Allergic Rhinitis: Diagnostic and Therapeutic Challenges

Case Study and Commentary, Anthony Montanaro, MD, and Stephen A. Tilles, MD

Introduction, Anthony Montanaro, MD

INTRODUCTION

Allergic rhinitis is a common medical condition that accounts for significant morbidity in pediatric and adult patients. In fact, it is the most common atopic disease in children and adults. Prevalence figures in the general population are variable but average between 10% to 15% [1]. One survey of 15,000 U.S. households established a 14.2% prevalence rate of physician-diagnosed allergic rhinitis [2]. Another survey of children in Tucson, Arizona, documented a prevalence of 43% [3]. While there are no standardized criteria for establishing a diagnosis of allergic rhinitis, it may be defined as an inflammatory condition of the nose mediated by allergen-specific immunoglobulin E (IgE) and presenting with sneezing, rhinorrhea, and nasal congestion and pruritus [4]. The occurrence of these symptoms on a seasonal basis can be referred to as “hay fever.” While hay fever is a classic misnomer since the condition is generally not caused by hay nor a cause of fever, this classical term describes an illness that can prominently affect a patient’s quality of life [5]. Seasonal allergic rhinitis is generally induced by allergens associated with airborne grass and tree or weed pollen. Indoor allergens such as dust mites, animal dander, or mold spores can result in perennial rhinitis.

In considering the diagnosis of allergic rhinitis and selecting appropriate management, a number of issues must be considered. The nature, extent, and duration of symptoms must be evaluated. If as-needed therapy is adequate, long-term therapy may not be indicated. Alternatively, if significant morbidity exists (e.g., impaired work or school performance), more aggressive pharmacologic measures are needed. In addition, allergic rhinitis may be complicated by other conditions such as paranasal sinusitis, otitis media, eustachian tube dysfunction, hearing loss, and asthma. When these comorbid features occur in a patient, chronic suppressive therapy frequently is indicated. It is important to remember that pharmacotherapy should be considered secondary to environmental control measures, as avoidance measures can dramatically decrease signs and symptoms of disease and need for medication. If an individual has an animal or dust mite sensitivity, environmental controls alone may be sufficient to control symptoms.

CASE STUDY

Initial Presentation

A 28-year-old man presents to the family practice clinic with a 1-year history of disabling nasal and ocular complaints.

History

The patient first presented to the clinic 3 months previously, 9 months after emigrating to Portland, Oregon, from Leningrad, Russia. He complained of perennial nasal congestion, rhinorrhea, sneezing, and nasal itch and was given samples of chlorpheniramine 4 mg to be taken twice daily on an as-needed basis. He was unable to tolerate chlorpheniramine due to excessive sedation so he elected to “suffer.” He has used no other over-the-counter medications.

The patient reports that he sneezes “100 times a day.” He complains of prominent postnasal drainage, intermittent cough, and bilateral ocular itch with intermittent swelling. He denies chest tightness or wheezing and has no exertional or nocturnal symptoms. He denies skin rash. The patient notes that although his symptoms bother him year-round, his symptoms of nasal congestion, sneezing, and ocular itch worsen between March and June. Perceived significant symptom triggering factors include passive smoke, dust, and perfume, but his symptoms sometimes occur in the absence of these triggers. For the past year he has owned a cat, who sleeps at the foot of his bed. The patient works on a computer assembly line in a clean room at a local high-tech manufacturing firm. He is a nonsmoker but is exposed to some passive smoke in the breakroom at work. His symptoms interfere with his work productivity and have been commented on by his supervisor.
Past medical history is significant for a history of chronic low back pain for which he takes ibuprofen as needed, averaging 2 to 4 tablets 4 to 5 days per week. He was treated with antibiotics for “sinusitis” 3 or 4 times in the past year. Surgical history is significant for bilateral inguinal herniorrhaphies 4 years ago. He currently takes no medications and has no known allergies. He denies over-the-counter nasal spray use and considers his olfaction to be normal.

Physical Examination
Physical examination reveals a well-developed, well-nourished man in no acute distress. Vital signs include a blood pressure of 125/75 mm Hg, a pulse of 72 bpm, and a respiratory rate of 8 breaths/min; respiration is nonlabored. HEENT examination reveals marked bilateral nasal turbinate erythema and edema. There is minimal conjunctival injection noted bilaterally. Examination of the pharynx reveals minimal cobblestoning of the posterior pharyngeal lymphoid tissue with thick postnasal drainage. Tympanic membranes are clear and freely mobile. Examination of the neck reveals no cervical lymphadenopathy. Examination of the heart and lungs is normal. Skin examination reveals no rashes.

• What are diagnostic considerations in patients with allergy symptoms?

Dr. Tilles:
Diagnostic Considerations
In temperate climates in the United States, a patient with sneezing, rhinorrhea, and nasal congestion between the months of March and June with nasal turbinate edema on examination very likely has tree and grass pollen allergy. The mechanism of the intermittent symptoms other times of the year usually cannot be determined without specific testing for allergic sensitivity. The presence of a cat in the home of this patient is of obvious concern, especially as its introduction into the environment corresponded with the onset of symptoms. The absence of obvious triggering of symptoms by cats by no means negates the possibility of cat allergy. Chronic exposure to an allergen typically results in a “tolerance” to the immediate effects of exposure (eg, eye itch, sneezing) while causing a more continuous complex of symptoms (eg, nasal congestion, postnasal drip). Dust mites and molds are the other perennial allergens likely present in this patient’s environment. His employment at a high-tech firm is not a likely source of significant allergen exposure, though if he had reported obvious symptomatic worsening at work, additional information would be necessary. His exposure to passive cigarette smoke represents an irritant exposure that may contribute to symptomatic worsening, especially during times when the nasal mucosa is inflamed due to factors unrelated to the workplace.

The most frequently seen disorders in the differential diagnosis of allergic rhinitis are nonallergic rhinitis and subacute or chronic paranasal sinusitis. The most common forms of nonallergic rhinitis include vasomotor rhinitis and nonallergic rhinitis with eosinophilia (NARES). Vasomotor rhinitis is not an inflammatory disease, and its management may be problematic [6]. It typically presents with rhinorrhea and nasal congestion exacerbated by a wide variety of triggers including spicy foods, alcohol, temperature changes, and exposure to newsprint. Oral decongestants, antihistamines, and topical anticholinergic agents are most often used to treat vasomotor rhinitis. NARES is an inflammatory disorder characterized by nasal eosinophilia that does not depend on allergen exposure. Nasal corticosteroid sprays are usually quite effective. Empiric treatment of nonallergic rhinitis with a nasal corticosteroid spray is normally used to discriminate vasomotor rhinitis from NARES, though obtaining a nasal smear stained for eosinophils is sometimes helpful.

Chronic sinusitis may occur as the consequence of allergic rhinitis or may arise independently. Since sinusitis treatment differs from rhinitis treatment and identifying sinusitis by physical examination is often difficult, imaging studies are often useful. Plain sinus radiographs are usually easily obtainable but lack sensitivity in identifying ethmoid sinus disease. A screening computed tomography (CT) scan of the paranasal sinuses provides impressive anatomic detail and remains the gold standard for identifying sinusitis. Many centers offer a screening sinus CT scan series at a price comparable to the cost of a 3-view sinus plain radiograph series (roughly $150 to $200).

Other diagnoses to consider when evaluating a patient with rhinitis include hormonal rhinitis, rhinitis medicamentosa, and nasal polypsis. Conditions that may be associated with hormonal rhinitis include pregnancy, menopause, menstruation, and hypothyroidism. Rhinitis medicamentosa is common and should be suspected when there has been chronic use of topical decongestant sprays. Patients must be specifically asked about decongestant sprays because they may not consider these sprays to be medication. Nasal polyps often accompany chronic sinusitis and usually are not associated with atopy [7].

Diagnosis and Trial of Therapy
Based on the patient’s history and physical examination, the physician concludes that the patient has perennial allergic rhinitis with seasonal worsening. The seasonal symptoms are likely due to tree and grass pollen exposure, while the perennial symptoms could be due to dust mites, the cat, and/or mold. The physician prescribes a trial of a nonsedating antihistamine.
What pharmacologic agents are used to treat allergic rhinitis?

Dr. Montanaro:

Antihistamines, decongestants, and intranasal corticosteroids are the 3 main medications used in treatment of allergic rhinitis.

Antihistamines

Oral antihistamines are effective in reducing allergic symptoms such as nasal itch, sneezing, and rhinorrhea. The mechanism of action of antihistamines primarily is blockade of histamine, (H1) receptors. Second-generation antihistamines have additional anti-inflammatory effects such as diminished eosinophil chemotaxis and decreased expression of intracellular adhesion molecules (ICAM). The effectiveness of oral antihistamines in the treatment of seasonal and perennial allergic rhinitis has been well documented [8].

Like the case patient, many individuals are intolerant of the first-generation antihistamines. The significant sedating side effects of these antihistamines may impair performance, and the drugs have been associated with motor vehicle accidents and fatalities [9,10]. In addition to the sedating side effects, many first-generation antihistamines have anticholinergic effects that are poorly tolerated, particularly in geriatric populations. Second-generation antihistamines, on the other hand, are associated with less sedation and fewer anticholinergic side effects. In fact, fexofenadine and loratadine are not different from a placebo in their incidence of sedation, and neither of these agents has any significant anticholinergic activity. Cetirizine is associated with sedation in approximately 10% of individuals who take the drug. All of the newer antihistamines have significant costs, which can average $2.00 to $2.50 per day (Table 1).

Azelastine, an intranasal antihistamine, has been shown to be effective in controlling nasal itch, sneezing, and rhinorrhea. Azelastine can be used as an alternative to intranasal corticosteroids or non-sedating antihistamines, but it causes sedation in a small percentage of children and adults.

Decongestants

Nasal congestion can be a prominent feature of allergic rhinitis. Perennial allergic rhinitis characteristically presents with greater nasal congestion than seasonal allergic rhinitis. Patients frequently require an α-adrenergic decongestant in combination with or in addition to their antihistamine, since antihistamines have a negligible effect on congestion. Both fexofenadine and loratadine are available as combination products that include high doses of pseudoephedrine. Clinicians must be aware of the potential side effects of these sympathomimetic agents, which may include glaucoma, bladder outlet obstruction, hypertension, and cardiac dysrhythmias [11]. Topical sympathomimetics containing...
pseudoephedrine or phenylpropanolamine are rapidly active and effective but have well-known rebound symptoms with their discontinuation after 5 days of use.

**Inhaled Corticosteroids**

Intranasal corticosteroids (Table 2) have been shown to be the most effective medication for control of the nasal symptoms of allergic rhinitis. In fact, there have been no studies that have shown nonsedating antihistamines to be superior in efficacy; evidence also suggests that they are more cost-effective than oral antihistamines [12]. However, as some patients find oral therapy easier to comply with, many practitioners use oral antihistamines as first-line therapy. In addition, most patients who have severe ocular or pharyngeal complaints may obtain better control of these extranasal side effects with oral therapy.

Inhaled corticosteroids are generally safe and easy to use. Most agents can now be used on a once-daily basis. While these agents are generally extremely well-tolerated, there are some patients who develop local side effects such as nasal septal bleeding and irritation. There have been rare cases of nasal septal perforation associated with the use of intranasal corticosteroids. Patients on inhaled corticosteroids should be instructed on potential local and systemic side effects. There have been recent concerns regarding the use of nasally inhaled beclomethasone and the potential impact of linear growth in adolescents [13].

Some patients may require systemic corticosteroids for the treatment of severe seasonal allergic rhinitis. Systemic corticosteroids can be safely and reasonably utilized by primary care physicians when conservative measures fail. When systemic corticosteroids are necessary, they should be used for short periods of time (ie, 3 to 5 days). In our practice, we typically use 1 mg/kg/day of prednisone in children and 20 to 40 mg of prednisone in adults. We avoid the use of long-acting intramuscular corticosteroids due to the unpredictable nature of their systemic side effects.

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**Table 2. Some Corticosteroid Nasal Sprays for Allergic Rhinitis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose per Inhalation</th>
<th>Initial Adult Dosage</th>
<th>Wholesale Cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beconase—Glaxo Wellcome</td>
<td>42 µg</td>
<td>1 spray each nostril 2–4 times/day</td>
<td>$24.62</td>
</tr>
<tr>
<td>Vancenase Pockethaler—Schering</td>
<td>42 µg</td>
<td>1 spray each nostril 2–4 times/day</td>
<td>$25.56</td>
</tr>
<tr>
<td>Beconase AQ‡—Glaxo Wellcome</td>
<td>42 µg</td>
<td>1 or 2 sprays each nostril twice/day</td>
<td>$25.24</td>
</tr>
<tr>
<td>Vancenase AQ Double Strength‡—Schering</td>
<td>84 µg</td>
<td>1 or 2 sprays in each nostril once/day</td>
<td>$25.29</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinocort—Astra</td>
<td>32 µg</td>
<td>2 sprays each nostril twice/day</td>
<td>$43.40</td>
</tr>
<tr>
<td>or 4 sprays each nostril once/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td>25 µg</td>
<td>2 sprays each nostril twice/day</td>
<td>$47.80</td>
</tr>
<tr>
<td>Nasalide—Dura</td>
<td></td>
<td></td>
<td>$43.85</td>
</tr>
<tr>
<td>Nasarel‡—Dura</td>
<td></td>
<td></td>
<td>$43.85</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flonase‡—Glaxo Wellcome</td>
<td>50 µg</td>
<td>2 sprays each nostril once/day</td>
<td>$46.18</td>
</tr>
<tr>
<td>or 1 spray each nostril twice/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasonex‡—Schering</td>
<td>50 µg</td>
<td>2 sprays each nostril once/day</td>
<td>$48.23</td>
</tr>
<tr>
<td>Triamcinolone acetoniode</td>
<td>55 µg</td>
<td>2 sprays each nostril once/day</td>
<td>$46.93</td>
</tr>
<tr>
<td>Nasacort—Rhone-Poulenc Rorer</td>
<td></td>
<td></td>
<td>$37.22</td>
</tr>
</tbody>
</table>

Adapted with permission from Mometasone furoate nasal spray for allergic rhinitis. Med Lett Drugs Ther 1999;41:17.

*Manufacturers generally recommend trying lower dosage for maintenance once the effectiveness of the drug has been established.

†Cost to the pharmacist for 30 days’ treatment at the lowest initial dosage for adults, according to wholesale price (AWP) listings in Drug Topics Red Book Update, January 1999.

‡Aqueous solution.
Other Agents
Cromolyn sodium, a so-called mast cell stabilizer, is now available over-the-counter but has significant limitations. It is effective in reducing allergic symptoms in many individuals, but its 4 times daily dosing, which is necessary in many cases, limits compliance and subsequent effectiveness.

Intranasal anticholinergics may be helpful in patients who have primary anterior rhinorrhea but have little benefit for nasal congestion. Nonetheless, nasally applied ipratropium bromide can be helpful in patients with minimal side effects. Although leukotriene modifiers have recently been introduced for use in chronic asthma, their role in the treatment of chronic rhinitis remains to be defined.

Referral To Allergist
Three weeks after starting the nonsedating antihistamine, the patient calls to report minimal symptom improvement. As the patient has prolonged manifestations of rhinitis and impaired sleep and work performance, the physician refers him to an allergy clinic.

- When is an allergy consultation indicated?
- What tests may help confirm or characterize the diagnosis of allergic rhinitis?

Dr. Tilles:
Indications for Referral
An allergy consultation is indicated when symptoms persist, comorbidities are present, or when symptoms impair quality of life. A complete list of indications for referral has been developed by a joint task force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology [14] and is shown in Table 3.

Allergy Testing
In most circumstances, skin testing is the most cost-effective method for determining relevant specific allergic sensitivities. Epicutaneous (also called “prick” or “scratch”) skin testing for inhalant allergen sensitivity is very sensitive and specific when done in the appropriate clinical setting [15]. At a cost of several dollars per allergen, a screening panel of up to 25 allergens may cost less than $100. Intracutaneous (or intradermal) skin tests are more sensitive but less specific than epicutaneous skin tests. Intracutaneous skin tests are generally used to retest allergens that were negative by the epicutaneous method if the patient had a high pretest probability of allergic sensitivity to that allergen.

The other common methods for identifying allergic sensitivities use in vitro immunologic techniques to quantify specific IgE in serum and include radioallergosorbent testing (RAST) and enzyme-linked immunosorbent assays (ELISA). Compared with skin testing, these techniques have a similar sensitivity but are much more expensive per allergen tested. Allergen RAST or ELISA is useful when either skin testing is contraindicated or only 1 or a few allergens are suspected and skin testing is not immediately available [16].

Results of Skin Testing
A screening panel of epicutaneous skin tests reveals reactivity to tree pollen and grass pollen. There are negative tests to weed pollen, molds, cat hair, and dog dander. Intracutaneous skin tests to dust mites and cat are negative. The results confirm the diagnosis of seasonal allergic rhinitis. The symptoms experienced outside of the tree and grass pollen season do not appear to be due to allergic sensitivities and remain unexplained.

- What environmental control measures should be implemented?
- Is a change in pharmacotherapy indicated?

Dr. Tilles:
Environmental Control Measures
Depending on the patient’s specific allergen reactivity, simple environmental control measures often will alleviate symptoms in days to weeks without additional treatment. Environmental control measures are most effective for indoor allergens [17], and there is considerable geographic variation in the types of allergens found inside homes. This is primarily due to relative humidity, since both dust mites and molds thrive in areas where the humidity averages well

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Table 3. Indications for Allergy Referral

| Prolonged manifestations of rhinitis |
| Complications of rhinitis (eg, otitis media, sinusitis, nasal polyposis) |
| Comorbid condition (eg, asthma) |
| Previous treatment with oral corticosteroids |
| Symptoms interfere with functioning (eg, sleep disturbances, impaired school or work performance) |
| Symptoms significantly decrease quality of life |
| Effective treatment produces adverse events |
| Need for further definition of allergic or environmental triggers |
| Need for more intense education |
| Multiple medications required over a prolonged period of time |
above 50%. Dust mite environmental control measures focus on the bedroom and include obtaining specialized encasings for the mattress and pillow, washing linen in hot water (130°F), and removing the carpet. Mold contamination is often invisible, thus its presence, like dust mites, must be deduced. Sources of humidity or water intrusion in the home are often responsible for high levels of indoor mold, so patients must be asked to check for water leaks from their roof, basement, or plumbing. Heated fish aquariums may also raise the humidity enough to promote dust mite and/or mold growth.

Altering exposure to pets has the most dramatic potential for reducing symptoms in sensitized patients. Removing the pet from the home results in a rapid reduction in detectable allergen and symptoms over several months, though cat allergen may persist in a carpet for up to 1 year following removal of the animal. Other measures such as excluding the animal from the bedroom or bathing it weekly to reduce allergen shedding are less effective but worth doing if the presence of the animal in the home is not negotiable [17].

Since the patient in this case had negative skin tests to dust mites, molds, and cat, none of the environmental control measures discussed above are likely to benefit him. The relevant allergens in this case are pollens. Environmental control measures for pollens include keeping the windows closed and using air conditioning whenever possible in both the home and automobile. These measures are at best partially effective, as the pollen season spans many weeks and avoiding pollen exposure in other places is not practical. Environmental control measures unrelated to allergen exposures include avoidance of “irritants” (eg, the passive smoke encountered in the workplace breakroom).

**Modification of Pharmacotherapy**

Since the patient is being evaluated during the pollen season and has skin test reactivity to tree and grass pollen, it may be reasonable to continue the patient on the second-generation antihistamine but add intranasal corticosteroids to the regimen.

**Follow-up**

Three weeks later, the patient calls to report no further improvement. Because of the minimal response to the pharmacotherapy and because most of his symptoms are perennial, other diagnoses are considered. Since chronic sinusitis may also present with similar symptoms, a screening sinus CT scan series is ordered.

The sinus CT reveals bilateral severe maxillary and ethmoid mucosal disease without air-fluid levels. A decongestant is substituted for the antihistamine and a 21-day course of trimethoprim/sulfamethoxazole is started. The nasal corticosteroid is continued. The patient responds dramatically to this treatment and is able to wean off all medications after the pollen season.

- What is the effect of treatment on the natural history of allergic rhinitis?
- What is the role of immunotherapy in treatment of allergic rhinitis?

**Dr. Tilles:**

**Natural History of Allergic Rhinitis**

Allergic rhinitis in adults is a chronic disease, and untreated patients typically endure symptoms for decades [15]. However, symptom severity and skin test reactivity both tend to decrease with aging [18], and some patients have persistent symptoms while losing skin test reactivity. This suggests that in a minority of individuals, allergic rhinitis may be replaced by nonallergic rhinitis over time.

Comprehensive treatment of allergic rhinitis typically achieves a dramatic reduction in symptoms and improvement in quality of life, though with continued exposure to unavoidable allergens (eg, pollen), low-level symptoms often persist. Treatment with medications controls symptoms but has not been shown to alter the natural history of allergic rhinitis. On the other hand, properly administered immunotherapy induces an immunologic tolerance that usually retains its efficacy after therapy is discontinued [19,20]. The duration of this tolerance is variable, but typically is more than 5 years.

**Allergen Immunotherapy**

Allergen immunotherapy has been shown to be efficacious for allergic rhinitis, allergic asthma, and hymenoptera venom (stinging insect) allergy. According to a recent World Health Organization position paper [19], immunotherapy for allergic rhinitis is indicated for subjects (1) in whom antihistamines and topical medications insufficiently control symptoms; (2) who do not wish to be on pharmacotherapy; (3) in whom pharmacotherapy produces undesirable side effects; (4) who do not wish to receive long-term pharmacologic treatment. The efficacy of the method employed by board-certified allergy/immunology specialists has been validated by many controlled clinical trials and is actually more properly termed “allergen immunotherapy vaccination” because it causes a specific and often permanent immunologic change. The procedure involves the subcutaneous administration of increasing quantities of relevant allergens, usually on a weekly basis. The final or “maintenance” dose is often 100,000 times greater than the starting dose. Once clinical efficacy is apparent (usually...
several months after achieving the maintenance dose), the injection frequency is reduced. Immunotherapy injections should be continued for 3 to 5 years, after which a long-lived (and often permanent) tolerant state generally persists even if the injections are stopped. While allergen immunotherapy is generally safe when properly administered, the potential for life-threatening anaphylactic reactions demands that injections be performed in a suitable facility with resuscitation equipment available. The cost of immunotherapy varies, though each treatment allergen vial typically costs around $100, includes up to 15 doses of the allergen vaccine, and often provides months of therapy.

There are no well-controlled long-term allergic rhinitis clinical studies comparing the cost-effectiveness of immunotherapy with pharmacotherapy. Unless the patient’s symptoms respond adequately to first-generation antihistamines and decongestants, the cost of pharmacotherapy for perennial allergic rhinitis frequently exceeds $1000 annually. Immunotherapy is also expensive initially, since it requires a consultation, testing, and a build-up phase involving 5 to 10 vials of allergen extract. However, once the patient has reached the maintenance dose, the injection frequency decreases and the need for medication is usually drastically reduced. The cost (but not the benefit) ceases after 3 to 5 years when the injections are discontinued. All of these factors suggest that immunotherapy is a cost-effective long-term treatment for perennial allergic rhinitis.

Epilogue
The patient no longer experiences symptoms perennially. He continues to experience severe seasonal rhinitis symptoms, but these are well-controlled with the second-generation antihistamine plus a nasal corticosteroid spray.

References