is simply a protein carrier, and the protein allergen complex actually comprises the actual antigen.

The mechanism of allergic response involves binding of allergen to IgE bound to mast cells and basophils. This interaction in turn elicits the release of preformed mediators. Preformed mediators elicit an immediate response, which is responsible for the acute symptoms of itching, sneezing, wheezing, and cough. Additionally, signaling cascades are

initiated, which lead to propagation of the immune response including further inflammation and the sequelae of the late phase response.

Allergic disorders represent a global health problem. Allergic rhinitis is thought to affect around 15 million individuals in the United States, though it is likely under-reported because patients either frequently do not recognize their symptoms or they self-medicate with over-the-counter preparations. Asthma is less common but still affects around 5 million individuals in the United States. Atopic dermatitis is frequently associated with allergic rhinitis and asthma, as is allergic conjunctivitis. These disorders represent significant societal in-indirect and direct costs. Direct costs have, and will continue to escalate primarily due to the advancements in pharmacotherapy.

As a direct result of improved understanding of the pathophysiology of allergy and the recognition of the interaction between allergy and other illness, clinical practice guidelines have been developed which allow for efficient evaluation and therapy of these disorders. The overlap between allergic rhinitis and asthma has becoming increasingly apparent, and this has led to recognition that failure to treat one aspect of the global airway disorder may prevent sustained symptom relief. Complications of allergies manifested in the airways, such as sinusitis, otitis, allergic bronchopulmonary aspergillosis, and others, have been further defined, allowing for more effective management. The identification of the mechanisms of allergic disorders has identified several potential targets for therapy. These factors make the field of allergy exciting for both patients and practitioners.

The objective of this monograph is to provide an overview of the scope of allergic disorders, and review the current understanding of the mechanism of the allergic response. Due to the extensive nature of the topic, we will limit our discussion to systemic reactions eliciting an IgE-mediated response. Further, the intimate relationship between organs involved will be reviewed, particularly the relationship between allergic rhinitis and asthma. Part I includes the current evaluation, including historical features, exposures, physical exam findings, and ancillary diagnostic options will be reviewed. Part II discusses current therapeutic options, including the most recent additions to the therapeutic armamentarium will be reviewed. A stepwise approach to diagnosis and management of allergic disorders will be outlined. Finally, the discussion will also seek to familiarize clinicians with targeted treatment modalities on the horizon.

Introduction

Allergic reactions were described in Egyptian times, and an understanding of the body's reaction to external stimuli has been known for nearly 200 years. The term "allergy" was actually coined in 1906 by Viennese pediatrician Baron Clemens von Pirquet, and is derived from the Greek "allos" meaning changed or altered state, and "ergon" meaning reaction or reactivity.[1] Von Pirquet used the term after observing patients who developed an altered reaction to subsequent doses of horse serum or cowpox vaccine. Prior to this, the first description of hay fever was made in 1819, and rudimentary skin testing was described in 1869. Anaphylaxis, probably similar to what von Pirquet described in coining the term, was described in 1902, as a direct result of skin testing and immunotherapy. The identification of cellular and molecular mediators has occurred in the last 80 years, with the discovery of histamine as a component of the allergic response being made in the 1920s. The first antihistamine was synthesized in the late 1930s, and despite the phenomenal progress in the pharmacotherapy of allergy, histamine remains the most vulnerable mediator in the allergy cascade. The primary source of histamine, the mast cell, was identified in the 1950s, and the role of IgE was described in the 1960s. Leukotrienes, the most recent significant pharmacotherapeutic targets, were identified in the 1980s. In the last 15 years, however, molecular and genetic research techniques have illuminated the pathophysiology of the allergic response. This progress has led to a deeper understanding of the differences between immunologically and nonimmunologically mediated events, as well as providing new targets for pharmacotherapy.

Persons with IgE-mediated allergic disorders are frequently termed "atopic." Manifestations of atopy include primarily conjunctivitis, rhinitis, asthma, and eczema. Any organ system may be involved, however, and severe reactions may lead to anaphylaxis and death. IgE-mediated systemic reactions result from external stimuli, including pollens, dusts, mites, latex, insect stings, foods, and certain drugs. Hypersensitivity reactions that are non-IgE mediated can occur, and some are not immunologically mediated. Nonimmunologically mediated reactions are frequently a cause of rhinitis, but also can lead to bronchial, ocular, cutaneous, and gastrointestinal responses. Differentiating immunologically from nonimmunologically mediated systemic reactions can be particularly difficult to

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identify due to the overlap in physical findings, and may require extensive investigation into the history of the events. It is imperative, however, to distinguish these reactions, as their management does not necessitate and may not respond to standard allergy therapy.

Due to the multitude of manifestations, primary care physicians as well as specialists in allergy/immunology, otolaryngology, pulmonary medicine, ophthalmology, dermatology, and others typically treat allergies. By using a systematic approach of reduction of inflammation, inhibition of mediators, and even modification of the immune response, allergic disorders may be more adequately and effectively treated.

Allergic diseases are present worldwide and appear to be increasing in prevalence. A large study conducted in Sweden demonstrated that the number of children with allergic rhinitis, asthma, or eczema doubled over a 12-year period.[2] As allergic disorders have a wide range of systemic manifestations, often with considerable overlap, it is difficult to assess the prevalence of the spectrum of allergic disorders. Allergic rhinitis, allergic asthma, and allergic eczema or atopic dermatitis likely represents the most significant manifestations for which individuals seek medical care. Estimates on the prevalence of these individual manifestations are the only reliable indicators of disease activity. Unfortunately, it is often difficult to obtain true measures of these disorders due to the variability of definitions used in epidemiologic studies and shortcomings of the methods used to calculate the incidence and prevalence of allergies. Many of these studies are based on patient or physician questionnaires from clinical diagnoses, with few including objective data. Objective tests including skin testing and serum specific IgE testing are variably used in clinical practice and are not commonly used in epidemiologic studies. Furthermore, patients may not seek medical attention for certain aspects of allergic spectrum disorders, often choosing to self-treat with over-the-counter medications.

Several national and multinational studies are underway that attempt to further characterize the incidence and prevalence of allergic spectrum disorders. These include the second Health and Nutrition Examination Survey (NHANES II), the European Community Respiratory Health Survey (ECRHS), the International Study on Asthma and Allergy in Childhood (ISAAC), the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), and the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen (SCARPOL). Additionally, the National Health Interview Survey is conducted annually in the United States. Data from these studies indicate a wide variance in incidence and prevalence of allergic disorders worldwide.

Currently, data from the National Health Interview Survey and the National Ambulatory Medical Care Survey provide the most accurate information on incidence, prevalence, mortality, and cost of allergic disorders in the United States. These data are compiled from surveys of patients and providers. The NHIS is conducted yearly. Based on 1996 data, there were 23.7 million cases of allergic rhinitis,[3] and in 1999 there were 16.7 million office visits related to allergic rhinitis.[4] Using data from the 1996 Medical Expenditure Panel Survey, the direct cost of allergic rhinitis was estimated at $3.4 billion. Nearly half of this cost was attributed to prescription medications. Of those dollars attributed to prescription medication, 50% went to second-generation antihistamines, 25% to intranasal corticosteroids, and 5% to first-generation antihistamines.[5]

Data from worldwide studies indicate that more than 150 million individuals are affected by asthma.[6,7] The 2001 National Health Interview Survey identified 31.3 million people in the United States who had been diagnosed with asthma during their lifetime. This total represented 22.2 million adults and 9.2 million children. It is important to note that these figures estimate prevalence. Beginning with the 2001 survey, estimates of incidence were attempted. A total of 20.3 million people reported a current diagnosis of asthma, which included 6.3 million children and 14 million adults. In 2000, there were 10.4 million office visits and 1.8 million emergency department visits for asthma. Of these visits, there were 465,000 hospitalizations and 4487 deaths.[8] Data from the 1997 study indicate that asthma was responsible for 3.7 school absence days per year in children aged 5-17 years and 2.5 work absence days per year in adults from 1994-1996.[9] Asthma mortality has decreased over the last 5 years but continues to be nearly 3 times higher in black males than white males, and 2.5 times higher in black females than white females. Estimates of the cost of treating asthma vary widely. The most recent published studies are from the 1987 National Medical Expenditure Survey. With inflation to 1994 dollars, the estimated direct and indirect cost was 5.8 billion, represented by 5.1 billion in direct costs and 673 million in indirect cost.[10]

While allergic rhinitis and asthma have societal implications both from a quality-of-life and economic burden standpoint, atopic dermatitis is a highly prevalent disorder with great potential effect with respect to quality of life. Atopic dermatitis is a highly pruritic chronic inflammatory disorder that generally presents in early childhood but may persist into adulthood. IgE-mediated atopic dermatitis is often referred to as extrinsic type, affects 70-80% of patients, and is often associated with dust mite allergy and food allergy. Intrinsic atopic dermatitis is non-IgE mediated and affects 20-30% of patients.[11] Atopic dermatitis has lifetime prevalence in children of 10-20% and a prevalence of 1-3% in adults.[12] As with other allergic disorders, prevalence has increased in the last few decades, mostly in industrialized countries. Cost estimates on the treatment of atopic dermatitis vary widely, with medication cost representing the bulk of the cost.

Clearly, with the large number of patients affected and the high costs associated with absenteeism and treatment, allergic disorders required a focused, effective approach to diagnosis and treatment.

Etiology

The etiology of all allergic diseases remains to be fully defined. There is overwhelming evidence of a relationship between allergic rhinitis, asthma, and eczema both in epidemiologic studies and in studies of inflammatory mediators responsible for the individual disorders. The role of genetic and environmental factors is the study of intense investigation. Genetic predisposition toward allergic disorder has been posited for more than 100 years based on the observations that these disorders tend to run in families. The heritability of allergic disorders has been strengthened by studies of twins, and, more

recently, by molecular studies of the genome. The postulate that environmental stimuli are responsible for allergic disorders stems from observations that exposures to certain infections and allergens are common in persons who develop these disorders.

Twin studies of asthma, allergic rhinitis, and eczema have identified a predisposition to these disorders. In one study of 7000 same sex twin pairs, concordance rates for asthma were 19% in monozygotic twins compared to 4.8% in dizygotic twins.[13] This finding is further supported by a twin study of the prevalence of asthma, seasonal rhinitis, skin-test response, total serum IgE, and specific IgE as measured by RAST. In this study monozygotic twins reared apart or together showed a greater concordance than dizygotic twins reared apart or together.[14] While the definition of the allergic phenotype may be different in each of these studies, there is clearly a genetic predisposition to the spectrum of disorders.

As the field of molecular genetics has expanded, several genomic screening studies of the allergic phenotype have been conducted. Chromosomal linkage studies have identified chromosomes 4-7, 11-14, and 16 with association to asthma and allergic disorders. Candidate genes associated include the interleukins identified in the allergy cascade, as well as other intracellular mediators and cell surface receptors.[15] These studies have associated chromosomes with certain phenotypes. For instance, markers on chromosome 4 are associated with bronchial hyperreactivity; 6 with total serum IgE and eosinophilia; 7 with total IgE, eosinophilia, and bronchial hyperreactivity; 11 with total IgE, positive allergy skin test, and asthma; 13 with atopy; and 16 with total IgE, bronchial hyperreactivity, and asthma.[16] As with many disorders, linkage with the HLA genes has also been identified. While the sum of these data points to a genetic etiology of allergic disorders, there has clearly been no definitive marker for the spectrum of disorders. As data accumulate, it is likely that we will see a genetic predisposition to these disorders that is activated through environmental mechanisms.

Another aspect of genetic susceptibility involves the differential response of individuals to standard therapy. Several studies have identified a genetic linkage to β-adrenergic therapy response. Evidence indicates several polymorphisms exist in the β- 2 adrenergic receptors. Individuals who are homozygous for the glycine 16 variant (which leads to significant down regulation) show a reduced response following chronic dosing with beta agonists.[17,18] Approximately 35% of Caucasians have this genotype; therefore, a significant number of patients with asthma likely have altered response to β-agonists. Environmental associations with allergic rhinitis and asthma have arisen out of observation that western cultures and more modern societies tend to have a higher prevalence of these disorders. In recent years, a phenomenon known as the "hygiene hypothesis" has arisen. This hypothesis relates to the theory that naturally occurring infections and microbial exposures can immunize against the development of allergies, and that reduction in infection and microbial exposures contributes to the rise in prevalence of allergies via a shift in the T-helper population to a predominance of T_H2 type. This phenomenon is most strikingly represented in comparative studies in former East and West Germany demonstrating that lifestyle and environment play a major role in the expression of allergic disorders.[19-21] The association of cockroach sensitivity and its relation to asthma has been present since the 1960s.[22] Multiple groups also described dust mite exposure as a potential etiology to allergy and asthma in the 1960s.[23,24] Further environmental associations include pollens, animal danders, fungal allergens, tobacco smoke, and air pollution. Several drugs, with aspirin being the prototype, are associated with allergic symptoms, although typically not via an IgE mechanism.

While exposure to these environmental agents later in life is associated with increasing allergy symptoms, early exposure to naturally occurring viruses, parasites, and toxins has clearly been associated with lower rates of allergy. A US study of individuals with early prior exposure to hepatitis A, *Toxoplasma gondii*, and herpes simplex I showed lower rates of allergic disorders.[25] Similar studies have shown associations with intestinal flora exposure, parasitic exposure, and endotoxin exposure. All of these "less hygienic" exposures potentially modulate the immune response in a time and dose-dependent manner.

Pathophysiology

Our understanding of the systemic reaction to allergens has increased dramatically over the last decade and has been recently reviewed.[26,27] The central cellular components include CD4+ T lymphocytes (T_H2), antigen presenting cells such as dendritic cells and Langerhans' cells, eosinophils, basophils, macrophages, and mast cells. The central immunoglobulin is IgE, though IgG4 may play a limited role. There are many cellular mediators with histamine as the most well described and most effectively modified in current pharmacotherapy. Other mediators include leukotrienes, interleukins, GM-CSF, and several chemokines. The immunologic response occurs in 2 phases. The immediate response, of Gell & Coombs Type I, occurs as an IgE-mediated response. A late response often occurs in both allergic rhinitis and asthma and is due to the recruitment of inflammatory cells and their mediators.

The initiation of an allergic response begins with sensitization to an antigen. Antigens are inhaled, ingested, or exposed, and are internalized by antigen-presenting cells (APC)—typically Langerhans' cells and macrophages—where they are processed and ultimately displayed on the cell surface in association with major histocompatability complex (MHC). The APC is then capable of engaging undifferentiated T cells and B cells. The undifferentiated T cell in atopic individuals differentiates into a T_H2 cell and produces cytokines, such as IL-4, the IgE switch cytokine, and an array of other cellular mediators. B cells, under the influence of cytokines from the T_H2 cell, mature into a plasma cell producing IgE antibodies.

In atopic individuals, the stage is then set for the immediate response. Allergen re-exposure results in binding to IgE, which is bound to mast cells and basophils via high affinity IgE receptors (FcεRI). Activation and signaling the mast cell to release preformed mediators such as histamine, enzymes, hydrolases, and proteoglycans. Several proinflammatory mediators are also synthesized on allergen exposure, and

Table 1.

Mediator	Actions
Histamine	Increased vascular permeability, vasodilation, increased mucus production, bronchoconstriction, activation of nociceptive neurons
Proteases	Degradation of tissue, activation of protein precursors, increased mucus production, generation of bradykinins
Arachidonic acid derivatives	
Leukotrienes (B_4, C_4, D_4)	Increased vascular permeability, increased mucus production, bronchoconstriction, neutrophil/eosinophil chemoattractant (B_4), increased leukocyte adhesion molecule expression (B_4)
PGD_2	Increased vascular permeability, bronchoconstriction (increased transient airway hyperresponsivity)
Thromboxane A_2	Bronchoconstriction
Cytokines	
IL-3	Hematopoietic growth factor, chemoattractant for basophils
IL-4	Increased IgE production, increased differentiation of T_H2 from T_H0 CD4+ cells
IL-5	Increased eosinophil proliferation and differentiation, chemoattractant for eosinophils and basophils
IL-9	Increased IgE production, development/accumulation of eosinophils/basophils, mast cell development, increased mucus production, bronchoconstriction
IL-13	Increased IgE production, development/accumulation of eosinophils/basophils, mast cell development, increased mucus production, bronchoconstriction
TNF-α	Potent stimulator of inflammatory cascade, up-regulation of leukocyte adhesion molecules on endothelium
GM-CSF	Increased proliferation of granulocytes
Platelet activating factor	Eosinophil/neutrophil chemoattractant, increased vascular permeability
Secreted Phospholipase A_2	Arachidonic acid release, IL-6 & IL-8 production, β-glucuronidase production

these include prostaglandins (PGD2), leukotrienes (C4, D4, E4), platelet activating factor, bradykinin, phospholipases, and cytokines (TNF-α, IL-4, IL-5, IL-6, IL-10, and IL-13). Similar responses are thought to occur in the less well-studied basophil. These resultant mediators induce venule permeability leading to airway edema, smooth muscle activation leading to bronchoconstriction, and increased mucus secretion. These effects result in the clinical syndrome of the immediate allergic response, which includes wheezing, nasal itching, sneezing, and rhinorrhea.

In addition to the inflammatory effects produced by mast cell and basophil activation, neuronal responses are also responsible for part of the immediate response. Nociceptive type C neurons are activated by histamine, which then depolarize leading to release of substance P, calcitonin gene-related peptide, and neurokinin A.[28] These neuronal-derived mediators appear to induce production of cytokines and other mediators similar to those produced by mast cells and basophils. Additionally, however, parasympathetic reflexes are initiated, which may have a significant effect on mucous production.

Subsequent to immediate phase phenomena, there is a continuation of the cascade initiated by the mast cell activation. Leukotrienes and platelet-activating factor stimulate the influx of inflammatory cells, and the release of multiple cytokines. This influx of inflammatory cells likely occurs through the activation and expression of adhesion molecules and selectins on endothelial cells and integrins and selectins on leukocytes. While the mechanism of this response is still the subject of investigation, the accumulation of leukocytes (predominantly eosinophils) in the airway is thought to result in late phase responses. Late phase mediators are responsible for symptoms including further wheezing, sustained blockage of the nose, and eczema.

The mediators of the immediate and late response are increasingly being targeted for specific pharmacotherapy. These mediators act at various points along the inflammatory cascade, and identification of the rate limiting steps in that cascade should lead to the most effective therapies. A brief description of the actions of some of these mediators is illus-

trated in Table 1.

The fundamental basis of the allergic response has been postulated to be the imbalance of T_H1 and T_H2 responses, with atopic individuals having a T_H2 predominant response to environmental allergens. These observations have been made in part by the identification of cytokines produced by the individual cell types. T_H1 cells generate IFN-γ, IL-2, and TNF-β while T_H2 cells generate IL-4, IL-5, IL-13, and others. Nonatopic individuals respond to allergens by generating allergen-specific IgG antibodies via a T_H1 mediated response, and atopic individuals generate IgE via a T_H2 mediated response.[29]

Through various studies, it appears that intrauterine and early childhood immunologic mechanisms are T_H2 predominant. Through mechanisms that are still under investigation, we know that in most individuals, there is a transformation to a T_H1-predominant immunological response sometime in early childhood. As previously discussed, this transformation is hypothesized to occur as a result of exposure to microbes and has been termed the hygiene hypothesis because of the observed rise in allergic disorders, predominantly in western societies.[30,31] Macrophages that engulf microbes release IL-12, which is a stimulant to the production of interferon-γ by T_H1 and natural killer cells. IFN-γ is thought to be the primary stimulus toward the "allergy protective" T_H1 response. As previously discussed, this transformation may be driven by infectious exposures with some effect by genetic predisposition. In susceptible individuals, there is a persistent ineffective transformation to the T_H1 response leading to allergic symptoms.

The hygiene hypothesis is supported by the observation that infectious exposures may protect against asthma and atopy, and observations that children with older siblings and children in daycare were protected against the development of asthma.[32,33] These data, coupled with the previously noted data on infectious exposures, lend strong support to the causal relationship between the lack of natural exposures and the development of allergic syndrome disorders. Once these disorders are manifested, however, there is a definite association with exposure to endotoxin and exacerbation of symptoms.[34]

One seemingly contradictory observation is that of the increased prevalence of allergic disorders in inner-city individuals. Asthma prevalence is higher in urban populations than in rural populations, and this finding is not influenced by ethnicity or poverty.[35] Asthma severity, on the other hand, has been linked to ethnicity and poverty.[36] Those who are proponents of the hygiene hypothesis counter this argument by noting that inner city exposures are likely quite different from rural exposures, thus T cell transformation may not occur upon exposure to urban environmental antigens. Further, the increased severity of asthma in African American and lower socioeconomic classes is likely a result of increased exposure to endotoxin and other agents as a result of living conditions.

The T_H1/T_H2 transition phenomenon has been demonstrated at the cellular level in a recent long-term study of asthmatics. In this study, a cohort of asthmatic children and a control group were followed prospectively for approximately 35 years. Peripheral blood cytokines were stimulated in vitro, and cytokine production was assessed in these individuals at 7-year intervals. T_H1 (IFN-γ) responses were reduced in patients with persistent asthma, and returned to relatively normal levels in patients with resolved asthma. T_H2 responses (IL-5), on the other hand, were not reduced in patients with resolved asthma. The lack of dimunition of T_H2 response was attributed to persistent atopy, rather than asthma severity.[37]

Clinical Signs, Symptoms, Testing, and ddx

The significant manifestations of allergic disorders include allergic rhinitis, asthma, atopic dermatitis, urticaria, and the most severe manifestation—anaphylaxis. The clinical symptoms of each often co-exist, and therefore can occasionally be difficult to differentiate. Additionally, complications of allergic disorders, including anosmia, sinusitis, otitis media, lower respiratory tract infection, nasal polyps, and conjunctivitis can occur. A more severe entity that can co-exist in an allergic asthmatic is allergic bronchopulmonary aspergillosis, and involves irreversible bronchiectasis.

Rhinitis. Rhinitis is defined as inflammation of the membranes lining the nose, and is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage. Nasal symptoms develop for a number of reasons, including allergic, infectious, hormonal, and medication-related etiologies. A detailed history including contacts, exposures, occupation, and family history of atopy is necessary for proper diagnosis and treatment. It is particularly important to evaluate for infectious etiologies, as they do not generally require expensive inflammatory-modulating therapies. Common causes of rhinitis are listed in Table 2.

Classically, allergic rhinitis has been identified as either seasonal or perennial. Roughly half of patients experience symptoms for 4 or more months per year, and approximately 20% remain symptomatic more than 9 months per year. Seasonal allergic rhinitis is typically associated with outdoor allergens such as tree, grass, and weed pollens, as well as fungi. Perennial allergic rhinitis generally results from sensitivity to indoor allergens such as molds, dust mites, cockroaches, and pet danders. The classic descriptions of nasal symptoms in allergic disorders link rhinorrhea with seasonal allergic rhinitis, and nasal obstruction with perennial rhinitis.[39]

Allergic rhinitis is commonly associated with asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection, and conjunctivitis. Complications of chronic rhinitis include loss of smell, snoring and sleep problems, postnasal drip, chronic cough, as well as headache and fatigue. Consideration of these complications is necessary when the chief complaint centers around rhinitis symptoms, and an investigation into allergic symptoms should be made when the presenting complaint is one of the above listed symptoms and or a strong family history of atopy is noted.

Historical features that point to allergic rhinitis include symptoms of itching, sneezing, and rhinorrhea associated with seasons of the year or specific exposures. Typically, patients who suffer from outdoor allergies have been symptomatic at the same time each year over several years. The timing of symptoms is often helpful; for example, in Kentucky, with persons sensitive to tree pollens become symptomatic in the early spring, symptomatic to grasses in early summer, and symptomatic to ragweed and other summer weeds in the late summer

persisting until first frost. However, seasonal pollens and molds vary due to geographical location. For instance, the Pacific Northwest is the only locale in the continental United States that lack significant levels of ragweed pollen. Of patients with allergic rhinitis, 75% react to ragweed pollen, 40% to grass pollens, and 9% to tree pollens.[40] The most common clinically relevant aeroallergens in North America are listed in Table 3. Onset of allergic rhinitis often occurs in childhood but persons may develop symptoms at any age. And if a history of change in living conditions or moving to a new region of the country is given by a patient, allergic rhinitis should be considered.

Table 2. Differential Diagnosis of Rhinitis

Allergic
- Seasonal allergic rhinitis
- Perennial allergic rhinitis

Nonallergic
- Infectious rhinitis
- Vasomotor rhinitis
- Nonallergic rhinitis with eosinophilia syndrome (NARES)

Occupational rhinitis

Hormonal rhinitis
- Pregnancy-associated rhinitis
- Hypothyroidism

Drug-induced rhinitis
- ACE inhibitors
- Reserpine
- Guanethidine
- Phentolamine
- Methyldopa
- Beta blockers
- Chlorpromazine
- Aspirin and NSAIDs
- Oral contraceptives
- Rhinitis medicamentosa (overuse of oxymetazoline or phenylephrine)
- Cocaine

Rhinitis associated with food ingestion

Nasal polyps

Other
- Nasal septal deviation
- Tumors
- Adenoidal hypertrophy
- Hypertrophy of nasal turbinates
- Foreign body
- Vasculitis
- Atrophic rhinitis

Adapted from: Bousquet J, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-S334.

Indoor and perennial sensitivities are somewhat more difficult to identify and often present as persistent upper respiratory infections or chronic cough. Symptoms are often prolonged and associated with specific exposures. For instance, patients may notice that symptoms are present with exposure to certain parts of a house, eg, molds in a basement. Alternatively, patients may note that symptoms improve when environmental conditions change, such as going on vacation, going to work, weekends/holidays, etc.

In general, patients with rhinitis should be questioned regarding the pattern, chronicity, and seasonality of symptoms, as well as response to medications, presence of coexisting conditions, occupational exposure, family history of atopic disease, and detailed environmental/exposure history. Consideration for the reduction in the quality of life of the allergic patient must be recognized, since the effects of fatigue, headache, cognitive impairment, loss of smell, snoring and sleep problems, postnasal drip or chronic cough, and sedation can be enormous. Associated asthma, conjunctivitis, or dermatitis should also be considered. Patients with occupational rhinitis may be particularly difficult to diagnose due to the frequency of exposure and the multitude of unknown exposures in the workplace.

Risk factors for development of allergic rhinitis include family history of atopy, serum IgE ≥ 100IU/mL before age 6, higher socioeconomic class, exposure to indoor allergens such as animals and dust mites, and the presence of a positive allergy skin prick test. For others with new onset of symptoms, a careful analysis of other etiologies must be considered—especially that of infectious causes of rhinitis. Infectious causes can be similar in that patients suffer from sneezing, rhinorrhea, and even itching. Nasal drainage can be clear or colored, and is of little benefit in the diagnosis of various causes of rhinitis.

The physical examination in patients with allergic rhinitis is typically notable for abnormalities in the conjunctiva, nasal mucosa, and even skin. Examination of the nose should include observation of the visible components of the nose (septum, inferior turbinates, and possibly middle meatus), color and condition of the mucosa, and presence of secretions. The classic findings of pale, boggy nasal mucosa are often present, but mucosal erythema also occurs. Frequently, the mucosa is edematous with increased vascularity, and an allergic nose often bleeds. A careful examination of the nose infrequently reveals nasal polyps, but when present, warrants evaluation for aspirin sensitivity and asthma. Another common observation in children is the "allergic salute," the upward rub of the palm across the tip of the nose. A frequently associated finding with the allergic salute is the nasal crease, a transverse line below the bridge of the nose that is caused by frequent rubbing. Clear nasal drainage is frequently present, but purulent nasal drainage is possible, signifying white blood cell presence rather than bacteria. Transillumination of the sinuses has been considered a rapid, simple technique for evaluating sinus involvement. Unfortunately, this technique is neither sensitive nor specific. Examination of the posterior pharynx

can demonstrate signs of postnasal drip and hyperplasia of lymphoid tissue. Examination of the eyes can reveal conjunctival erythema, tearing, and edema of the lids. Suborbital edema is often termed the, "allergic shiner." Dennie-Morgan lines are linear folds or lines in the lower eyelid due to edema. A pale, cobblestone appearance of the conjunctiva also can occur. Examination of the tympanic membranes is necessary to evaluate for a concomitant serous otitis or frank otitis media. The neck exam may reveal mild cervical adenopathy.

Diagnostic tests for allergic rhinitis are somewhat limited. Total serum IgE is helpful if it is markedly elevated, but the test has low sensitivity and specificity. Similarly, total serum eosinophil count in excess of 500 cells/mm^3 is suggestive of allergic etiologies, but normal eosinophil counts do not rule out allergies, and elevated eosinophil counts can be seen in a number of other conditions (parasitic infections, drug effects, neoplasms, Addison's disease, and collagen vascular disease). The routine evaluation of IgE and eosinophil counts has been discouraged by many practitioners and is not recommended in the position paper by the Joint Task Force for the diagnosis and management of rhinitis.[42]

While the diagnosis of allergic rhinitis is often made on clinical grounds, in patients who have failed avoidance therapy and pharmacotherapy, *in vivo* testing such as skin testing, or *in vitro* testing, such as radioallergosorbent testing (RAST) and enzyme-linked immunosorbent assay (ELISA), may be indicated. Examination of the nasal secretions by cytologic methods in order to identify nasal eosinophilia has also been used. This study is of limited value, however, because it is present not only in allergic rhinitis, but also in vasomotor and nonallergic rhinitis with eosinophilia syndrome (NARES).

Skin testing is advantageous in that the results are immediate, accurate, reproducible, and diagnostic when performed correctly and correlated with a patient's environmental history. Allergy skin testing involves pricking the skin after preparations of common allergens are dropped onto the skin (prick method). An intradermal method is often completed if prick testing is negative. A positive test is identified as a wheal and flare seen within 20 minutes. This wheal and flare is identical to that produced by histamine and is representative of inflammatory and neurogenic effects. Positive reactions indicate sensitization to the allergen and presence of allergen-specific IgE. The late-phase reaction can also occur and is represented by late diffuse edema and slight induration at the site of the wheal and flare. The intensity of the late-phase response generally correlates with the immediate reaction. It begins 1-2 hrs after challenge, peaks at 6-12 hrs, and resolves in 24-48 hrs. Antihistamines, imipramines, and phenothiazines, can cause false-negative results and must be discontinued up to 10 days prior to skin testing. All tests should include a negative and positive control, and all test results should be correlated to the patient's environment.

RAST testing is a means to identify and quantify allergen-specific IgE. It involves taking patient serum and mixing it with a purified allergen adsorbed to an inert substance. If allergen-specific IgE is present, it binds to the protein. Free antibodies are then washed away, and the solid phase is incubated with I^{125}-labeled, purified antihuman IgE. Free radiolabel is washed away, and the amount of radioactivity measured from the solid phase represents the quantity of allergen-specific IgE present in the serum. RAST is somewhat expensive and has moderate sensitivity. It is best reserved for patients with equivocal skin prick testing or those who cannot undergo skin testing.

Radiographic examinations, such as plain sinus radiographs or computerized tomography of the sinuses, are not recommended for routine evaluation of nasal congestion or drainage. CT scans may be useful to exclude sinusitis, eliminate other conditions or complications, or to evaluate patients who do not

Table 3. Major Clinically Relevant Aero-allergens of North America

Tree pollen
Chinese elm; Siberian elm, elm
Red oak, white oak
Paper birch
Alder
Box elder, red maple
Eastern cottonwood
Sycamore
White ash, olive
Black walnut
Mulberry
Mountain cedar
Pecan

Grass pollen
Rye
Timothy
Meadow fescue
Bermuda
Johnson
Bahia

Weed pollen
Short ragweed
English (narrow leaf) plantain
Mugwort
Russian thistle
Burning bush
Sheet (red) sorrel
Red root pigweed

Indoor aero-allergens
Cat epithelium
Dog epithelium
Arthropods (domestic mites)
Insects (German cockroach)

Fungi
Alternaria alternate
Cladosporium
Penicillium
Aspergillus fumigatus
Epicoccum nigrum

Adapted from: Li JT, et al, eds. Allergen Immunotherapy: A practice parameter . Ann Allergy Asthma Immunol. 2003;90(Suppl 1):1-40.

respond to conventional treatment.

In assessing severity of rhinitis or response to symptoms, there are few reliable tools available. For research purposes, rhinitis specific visual analogue scales have been developed. Practically, however, patient satisfaction with therapy seems to be the main indicator of disease status. A system of grading intensity and severity of symptoms has been put forward in the recent review of allergic rhinitis and its effect on asthma by Bousquet and colleagues (*see Table 4*).

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Table 4. Severity of Allergic Rhinitis

Intermittent

Less than 4 days/week

Or for less than 4 weeks

Mild

Absence of:

- sleep disturbance
- impairment of daily activities, leisure, and/or sport
- impairment of school or work
- "troublesome" symptoms

Persistent

More than 4 days/week

And for more than 4 weeks

Moderate/severe

Presence of:

- sleep disturbance
- impairment of daily activities, leisure, and/or sport
- impairment of school or work
- "troublesome" symptoms

Adapted from: Bousquet J, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl): S147-S334.

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CME Questions

30. Allergic diseases have increasing world-wide prevalence.
    a. True
    b. False

31. According to the 1996 Medical Health Expenditure Survey, to what is attributed the greatest percentage of resource of the $3.4 spent on allergic rhinitis?
    a. Physician visits
    b. Over-the counter therapies
    c. Second generation antihistamines
    d. Intranasal steroids

32. Allergic diseases are due (at least in part) to an imbalance of TH1/TH2 CD4+ T lymphocytes.
    a. True
    b. False

33. Which of the following are included in the differential diagnosis of rhinitis?
    a. Seasonal allergic rhinitis
    b. Perennial allergic rhinitis
    c. Pregnancy associated rhinitis
    d. Nasal polyps
    e. All of the above

34. Of patients with allergic rhinitis, the majority react to:
    a. ragweed pollen.
    b. grass pollen.
    c. tree pollen.

Answers: 30.(a); 31.(c); 32.(a); 33.(e); 34.(a)

In Future Issues:

Allergies and Allergy Therapy—Part II
David M. Hiestand, MD, PhD,
and Barbara Phillips, MD, MPH

PHARMACOLOGY WATCH

Eplerenone Cleared for CHF Patients with Sustained MI

The FDA has approved Pfizer's eplerenone (Inspra) for the treatment of congestive heart failure (CHF) in patients who have sustained a myocardial infarction. The drug is a selective aldosterone blocker, a new class of drug for the treatment of CHF. It differs from spironolactone in that it selectively blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors. The approval of eplerenone for the treatment of CHF was based primarily on the findings of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which was published in the April 2003 issue of the *New England Journal of Medicine*. In EPHESUS, nearly 7000 patients with acute myocardial infarction and left ventricular dysfunction and heart failure were randomized to eplerenone 25 mg per day titrated up to 50 mg per day or placebo. Both groups also received optimal medical therapy. Following 16 months of follow-up, there was a significant reduction in death rate (RR, 0.85; 95% CI, 0.75-0.96; P = 0.008) in the eplerenone group. The drug also resulted in significant reductions in cardiovascular deaths and sudden cardiac death (*N Engl J Med*. 2003;348:1309-1321). The drug appears to be well tolerated with the primary adverse events being hyperkalemia and increased creatinine levels. Because of the selectivity of the drug for the mineralocorticoid receptor, there is no reported increase in menstrual disorders, gynecomastia, or impotence with eplerenone, adverse reactions that are frequently associated with spironolactone usage. Pfizer will make the drug available through an early access program by December 2003. Eplerenone was previously approved for treatment of hypertension alone or in combination with other antihypertensive agents.

No Adverse Effect with Concomitant Aspirin and ACE Inhibitor Use in CHF Patients

Aspirin does not adversely affect survival in patients with stable CHF who were being treated with an ACE inhibitor, according to a French study published in October. This study contradicts earlier studies, which raised concern about the concomitant use of aspirin and ACE inhibitors in CHF patients. In a retrospective analysis, 755 stable patients with left ventricular systolic dysfunction were followed for nearly 5.5 years. Most patients were on an ACE inhibitor and 317 were on aspirin, the majority on low-dose aspirin (< 200 mg/d). End points included cardiac-related deaths, version transplants, nonurgent transplants, and noncardiac deaths. The analysis revealed no relationship between the use of aspirin and survival among patients taking ACE inhibitors. Brunner-La Rocca and colleagues conclude that aspirin is not harmful for heart failure patients who are taking ACE inhibitors (*Chest*. 2003; 124:1192-1194, editorial 1250-1258).

HIV Treatment Shows High Failure Rate

A once-daily, triple nucleoside reverse transcriptase inhibitor (NRTI) HIV treatment regimen has seen a high number of treatment failures and HIV

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resistance. The rate of virologic failure reached 91% along with a high rate of HIV resistance to NRTIs in treatment-naive patients. Gilead Sciences has taken the step of notifying health-care professionals to discontinue the regimen in a "Dear Doctor" letter. The treatment failures were seen with a regimen containing didanosine enteric-coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead) in HIV-infected treatment-naive patients. Tenovir DF is no longer recommended for use in combination with didanosine and lamivudine in treatment-naive or experienced patients with HIV infections. The FDA is also recommending that patients currently on this regimen should be considered for treatment modification (http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#viread [Accessed Nov. 5, 2003]).

New Psoriasis Treatment Approved

The FDA has approved the second biologic for the treatment of psoriasis. Genentech's efalizumab (Raptiva) was approved for the treatment of moderate-to-severe psoriasis in October. It joins Biogen's alefacept (Amevive), which was approved in January 2003 and will probably soon be joined by Amgen's rheumatoid arthritis drug etanercept (Enbrel), which is also seeking approval for the treatment of psoriasis. Efalizumab is a humanized therapeutic antibody that blocks the activation, reactivation, and trafficking of T-cells that lead to the development of psoriasis symptoms. The drug requires a once-a-week self-injection and will cost $14,000 a year.

THG Controversy Gains Steam

The FDA has issued a warning regarding tetrahydrogestrinone (THG), a synthetic "designer" steroid, which is derived by simple chemical modifications from another anabolic steroid. Little is known about the safety of the drug or its structure, but its relationship to better-known products suggests that it may represent a considerable health risk. THG has been marketed as a dietary supplement; however, the FDA has determined that it is an unapproved drug and as such cannot be legally marketed. Urine assays have recently been developed for THG, and testing of athletes has revealed some disturbing findings. Four US Olympic athletes, as well as Britain's leading sprinter, have tested positive in the initial assay—further tests are to follow. A San Francisco grand jury is looking into a California nutritional supplement manufacturer that may be the source of the drug. The FDA statement is available at www.fda.gov/bbs/topics/NEWS/2003/NEW00967.html (accessed Nov. 5, 2003).

New Study Examines Sulfonamide Nonantibiotics

Is it safe to use a sulfonamide-based nonantibiotic in patients who have an allergy to sulfonamide antibiotics? A large retrospective cohort study from the United Kingdom looked at this issue and suggests that penicillin allergy is as likely or more likely to be associated with nonantibiotic sulfonamide reactions as a history of sulfonamide antibiotics allergy. Nearly 10% of patients with a history of allergy to a sulfonamide antibiotic had an allergic reaction after receiving a sulfonamide nonantibiotic compared to only 1.6% of patients who have no history of allergy to sulfonamide antibiotics. Patients who had a history of hypersensitivity to penicillin were most likely to have an allergic reaction to a sulfonamide nonantibiotic (adjusted odds ratio, 0.6; 95% CI, 0.5-0.8). Strom and associates conclude that there is a relationship between hypersensitivity to sulfonamide antibiotics and subsequent allergic reaction with sulfonamide nonantibiotics such as thiazide diuretics; however, this risk seems to be due to a predisposition to allergic reactions rather than a cross reactivity between sulfonamide-based drugs (*N Engl J Med*. 2003;349:1628-1635).

FDA Actions

Novavax Inc has received FDA approval to market a new topical estrogen therapy for the treatment of hot flashes in menopausal women. The white lotion is an emulsion of estradiol topical that women apply only to their legs, thighs or calves on a daily basis. The topical preparation is absorbed through the skin allowing estradiol to bypass enterohepatic circulation. Estradiol topical emulsion will be marketed under the trade name Estrasorb.

The FDA has issued an approvable letter to Cephalon, Inc. regarding expanded indications for modafinil (Provigil). The drug is currently approved for excessive daytime sleepiness associated with narcolepsy. The letter states that modafinil is approvable for improving wakefulness in patients with excessive sleepiness associated with shiftwork and in patients with obstructive sleep apnea/hypopnea syndrome. Cephalon had also sought approval for other causes of excessive sleepiness including jet lag; however, the FDA panel could not come to agreement on that recommendation. ■