

Allergic Rhinitis

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atopic conditions, sinusitis, otitis media, and sleep apnea. Primary care physicians should be well adept at recognizing and initiating empiric first-line therapy for chronic rhinitis. Allergen avoidance, topical nasal steroids, and antihistamines may be sufficient for some patients. In most cases, referral to a board-certified allergy specialist for skin testing and targeted management is indicated. It is essential to make sure that patients abstain from using antihistamines at least 1 week prior to reporting to the allergist for skin testing in order to avoid false-negative results. Traditional subcutaneous allergen immunotherapy, when performed by an experienced allergist, affords relief in >75% of cases. The growing armament of treatment options for refractory allergic rhinitis includes oral and sublingual immunotherapy, recombinant allergens, conjugated DNA vaccines, and anti-immunoglobulin E monoclonal antibody. *Mt Sinai J Med* 78:634–644, 2011. © 2011 Mount Sinai School of Medicine

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ABSTRACT

Allergic rhinitis is a costly disease associated with significant morbidity. It impacts the quality of life of millions of individuals, particularly in industrialized nations, and it is on the rise. Lost productivity and total healthcare expenditure exceeds several billion dollars annually in the United States, with an estimate of >\$6 billion spent on prescription medications alone. It is also associated with asthma and other

The term rhinitis refers to a mixed group of nasal disorders characterized by ≥ 1 of the following symptoms: sneezing, nasal pruritus, rhinorrhea, and/or nasal congestion. It is also frequently associated with postnasal drip, cough, fatigue, and irritability. Chronic rhinitis can be divided into 2 broad categories: allergic and nonallergic.

Allergic rhinitis is the most common type of rhinitis. It is defined as an allergen-induced symptomatic disorder of the nose that is characterized by an immunoglobulin E (IgE)-mediated inflammatory reaction. It is often subdivided into seasonal or perennial, based on the timing of symptoms. Perennial allergic rhinitis is caused mainly by indoor allergens such as dust mites, molds, animal dander, and cockroach, which are effectively present all year round. Seasonal allergic rhinitis is associated with tree, grass, and weed pollens, and is sometimes referred to as “hay fever.” However, due to the increasing number of patients with mixed symptoms that are irrespective of season, a new classification was determined.

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Table 1. Skin Test Results.

Condition	Symptoms of Rhinitis	Allergen Skin Test Result
Allergic rhinitis	Yes	Positive
Nonallergic rhinitis	Yes	Negative
Sensitized*	No	Positive
Normal patient	No	Negative

*Patients without symptoms of rhinitis are not usually skin tested.

Allergic nasal disease is now characterized as intermittent or persistent, and mild or moderate to severe (Table 1).¹ Moderate to severe symptoms may result in abnormal sleep and interference with daily activities. In the absence of these disruptions, symptoms are considered mild.

Nonallergic rhinitis refers to any rhinitis that is not induced by an allergen and includes infectious, hormonal, occupational, and other causes. Recent studies suggest that 40%–87% of patients with rhinitis may have a combination of both allergic and nonallergic pathology. Furthermore, almost half of patients with allergic rhinitis have nonallergic triggers.^{2–4}

Chronic rhinitis patients tend to have an increased susceptibility to upper respiratory infections, and complications of the disease include sinusitis, anosmia, obstructive sleep apnea, and otitis media. Approximately 40% of patients with allergic rhinitis have asthma, and as many as 78% of asthmatics have allergic rhinitis.^{5–7} Research suggests a common pathophysiology for the 2 diseases.

Chronic rhinitis accounts for $\geq 2.5\%$ of all general clinician visits.^{7,8} In terms of quality of life, approximately 10,000 children are absent from school on any given day, amounting to 2 million lost school days per year secondary to allergic rhinitis.⁸ In a study of >8000 employees from 47 employers, including several Fortune 500 corporations spanning a broad range of sectors (energy, production technology, healthcare, and government), 55% had symptoms of allergic rhinitis. They subsequently missed an average of 3.6 days per year of work, and were unproductive for 2.3 hours per workday when experiencing symptoms.⁹ In the Medical Outcomes Study Short-Form Health Survey, patients with allergic rhinitis had similar impairments of energy, general health perception, and physical and emotional limitations as did patients with asthma.^{10,11} In terms of social functioning, patients with allergic rhinitis had significantly lower scores than asthmatics alone.

In the year 2000, >\$6 billion was spent on prescription medications for allergic rhinitis.^{12–14} Almost twice this amount was spent on over-the-counter medications.¹² The diagnosis of allergic

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rhinitis accounts for >\$1.1 billion in clinician billing.⁷ These numbers do not reflect the additional out-of-pocket expense for patients who seek herbal remedies¹⁵ and Eastern therapies such as acupuncture¹⁶ to help with their symptoms.

EPIDEMIOLOGY

Allergic rhinitis is found in approximately 10%–30% of the general population and is on the rise, particularly in industrialized nations.^{17,18} An estimated 30 million to 60 million individuals in the United States are affected annually.^{4,19} The prevalence is highest in school-aged children, at >40%⁴; is lowest in children aged <5 years, and has a second peak in the early adult years before declining. The highest rate of symptom increase occurs between the ages of 12 and 15, and tends to be slightly more common in males.²⁰ Proposed risk factors for the development of the disease include family history of atopy, birth during the pollen season,²¹ exposure to high concentrations of indoor allergens or maternal smoking in the first year of life, and early use of antibiotics.^{22,23} Additionally, studies have shown that higher socioeconomic status, ethnicity other than white,²⁴ late entry into daycare,^{25,26} firstborn status, and lack of other siblings may also play a role. Higher serum IgE levels before the age of 6 years and the presence of positive allergen skin-prick tests are also associated with a higher incidence of allergic rhinitis development.²²

PATHOPHYSIOLOGY AND GENETICS

Allergic rhinitis is a disease of specific IgE overexpression. When allergens such as dust mite, cockroach residue, animal dander, mold, and pollen are inhaled, allergenic proteins are absorbed into nasal tissue. This leads an increase in allergen specific IgE production over weeks.

Re-exposure and inhalation of the allergens cause a rapid and specific IgE-mediated response, leading to the degranulation of mast cells and basophils. Histamines as well as tryptase, leukotrienes, and prostaglandins are subsequently

released. This results in edema, nasal occlusion, and pooling of blood in cavernous sinusoids—the number-one cause of congestion in allergic rhinitis.²⁷ During ongoing prolonged allergen exposure, the nasal mucosa becomes progressively more inflamed and hypersensitive to allergen, known as the priming effect. Over time, less and less allergen is required to produce symptoms.

The development of allergic disease has been attributed to both genetic and environmental causes.²⁸ Data to support the notion that vaccinations or overly clean households devoid of pathogens (the so-called hygiene hypothesis) leads to the development of allergy in industrialized nations has been mixed.^{29,30} Multiple genetic loci have been implicated, especially chromosome 6, but also chromosomes 2, 5, 7, 11, 13, 16, and 20.^{31–33}

In one study, development of atopic disease in the absence of parental family history was only 17%; however, when 1 parent or sibling was atopic, the risk increased to 29%.³⁴ When both parents were atopic, the risk for developing an atopic disorder in the next generation was 47%.³⁴ It was found that genes that control the IgE response are located within the major histocompatibility complex on chromosome 6, and dysregulation of these genes is responsible for IgE hyperactivity. There also appears to be an association between allergic rhinitis and overexpression of T helper 2 type T-cell responses.^{35,36}

DIFFERENTIAL DIAGNOSIS

Making the diagnosis of allergic rhinitis requires a careful history, physical examination, and appropriate confirmatory skin testing for suspected allergens. Family or personal history of an allergic condition and the presence of a seasonal component to symptoms places allergic rhinitis high on the differential. However, it is important to note that many symptoms of allergic rhinitis overlap with symptoms of nonallergic rhinitis and various anatomic abnormalities of the upper airway. The following nonallergic conditions warrant mention in the differential diagnosis.

Nonallergic Rhinitis With Eosinophilia Syndrome

Nonallergic rhinitis with eosinophilia syndrome (NARES) is one of the most difficult to distinguish from allergic rhinitis upon history alone. These patients experience persistent nasal symptoms characterized predominantly by congestion, but also include sneezing, profuse watery rhinorrhea, pruritus, and occasional anosmia.⁴ Eosinophils are present on nasal smear, but patients lack evidence of allergic sensitization based on skin testing (Table 2) or serum IgE levels to environmental allergens. However, on the molecular level, these patients exhibit an increase in IgE bound to mast cells as well as elevated levels of tryptase.^{37–39} Patients tend to be middle-aged adults. Rare in children, NARES accounts for <2% of children with nasal eosinophilia.⁴⁰

Nonallergic Rhinitis Without Eosinophilia

Nonallergic rhinitis without eosinophilia (NAR) is also referred to as idiopathic rhinitis or vasomotor rhinitis. Symptoms include nasal obstruction and increased nasal secretions. The key in history-taking is that in patients with NAR, sneezing and pruritus is less common. Nasal symptoms tend to occur in response to environmental conditions such as temperature or humidity shifts, passive tobacco smoke, odors such as perfumes or cleaning materials, and even sexual arousal and emotional factors. The symptoms of nasal hyper-reactivity are caused by nonallergic triggers, although occasionally a patient may also have an allergic component to their symptoms, known as mixed rhinitis.

Acute Infectious Rhinitis

It is important not to confuse allergic rhinitis with a simple viral or bacterial infection. Often these patients initially complain of rhinitis and constitutional symptoms, followed by a cough by the fourth or fifth day with resolution of the rhinitis. When symptoms last longer than a few weeks, however, it is difficult

Table 2. Classification of Allergic Rhinitis.

Classification	Duration of Symptoms	Symptom Severity	Complications
Intermittent rhinitis	<4 days/week or <4 weeks	Mild	No impairments
Persistent rhinitis	>4 days/week or >4 weeks	Moderate to severe	Disrupted sleep, decline in cognitive processing, psychomotor speed, verbal learning, memory*

*Any one of these complications constitutes moderate to severe rhinitis.

to distinguish the condition from allergic rhinitis. In refractory cases, an otolaryngology consultation may be beneficial to obtain a culture if the clinical picture is suggestive of an infective etiology. Notably, many patients with allergic rhinitis also frequently develop sinus infections.

Rhinitis Medicamentosa

Rhinitis medicamentosa arises from the overuse of decongestant, vasoconstricting nose drops as well as regular usage of cocaine. Patients who present with chronic nasal congestion should be questioned about usage. Symptoms should resolve within days of discontinuation. The adjunctive use of topical and at times oral steroids may be necessary to wean patients from chronic nasal decongestant use.

Medication-Induced Rhinitis

Rhinitis is also a side effect of certain medications such as antihypertensive beta-blockers, alpha-blockers, and hydralazine, as well as erectile dysfunction medications and certain psychotropics such as chlorpromazine, amitriptyline, and alprazolam. Aspirin and other nonsteroidal anti-inflammatory medications commonly cause rhinitis. Clinicians should be aware of the distinct clinical syndrome of aspirin sensitivity, asthma, and nasal polyposis. This constellation of symptoms is more commonly known as Samters triad.⁴¹

Hormones

Rhinitis of pregnancy characteristically begins at the end of the first trimester, and then disappears within a few weeks after delivery. Thirty percent of women with known allergic rhinitis may experience a worsening of their symptoms during pregnancy.⁴² Females may also experience rhinitis in association with taking oral contraceptive pills, as well as at various times of the month associated with their menstrual cycle.

Atrophic Rhinitis

Most common in the elderly, atrophic rhinitis is characterized by progressive atrophy of nasal tissue. Patients experience nasal congestion and perceive a persistent bad odor. This condition is commonly seen in patients who have had overaggressive resection of sinonasal tissue and the humidifying properties of the nose are compromised, resulting in chronic crusting and congestion.

Food-Induced Rhinitis

Although some clinicians believe that food allergens may be significant factors in the cause of persistent allergic rhinitis, a direct immunologic relationship between ingested foods and persistent rhinitis symptoms has been difficult to establish. Rarely, however, hypersensitivity to dietary proteins may induce the symptoms of allergic rhinitis.⁴³ More common is a condition known as gustatory rhinitis that is cholinergically mediated. The result is watery rhinorrhea immediately after the ingestion of particular foods. The most common food culprits are hot and spicy foods, cinnamon, and peppermint. Ethanol in beer, wine, and other alcoholic drinks can also produce symptoms of rhinitis, presumably through pharmacologic nasal vasodilation.

Other conditions that are less common but deserve mention include cerebrospinal fluid rhinorrhea, which is most commonly associated with a history of trauma but in a small percentage of patients has occurred spontaneously, as well as rhinitis associated with systemic inflammatory diseases such as amyloidosis, sarcoidosis, Churg-Strauss syndrome, and Wegners granulomatosis. Lastly, cystic fibrosis must be included on the differential, particularly when polyps are noted on physical exam.

DIAGNOSIS

Physical Exam

Careful physical examination of the nasal cavity should be performed to exclude septal deviation, foreign bodies, tumors, and nasal polyps. Of note, patients with active allergic rhinitis frequently have a pale bluish hue to their nasal mucosa, with turbinate edema. If nasal rhinoscopy is performed, one may see cobblestoning of the posterior pharynx. Figure 1 demonstrates gross anatomical images performed by rhinoscopy of a normal subject, allergic rhinitis, nasal polyps, and sinusitis. Chronic rhinosinusitis tends to be associated with mucopurulent discharge, whereas chronic rhinitis may reveal pale mucosa or clear discharge (Figure 1).

Confirming Diagnosis

After a careful history is performed, some clinicians may feel comfortable initiating empiric treatment for allergic rhinitis. However, when patients are refractory to treatment and/or have severe persistent

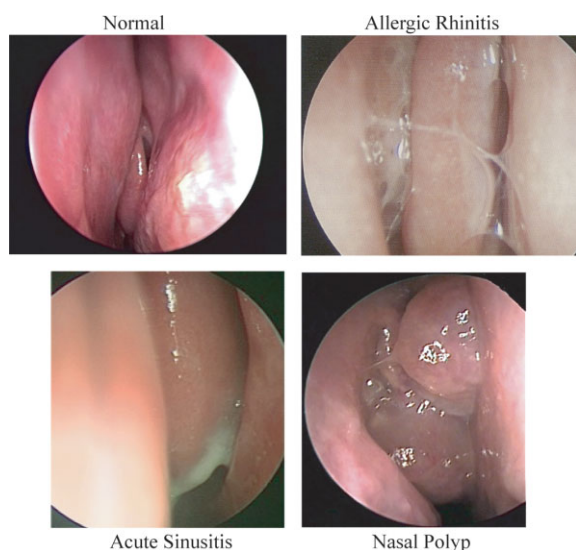


Fig 1. Rhinoscopic images of the nose and sinus reveal a normal subject, allergic rhinitis, the mucopurulent discharge associated with sinusitis, and a pearly white nasal polyp.

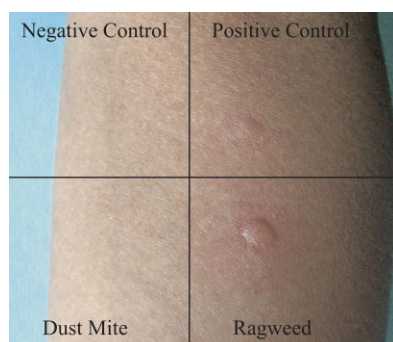


Fig 2. Skin prick testing of the forearm. A raised erythematous wheal indicates a positive test. The subject as shown was positive to histamine control and ragweed, and negative to saline control and dust mite. All skin test reagents were obtained from ALK-Abelló (Round Rock, TX).

symptoms, referral to an allergist for skin testing is recommended (Figure 2). It is essential to remember that before seeing an allergist, patients must discontinue antihistamines for ≥ 1 week—and possibly longer, depending on the antihistamine—to avoid false-negative skin test results. Negative allergen skin testing excludes the diagnosis of allergic rhinitis (Table 2), although it is important to note that in

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pediatric patients, symptoms may be present before positive skin tests appear.

Skin testing is useful in determining the reactivity of the patient against specific suspected allergens, and can ultimately help direct immunotherapy if it is indicated. Skin testing should only be carried out by a specialist because patients with allergic rhinitis may demonstrate positive skin tests to allergens other than those that are clinically relevant. Additionally, results may be altered by placement technique, the type of device used for testing, and the quality of extracts utilized.^{44,45}

Serum tests for IgE-specific allergen antibodies (referred to as fluorezymeimmunoassay or ImmunoCAP and more classically known as radioallergosorbent test or RAST) has limited utility and often results in data that is difficult to interpret in allergic rhinitis. In fact, as many as 25% of patients with a positive skin prick test have a negative serum IgE immunoassay for the same allergen.⁴⁶ Skin testing generally is more cost-effective and has a higher sensitivity. Immunoglobulin E antibody testing is indicated when high-quality extracts for skin testing are not available, when a negative control skin test is consistently positive, antihistamine therapy cannot be discontinued (which could result in false-negative results), when there is concern for anaphylaxis, or if widespread skin disease is present.

Total serum IgE levels and eosinophil count are typically not indicated in the diagnosis because they are neither sensitive nor specific for allergic rhinitis. Nasal cytology might aid in differentiating allergic rhinitis and NARES from other forms of rhinitis, however only if the correct procedure for collection is followed and the appropriate stains used.

MANAGEMENT

Avoidance

Comprehensive allergen-avoidance techniques are an effective first-line approach to reduce symptoms of allergic rhinitis in patients with documented positive skin tests.

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Dust Mite Avoidance

Dust mites tend to thrive in humid environments and create nests in sofas, carpets, bedding, and any woven material. It is predominantly the fecal material of the dust mite that triggers an allergic response^{47,48} and exposure to allergen occurs when an individual is in close proximity to debris during time spent in bed, on the floor, or on upholstered furniture, not simply from breathing in the air.⁴⁹ In fact, dust mite debris is undetectable in the air just 15 minutes after vigorous disturbance of a dust mite nest.⁵⁰ Therefore, the key to dust mite avoidance is creating an environment that is not conducive to dust mite nesting, such as the removal of carpets or curtains and removal of stuffed toys from rooms. Dust-proof covers on pillows and mattresses has a clinically modest but clearly measurable effect.⁵¹ The use of high-efficiency particulate air (HEPA) filtration is not effective, although wearing a mask while cleaning may be useful. Because dust mites thrive in moist environments, patients should control humidity to <50%⁵² by either using air conditioning in humid environments (more effective than dehumidifiers) or simply opening windows in drier environments. Bedding should be washed weekly in hot water (140°F) and dried under high heat in an electric dryer.⁵³ If it is not feasible to remove carpets, they should be vacuumed and/or cleaned frequently. Studies on treatment of carpets with insecticide or allergen denaturing proteins on reducing allergy symptoms are mixed, but do show a modest benefit.^{54–57} It is the combination of these avoidance measures that may provide the greatest reduction in symptoms.

Mold Avoidance

The key to indoor mold control is reducing humidity. This can be done by covering cold, moist surfaces such as water pipes with insulation, as well as increasing ventilation. A number of academic and federal agencies have developed guidelines for controlling mold in the home, and additional information can be found at the US Environmental Protection Agency Web site at <http://www.epa.gov/mold>. Visible mold should be removed from surfaces with detergent and water (bleach is unnecessary), and any areas where mold is imbedded should be removed or replaced.

Cockroach Avoidance

Although there are few studies looking at cockroach allergen in allergic rhinitis, most experts agree that the allergen should be eradicated. Currently, the focus is on keeping kitchens free of open food or unwashed

dishes, and bathrooms clean and dry. In addition, placing multiple baited traps is recommended.^{58,59}

Pet Dander Avoidance

There is irrefutable evidence that removal of pets from the home is the best way to control allergens from animals.⁶⁰ When cats are removed from the house, allergen may persist for up to 6 months,⁶⁰ so confining the animal to a single room in the house is not a sufficient avoidance measure. Daily cleaning or bathing of cats is not practical. Notably, the use of HEPA air filters is only useful after the pet is removed from the home, in conjunction with thorough cleaning. If the animal is still present, the filters can actually circulate and increase the quantity of allergen.^{61,62} The majority of people allergic to cat are sensitized to the Fel d 1 protein. A putative hypoallergenic cat Allerca is said to be under development commercially by breeding naturally deficient Fel d 1 cats. These cats cost as much as \$8000 or more; however, there is no peer-reviewed published data to support the claim that breeding low-Fel d 1 cats is successful or that these cats are better tolerated by allergic patients. Currently, there is no such thing as a true hypoallergenic cat or dog.

Outdoor Allergen Avoidance

Pollens in particular are very difficult to control because of their prevalence in the environment. On high-pollen-count days, patients with pollen and outdoor mold allergies should keep windows closed, use air conditioners to filter the air, and also stay inside as much as possible. Some clinicians recommend showering before bed to remove allergens in the hair and scalp.

Pharmacotherapy

Symptoms of allergic rhinitis can range from mild annoyance to severe debilitation. Because of the large selection of over-the-counter medications available to treat nasal and sinus symptoms, patients may self-medicate without actually knowing what they are treating. Often patients may have significant side effects to these medications, such as sleep disturbances, drowsiness, and rebound nasal congestion, in addition to large out-of-pocket expenses. Establishing a diagnosis and individualizing a patient's medication regimen is critical to managing this disease.

Nasal steroids are the mainstay of treatment for allergic rhinitis, and are first-line for moderate

to severe allergic rhinitis.⁶³ They are effective as monotherapy and improve all nasal symptoms, including congestion, sneezing, rhinorrhea, and itching.¹⁹ Multiple head-to-head trials have demonstrated their superior efficacy over antihistamines and leukotriene receptor agonists, even when these medications are used in combination.^{64,65} Nasal steroids are most effective if used on daily basis, even when symptoms are not present.⁶⁶ Systemic steroid therapy should only be used in the short term for severe cases of allergic rhinitis where standard intranasal steroid therapy is unsuccessful. Short courses of oral steroids for 3–7 days to open up severely obstructed, inflamed nasal passages can be appropriate, but is not for usage on a chronic basis.

Multiple studies have demonstrated safety of nasal steroids, particularly in children where there was initially a concern for systemic side effects, as well as a concern for bone fracture, glaucoma, and diabetes development in adults.⁶⁷ At the appropriate dosage, and particularly with second- and third-generation nasal steroids that have limited bioavailability (<1%) these medications are safe to use daily.^{68,69} However, due to lack of long-term data and the potential for a dose-accumulation effect over time, physicians should monitor patients closely.⁷⁰ Side effects include nasal drying, crusting, and bleeding. Septal perforation is a concern, particularly when patients inappropriately administer the spray. It is important to instruct patients to keep their head down, and point the tip of the spray away from the septum.⁷¹

For mild intermittent or mild persistent rhinitis, oral antihistamines (H1 blockers) are appropriate on an as-needed or daily basis, respectively. Second-generation H1 blockers are preferred as they are less sedating and have fewer anticholinergic effects. While not as efficacious as nasal steroids, they have a quicker onset of action and can help with ocular symptoms, and provide an alternative if patients cannot tolerate nasal sprays. Leukotriene receptor antagonists such as montelukast can be used for both intermittent or persistent allergic rhinitis. They can be useful adjuvant therapy when concomitant asthma is present. Intranasal cromolyn, a mast cell stabilizer, can be used prophylactically for the prevention of intermittent, or seasonal allergic rhinitis. However, patients should understand that cromolyn is not a medication for immediate symptom relief following acute allergen exposure, but rather it functions to prevent symptoms from occurring during allergy season. Cromolyn spray is not as effective as intranasal steroid, must be used 3–4× daily, and is slightly less effective than nasal antihistamine, but has a slightly better side-effect profile.⁷²

Oral decongestants such as pseudoephedrine reduce nasal congestion temporarily; however, patients should be educated that they should not be used regularly. Side effects include insomnia, palpitations, irritability, and hypertension. Nasal decongestants should also be avoided, as they can cause severe rebound rhinitis when discontinued.

Ipratropium nasal sprays are effective for cases of mixed rhinitis as well as nonallergic rhinitis, but they are suboptimal for pure allergic rhinitis management.

Immunotherapy

It has been 100 years since the discovery of the concept of allergen immunotherapy, and its effectiveness and safety has improved over time with the advent of extract standardization and research into mechanisms of action.^{73–76} Allergen immunotherapy is defined as

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the repeated administration of specific allergens to patients with IgE-mediated conditions to provide protection against allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.⁷⁶ Allergen immunotherapy should be considered for patients who continue to have moderate to severe symptoms despite maximal appropriate therapy or have coexisting conditions such as asthma or chronic sinusitis that are debilitating.⁷⁷

In general, allergen immunotherapy is well tolerated; however, adverse reactions may occur and include local skin irritation at the site of injection as well as systemic reactions that occur in approximately 5%–10% of patients. One to three percent of these systemic reactions are considered moderate to severe. Rarely, patients have died from anaphylaxis secondary to allergy immunotherapy.^{76,78}

Subcutaneous allergen immunotherapy (SCIT) is effective in approximately 75% of cases,^{79–81} and has the advantage of actually changing the course of disease and potentially decreasing the number of

medications a patient requires for control of symptoms. Subcutaneous allergen immunotherapy has also been shown to be cost-effective, particularly for patients who are on multiple medications.^{77,82} However, allergen immunotherapy requires a long-term commitment of weekly to monthly injections for approximately 3–5 years, and therefore is not

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appropriate for patients who will frequently miss injection visits.

New research has been undertaken using sublingual allergen immunotherapy (SLIT), which may have even fewer systemic side effects than SCIT. Although oral and sublingual itching and swelling frequently occurs, SLIT is considered a safe alternative to traditional immunotherapy.^{83–85} Currently, within the United States, there is no consensus on a therapeutic dose or overall feasibility of SLIT, although it is used regularly in Europe.

Omalizumab (a monoclonal anti-IgE antibody) has been shown to be effective for allergic rhinitis, even at very low dosages,⁸⁶ but it is not cost-effective for this condition. In patients with allergic rhinitis and concomitant, uncontrolled asthma, however, it should be considered.⁸⁷

Future therapies include the use of recombinant allergens, adjuvants, and DNA vaccines. Amb a 1, the major allergen in ragweed pollen, when combined into a vaccine with bacterial DNA (CpG) and given subcutaneously, was highly effective in treating a cohort of subjects with allergic rhinitis to ragweed.^{88,89} Of note, these patients were effectively treated with just 6 weekly injections with the Amb a 1-CpG vaccine.

One study on intranasal vaccines containing DNA oligodeoxynucleotides curbed allergic hyper-reactivity in mice.⁹⁰ Another study, in humans, looked at injecting allergen extract directly into lymph nodes. The method was highly effective, used less extract than what is used in traditional SCIT, and required only 4 injections.⁹¹ The addition of adjuvants such as monophosphoryl lipid A to immunotherapy extracts works to further modulate the immune system of the

allergic patient and thus enhance response to therapy. In one study, patients receiving monophosphoryl lipid A + allergen extract only required 4 injections to achieve clinical efficacy, compared with the 15–30 injections with traditional SCIT.⁹² Basic and clinical research in the field is ever-growing, and will likely increase the number of safe and effective management options for a variety allergic disease entities.

DISCLOSURES

Potential conflict of interest: Satish Govindaraj is on the speakers bureau for GlaxoSmithKline.

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