Evaluation and treatment of the patient with allergic rhinitis

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KEY POINTS FOR CLINICIANS

- Physical clues to allergic rhinitis include boggy, pale, or "bluish" nasal turbinates, with watery discharge on nasal speculum exam. Patients may also have a nasal crease on the external nose caused by repeated rubbing or itching (the so-called "allergic salute").
- Skin prick testing can detect IgE antibodies in patients with reliable histories of exposure to allergens.
- Intranasal corticosteroids are superior to other medications in achieving desired clinical outcomes, including quality of life.
- For some cases of allergic rhinitis, subcutaneous immunotherapy can achieve clinical remission for up to 3 years after cessation of therapy.

While allergic rhinitis is merely a nuisance to most people afflicted by it, the condition can lead to complications if it is severe or exists undetected for too long. In this article, I review the most reliable means of diagnosing allergic rhinitis, and outline a recommended approach to treatment.

PREVALENCE AND PATHOPHYSIOLOGY

An estimated 20 to 40 million Americans are affected by allergic rhinitis. The actual prevalence of the condition is difficult to discern as many sufferers self-medicate without seeking medical care. One survey stated that up to 92% of patients had self-medicated prior to seeking medical care.[1] Even when accounting for self-treatment, allergic rhinitis is the most commonly encountered form of chronic rhinitis, representing about 3% of all primary care office visits.[2,3] Direct and indirect clinical costs run between $1.2 and $5.3 billion per year.[4-6] Although the disease can develop in persons of any age, in 80% of cases symptoms will develop before the patient is 20 years old.[5] Symptoms often wane as a patient grows older, and it is uncommon for persons older than 65 to experience new onset of allergic rhinitis.[3,7]

Allergic rhinitis stems from a type I hypersensitivity reaction.[4] During an initial sensitization phase, the immune system identifies an allergen as foreign and generates specific antibodies to act against that allergen. Atopic patients exhibit an exaggerated response, generating high levels of Type 2 T-helper (Th2) cells and, subsequently, IgE antibodies.[8] On re-exposure to the allergen, specific IgE antibodies bound to mast cells form cross-links resulting in mast cell degranulation and the release of histamine and other chemical mediators. The patient then immediately develops such allergy symptoms as itching, sneezing, and rhinorrhea. A cellular inflammatory response, chiefly involving eosinophils, monocytes, and basophils, characterizes the secondary phase of the allergic reaction. Nasal congestion tends to dominate this later response phase.

Seasonal allergic rhinitis is usually triggered by pollens or molds. Perennial allergic rhinitis, triggered by dust mites, molds, cockroach or animal allergens, is defined as occurring 9 months out of the year.[9]

CLINICAL EVALUATION

The diagnosis of allergic rhinitis is usually made on the basis of the patient's history and the results of your physical examination. In addition to classic symptoms of nasal congestion, itchy nose, sneezing, rhinorrhea, or itchy, watery eyes, patients may also complain of chronic cough, dry scratchy throat, otal-

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gia, or recurrent sinusitis.[4] Other important historical considerations include a family history of allergic rhinitis, a history of other atopic disease, previous treatment experiences, and suspected triggers.[5]

Physical clues to allergic rhinitis include boggy, pale, or "bluish" nasal turbinates, with watery discharge on nasal speculum exam. Patients may also have a nasal crease on the external nose caused by repeated rubbing or itching (the so-called "allergic salute"). Chronic nasal congestion may also precipitate darkening of the skin under the eyes or "allergic shiners."[2,6] Concurrent conjunctivitis is common. Polyps, seen on direct nasal examination, may occur both in allergic and non-allergic patients.

No studies have evaluated the accuracy of the history or physical examination in confirming the diagnosis of allergic rhinitis. The differential diagnosis is extensive and includes infectious rhinitis, non-allergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, mechanical obstruction, vasomotor rhinitis, drug-induced rhinitis, and nasal polyps.[5]

Diagnostic Tests

Published guidelines from the American Academy of Asthma, Allergy and Immunology, as well as other expert panels, recommend confirmatory testing when allergic rhinitis is clinically suspected.[2,5,10] There is no evidence to support the superiority of this recommendation over an empiric trial of medication, and most primary care physicians choose to treat empirically based upon the history and physical examination.

Although further testing should be done when the diagnosis is unclear, be aware that there is uncertainty associated with allergy testing. Because an individual may become sensitized to an allergen without exhibiting symptoms of allergic rhinitis, there is no clearly defined reference standard for the confirmation of allergic rhinitis.[11] Likewise, a history of sensitivity is not always followed by expected IgE test results. Challenge methods developed for studies of airborne allergens are used as reference standards in the evaluation of clinical tests.[12]

Diagnostic tests include skin prick testing, intradermal testing, and in vitro blood tests. Nasal challenge testing, nasal smears, sinus transillumination, and nasopharyngoscopy are nonspecific tests. They are not recommended for routine evaluation but may be useful in selected cases when allergen-specific tests have failed to clarify the cause of the rhinitis. An expert panel has stated that no studies address the cost-effectiveness of any of these methods.[2]

Skin prick testing (SPT) is considered the most convenient and least expensive screening test. SPT can detect IgE antibodies in patients with reliable exposure histories.[13] Sensitivity and specificity are difficult to determine, for a number of reasons. First, as previously mentioned, there is no clearly defined reference standard.[11] Second, only 5 allergen extracts have been standardized for defined quantities known to induce biologic activity. Standardized extracts in the United States include ragweed pollen, cat dander, house dust mites, Hymenoptera venoms, and some grasses. All other extracts are local or regional preparations, and skin tests with nonstandard extracts are not necessarily reproducible.[11] Third, even with a single individual, there can be wide variation in skin reaction to the same reagent, depending on the device used.[14] As a result, correlation between SPT and inhalation challenges vary from 60% to 90%.[13]

Intradermal skin tests (IDST) are usually done when SPT yields a negative result despite a history compatible with allergic rhinitis.[13] The primary advantage of IDST is sensitivity afforded by a fixed concentration of allergen. Because of this sensitivity, not all reactions are clinically relevant.[13] In fact, IDST is often used as a reference standard in studies of the accuracy of SPT and in vitro tests.

Several in vitro assays of specific IgE antibodies are available. They are all modeled after the original radioallergosorbent tests (RAST); the term "RAST" is often used interchangeably with any type of in vitro blood test.[13] IgE antibody tests have a high false-positive rate, meaning the test is positive in patients without allergy symptoms. RAST tests are less sensitive than SPT, with a mean sensitivity of 75% and a range of approximately 50% to 95%.[13]

The 3 primary diagnostic tests for allergic rhinitis are usually compared with each other and not to a recognized standard. Table 1 summarizes data from a study that compared all 3 tests with subjects who were placed in a small room with 2 cats and their bed.[12] While this is one of very few studies that contrasts all 3 tests to a reasonable reference standard, the findings cannot necessarily be extrap-

TABLE 1

Accuracy of diagnostic tests for diagnosis of cat allergy[13]

Test	Sensitivity	Specificity	PV+	PV-	LR+	LR-
Skin prick test	79.2	90.6	92.6	74.3	8.4	0.2
Intradermal test	60.0	31.0	23.1	69.2	0.9	1.3
RAST	69.2	100	100	72.7	69.2	0.3

Note: Results are based upon any upper or lower symptoms when exposed to cat challenge. Intradermal test done if negative skin prick test. LR+ = positive likelihood ratio, LR- = negative likelihood ratio, PV+ = positive predictive value, PV- = negative predictive value.

olated to other airborne allergens.

In the hope of limiting referrals to allergists for testing, and reducing the uncertainty in making a diagnosis, one study looked at the RAST response to 19 allergens. The authors found that of all the patients who responded to any allergen, 95% exhibited responses specifically to grass pollen, dust mites, or cat dander. They went on to conclude that 96.3% of patients with allergic disease could be correctly identified with a combination of a standardized history (available in the study text), a total serum IgE of greater than 40 U/mL, and in vitro tests for cat dander, dust mites, and grass pollen.[15]

TREATMENT

Untreated allergic rhinitis can have a significant impact on quality of life. Patients are bothered by nose blowing, disrupted sleep, fatigue, and decreased concentration.[1] In one 1996 survey, 32 % of patients said that allergy attacks embarrassed them or interfered with their quality of life.[16] As a result, most patient-oriented studies on treatment evaluate the impact on health-related quality of life.[17]

The initial form of treatment is usually avoidance of the allergen, although this can be difficult. For animal allergens, washing pets and using high-efficiency particulate air (HEPA) filters have been shown to temporarily reduce the volume of airborne allergens but not to improve patient-oriented outcomes.[18,19] Removing the pet from the home is the only sure remedy.[18] More studies are needed to evaluate the benefit of multiple home treatments to reduce exposure to cockroach and fungal allergens.[18] A systematic review of several studies showed that maternal antigen avoidance during lactation reduced the incidence of atopic dermatitis in at-risk infants.[20] A meta-analysis of measures to avoid house-dust mites showed no clear benefit for patients with asthma[10] It is unclear if these findings can be extrapolated to other atopic conditions such as allergic rhinitis.

Intranasal corticosteroids. Intranasal corticosteroids are the most effective medication in the treatment of allergic rhinitis. Available preparations in the US include beclomethasone diproprionate, budesonide, funisolide, fluticasone propionate, mometasone furoate, and triamcinalone acetonide. A meta-analysis identified 16 randomized controlled trials (RCTs) that compared antihistamines with intranasal corticosteroids in a total of 2767 patients. Intranasal corticosteroids provided significantly greater relief from nasal discharge, sneezing, pruritis, and postnasal drip. There was no statistically significant difference between the 2 in reduction of eye symptoms.[21]

Although this review did not address quality of life, other studies have shown that both triamcinolone acetonide and fluticasone propionate are superior to loratadine in improving quality of life.[22,23] Few studies provide any guidance in choosing one intranasal steroid over another. Generally, they are of equal efficacy in patient-oriented outcomes.[24,25] Although intranasal corticosteroids are considered daily or "maintenance" medications, a single small RCT of 26 patients showed that fluticasone propionate improved quality of life and reduced symptoms compared with placebo when used on an as-needed basis over a 4-week period.[26] More studies are needed to confirm this preliminary finding, though.

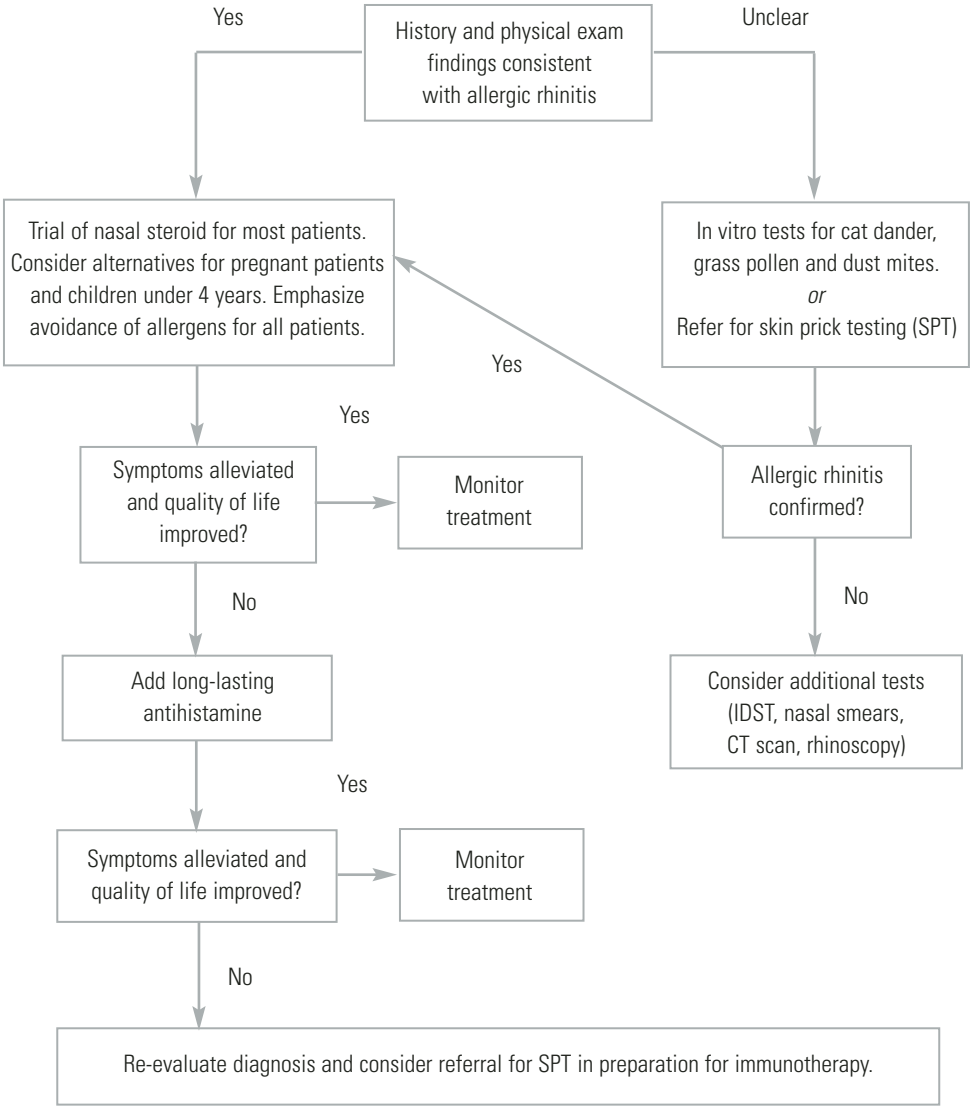
Antihistamines. Although not as effective as intranasal steroids, antihistamines do reduce symptoms of rhinorrhea, sneezing, and itching.[27] First-generation antihistamines (diphenhydramine, chlorpheniramine, etc.) are lipophilic and cross the blood-brain barrier, resulting in varying degrees of anticholinergic side effects. Placebo-controlled studies have confirmed that these agents cause psychomotor retardation, sleepiness, and decreased work production.[5,28] Specifically they seem to affect attention, memory, and vigilance. These symptoms may persist even after an overnight period of sleep.[28,29] Second-generation antihistamines (fexofenadine, loratadine, etc.) do not penetrate the brain as well and are less likely to cause central nervous system effects.

However, a recent RCT involving 63 elementary school students challenges findings from previous studies. Children who received diphenhydramine, 25 mg twice daily, performed no differently on computerized reaction-time tests or multiple-choice learning tests than did children who received placebo or loratadine, 10 mg daily.[30] Another RCT involving 845 patients from ages 12 to 65 years evaluated quality of life as well as work and school performance of patients who received fexofenadine or placebo. While quality-of-life scores and work performance improved significantly with fexofenadine, there was no significant difference between the groups in school performance.[31] Direct comparisons of antihistamines are rare and the results are conflicting. There are no data to show that one of the first-generation antihistamines is superior to the others. Similarly, second-generation drugs are no more effective than the older medications; they only have fewer side effects. Among the second-generation antihistamines, fexofenadine and cetirizine appear to be more effective then loratadine.[29]

Decongestants. Systemic and topical decongestants relieve the congestion that accompanies the secondary phase of an allergic reaction.[4] They have limited effects on other allergic symptoms and, as a result, are often used in combination with antihistamines.[32] When used for more than 10 days, topical

FIGURE

A guide to evaluation and treatment of allergic rhinitis



SPT= skin prick testing; IDST =Intradermal skin testing

decongestants (oxymetazoline, xylometazoline) are associated with rebound congestion (rhinitis medicamentosa).[33]

Leukotriene receptor antagonists. Although not approved by the FDA for treatment of allergic rhinitis, the leukotriene receptor antagonist montelukast was shown in a randomized double-blinded trial to be as effective as loratadine in relieving symptoms. There was minimal additional benefit in using the medications concomitantly.[34]

Cromolyn sodium. Cromolyn sodium has been shown to prevent the onset of allergic rhinitis symptoms in multiple placebo-controlled trials.[35] It is extremely safe but requires regular use and is not as effective as other medications for acute symptoms. Direct comparison studies have shown that cromolyn is not as effective as intranasal corticosteroids.[35,36]

Immunotherapy. Subcutaneous immunotherapy (SIT) is recommended by all guidelines for patients who fail to respond to pharmacotherapy and aller-

gen avoidance.[2,5,10,27] It is recommended in particular for allergic rhinitis secondary to ragweed, grasses, molds, and dust mites. Immunotherapy induces the creation of protective IgG and inhibits the inflammatory response to allergens.[27] SIT requires specific allergen confirmation with either a skin test or in vitro assay. Preparation of SIT doses should be done by a practitioner well trained in mixing and diluting extracts.[5,37] Forty-three placebo-controlled, double-blind studies have evaluated the efficacy of SIT for 12 different allergens since 1980.[10] Thirty-two trials showed clinical efficacy, which can be long lasting. A study of patients treated for 3 to 4 years with immunotherapy for grass pollen allergy showed continued clinical remission for at least 3 years after treatment was stopped.[38]

TABLE 2

Evidence to support treatment recommendations

Strength of recommendation	Treatment	Comment
A	Immunotherapy	Can have long lasting clinical benefit.
A	Intranasal corticosteroids	Consistently superior to antihistamines in head to head trials. Not clear if all steroids are equally effective.
A	Antihistamines	Effective, but inferior to intranasal steroids in most clinical outcomes.
A	Cromolyn sodium	Intranasal steroids superior in all clinical outcomes.
B	Decongestants	Less effective than antihistamines in direct comparisons, many trials involve combination products.
D	Probiotics	Larger trials needed, limited evidence.
D	Herbal medications (licorice, gingko, ginseng)	Limited evidence.

Herbal therapies. Alternative approaches to the treatment of allergic rhinitis warrant further investigation. Herbal medications, such as licorice, gingko, and ginseng, are currently used to treat allergic rhinitis, although there are no large studies to confirm their effectiveness.[39]

Probiotics. Epidemiologic studies suggest that the increase in atopic disease may be related to a clean environment and widespread use of antibiotics in Western countries. The environment may deprive fetal and infant immune systems of bacterial antigens that stimulate type 1 T-helper (Th1) cells.[8] In light of this theory, Finnish researchers randomly assigned 159 pregnant women with a family history of atopy to receive capsules of Lactobacillus GG (a potentially beneficial bacteria or "probiotic") or placebo, beginning 2 to 4 weeks prior to delivery and continuing 6 months postpartum. Infants were followed for 2 years. Frequency of atopic dermatitis was reduced by 50% among those infants whose mothers received Lactobacillus.[40] Further study of this association in allergic rhinitis would be beneficial.

Treatment recommendations. Table 2 summarizes treatment-related evidence in the management of allergic rhinitis, and the Figure illustrates a proposed treatment algorithm. Another algorithm by the European Academy of Allergy and Clinical Immunology recommends initial therapy with oral or nasal antihistamines for mild disease, nasal corticosteroids for moderate disease, and both for severe disease.[10] This was a consensus opinion. Of the 2 most commonly used medications for allergy, nasal steroids are favored over antihistamines for overall safety, tolerability, effectiveness, and simplicity in all cases. In one study of 61 adults, patients were randomized to receive either a nasal steroid or an antihistamine as initial therapy, with the other agent reserved as "back-up." After 6 weeks, 86% of patients started on an antihistamine had added their steroid back-up, while 51% of the group started on a steroid remained on that agent alone.[41] Starting all patients on both an antihistamine and a nasal steroid is inappropriate.

PROGNOSIS

The long-term prognosis for allergic rhinitis is excellent. For most patients, the illness is primarily a nuisance with no significant morbidity. However, for patients whose rhinitis is moderate to severe and poorly controlled, there can be significant complications. These complications include asthma, sinusitis, otitis media, nasal polyposis, respiratory infections, and orthodontic malocclusions.[42] In one study of 605 children with allergic rhinitis, 21% had chronic otitis media with effusion (OME). Conversely, in another study of 259 children with OME, 50% had allergic rhinitis.[43] Even among patients without asthma, 20% to 30% will have bronchial hyper-responsiveness. Additionally, poorly controlled allergic rhinitis can contribute to sleep loss, daytime fatigue, and learning impairment.[44]

Potential complications related to long-term treatment in children remain controversial. In a 1998 study of intranasal beclomethasone, children receiving the study medication grew an average of only 5 centimeters (cm) in 1 year, compared with an aver-

age of 5.9 cm in the placebo group.[45] However, a similar study done 2 years later with intranasal mometasone showed no evidence of growth suppression.[45] Further studies are needed before the true impact of intranasal steroids on children can be determined.

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