### CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., Editor

# 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 35-year-old woman has a history of nasal congestion on most days of the year, dating back to her late teens. She has chronic nasal drainage, which is clear and thick. Her congestion is worst in the late summer and early fall and again in the early spring; at these times, she also has sneezing, nasal itching, and cough. Five years ago, she had an episode of shortness of breath with wheezing on a day when her nasal symptoms were severe, but this episode resolved spontaneously and has not recurred. Her eyes do not bother her. Over-the-counter oral antihistamines help her symptoms a little, as do nasal decongestants, which she uses occasionally. Her 6-year-old son has similar symptoms. How should this case be managed?

# THE CLINICAL PROBLEM

Allergic rhinitis is defined as symptoms of sneezing, nasal pruritus, airflow obstruction, and mostly clear nasal discharge caused by IgE-mediated reactions against inhaled allergens and involving mucosal inflammation driven by type 2 helper T (Th2) cells.<sup>1</sup> Allergens of importance include seasonal pollens and molds, as well as perennial indoor allergens, such as dust mites, pets, pests, and some molds. The pattern of dominant allergens depends on the geographic region and the degree of urbanization, but the overall prevalence of sensitization to allergens does not vary across census tracts in the United States.<sup>2</sup> Sensitization to inhaled allergens begins during the first year of life; sensitization to indoor allergens precedes sensitization to pollens. Because viral respiratory infections occur frequently in young children and produce similar symptoms, it is very difficult to diagnose allergic rhinitis in the first 2 or 3 years of life. The prevalence of allergic rhinitis peaks in the second to fourth decades of life and then gradually diminishes.<sup>3,4</sup>

The frequency of sensitization to inhalant allergens is increasing and is now more than 40% in many populations in the United States and Europe.<sup>2,5,6</sup> The prevalence of allergic rhinitis in the United States is approximately 15% on the basis of physician diagnoses<sup>7</sup> and as high as 30% on the basis of self-reported nasal symptoms.<sup>3</sup> Allergic rhinitis contributes to missed or unproductive time at work and school, sleep problems, and among affected children, decreased involvement in outdoor activities.<sup>7</sup> In addition, children with allergic rhinitis are more likely than unaffected children to have myringotomy tubes placed and to have their tonsils and adenoids removed.<sup>7</sup> The ability to control asthma in people with both asthma and allergic rhinitis has been linked to the control of allergic rhinitis.<sup>8</sup>

Most people with asthma have rhinitis. The presence of allergic rhinitis (seasonal or perennial) significantly increases the probability of asthma: up to 40% of people with allergic rhinitis have or will have asthma.<sup>9,10</sup> Atopic eczema frequently precedes allergic rhinitis.<sup>11</sup> Patients with allergic rhinitis usually have allergic conjunctivitis as well.<sup>12</sup> The factors determining which atopic disease will develop

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#### **KEY CLINICAL POINTS**

### ALLERGIC RHINITIS

- An estimated 15 to 30% of patients in the United States have allergic rhinitis, a condition that
  affects productivity and the quality of life in children and adults.
- Allergic rhinitis frequently coexists with asthma and other allergic diseases; most people with asthma have rhinitis.
- Intranasal glucocorticoids are generally the most effective therapy; oral and nasal antihistamines and leukotriene-receptor antagonists are alternatives. However, many patients do not obtain adequate relief with pharmacotherapy.
- Allergen immunotherapy should be used in patients with refractory symptoms or in those for whom pharmacotherapy is associated with unacceptable side effects.
- Two forms of allergen immunotherapy are now available: subcutaneous injections and rapidly dissolving sublingual tablets, the latter limited in the United States to the treatment of grass and ragweed allergy. Both forms of therapy generally provide sustained efficacy after the cessation of treatment.

in an individual person and the reasons why some people have only rhinitis and others have rhinitis after eczema or with asthma remain unclear. Having a parent with allergic rhinitis more than doubles the risk.<sup>13</sup> Having multiple older siblings and growing up in a farming environment are associated with a reduced risk of allergic rhinitis<sup>14,15</sup>; it is hypothesized that these apparently protective factors may reflect microbial exposures early in life that shift the immune system away from Th2 polarization and allergy.<sup>14,15</sup>

When persons are exposed to an allergen against which they are sensitized, cross-linking by the allergen of IgE bound to mucosal mast cells results in nasal symptoms within minutes (Fig. 1). This is due to the release of neuroactive and vasoactive substances such as histamine, prostaglandin D<sub>2</sub>, and cysteinyl leukotrienes.<sup>16</sup> During the next hours, through a complex interaction of mast cells, epithelial cells, dendritic cells, T cells, innate lymphoid cells, eosinophils, and basophils, Th2 inflammation develops in the nasal mucosa with the participation of a wide array of chemokines and cytokines produced by these cells.<sup>16,17</sup> As a consequence of mucosal inflammation, nasal symptoms can persist for hours after allergen exposure and the mucosa becomes more reactive to the precipitating allergen (priming) as well as to other allergens and to nonallergenic stimuli, such as strong odors and other irritants (nonspecific nasal hyperresponsiveness).18,19 Allergic rhinitis should be viewed as a constellation of these mechanisms and not as a simple acute reaction to allergen exposure.

#### STRATEGIES AND EVIDENCE

## DIAGNOSIS

The diagnosis of allergic rhinitis is often made clinically on the basis of characteristic symptoms and a good response to empirical treatment with an antihistamine or nasal glucocorticoid. Formal diagnosis is based on evidence of sensitization, measured either by the presence of allergen-specific IgE in the serum or by positive epicutaneous skin tests (i.e., wheal and flare responses to allergen extracts) and a history of symptoms that correspond with exposure to the sensitizing allergen. It is easier to diagnose the disease when seasonal symptoms are present or when the patient can clearly identify a single trigger than when symptoms are chronic or the patient reports more than one trigger, including allergens and irritants. Epicutaneous skin testing and testing for allergen-specific IgE have similar sensitivity, although they do not identify sensitization in an entirely overlapping group of patients.<sup>20</sup> The advantages of blood testing are that the patient does not need to stop taking antihistamines several days in advance and technical skills are not required to perform the test, whereas the advantage of skin testing is that it provides immediate results. Interpreting the results of either test requires knowledge of the allergens that are

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## Figure 1. Development of Allergic Sensitization, Immunologic Mechanisms of Nasal Reaction to Allergens, and Mechanisms of Symptom Generation in Allergic Rhinitis.

As shown in Panel A, sensitization involves allergen uptake by antigen-presenting cells (dendritic cells) at a mucosal site, leading to activation of antigen-specific T cells, most likely at draining lymph nodes. Simultaneous activation of epithelial cells by nonantigenic pathways (e.g., proteases) can lead to the release of epithelial cytokines (thymic stromal lymphopoietin [TSLP], interleukin-25, and interleukin-33), which can polarize the sensitization process into a type 2 helper T (Th2) cell response. This polarization is directed toward the dendritic cells and probably involves the participation of type 2 innate lymphoid cells (ILC2) and basophils, which release Th2-driving cytokines (interleukin-13 and interleukin-4). The result of this process is the generation of Th2 cells, which, in turn, drive B cells to become allergen-specific IgE-producing plasma cells. MHC denotes major histocompatibility complex. As shown in Panel B, allergen-specific IgE antibodies attach to high-affinity receptors on the surface of tissue-resident mast cells and circulating basophils. On reexposure, the allergen binds to IgE on the surface of those cells and cross-links IgE receptors, resulting in mast-cell and basophil activation and the release of neuroactive and vasoactive mediators such as histamine and the cysteinyl leukotrienes. These substances produce the typical symptoms of allergic rhinitis. In addition, local activation of Th2 lymphocytes by dendritic cells results in the release of chemokines and cytokines that orchestrate the influx of inflammatory cells (eosinophils, basophils, neutrophils, T cells, and B cells) to the mucosa, providing more allergen targets and up-regulating the end organs of the nose (nerves, vasculature, and glands). Th2 inflammation renders the nasal mucosa more sensitive to allergen but also to environmental irritants. In addition, exposure to allergen further stimulates production of IgE. As shown in Panel C, mediators released by mast cells and basophils can directly activate sensory-nerve endings, blood vessels, and glands through specific receptors. Histamine seems to have direct effects on blood vessels (leading to vascular permeability and plasma leakage) and sensory nerves, whereas leukotrienes are more likely to cause vasodilatation. Activation of sensory nerves leads to the generation of pruritus and to various central reflexes. These include a motor reflex leading to sneezing and parasympathetic reflexes that stimulate nasal-gland secretion and produce some vasodilatation. In addition, the sympathetic drive to the erectile venous sinusoids of the nose is suppressed, allowing for vascular engorgement and obstruction of the nasal passages. In the presence of allergic inflammation, these end-organ responses become up-regulated and more pronounced. Sensory-nerve hyperresponsiveness is a common pathophysiological feature of allergic rhinitis.

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seasonal pattern.

The differential diagnosis includes forms of rhinitis that are nonallergic in origin such as a noninflammatory rhinopathy (also known as vasomotor rhinitis) and nonallergic chronic rhinosinusitis.<sup>17</sup> In allergy clinics, only about one in four to five patients with rhinitis receives a diagnosis of nonallergic rhinitis, but this estimate is biased by the nature of referrals to such clinics; in the general population, the prevalence of nonallergic rhinitis is higher and may be close to 50% of all cases of rhinitis.<sup>21</sup> Some studies using nasal allergen-provocation testing as the diagnostic standard have suggested that more than half of patients classified as having nonallergic rhinitis on the basis of negative serum IgE or skin testing have "local allergic rhinitis" associated with production of allergenspecific IgE antibodies limited to the mucosa,<sup>22</sup> but this observation requires further study, and the measurement of allergen-specific IgE in nasal fluid is restricted to research.

Seasonal symptoms can be caused by viral infections, especially if the patient is a child or lives with children; rhinovirus has a marked peak in incidence in September and a smaller peak in the spring.<sup>23</sup> Allergic rhinitis can coexist with tamines have not shown superiority of any spe-

important in the geographic region and their nonallergic forms (mixed rhinitis), but sensitivity of the nose to nonspecific stimuli can be experimentally induced by allergen provocation in people with allergic rhinitis, which suggests that the "nonallergic" component may simply represent a state of nasal hyperresponsiveness rather than the coexistence of two distinct entities.<sup>24</sup>

# TREATMENT

# Pharmacotherapy

Pharmacologic treatment options include H<sub>1</sub>antihistamines, intranasal glucocorticoids, and leukotriene-receptor antagonists (Table 1). The majority of randomized trials of these agents have involved patients with seasonal allergic rhinitis, but the few trials involving patients with perennial allergic rhinitis support efficacy in that condition as well.

Therapy usually starts with oral antihistamines, frequently initiated by the patient, because a variety of these agents are available over the counter. Later-generation antihistamines are less sedating than older agents and are just as effective, so they are preferred.25,26 Because of their relatively rapid onset of action, antihistamines can be used on an as-needed basis. The few head-to-head trials of nonsedating antihis-

Table 1. Pharmacotherapy and Immunotherapy for Allergic Rhinitis.*	
Type of Symptoms	Recommended Treatment Options
Episodic symptoms	Oral or nasal $H_1\text{-}antihistamine,$ with oral or nasal decongestant if needed
Mild symptoms, seasonal or perennial	Intranasal glucocorticoid,† oral or nasal H1-antihistamine, or leukotriene- receptor antagonist (e.g., montelukast)
Moderate-to-severe symptoms‡	Intranasal glucocorticoid,§ intranasal glucocorticoid plus nasal H₁-antihista- mine,¶ or allergen immunotherapy administered subcutaneously or sub- lingually (the latter for grass or ragweed only)∥

\* Common or severe adverse effects are as follows: for oral antihistamines, sedation and dry mouth (predominantly with older agents); for nasal antihistamines, bitter taste, sedation, and nasal irritation; for oral decongestants, palpitations, insomnia, jitteriness, and dry mouth; for nasal decongestants, rebound nasal congestion and the potential for severe central nervous system and cardiac side effects in small children; for leukotriene-receptor antagonists, bad dreams and irritability; for nasal glucocorticoids, nasal irritation, nosebleeds, and sore throat; for sublingual immunotherapy, oral pruritus and edema, systemic allergic reactions (epinephrine auto-injectors are advised per the package insert), and eosinophilic esophagitis; and for subcutaneous immunotherapy, local and systemic allergic reactions (therapy should be administered only in a setting where emergency treatment is available).

† Intranasal glucocorticoids are more efficacious than oral antihistamines or montelukast, but the difference may not be as evident if the symptoms are mild.

‡ Moderate to severe allergic rhinitis is defined by the presence of one or more of the following: sleep disturbance, impairment of usual activities or exercise, impairment of school or work performance, or troublesome symptoms.

 $\S$  An oral H1-antihistamine plus montelukast is an alternative for patients for whom nasal glucocorticoids are associated with unacceptable side effects or for those who do not wish to use them; the efficacy of this combination is not unequivocally inferior to that of an intranasal glucocorticoid.

This combination is more efficacious than an intranasal glucocorticoid alone.

Allergen immunotherapy should be used in patients who do not have adequate control with pharmacotherapy or who prefer allergen immunotherapy.

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cific agent over another.<sup>27</sup> H<sub>1</sub>-antihistamines are also available as nasal sprays by prescription. The intranasal preparations appear to be similar to oral preparations in efficacy but may be less acceptable to patients owing to a bitter taste.<sup>28</sup> The effect of antihistamines on symptoms, especially nasal congestion, is modest.29 They can be combined with oral decongestants, and the combination can improve nasal airflow in the short term (on the basis of data from trials lasting 2 to 6 weeks), at the cost of some side effects.<sup>30,31</sup> Topical nasal decongestants are more effective than oral agents, but there are reports of rebound congestion (rhinitis medicamentosa) or reduced effectiveness beginning as early as 3 days after treatment,<sup>32</sup> and only short-term use is recommended. In one study, adding an intranasal glucocorticoid reversed the reduced effectiveness of a topical decongestant.33

Intranasal glucocorticoids are the most effective pharmacotherapy for seasonal allergic rhinitis, yet their overall efficacy is moderate.<sup>29,34</sup> Although the clinical effects appear within a day, the peak effect in cases of perennial rhinitis is not reached for several weeks.<sup>35</sup> The superiority of intranasal glucocorticoids over antihistamines in the treatment of perennial allergic rhinitis is uncertain.<sup>29</sup> There are insufficient data to determine whether the effectiveness differs among various intranasal glucocorticoids. For the ocular symptoms of allergy, intranasal glucocorticoids appear to be at least as effective as oral antihistamines.<sup>12</sup>

Because several nonsedating oral antihistamines and one intranasal glucocorticoid (triamcinolone acetonide [Nasacort]) are now available in the United States without a prescription, many patients are already using one or both of these options when they present to a health care provider. The effect of leukotriene-receptor antagonists on the symptoms of allergic rhinitis is similar to or slightly less than that of oral antihistamines, and some randomized trials have shown a benefit of adding the leukotrienereceptor antagonist montelukast to an antihistamine. Although the majority of trials have favored intranasal glucocorticoids over this combination, data are inconsistent<sup>36</sup>; this combination should be considered for patients whose symptoms are inadequately controlled with an antihistamine and who do not wish to use a glucocorticoid nasal spray. There is no

significant benefit of adding an oral antihistamine or montelukast to a nasal glucocorticoid. However, in randomized trials, the combination of an intranasal antihistamine plus an intranasal glucocorticoid has been shown to be superior to either agent alone.<sup>37</sup>

# Allergen Immunotherapy

In general population or general practice surveys, a third of children and almost two thirds of adults report partial or poor relief with pharmacotherapy for allergic rhinitis.7,38 The next step in treating such patients is allergen immunotherapy. Although allergen immunotherapy has traditionally been administered subcutaneously in the United States, rapidly dissolving tablets for sublingual administration were recently approved for treatment of grass and ragweed allergy.39,40 In subcutaneous immunotherapy, the patient receives the offending allergen (or allergens) in increasing concentrations, until a maintenance dose is reached. In sublingual immunotherapy, a fixed dose of allergen is delivered beginning 12 to 16 weeks before the anticipated start of the allergy season. In both cases, treatment continues with the maintenance dose for several years. Immunotherapy down-regulates the allergic response in an allergen-specific manner by a variety of mechanisms still being elucidated. In addition to having proven efficacy in controlling allergic rhinitis, immunotherapy also helps control allergic asthma and conjunctivitis.41

With immunotherapy, unlike pharmacotherapy, the effect persists after the discontinuation of therapy. The positive effects of a 3-year course of subcutaneous immunotherapy with grass extract were shown to persist at least 3 years after therapy was discontinued.42 A recent study of grass sublingual immunotherapy in which the allergen was given year-round also showed a sustained benefit after the discontinuation of treatment.<sup>43</sup> A disadvantage of subcutaneous immunotherapy is that as the dose of allergen is being built up, injections are required once or twice weekly; for maintenance therapy, monthly injections can be adequate. If there is improvement in the first year, injections are generally continued for at least 3 years. Data from randomized trials are lacking to guide decisions about the duration of therapy. Subcutaneous immunotherapy carries a risk of systemic reactions, which occur in 0.1% of injection visits, in

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rare cases leading to life-threatening anaphylaxis (1 reaction per 1 million injection visits).<sup>44</sup>

Although subcutaneous immunotherapy has not been compared with sublingual immunotherapy in large head-to-head trials, indirect comparisons suggest that subcutaneous immunotherapy is more effective for symptom relief.<sup>45</sup> However, sublingual immunotherapy has a clear advantage in terms of safety, with very few reports of anaphylactic reactions.<sup>46</sup> In contrast to subcutaneous immunotherapy, sublingual immunotherapy is given at home after the first dose, but that may not be as great an advantage as anticipated, because daily treatment is required; adherence to therapy for the recommended duration is lower with sublingual immunotherapy.<sup>47</sup>

#### AREAS OF UNCERTAINTY

The appropriate use, timing of initiation, and duration of immunotherapy remain uncertain. The general recommendation in the United States has been to start immunotherapy only for patients in whom symptom control is not adequate with pharmacotherapy or those who prefer immunotherapy to pharmacotherapy.<sup>25</sup> However, the Preventive Allergy Treatment Study, in which children with allergic rhinitis but without asthma were randomly assigned to subcutaneous immunotherapy or a pharmacotherapy control, showed that fewer children had new allergies or asthma after 3 years of immunotherapy, and this preventive effect persisted 7 years after therapy was discontinued.48 A similar large trial using sublingual immunotherapy is ongoing (ClinicalTrials .gov number, NCT01061203).

With subcutaneous immunotherapy, the standard practice in the United States is to administer multiple allergens (on average, eight allergens simultaneously in a single injection or multiple injections) because most patients are sensitized and symptomatic on exposure to multiple allergens.<sup>49</sup> It is not known whether multi-allergen therapy results in better outcomes than singleallergen therapy. Although some older studies suggest a benefit of multi-allergen immunotherapy, most trials showing the efficacy of immunotherapy involve a single allergen.

The role of allergen avoidance in the prevention of allergic rhinitis is controversial. Avoidance of seasonal inhalant allergens is universally recommended on the basis of empirical evidence, but the efficacy of strategies to avoid exposure to perennial allergens, including dust mites, pest allergens (cockroach and mouse), and molds, has been questioned. For abatement strategies to be successful, allergens need to be reduced to very low levels, which are difficult to achieve. Abatement usually requires a multifaceted and continuous approach, raising feasibility problems. Multifaceted programs have been effective in the management of asthma but have not been studied in allergic rhinitis.<sup>50</sup>

# GUIDELINES

Guidelines for the treatment of allergic rhinitis are available from the international community (Allergic Rhinitis and Its Impact on Asthma [ARIA] guidelines) and jointly from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology in the United States.25,26 Differences between the two sets of guidelines exist. For example, the ARIA guidelines do not recommend oral decongestants, even when combined with antihistamines, except as rescue medications, and they recommend nasal antihistamines only for seasonal use. Whereas the ARIA guidelines do not specifically endorse combinations of medications, the U.S. guidelines recommend a stepped-care approach that can include more than one medication. The U.S. guidelines were written before Food and Drug Administration approval of sublingual immunotherapy, and therefore this treatment is not discussed. The recommendations in this article are largely concordant with both sets of guidelines.

# CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette presents with perennial nasal symptoms and seasonal exacerbations that are typical of allergic rhinitis. She has a first-degree relative with similar symptoms, as is common in persons with allergic rhinitis. Her history of an episode of wheezing suggests the possibility of coexisting asthma, which in many cases can have an episodic, seasonal nature. Treatment of this patient may begin with an empirical treatment trial; testing for sensitization to relevant allergens in order to establish the diagnosis of allergic rhinitis is indicated if she does not obtain adequate relief. The choice of

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treatment should take into account symptom severity and previous use of medications (Table 1).

An intranasal glucocorticoid to be used on an ongoing basis should be prescribed. Combining a nasal antihistamine with an intranasal glucocorticoid could offer additive effects. In cases in which pharmacotherapy is ineffective or not acceptable to the patient, allergen-specific immunotherapy should be used. Sublingual immunotherapy, an option outside the United States for several years, is now available in this country but is limited to cases in which grass or ragweed is the major offending allergen. If other or additional major allergies are present in U.S. patients, subcutaneous immunotherapy is appropriate. As long as immunotherapy offers a benefit by the end of the first year, the minimum duration of therapy should be 3 years; its effects may be long-lasting after the cessation of therapy.

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#### REFERENCES

**1.** Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63:Suppl 86:8-160.

2. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol 2014;134:350-9.

**3.** Salo PM, Calatroni A, Gergen PJ, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2011; 127:1226-35.

**4.** Yonekura S, Okamoto Y, Horiguchi S, et al. Effects of aging on the natural history of seasonal allergic rhinitis in middle-aged subjects in South Chiba, Japan. Int Arch Allergy Immunol 2012;157:73-80.

5. Law M, Morris JK, Wald N, Luczynska C, Burney P. Changes in atopy over a quarter of a century, based on cross sectional data at three time periods. BMJ 2005;330: 1187-8.

**6.** Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2005;116: 377-83.

7. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009;124: Suppl:S43-S70.

 Cruz AA, Popov T, Pawankar R, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. Allergy 2007;62:Suppl 84:1-41.
 Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002;109:419-25.

**10.** Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudi-

nal population-based study. Lancet 2008; 372:1049-57.

**11.** Hopper JL, Bui QM, Erbas B, et al. Does eczema in infancy cause hay fever, asthma, or both in childhood? Insights from a novel regression model of sibling data. J Allergy Clin Immunol 2012;130: 1117-22.

**12.** Bielory L. Allergic conjunctivitis and the impact of allergic rhinitis. Curr Allergy Asthma Rep 2010;10:122-34.

**13.** Westman M, Kull I, Lind T, et al. The link between parental allergy and off-spring allergic and nonallergic rhinitis. Allergy 2013;68:1571-8.

14. McKeever TM, Lewis SA, Smith C, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands General Practice Research Database. Thorax 2001; 56:758-62.

**15.** Genuneit J, Strachan DP, Buchele G, et al. The combined effects of family size and farm exposure on childhood hay fever and atopy. Pediatr Allergy Immunol 2013; 24:293-8.

**16**. Barnes PJ. Pathophysiology of allergic inflammation. Immunol Rev 2011;242:31-50.

**17.** Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. Proc Am Thorac Soc 2011;8:106-14.

**18.** Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. J Allergy Clin Immunol 1989;84:492-501.

**19.** Sarin S, Undem B, Sanico A, Togias A. The role of the nervous system in rhinitis. J Allergy Clin Immunol 2006;118:999-1016.

**20.** Bousquet PJ, Castelli C, Daures JP, et al. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). Ann Epidemiol 2010;20:797-803.

Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. Allergy Asthma Proc 2001;22:185-9.
 Rondón C, Campo P, Togias A, et al. Local allergic rhinitis: concept, patho-

physiology, and management. J Allergy Clin Immunol 2012;129:1460-7.

**23.** Monto AS. The seasonality of rhinovirus infections and its implications for clinical recognition. Clin Ther 2002;24: 1987-97.

24. Walden SM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Antigen-provoked increase in histamine reactivity: observations on mechanisms. Am Rev Respir Dis 1991;144:642-8.

**25.** Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122: Suppl:S1-S84. [Erratum, J Allergy Clin Immunol 2008;122:1237.]

**26.** Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126: 466-76.

**27.** Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999;57:31-47.

**28.** Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. Pharmacotherapy 2007; 27:852-9.

**29.** Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. Ann Allergy Asthma Immunol 2010;104:13-29.

**30.** Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997;100:781-8. [Erratum, J Allergy Clin Immunol 1998; 101:792.]

**31.** Nathan RA, Finn AF Jr, LaForce C, et al. Comparison of cetirizine-pseudo-ephedrine and placebo in patients with seasonal allergic rhinitis and concomitant mild-to-moderate asthma: randomized, double-blind study. Ann Allergy Asthma Immunol 2006;97:389-96.

**32.** Graf P, Juto JE. Correlation between objective nasal mucosal swelling and esti-

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The New England Journal of Medicine

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mated stuffiness during long-term use of vasoconstrictors. ORL J Otorhinolaryngol Relat Spec 1994;56:334-9.

**33.** Vaidyanathan S, Williamson P, Clearie K, Khan F, Lipworth B. Fluticasone reverses oxymetazoline-induced tachyphylaxis of response and rebound congestion. Am J Respir Crit Care Med 2010;182:19-24.

**34.** Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;317:1624-9.

35. Bende M, Carrillo T, Vona I, da Castel-Branco MG, Arheden L. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. Ann Allergy Asthma Immunol 2002;88:617-23.
36. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol 2006;96:779-86.

**37.** Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol 2012; 129:1282-9.

**38.** White P, Smith H, Baker N, Davis W, Frew A. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for al-

lergen immunotherapy? Clin Exp Allergy 1998;28:266-70.

**39.** Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol 2014;112:146-53.

40. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013;131:1342-9. 41. Lin SY, Erekosima N, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for the treatment of allergic rhinoconjunctivitis and/or asthma: comparative effectiveness review. Rockville, MD: Agency for Healthcare Research and Quality, 2013 (http://www.ncbi.nlm.nih .gov/pubmedhealth/PMH0055886/pdf/TOC .pdf).

**42**. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.

**43.** Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129:717-25.

**44.** Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract 2014;2:161-7.

**45.** Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. J Allergy Clin Immunol 2012;130: 1097-107.

**46.** Nelson HS. Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective? J Allergy Clin Immunol Pract 2014;2:144-91.

**47.** Kiel MA, Roder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Molken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013;132:353-60.

**48.** Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.

49. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. Ann Allergy Asthma Immunol 2009;103:451-59.
50. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351: 1068-80.

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