CLINICAL PRACTICE

Allergic Rhinitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A Baltimore college student has rhinorrhea, sneezing, nasal congestion, and itchy, watery eyes in the spring. He reports having had similar symptoms the previous spring. Over-the-counter allergy pills have failed to help his symptoms and caused dry mouth and somnolence. He wants relief and assurance that he will not be ill, have dry mouth, or feel drowsy during final examinations. On physical examination, his conjunctivae are injected, and his nasal mucous membranes are pale, wet, and boggy. What are your recommendations?

THE CLINICAL PROBLEM

Characteristics of allergic rhinitis and conjunctivitis[1] include sneezing, watery rhinorrhea, and nasal congestion; itchy palate; and itchy, red, and watery eyes. Blockage of the eustachian tubes, cough, and a sensation of pressure in the sinuses result from edema and venous engorgement of the nasal mucosa.[2,3] Allergic rhinitis occurs when inhaled allergens interact with IgE antibodies on cells in the airway.[4] Estimates of the prevalence of allergic rhinitis in the United States range from 8.8 percent[5] to 16 percent.[6]

STRATEGIES AND EVIDENCE

EVALUATION

History and Physical Examination

The history helps establish seasonality, year-to-year persistence, potentially inciting factors, and complicating conditions (including sinusitis, nasal polyps, and asthma). These conditions occur more frequently in patients with allergic rhinitis than in control populations; in one study, 19 to 38 percent of patients with allergic rhinitis were found to have coexisting asthma.[7]

The diagnosis can generally be made on the basis of the history and physical examination. The examination should easily detect signs of rhinitis and conjunctivitis and may reveal wheezing suggestive of associated asthma. Spirometry is useful in detecting subclinical asthma, and computed tomography most reliably reveals sinusitis in patients with symptoms of refractory rhinitis. Additional testing may be helpful if the diagnosis is uncertain or if the response to therapy is suboptimal. For example, blood or nasal eosinophilia suggests an allergic cause, whereas neutrophilia points to an infectious cause.

The severity of allergic rhinitis is assessed[2] by assigning numerical values for eye symptoms, nasal itching, sneezing, rhinorrhea, and nasal congestion (with 0 denoting none, 1 mild, 2 moderate, and 3 severe), taking into account subjective intensity and whether these symptoms interfere with sleep, leisure, and school or work activities, or the duration of symptoms each day (with 0 denoting none, 1 denoting less than 30 min-

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utes, 2 denoting 30 minutes to 2 hours, and 3 denoting more than 2 hours).

Allergy Testing

Allergy testing is performed in order to confirm which allergens are relevant to the symptoms and which should be included in immunotherapy regimens. Culpable allergens can be identified by skin or in vitro tests for the presence of allergen-specific IgE antibodies.[1] A patient with an annual recurrence of symptoms is likely to be reacting to seasonal pollen or other environmental triggers. Allergens contained in dust-mite excreta, in the epidermis and saliva of furred pets, in cockroach bodies, and in fungal spores are present year-round. Testing is typically performed with a set of allergens relevant to the patient's environment. For example, a cat owner in Maryland with year-round symptoms might be tested with extracts of pollen from local trees, grasses, and weeds, as well as with allergens from house-dust mites, cockroaches, mold spores, and cats. The wheal and erythema response 15 to 20 minutes after the "prick" or intradermal application of the allergen is compared with negative (saline) and positive (histamine) controls.

In alternative procedures, in vitro tests for serum IgE antibody to allergens — including varieties of the radioallergosorbent test and enzyme-linked immunosorbent assay — estimate the amount of allergen-specific IgE antibody in a patient's serum, with sensitivity and specificity equal to that of skin testing. Although skin testing carries a very small risk of a systemic allergic reaction,[2] the immediacy of test results, which enables the practitioner to recommend strategies for allergen avoidance and provide the basis for an allergen immunotherapy regimen, is appealing.

ALLERGEN AVOIDANCE AND PHARMACOTHERAPIES

Treatment strategies depend on modulation of the immune response so as to interfere with the function of IgE antibodies, interruption of the release of antigen-induced autacoids (histamine and eicosanoids) from IgE-sensitized cells, inhibition of the autacoid effect at receptor sites, and the resolution of allergic inflammation.

Allergen Avoidance

Although allergen avoidance is generally included in a treatment plan for allergic rhinitis, controlled trials of the avoidance of outdoor allergens by staying indoors are not feasible. Limited studies, which were reviewed in a meta-analysis[8] of the avoidance of house-dust mites with the use of high-efficiency particulate air (HEPA) filters (in one study), acaricides (in two studies), and mattress covers and hot-water laundering of bedding (in one study), demonstrated that active treatment reduced both the levels of house-dust mites and rhinitis symptom scores. In children with allergen-driven asthma, environmental interventions reduced wheezing in proportion to the reduction in the levels of cockroach and house-dust-mite allergens; however, effects on allergic rhinitis were not evaluated.[9]

Randomized trials involving patients with allergic rhinitis showed the effectiveness of several therapeutic approaches (Table 1).[2,10-14]

Oral Antihistamines

Antihistamines[21] were introduced more than 50 years ago for the treatment of allergic rhinitis. However, although these first-generation antihistamines are clinically effective, their use is limited by their anticholinergic and sedative effects, such as impaired performance of tasks,[2] although some data suggest that the magnitude of the effects on performance has been overstated.[22] More recently, second-generation antihistamines lacking substantial sedative properties have largely supplanted the earlier drugs (Table 1). Antihistamines substantially reduce symptoms of nasal itching and watery eyes and have moderate but clinically and statistically significant effects in reducing rhinorrhea and sneezing. However, these agents have minimal effects on the symptoms of nasal congestion.[2,23] Clinical trials comparing various second-generation antihistamines demonstrate approximate equivalence in the reduction of symptoms, with only small and inconsistent statistical differences.[21,24] There is no evidence that any particular drug in this class is superior on the basis of the type of allergen inciting symptoms.

Some observers have suggested a combination of a first-generation over-the-counter antihistamine (all of which are soporific) at bedtime and a second-generation antihistamine during the day. However, the efficacy and side effects of such regimens have not been rigorously evaluated, and next-day sedation has been observed with such a regimen.[25]

Nasal Corticosteroids

Nasal corticosteroids are recommended as first-line therapy for moderate-to-severe allergic rhinitis.[2] Second-generation antihistamines are gener-

Table 1. Therapies for Allergic Rhinitis.*

Class of Agents	Method of Action	Indication	Examples and Adult Doses	Major Side Effects
Second-generation antihistamine†	Blocks H_1 receptors; inhibits autacoid release	Reduces sneezing, ocular and nasopharyngeal itching, rhinorrhea	Fexofenadine (Allegra), 180 mg once daily; cetirizine (Zyrtec), 5–10 mg once daily; loratadine (Claritin, Alavert), 10 mg once daily; desloratadine (Clarinex), 5 mg once daily; azelastine (Astelin), 2 sprays/nostril twice daily	Mild sedation, dry mouth in minority of patients‡
Nasal corticosteroid	Inhibits influx of inflammatory cells	Reduces sneezing, ocular and nasopharyngeal itching, rhinorrhea, mucosal congestion	Beclomethasone (Beconase), 1–2 sprays/nostril twice daily; budesonide (Rhinocort), 1–4 sprays/nostril once daily; fluticasone (Flonase), 2 sprays/nostril once daily; mometasone (Nasonex), 2 sprays/nostril once daily; flunisolide (Nasalide), 2 sprays/nostril two or three times daily; triamcinolone (Nasalcort), 2 sprays/nostril once daily	Nosebleed, nasal septal perforation, other systemic corticosteroid effects§
Leukotriene-receptor antagonist	Blocks leukotriene receptors	Reduces mucosal inflammation	Montelukast (Singulair), 10 mg once daily	Elevated levels of AST, ALT, bilirubin¶
Anticholinergic agent	Blocks acetylcholine receptors	Reduces copious rhinorrhea	Ipratropium (Atrovent Nasal), 2 sprays/nostril two or three times daily	Headache, nosebleed
Mast-cell stabilizer	Inhibits histamine release (animal evidence)	Reduces rhinitis symptoms	Cromolyn (Nasalcrom), 1 spray/nostril three or four times daily	Sneezing, nasal irritation, nosebleed
Topical agents for ocular use				
Mast-cell stabilizer	Inhibits histamine release (animal evidence)	Relieves allergic conjunctivitis	Cromolyn (Crolom), nedocromil (Alocril), lodoxamide (Alomide), dose varies with agent	Ocular discomfort
Antihistamine	Blocks H_1 receptors; inhibits autacoid release	Relieves allergic conjunctivitis	Various antihistamines, 1 drop two or three times daily	Ocular discomfort
Nonsteroidal antiinflammatory drug	Unknown	Relieves allergic conjunctivitis	Ketorolac (Acular), 1 drop four times daily)	Ocular discomfort

α-Adrenergic agonist	Acts as vasoconstrictor	Relieves nasal congestion	Pseudoephedrine (Sudafed), 30–60 mg every 4 hr; slow-release, 120 mg every 12 hr or 240 mg every 24 hr	Arrhythmias, hypertension, insomnia, nervousness
Oral corticosteroid	Inhibits influx of inflammatory cells	May be considered for severe symptoms unresponsive to nasal corticosteroids, especially congestion	Prednisone (Deltasone), 7.5–15 mg daily; methylprednisolone (Medrol), 6–12 mg daily; triamcinolone (Aristocort), 6–12 mg daily	Systemic corticosteroid effects, adrenal suppression if used for >2 wk
Injected depot corticosteroid	Inhibits influx of inflammatory cells	May be considered for severe symptoms unresponsive to nasal corticosteroids, especially congestion	Triamcinolone (triamcinolone acetonide), 80 mg preseason	Systemic corticosteroid effects, adrenal suppression
Allergen immunotherapy‖				
Aqueous (administered subcutaneously)	Modulates immune response	Relieves symptoms unresponsive to antihistamines and nasal corticosteroids	Doses not standardized; maintenance immunotherapy with 5–20 μg of major allergens per injection**	Systemic reactions including anaphylaxis
Alum-precipitated or formaldehyde-treated ("allergoid") (administered subcutaneously)††	Modulates immune response	Relieves symptoms unresponsive to antihistamines and nasal corticosteroids	Doses not standardized	Systemic reactions (low rate)
Sublingual	Modulates immune response	Relieves symptoms unresponsive to antihistamines and nasal corticosteroids	Doses not standardized	Low risk of systemic reactions

* All drugs listed in this table have proved superior to placebo in randomized trials.[2,10-14] Loratadine, cetirizine, budesonide, montelukast, nedocromil, lodoxamide, ipratropium, and cromolyn are in the Food and Drug Administration's Pregnancy Category B, which is defined as drugs that have not been shown to pose a risk to the fetus in studies in animals and that have not been adequately tested in pregnant women. All other drugs, except for allergen immunotherapy, are in Category C, which is defined as drugs that have been shown to have an adverse effect on the fetus in studies in animals and that have not been adequately tested in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.[15,16] Allergen immunotherapy is not classified according to these pregnancy criteria.[15-17]

† First-generation antihistamines are not listed because, although they are effective, they are less selective and are associated with considerable sedation and anticholinergic side effects. Antihistamines are generally the first-line agent for mild symptoms. Oral forms are available for all drugs except for azelastine nasal spray. Loratadine is the only second-generation antihistamine that is currently available over the counter.

‡ Most orally administered second-generation antihistamines are free of significant side effects. Somnolence and dry mouth are possible when amounts exceeding recommended doses are taken. Cetirizine at a dose of 10 mg has been associated with psychomotor impairment.[18]

§ Beclomethasone may cause delay in obtaining normal height in children.

¶ AST denotes aspartate aminotransferase, and ALT alanine aminotransferase.

‖ Although immunotherapy is not known to harm the fetus, it is not initiated during pregnancy in order to avoid the risk of harm to the fetus from a systemic allergic reaction; for the same reason, immunotherapy doses are not increased and are often reduced until the postpartum period.

** Data are from Ewbank et al.[19]

†† Data are from Bousquet et al.[20]

ally preferred for the treatment of mild allergic rhinitis owing to their safety and ease of use, although nasal corticosteroids are also considered safe.

Symptoms, including nasal congestion, are better relieved by nasal corticosteroids than by placebo.[2] A meta-analysis has compared the effects of oral antihistamines and nasal corticosteroids with respect to symptoms of allergic rhinitis. There was a clinically and statistically significant benefit to nasal corticosteroids over antihistamines for nasal congestion and sneezing. In contrast, there was no significant difference between nasal corticosteroids and antihistamines in relieving ocular symptoms.[10] Similar results were obtained in a meta-analysis of nasal antihistamines and nasal corticosteroids.[11]

The Montreal protocol, an international treaty to protect the ozone layer, dictates the eventual replacement of medications using chlorofluorocarbon-based propellants. Aqueous preparations of nasal corticosteroids with negligible systemic activity have replaced Freon-propelled products. Recently, the Food and Drug Administration has approved a product using hydrofluoroalkane as the propellant.[26] All nasal corticosteroids have been more effective than placebo in preventing symptoms of rhinorrhea and nasal obstruction when used daily during periods of allergen exposure.[27] Table 1 lists currently available preparations.

Nasal corticosteroids have relatively few adverse effects.[27-30] The most common effect is epistaxis, which occurs in 10 percent of cases[31] and rarely requires discontinuation of the drug. A delay in the attainment of normal height has been reported in children using intranasal beclomethasone but not other nasal corticosteroids[29]; increased intraocular pressure and posterior subcapsular cataracts have been reported in adults.[28,30] However, these complications are uncommon and less likely with doses administered intranasally than with the higher doses sometimes used for oral inhalation in asthma.[28,30]

Antihistamines Combined with Nasal Corticosteroids

Data are lacking from rigorous studies to demonstrate that combination therapy with antihistamines and nasal corticosteroids is superior to nasal corticosteroids alone. Because antihistamines and nasal corticosteroids influence different pathogenetic mechanisms, patients with moderate or severe symptoms are commonly treated with both. In practice, combination therapy is often used for patients who do not have a response to a single agent. In a study testing an algorithm for management, such therapy was the standard for patients with moderate or severe rhinitis.[32] After control of symptoms with the use of combination therapy, it is reasonable to attempt to discontinue one of the agents when symptoms have abated.

Leukotriene-Receptor Antagonists

The leukotriene-receptor antagonist montelukast is superior to placebo in relieving nasal symptoms in patients with allergic rhinitis.[12] However, the drug is relatively weak as monotherapy. A meta-analysis demonstrated that, as compared with placebo, montelukast induced a moderate but significant reduction in scores for daily symptoms of rhinitis; in comparison, nasal corticosteroids induced a significant and substantial reduction in symptom scores.[12] Thus, montelukast's role is generally as an adjunct in the treatment of a patient who does not have an adequate response to an antihistamine, a nasal corticosteroid, or both. However, there are no clear data demonstrating that leukotriene-receptor antagonists combined with either antihistamines or nasal corticosteroids reduce symptom scores more than the antihistamines or corticosteroids alone.

Mast-Cell Stabilizers

The cromone cromolyn is available over the counter for intranasal use. It has proved to be significantly better than placebo at reducing nasal symptoms in some trials, but data are inconsistent, and its effects are modest. Cromolyn may be more effective when administered just before exposure to an allergen,[2] such as when a person with a sensitivity to feline allergens visits a cat owner.

Ophthalmic Preparations

The mast-cell stabilizers, ocular antihistamines, and the nonsteroidal antiinflammatory drug ketorolac are all used topically in ophthalmic preparations for allergic conjunctivitis (Table 1). Randomized, controlled trials have demonstrated that these agents significantly reduce ocular symptoms, including itching, and improve sleep.[33] For predominantly ocular symptoms, one of these preparations alone may suffice. Patients with refractory ocular symptoms should be referred to an ophthalmologist.

Intranasal Agents

Nasal antihistamines are considered to be similar in efficacy to oral antihistamines,[2,10,11] and one trial suggested that nasal antihistamines relieve total nasal symptoms (and rhinorrhea, specifically) more effectively than oral antihistamines.[34] Nasal ipratropium, a quaternary ammonium compound related to atropine, relieves rhinorrhea in patients with allergic rhinitis, with effects similar to those of nasal corticosteroids in one study.[35]

α-Adrenergic Agonists

Pseudoephedrine, an α-adrenergic–receptor agonist, counters vascular engorgement of the turbinates, improving nasal air flow.[36] There have been few evaluations of pseudoephedrine alone. In one study, the combination of pseudoephedrine and an antihistamine was significantly more effective in reducing total nasal symptoms, including nasal congestion, than was either agent alone.[37] Another report showed that the combination of an antihistamine and pseudoephedrine was at least as effective as nasal beclomethasone for nasal symptoms and was superior for relief of ocular symptoms.[38] Some patients with severe nasal congestion that is resistant to treatment with a nasal corticosteroid may respond to a combination of antihistamine and pseudoephedrine. However, pseudoephedrine should be used cautiously in patients with coronary artery disease, hypertension, diabetes, or hyperthyroidism and in those receiving monoamine oxidase inhibitors, given its sympathomimetic effects. The drug may also aggravate narrow-angle glaucoma and symptoms of bladder-neck obstruction.[36]

Systemic Corticosteroids

Rarely, patients with severe symptoms who do not have a response to or are intolerant of other medications may be treated with either oral or injected systemic corticosteroids. Treatment regimens include either a preseasonal intramuscular injection of a dose of depot corticosteroids (the equivalent of 100 mg of prednisone) or oral corticosteroids, administered for several weeks in either alternate-day or daily doses of the equivalent of 7.5 to 15 mg of prednisone, although starting doses as high as 20 to 40 mg of prednisone per day may be required for complete relief of symptoms.[39] One controlled trial showed that the depot injection was more efficacious than oral therapy,[40] but there is concern that suppression of endogenous corticosteroids might be greater with parenteral injections. The well-recognized risks associated with the prolonged use of corticosteroids make other therapies preferable.

Algorithm-Guided Treatment

A recent controlled study[32] found that therapy directed by a set of simple guidelines was more effective than therapy chosen by physicians. The selection of a regimen — either an oral antihistamine (for mild rhinitis) or a combination of oral antihistamine and intranasal corticosteroid (for moderate or severe rhinitis) — was based on a visual-analogue scale of 0 to 100 mm for the severity of symptoms of nasal discharge, nasal congestion, and sneezing. Patients whose scores were 50 mm or more for any one of the symptoms were categorized as having moderate-to-severe disease. In addition, ocular cromone was used for moderate or severe conjunctivitis on the basis of a visual-analogue scale for severity of conjunctivitis. The study predominantly included patients with moderate or severe rhinitis. Patients who were randomly assigned to receive treatment as outlined in the algorithm had significantly less severe symptoms and better indexes of quality of life than those in the control group, perhaps because 84 percent of the patients received inhaled corticosteroids, as compared with 32 percent in the control group.[32]

Allergen Immunotherapy

According to expert guidelines, allergen immunotherapy should be considered for patients who continue to have moderate-to-severe symptoms despite therapy, who require systemic corticosteroids, who have an inadequate response to the recommended doses of nasal corticosteroids, or who have coexisting conditions such as sinusitis, asthma, or both.

Subcutaneous allergen immunotherapy consists of an open-ended schedule of weekly doses of a solution containing the culpable allergens that gradually increase to an optimal maintenance dose (Table 1).[19] Maintenance doses are often given at intervals ranging from two to six weeks; data are lacking to compare various dosing frequencies. The magnitude of symptom reduction during immunotherapy is variable, although in some trials patients had a reduction of more than two thirds in symptoms and medication scores.[41] Immunotherapy may also confer long-term benefits; it is the only intervention for allergic rhinitis that alters the natural history of disease.

In one study of adults with allergic rhinitis who

Table 2. Expert Guidelines for the Treatment of Allergic Rhinitis.

Source of Guidelines	Allergy Report[54]	Joint Task Force on Practice Parameters for Rhinitis[23]	European Academy of Allergology and Clinical Immunology[55]	Allergic Rhinitis and Its Impact on Asthma (ARIA)[2]
Type of statement	Expert panel	Expert panel	Consensus statement	Expert panel
Diagnostic testing for IgE antibody	Indicated if symptoms persist, if quality of life is affected, or if immunotherapy is considered	Indicated to confirm allergic cause and to identify allergens to avoid, or for immunotherapy	No comment	Indicated to confirm allergic cause
Allergen avoidance	Indicated for all patients	Indicated for all patients, including the use of air conditioning for control of outdoor allergens	Indicated for all patients	Indicated for all patients
Antihistamine				
First-generation (oral)	Not recommended	Not recommended	Not recommended	Not recommended
Second-generation (oral, intranasal, or ophthalmic)	Indicated as mainstay for mild-to-moderate disease and in combination with nasal corticosteroids for severe disease; ophthalmic preparation indicated for conjunctivitis	Indicated as first-line therapy and for prophylactic use, but not effective alone for nasal congestion	Indicated as first-line therapy, but not effective alone for nasal congestion	Indicated as first-line therapy, but not effective alone for nasal congestion; ophthalmic preparation indicated for conjunctivitis
Decongestant (oral)	Indicated in combination with antihistamine	Indicated to reduce nasal congestion in combination with oral antihistamine	Indicated in combination with antihistamine to treat nasal congestion but for no more than 10 days	Indicated in combination with antihistamine to treat nasal congestion but for no more than 10 days
Corticosteroid				
Nasal	Indicated as primary agent for severe disease and for nasal obstruction, but relief is less rapid than with antihistamines	Indicated especially for severe disease	Indicated as first-line treatment for moderate or severe or persistent disease, despite slow onset of action (12 hr); effective for nasal congestion, particularly in perennial allergic rhinitis	Indicated as first-line treatment for moderate or severe disease, despite slow onset of action (12 hr); effective for nasal congestion
Oral or depot	Oral therapy: indicated for up to 7 days for severe symptoms or to control symptom exacerbations; depot therapy: not recommended	Oral therapy: indicated for severe or intractable disease; depot therapy: not recommended because of potential side effects	Oral therapy: only as last resort; depot therapy: may be more effective than oral therapy, according to some data	Oral therapy: as last resort if other treatments ineffective; depot therapy: may be more effective than oral therapy, but ability to adjust dosage is reduced

Mast-cell stabilizer (intranasal or ophthalmic)	Safe and effective but less effective than antihistamine or nasal corticosteroid; ophthalmic preparation recommended for conjunctivitis	Safe and effective in some patients, especially if begun early in season	Safe and effective, but less effective than antihistamine and nasal corticosteroid	Safe and effective, but less effective than antihistamine and nasal corticosteroid; ophthalmic preparation recommended for conjunctivitis
Intranasal anticholinergic	Ipratropium indicated to reduce rhinorrhea not controlled by other medications	Indicated to reduce rhinorrhea, but no effect on other symptoms	Indicated for perennial allergic rhinitis, but reduces only nasal hypersecretion	Ipratropium indicated to reduce nasal hypersecretion
Leukotriene-receptor antagonist	No comment	No comment	No comment	Indicated with modest evidence of efficacy
Allergen immunotherapy				
Subcutaneous	Indicated if response to primary therapy is poor, if compliance with pharmacotherapy is low, or if complications (asthma, sinusitis, otitis) are present	Indicated if symptoms are severe or protracted or if other treatment fails; to prevent progression or the development of complicating illnesses	Indicated if only 1 or 2 relevant allergens and pharmacotherapy and avoidance therapy are insufficient; risk of systemic effects	Indicated for severe or persistent disease if avoidance therapy and pharmacotherapy have insufficient response or side effects
Sublingual	No comment	No comment	Indicated for same conditions as subcutaneous allergen immunotherapy and for seasonal allergic rhinitis; may be safer than subcutaneous immunotherapy	Indicated for same conditions as subcutaneous allergen immunotherapy for patients who have systemic reactions or poor compliance or refuse injections
Referral to allergist–immunologist or other specialist	Indicated if response to environmental control is poor, if >2 courses/year of oral corticosteroids are required, if complications of rhinitis are chronic or recurrent (e.g., sinusitis, eustachian-tube dysfunction, asthma), or if immunotherapy is considered	Indicated if response to drugs is poor; if immunotherapy is considered, if there are complications of rhinitis (e.g., sinusitis), if systemic corticosteroids are needed to control symptoms, or if symptoms persist for >3 mo	No comment	Indicated if treatment result is inadequate after 3 mo

were treated with immunotherapy, a reduction of two thirds in symptoms and medication scores persisted for at least three years after the termination of treatment.[41] A number of studies have shown persistent effects after allergen immunotherapy was stopped.[42] In addition, in a study of children between the ages of 6 and 14 years with allergic rhinitis, those who had been treated with immunotherapy had a significantly lower rate of the development of asthma than those who had not been so treated (25 percent vs. 45 percent after three years of immunotherapy).[43] In the subgroup of children who were sensitized to only a single allergen (house-dust mite), as distinguished from those sensitized to multiple allergens, the likelihood that IgE antibodies would develop into new allergens was markedly lower among patients who had undergone immunotherapy than among those who had not.[44,45] The mechanisms underlying these effects are not fully understood.

However, the risk of systemic reactions during immunotherapy is substantial. Approximately 5 to 10 percent of patients who receive allergen immunotherapy have systemic reactions, which are moderately severe in 1 to 3 percent of patients; rarely, patients have even died from anaphylaxis.[2,23,46,47] Other problems with immunotherapy include the nuisance of frequent injections and uncertainty regarding the optimal strength of extracts and the stability of allergen mixtures.[48] Thus, despite its benefit and evidence that it is cost-effective,[23] immunotherapy is generally considered a second-tier therapy. Issues concerning immunotherapy in pregnancy are addressed in Table 1.

Subcutaneous immunotherapy with allergens modified by precipitation with alum or chemically treated with formaldehyde or glutaraldehyde ("allergoids")[20] is used in Europe, although not in the United States. There are data indicating that its efficacy is equivalent to that of standard subcutaneous immunotherapy.[20]

Allergen immunotherapy can also be administered sublingually. Although mild oral and sublingual itching occurs, there have been no reports of systemic reactions to this therapy despite extensive use in Europe. The rarity of systemic reactions suggests that this therapy is safer than subcutaneous immunotherapy. However, the efficacy of sublingual therapy is apparently less than that of subcutaneous immunotherapy.[49] Sublingual immunotherapy is not yet available in the United States.

AREAS OF UNCERTAINTY

Long-term effects of immunotherapy (for example, the potential to reduce the risk of the development of asthma) require further study. Another potential approach is the administration of a humanized monoclonal anti-IgE antibody (omalizumab). In a placebo-controlled trial, this treatment resulted in a reduction in symptoms of more than 50 percent,[14,50] and the combination of omalizumab and allergen immunotherapy had at least additive effects.[51] However, this agent is not currently approved for the treatment of allergic rhinitis and is costly.

Recent experimental approaches to immunotherapy for allergic rhinitis have involved the use of agents that stimulate the innate immune system through specialized toll-like receptors (TLRs) — either TLR9 (stimulated by immunostimulatory sequences of DNA)[52] or TLR4[53] — or immunization with peptides of allergens. TLR9 stimuli have been provided either alone or conjugated to allergens. Further work is required to evaluate the efficacy and safety of such therapies and to determine whether the preparation of large numbers of conjugated allergens is feasible.

GUIDELINES

Four sets of guidelines from expert panels, two in the United States and two in Europe, are shown in

Table 3. Treatment Outline for the Management of Allergic Rhinitis.

Verify the cause of allergic symptoms with the use of history and tests
Reduce exposure to allergens
Start an inhaled nasal corticosteroid, an oral second-generation antihistamine, or both*
For resistant nasal symptoms, add a leukotriene-receptor antagonist; for resistant itching or tearing eyes, add an ocular antihistamine, mast-cell stabilizer, or nonsteroidal antiinflammatory drug
Consider immunotherapy if quality of relief with medication is inadequate, to forestall progression of disease, or if patient is affected by allergy-induced complicating illnesses (e.g., sinusitis and asthma)

* An antihistamine may be combined with an α-adrenergic agent if nasal congestion is prominent. Azelastine nasal spray is an alternative to an oral antihistamine.

Table 2.[2,23,54,55] These guidelines are in general agreement with one another and with the discussion in this article.

SUMMARY AND CONCLUSIONS

Mild symptoms of allergic rhinitis are easily ameliorated with either an oral antihistamine or a nasal corticosteroid alone. For patients with moderate-to-severe symptoms of allergic rhinitis with nasal congestion as a predominant finding, such as the student in the vignette, therapy should generally be started with the daily use of a nasal corticosteroid, which would reasonably be combined with a second-generation oral antihistamine (Table 3). Therapy should be started before the anticipated appearance of allergens and continue during the time of likely exposure. In the case described, this would mean starting before the appearance of tree pollen in the Baltimore area (usually in early March) and continuing through the peak of the grass-pollen season in May and June. If eye symptoms persist, an ocular antihistamine could be added. If symptom relief is incomplete, if there is a need for a high inhaled dose of a corticosteroid or a systemic corticosteroid, or if rhinitis is complicated by asthma or sinusitis, the initiation of immunotherapy (on the basis of the patient's history and allergy testing) before the next season of symptoms should be considered.

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