

Respiratory disease:

Addressing the underlying cause

**Clinical rationale
for obtaining
a precise diagnosis**

Leonard M. Fromer, MD

**Implications
for management:
Four case discussions**

Steven A. Green, MD
Caryl Heaton, DO
Susan M. Pollart, MD

Respiratory disease: Addressing the underlying cause

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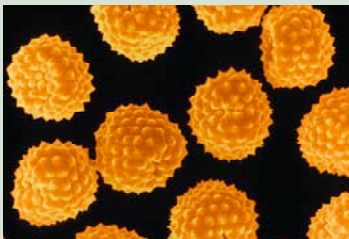
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Scanning electron micrograph of ragweed pollen.
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Introduction

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The patient with symptoms of respiratory disease is one of the most common—and potentially confusing—problems to confront the family physician. Of the estimated 74 million Americans with rhinitis, 35 million have allergic rhinitis,¹ 17 million have nonallergic rhinitis,² and 22 million have mixed (combined allergic and nonallergic) rhinitis.³ Of the 17 million Americans with asthma, 10 million are thought to have allergic asthma.⁴ We recognize that the spectrum of illness caused by either condition is very broad, but, in general, asthma carries the greater risk. Rhinitis, although usually benign, is a frequent and uncomfortable symptom.

The task for family physicians is to appropriately evaluate and treat the varied presentations of asthma and rhinitis.⁵ Our apparent dilemma is how to assess effectively the severity of illness and how to differentiate the allergic from nonallergic presentation. The only readily available objective measure of severity has been the pulmonary function test, which is usually reserved for patients with symptoms suggestive of asthma. Skin testing has long been used to determine the presence of atopy but has largely remained the domain of the allergist. We now, however, have blood tests for specific immunoglobulin E (IgE) available to us, giving us new possibilities for diagnosis and treatment.

Management of patients with respiratory symptoms and possible allergic disease can be approached in 2 ways. In one, a clinical history and physical examination that indicate a high probability of allergy are followed by empiric drug therapy. Blood or skin testing for specific IgE is considered for patients with inadequate responses. In the other approach, specific IgE levels are measured when the history and physical suggest a low probability of allergy. This is because specific IgE testing is very sensitive and, to recall *SnNOUT* and *SpPIN*, a *SeNsitive* test, when *Negative*, rules a disease *OUT*. For example, if the history suggests irritant (eg, perfume) or vasomotor rhinitis, IgE testing is actually most useful for ruling out allergy.

Millions of dollars are spent every year on prescriptions for nasal corticosteroids and nonsedating antihistamines given to patients who do not have

allergic disease. An evidence-based approach to diagnosis and treatment is clearly needed, and this should include some form of objective testing, particularly when empiric therapy fails.

Further complicating allergy management, avoidance measures have recently been shown to be of questionable value (see page S25). If the environment cannot be changed sufficiently to effect a clinical difference, why perform skin or blood testing to identify specific allergens? The answer, while not supported by evidence, may lie in modifying the environment for multiple rather than single allergens and in the concept of the allergic threshold, as described by Leonard M. Fromer, on page S4. Only skin or blood IgE testing can help us accurately identify allergens for avoidance and threshold reduction.

The “united airway” is another concept with relevance to respiratory disease, both allergic and nonallergic. The concept of the united airway presumes that the 2 conditions share a common etiology—they share the same genetic predisposition, a physiologically “continuous” respiratory mucosa, and an inflammatory response that involves the same molecular and cellular components.⁶ Indeed, over the years, it has become apparent that both conditions respond to similar, if not the same, medications.

Dr Fromer begins this supplement by placing specific IgE testing within the framework of overall management of the patient with allergy-like symptoms. The case discussions that follow illustrate and expand on many important points in both the workup and treatment. Until studies are conducted that help us understand more fully the costs and outcomes of the different management approaches to the patient with potentially allergic respiratory disease, we need to continue to use the best of the evidence and the best of the “art.”

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Clinical rationale for obtaining a precise diagnosis

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■ THE SCOPE OF THE PROBLEM

Allergic diseases present as a constellation of symptoms and signs that overlap with many nonallergic etiologies. For example, undifferentiated upper respiratory symptoms may represent seasonal or perennial allergic rhinitis. In a nonallergic patient, the same symptoms may stem from myriad etiologies, including infectious, vasomotor, or anatomic conditions. The challenge is to establish an accurate diagnosis, because appropriate management of various allergy-like symptoms may differ substantially at times. Indeed, the increasing specificity of treatments and the rising costs of pharmacotherapy lend special weight to diagnostic precision.

In the United States, 40 to 50 million people have allergic disease.¹ In 2001, for example, 12.3 million office visits were coded for chronic rhinitis, 10.1 million for allergic rhinitis, and 11.3 million for asthma.² These numbers do not include other conditions with a possible allergic component, such as atopic dermatitis, and some cases of conjunctivitis and otitis media. Allergic diseases in some form are the sixth leading cause of chronic disease in the United States.³

■ CLINICAL CONCEPTS

Allergy march. IgE-mediated allergic disease progresses in a predictable manner sometimes called “the allergy march” (Figure 1). The formation of IgE antibodies starts early in life, and the antibodies can often be detected before clin-

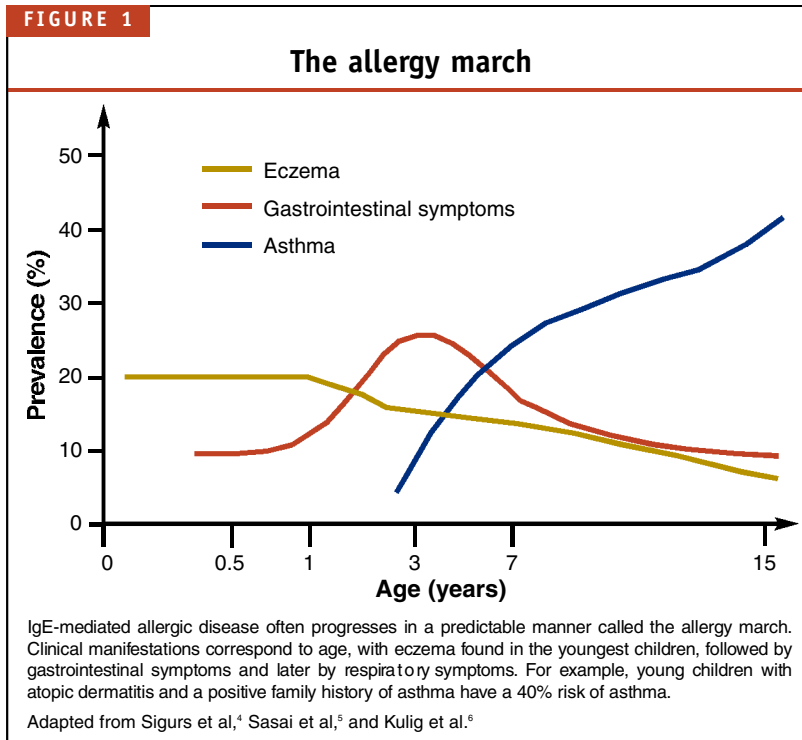
PRACTICE RECOMMENDATIONS

- In patients with a low probability of allergy (based on history and physical examination), specific IgE testing is useful to detect occult allergens. (strength of recommendation: C)
- In patients with a moderate or high probability of allergy, testing may help direct treatment; however, negative testing is not highly accurate, and a trial of empiric therapy should be considered. (SOR C)

ical symptoms emerge. Food antigens have the earliest sensitization, and it frequently precedes problems with inhalant allergens.⁴ Sasai et al showed that the presence of antibodies to egg white at 6 months of age was a strong predictor of future allergy to house dust mite ($P=.0001$ [level of evidence: 3]).⁵ Young children with a diagnosis of atopic dermatitis and a positive family history of asthma have a 40% risk of subsequent asthma.⁶

Allergic threshold. Allergic sensitization is a cumulative process, rather than an “all or nothing” phenomenon. When the allergen load accumulates beyond an individual’s threshold of tolerance, clinical symptoms become evident (Figure 2). Clinical manifestations correspond to age, with eczema predominating in the youngest age group, followed by gastrointestinal symptoms and later by respiratory symptoms.⁷

While the most recent allergen exposure precipitates symptoms, multiple allergens may



be responsible for pushing a patient beyond the symptomatic threshold. For example, the patient described in Figure 2 may be sensitized to mold, dust-mite, and cat allergens, but symptoms appeared only after a cat was obtained as a pet. Reducing the level of mold and dust-mite exposure (eg, by avoidance) may be sufficient to relieve symptoms and allow the patient to keep the cat.

The concept of the allergic threshold was suggested in studies by Boner et al of children with allergic asthma who were moved back and forth from a low-altitude, allergen-rich environment to a high-altitude (1,756 m), allergen-free environment in the Italian Alps.^{8,9} Clinical improvement (ie, improved pulmonary function test results and decreased need for medication) was noted at high altitude, as were decreased serum levels of total IgE and eosinophil activation (LOE: 3).

■ IS IT REALLY ALLERGY?

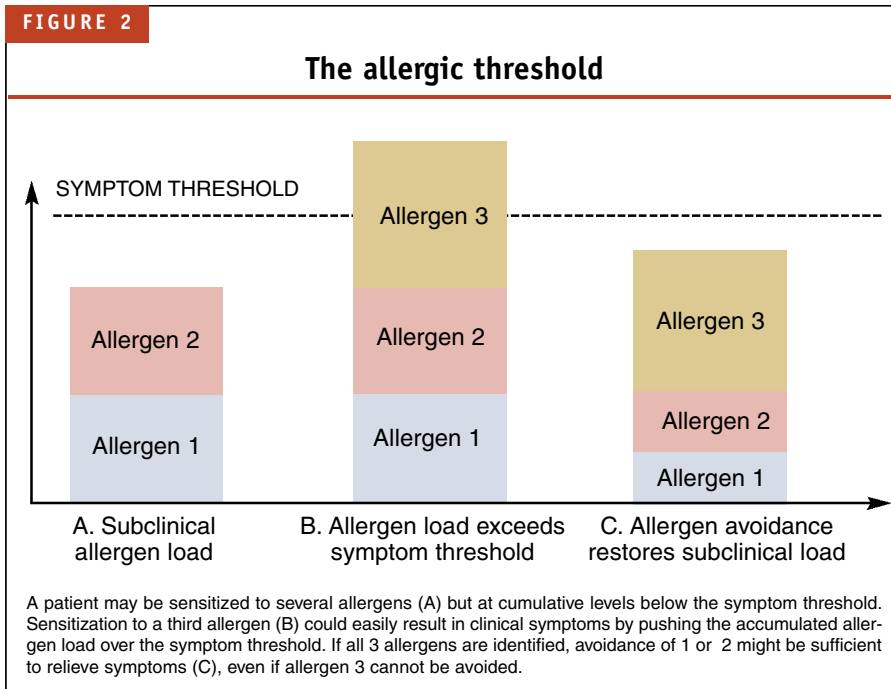
Despite the millions of people who have bona fide allergic disease, many millions more

think they do. A study by Szeinbach et al conducted in a managed care organization suggests that as many as two-thirds of patients with allergic symptoms may be misdiagnosed.¹⁰ The investigators identified 244 patients who were being treated with nonsedating antihistamines for allergic rhinitis. Specific IgE blood testing determined that only 35% of these patients had abnormally elevated IgE levels; the remaining 65% did not.

Thus, in this study nearly two thirds of the patients who took antihistamines presumably did not need them. Indeed, without diagnostic

testing, it is often difficult to accurately differentiate allergic from nonallergic conditions. In a study by Williams et al, when the diagnosis of specific allergic sensitization by history and physical examination alone was compared with results from skin-prick and blood testing for specific IgE, the ability of allergy specialists to accurately predict allergic sensitization rarely exceeded 50% (LOE: 3).¹¹

With respect to respiratory symptoms, a recent report from the Agency for Healthcare Research and Quality (AHRQ) stated, "No studies were found that specifically sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms, signs on physical examination, or the presence or absence of comorbid conditions. The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature.... No diagnostic test has been specifically developed to diagnose nonallergic rhinitis. Given the absence of studies to differentiate nonallergic rhinitis, diagnostic testing rather than symptoms or signs is



necessary to differentiate isolated vasomotor or nonallergic rhinitis from allergic rhinitis.”¹²

The correct management paradigm? Many clinicians manage allergic disease by identifying allergy-like symptoms, obtaining a history suggestive of allergic disease, and prescribing pharmacotherapy. Such a strategy is both safe and consistent with patient expectations, although it contradicts a basic disease management paradigm (Figure 3). In hypercholesterolemia or diabetes, for example, laboratory test results supplement findings from the history and physical examination; all 3 help guide treatment decisions. With allergic diseases, however, clinicians frequently progress directly from signs and symptoms to pharmacotherapy, even when diagnostic evidence is readily available. Empiric management may result in unnecessary repeat office visits, inappropriate medication, greater costs, and unnecessary referrals.^{9,11}

■ SPECIFIC IgE TESTING

There are several reasons why specific IgE testing might be considered in patients with

allergy-like symptoms (Table 1). First, the history and physical examination alone often lead to an incorrect diagnosis.¹¹ Similarly, testing alone is insufficient to establish a diagnosis in the absence of clinical signs and symptoms. Second, different diagnoses mandate different treatments. In allergic patients, it is essential to identify specific allergens before instituting avoidance measures, for example. In nonallergic patients, the search for a cause

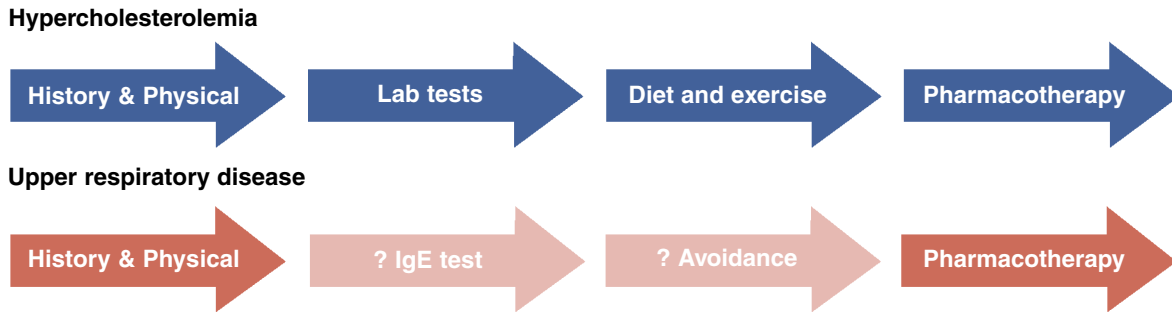
should continue since antihistamines are unlikely to relieve symptoms.¹³

Finally, the proper tools for testing are available in primary care. Before the advent of the radioallergosorbent test (RAST) in the 1970s, skin testing was the only method of confirming IgE-mediated allergy and it usually required referral to an allergist. First-generation RAST technology made specific IgE blood testing more widely available, but was hampered by a high number of false negatives. Accuracy was improved in the second-generation blood tests (Figure 4), and now third-generation assays allow primary care clinicians to approximate specialists in diagnostic precision (LOE: 3).¹⁴ A 1997 workshop panel chaired by Selner and Sullivan recommended selective use of specific IgE blood testing by primary care physicians, calling the tests well standardized, easily used, and effective in diagnosis of allergy (LOE: 3).¹⁵

Published guidelines for allergic rhinitis and asthma recommend skin or blood testing when symptoms are persistent and/or have a significant impact on the quality of life, to

FIGURE 3

Disease management paradigms



A common paradigm for diagnosis and management of disease begins with the patient history and then progresses to the physical examination and laboratory testing. These 3 form the basis for prescription of lifestyle modification (if applicable) and drug therapy. With allergic diseases, however, clinicians frequently jump directly from symptoms to pharmacotherapy.

identify unsuspected sensitivities, and to guide immunotherapy.^{3,16} Negative results can be as informative as positive results, ruling out allergy as the cause of symptoms.

Which test you choose is less important than understanding its strengths and limitations. Both methods depend on the use of standardized allergen source materials, test devices, and the proficiency of the individuals performing the test. In addition, both methods require clinical

training and experience in choosing items for testing and in interpreting and applying results.

Skin testing. Skin testing has been in widespread clinical use for decades; in the hands of a trained and skilled clinical specialist, the procedure is safe, sensitive, and economical. The precision of skin testing depends on the quality of allergen extracts and repeatable testing technique. Skin testing is most often performed by allergists; it is only to be done in offices prepared to invest in staff, training, and materials and to deal with life-threatening anaphylaxis. Skin test results reflect the complex interactions between IgE antibodies, activated immune system cells, responsiveness of the skin, and irritation to the skin.⁷ Skin testing cannot be used in patients with generalized skin disorders or in patients who cannot discontinue certain medications (eg, antihistamines, tricyclic antidepressants, and β -blockers), or if there is a risk of anaphylaxis (eg, in patients who may be sensitized to bee venom or latex but who need confirmatory testing).¹⁵

Blood testing. Current blood tests for allergen-specific IgE provide efficacy equivalent to skin testing and can be performed in the primary care office or sent to a reference laboratory.¹⁷ Serum separated from the patient's blood sample is incubated with allergens bound to a solid support (eg, paper disk, cellu-

TABLE 1

Testing for specific IgE with a skin or blood test

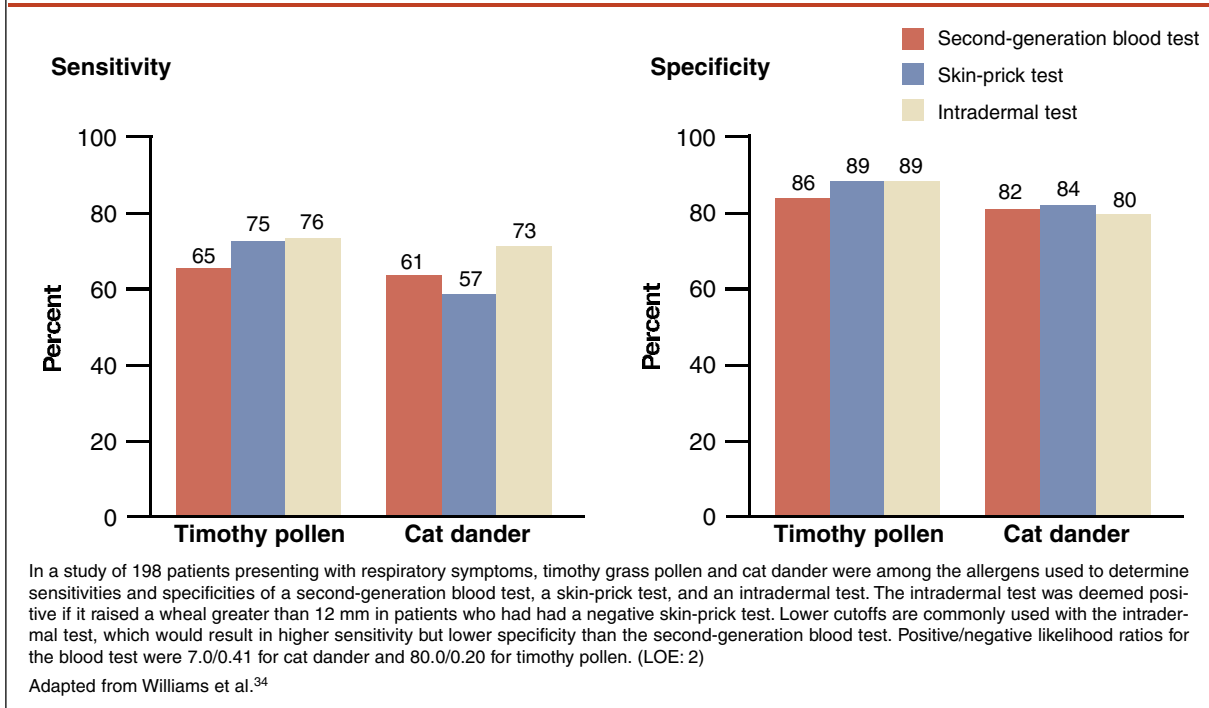
Specific IgE testing should be considered

- To identify avoidance measures
- To distinguish between allergic, nonallergic, and mixed disease
- To limit use and expense of antihistamines in nonallergic patients
- To select cost-effective drug therapy
- To identify complex cases that need referral to an allergist
- When symptoms are not controlled by avoidance and medication
- When symptoms are sufficiently chronic or recurrent to impact quality of life
- When antiallergic medication is not tolerated or desired

Adapted from Høst et al,³² Hedges and Pollart.³³

FIGURE 4

Selected sensitivities and specificities of skin and second-generation IgE blood tests



lose polymer sponge, soluble polymer matrix) (Figure 5). If IgE for a specific allergen is present, it combines with support-bound allergen to form an antigen-antibody complex. All other nonspecific IgE is washed away. The antigen-antibody complex is marked by adding anti-IgE, and the subsequent anti-IgE-antibody-antigen complexes are measured. Blood testing is calibrated to World Health Organization reference preparations to give reproducible results, and must be performed in compliance with the Clinical Laboratory Improvement Act of 1988 (CLIA-88). Blood testing can be performed on small children, pregnant women, and patients at risk for anaphylaxis.¹⁸

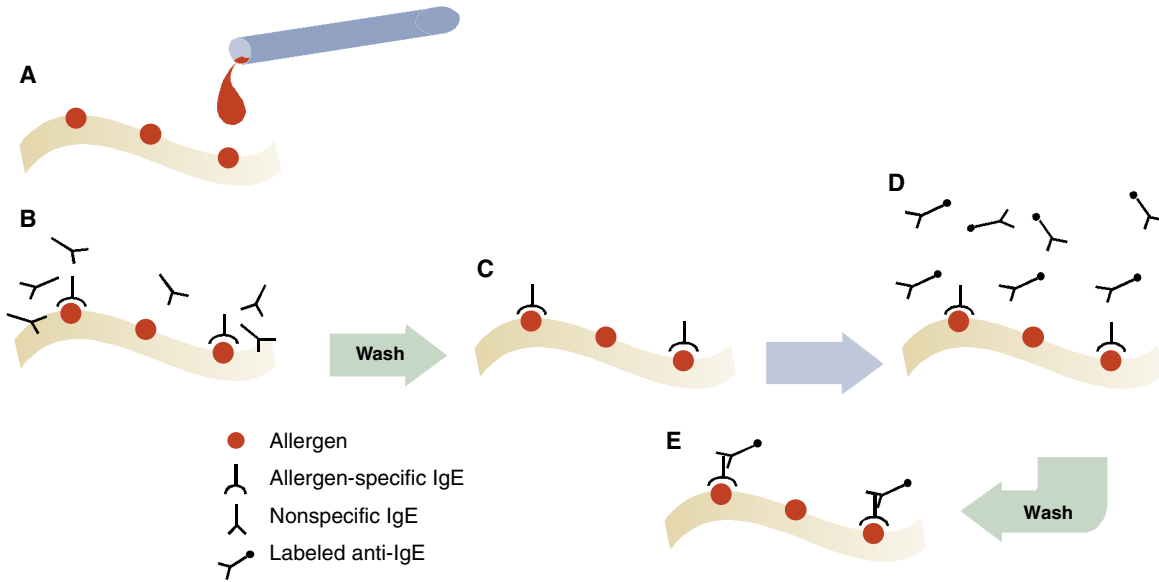
Wood et al compared skin tests (skin-prick and intradermal) with a third-generation blood test, evaluating their relative sensitivity, specificity, and positive and negative predictive value (Table 2).¹⁹ The blood and skin-prick tests were comparable, exhibiting high levels of sensitivity, specificity, positive predic-

tive value (PPV), and negative predictive value (NPV). However, noted the investigators, intradermal testing “added little to the diagnostic evaluation;” its NPV was comparable to that of skin-prick and blood tests, but its PPV was very low (LOE: 2).

Poon et al, in a review of the literature, found that results from blood and skin testing were highly correlated; that is, their diagnostic efficacies were similar (Figure 6).²⁰ The 2 tests gave the same diagnosis in 68% to 95% of cases, depending on the type of tests compared. When the comparison was restricted to second-generation blood tests and skin tests, correlation ranged from 87% to 95%. However, lacking an independent gold standard, the investigators concluded that it is not possible to determine absolutely the sensitivity and specificity of either test, thereby thwarting any conclusion as to which test is more accurate (LOE: 3). They did note that blood testing offered more standardization than did skin testing.

FIGURE 5

Detection of allergen-specific IgE with a blood test



In the first step of a specific IgE blood test, the patient's serum is incubated with allergens bound to a solid support (A). In the radioallergosorbent test (RAST), a paper disk functions as the allergen-support structure, whereas second- and third-generation serologic assays employ supports with greater allergen-binding capacities (eg, cellulose sponge, polystyrene, liquid-phase carrier). Allergen-specific IgE from the patient's serum binds to allergen to form antibody-antigen complexes (B). After nonspecific IgE has been washed away (C), labeled antibodies specific for human IgE are added, resulting in the formation of anti-IgE-antibody-allergen complexes (D). The radiolabeling used in earlier RASTs was replaced with enzyme (eg, fluorescent, colorimetric) or chemiluminescent labeling in more recent assays. Another washing removes unbound anti-IgE-antibody, and the remaining labeled complexes (E) are measured.

Adapted from Poon et al.²⁰

TABLE 2

Predictive value of skin and blood tests for cat allergy

	Skin-prick test (95% CI)	Third-generation blood test (95% CI)	Intradermal test (95% CI)
Sensitivity (%)	93.6 (±4.3)	87.2 (±6.9)	60.0 (±15.3)
Specificity (%)	80.1 (±7.1)	90.5 (±6.1)	32.3 (±14.7)
Positive predictive value (%)	90.1 (±5.3)	91.1 (±5.9)	12.0 (±10.2)
Negative predictive value (%)	87.1 (±6.0)	86.4 (±7.1)	84.6 (±11.3)
Likelihood ratio (positive/negative)	4.9/0.08	9.4/0.14	0.9/1.2

In this study of 120 patients, skin-prick tests (SPT) for cat-allergen-specific IgE were positive in 81 patients, and intradermal tests (IDT) were positive in 26 of 39 patients with a negative SPT. A third-generation blood test (BT) was performed in 89 patients; results were positive in 45 of 51 patients with a positive SPT and negative in all patients with a negative SPT. Subsequent challenges to cat allergen were positive in 38 of 41 patients with a positive SPT, 10 of 39 with a negative SPT, 6 of 26 with a positive IDT, 4 of 13 with a negative IDT, 27 of 27 with a positive BT, and 12 of 44 with a negative BT. (LOE: 2)

CI = confidence interval. Adapted from Wood et al.¹⁹

Position papers published in the 1980s and 1990s by various medical organizations (including the American Medical Association, the American College of Physicians, and 4 allergy associations) almost all stated that the correlation between skin and blood tests is good.²⁰ However, they do not agree on the relative sensitivity and specificity of the tests.

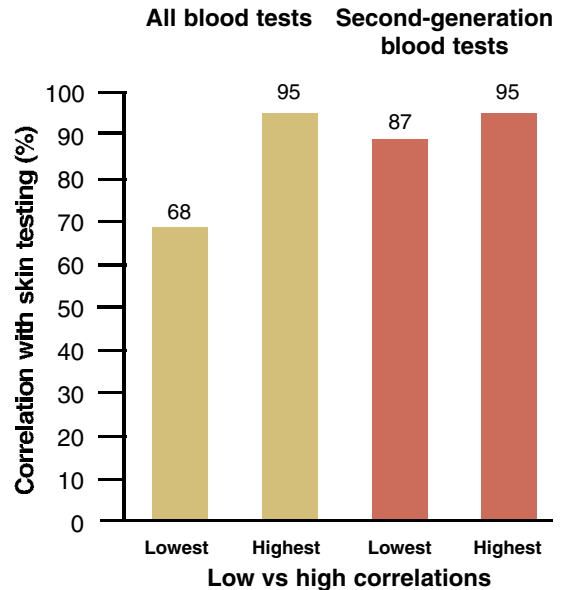
More recently, an evidence-based analysis of comparative studies stated that skin and blood (eg, Pharmacia CAP and UniCAP) tests “have similar diagnostic performance.”²¹ Positive likelihood ratios (PLRs) for skin-prick tests ranged from 3.23 to 16.17 and negative likelihood ratios (NLRs) from 0.03 to 0.51. Intradermal tests had PLRs of 0.89 to 8.80 and NLRs of 0.05 to 1.24. Blood tests had PLRs of 3.39 to 80.0 and NLRs of 0.09 to 0.84. The studies tested selected groups of allergens and used different “gold” standards. The investigators concluded that either skin tests or well-performed blood tests are reasonable choices for diagnosis, counseling, and follow-up.

A review of costs showed that a single skin test (ie, for 1 allergen) was less expensive than a single blood test.²⁰ But overall cost per patient appeared to be comparable since more allergens typically were used with skin testing. The 1996 Medicare Standard Analytical File showed that the median number of skin-prick tests was 50 per patient (median charge, \$255), while the median number of blood tests was 24 per patient (median charge, \$320).

Not all blood tests are equal. Several types of specific IgE blood tests are available, and not all of them perform equally well. Williams et al analyzed the accuracy and precision of specific IgE testing on 26 masked serum samples sent to 6 laboratories that used 5 different assays to detect 17 aeroallergens.²² Analysis of 12,708 test results showed considerable variation among laboratories, testing technologies, and allergens. A third-generation blood test used in 2 different laboratories performed closest to an

FIGURE 6

Diagnostic efficacy of IgE blood tests compared with skin tests



Based on a review of the literature, Poon et al determined that results from blood and skin tests were highly correlated. They gave the same diagnosis in 68% to 95% of cases, and when the comparison was restricted to second-generation blood tests, correlation ranged from 87% to 95%. Given the lack of an independent gold standard for detecting allergens, it is not possible to determine the overall sensitivity and specificity of either type of test. (LOE: 3). Assessments of third-generation specific IgE blood tests are shown in Table 2 and Figure 7.

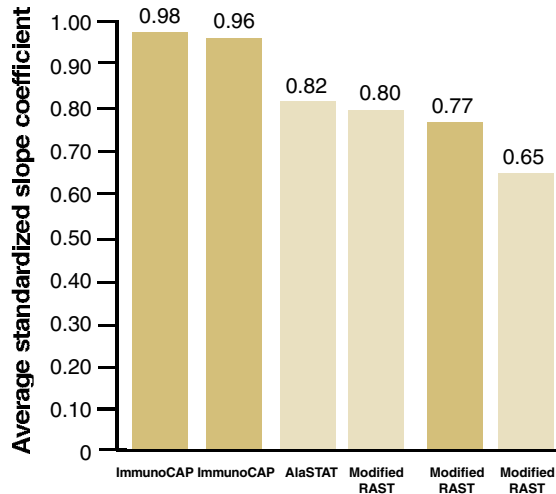
Adapted from Poon et al.²⁰

ideal statistical standard and proved consistently superior to other assays (Figure 7). The study found that only the third-generation blood test was capable of measuring specific IgE over a large range with precision and accuracy, and the investigators supported its use, for the time being, as a standard for quantitative measurements of specific IgE (LOE: 3).

Choosing a blood test. At least 15 blood tests have received FDA approval, and the number of available tests continues to increase. Hamilton noted in an editorial that the physician ordering a blood test assumes responsibility for choosing the best test.²³ Several suggestions were offered: Choose a laboratory that is CLIA-88 certified, and request a copy of its CLIA-88 certificate. Assess the laboratory’s technical skill and the

FIGURE 7

Comparison of selected specific IgE blood tests



To assess the precision and accuracy of commercial blood tests for specific IgE, 26 undiluted serum samples containing variable levels of specific IgE to 17 common allergens were sent on 3 different occasions to 6 laboratories. The laboratories used 5 different assays: 2 used ImmunoCAP (cellulose sponge), 1 used AlaSTAT (liquid-phase carrier), and 3 used modified radioallergosorbent tests (RAST; paper disks). A total of 12,708 test results were obtained. Because of the differences in scaling values for the assays, the average standardized slope coefficient (ASSC) across all allergens was used to evaluate overall performance of the assays and laboratories. A theoretical ideal assay with an ASSC of 1.00 was used for comparison. The ASSCs were 0.98 and 0.96 for ImmunoCAP, 0.82 for AlaSTAT, and 0.80, 0.77, and 0.65 for the modified RASTs. The overall results of AlaSTAT and modified RASTs were significantly different ($P=.01$) from those of the ideal standard while the results of ImmunoCAP were not. The investigators concluded that data from different assay systems are not interchangeable. (LOE: 3)

Adapted from Williams et al.²²

assay and allergen reagents that it uses; this can be achieved by reviewing the laboratory's Diagnostic Allergy (SE) Proficiency Survey. To participate in this survey, which is administered under the auspices of the American College of Pathologists, the laboratory completes an analysis of 5 serum samples that are submitted every 17 weeks. Hamilton recommends reviewing the Participant's Summary as well as the last year's SE Survey data on diagnostic performance (eg, sensitivity and specificity).

Total IgE. Most laboratories also report total IgE levels, although this information often is of little practical value. If skin or blood

test results for specific allergens are negative, prescribing an antihistamine on the basis of a high total IgE level may be misguided.

There are instances in which measurement of total serum IgE may be helpful. Some patients with a high total IgE level and no allergic symptoms may have a nonatopic condition known to be associated with elevated IgE (Table 3).³ An elevated total IgE may be a warning that important allergens have been missed. For example, in a patient with rhinitis or asthma and a total serum IgE of 600 IU/mL but no positive tests for specific inhalant allergens, it may be helpful to test for a wider range of allergens than those included in the test panel (LOE: 3).¹⁵

MANAGEMENT

There are 2 approaches to managing patients with respiratory symptoms and possible allergic disease (Figure 8); choosing between them depends largely on findings from the history and physical examination. For example, Gendo and Larson noted that, in patients with possible allergic rhinitis, historical items with the best diagnostic accuracy include a family or personal history of allergy and correlation of symptoms to animal dander and pollen. PLRs range from 3 to 5 for each of these factors.²¹ However, the absence of any factor cannot definitively rule out allergic rhinitis because their NLRs are not low (0.40 to 0.81).

Thus, in patients with a low probability of allergy (eg, atypical signs and symptoms, no history of allergy, no identifiable allergic triggers), specific IgE skin or blood testing is performed before treatment decisions are made. A positive test result is likely to be a true positive in such cases.²¹

In patients with an intermediate or high probability of allergy (based on history and physical), a substantial number of specific IgE test results will be false-negative.²¹ Empiric drug therapy is therefore warranted in this group with testing reserved for those who do not respond. Delayed testing in such cases has

TABLE 3

Nonatopic conditions associated with elevated total serum IgE levels

- Some immunodeficiencies (eg, HIV infection)
- IgE myeloma
- Drug-induced interstitial nephritis
- Graft-versus-host disease
- Parasitic diseases
- Hyper-IgE syndrome (dermatitis, recurrent pyogenic infection)

Adapted from AAAAI.³

more value as a guide for allergen avoidance and immunotherapy than as a diagnostic tool.

Avoidance therapy. Avoidance is an important first-line therapy in allergic patients, but it can achieve its full potential only when the offending allergen triggers have been identified. Studies on the efficacy of avoidance therapy have had conflicting results (see discussion by Caryl Heaton, DO, on page S25), in part because it may be impossible to completely avoid some allergens. In addition, because patients often are allergic to multiple allergens, symptoms may be caused by allergens other than the one that is being avoided.

Among the studies that have shown allergen avoidance to be efficacious, one by Nishioka et al found that avoidance prevented sensitization to house-dust mites in infants with atopic dermatitis. The 57 infants in this study had high levels of IgE against egg white, cow's milk, or soybean but not against house-dust mites.²⁴ The families of 27 infants were given mite-impermeable quilt and mattress covers for all beds. After 1 year, serum levels of anti-dust-mite IgE were significantly lower in infants who slept on protected bedding (0.7 U/mL vs 2.5 U/mL, $P<.05$), and fewer of these infants had positive skin-prick tests to dust-mite allergen (31% vs 63%, $P<.02$) (LOE: 3).

In another such study, the use of mite-

impermeable bed covers was associated with a decreased need for inhaled corticosteroids in children (aged 6 to 15 years) with asthma and dust-mite allergy.²⁵ After 1 year, the mean daily dose of inhaled steroids had decreased from 408 μg to 227 μg ($P<.001$) in the 26 children who used impermeable bed covers, whereas dosage did not change in the 21 children in the control group. Daily steroid intake decreased by 50% or more in 73% of children who used impermeable covers and in 24% of those who did not ($P<.01$) (LOE: 3).

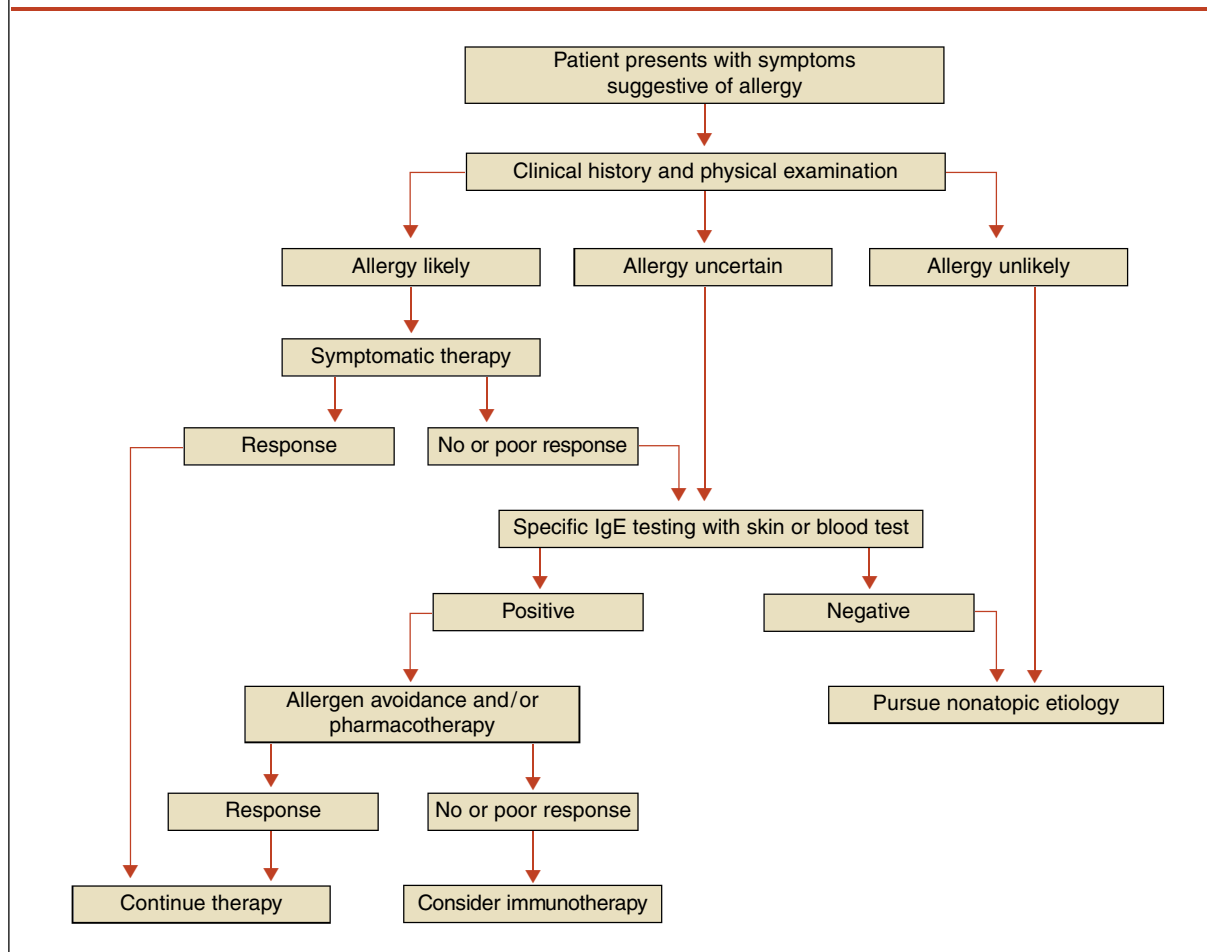
Pharmacotherapy. With regard to drug therapy for allergic rhinitis, the AHRQ stated "The overwhelming majority of studies clearly favor the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are true for both seasonal allergic rhinitis and perennial allergic rhinitis" (SOR: A).¹² This report of the AHRQ Evidence-Based Practice Program reviewed 9 studies (1 meta-analysis and 8 recent clinical studies).

Cromolyn sodium can be used prophylactically to treat seasonal allergies (SOR: A).¹³ Two new medications have been made available for allergic upper respiratory conditions. Montelukast, a leukotriene receptor antagonist, is now approved for treatment of seasonal allergic rhinitis; this agent and zafirlukast had been approved earlier for prophylaxis and chronic treatment of asthma (LOE: 1).²⁶⁻²⁷ Omalizumab, an anti-IgE monoclonal antibody given subcutaneously every 2 or 4 weeks, has been approved for treatment of moderate-to-severe allergic asthma in patients with positive skin or blood test reactivity to a perennial aeroallergen.²⁸

A Cochrane review of 8 trials that included 2,037 patients with mild-to-severe allergic asthma and high levels of IgE found that, compared with placebo, omalizumab reduced the incidence of asthma exacerbations and significantly increased the numbers of patients who were able to reduce or stop inhaled corticosteroids.

FIGURE 8

Management of patients with allergy-like symptoms



teroids (LOE: 1).²⁹ Intravenous and subcutaneous omalizumab reduced free IgE levels by 98% to 99%. Odds ratios for treatment efficacy were: 2.50 (95% confidence interval (CI), 2.00–3.13) for complete withdrawal from corticosteroids; 2.50 (95% CI, 2.02–3.10) for reducing daily steroid intake by more than 50%; 0.46, (95% CI, 0.35–0.61) for fewer asthma exacerbations while on the pretreatment steroid regimen; and 0.46, (95% CI, 0.36–0.59) during steroid reduction.

Immunotherapy. Although rare, severe systemic reactions can occur during immunotherapy.³⁰ Because these reactions can be fatal, immunotherapy should be performed by trained specialists in settings where the risk of

anaphylaxis is minimized (eg, with patient selection), its symptoms are readily recognized, and the necessary medications and equipment are on hand for prompt treatment (SOR: C).

Nonallergic disease. Oral antihistamines are usually ineffective in patients with nonallergic disease.¹³ Patients taking a combined antihistamine plus decongestant may respond to the decongestant component of the drug. Intranasal azelastine, an H₁ antihistamine, is FDA-approved for the treatment of vasomotor rhinitis as well as seasonal allergic rhinitis (LOE: 1).³¹ Many of the nasal corticosteroid sprays are approved for the treatment of both allergic and nonallergic rhinitis.

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Implications for management: Four case discussions

Case 1: A young woman with nasal congestion and sneezing

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■ PRESENTATION

A 26-year-old woman presented to her family physician with an 8-month history of nasal congestion and sneezing. She self-medicated with her sister's cetirizine (10 mg/day for 2 weeks), which reduced her symptoms by about 20%. She was interested in knowing the cause of her symptoms and what could be done to treat them. However, she preferred not to take any medicines.

■ HISTORY

The intensity of the patient's symptoms varied (although they had worsened during the last few months) and were not accompanied by fever. Her nasal discharge was thick and yellow in the morning but cleared somewhat by midday. She also had recurrent sinus infections accompanied by facial pressure and fever; the most recent episode had occurred 6 months earlier. She did not have asthma and denied any medication allergies or illicit drug use. She smoked 10 cigarettes a day and owned a cat. Another physician had advised her to get rid of the cat, but she had not complied. The floors of her home were covered with wall-to-wall carpeting.

■ EXAMINATION

Review of systems was normal. The patient's nasal mucosa was swollen and pale; her posterior pharynx was erythematous but free of swelling or exudates.

Her neck was supple with no adenopathy or thyromegaly. Her lungs were clear, with no sign of wheezing. Her heart sounds were normal.

This case is representative of the many patients who self-medicate before seeing a physician; in some cases, symptoms have been present for years. Evaluation of congestion and sneezing should include a focused evaluation of symptoms and general evaluation of the medical history. The pattern, chronicity, and seasonality of symptoms and the presence of coexisting medical conditions, such as asthma, allergic conjunctivitis, or rhinosinusitis, should be determined. Additionally, a detailed environmental history, including occupational exposures, and identification of precipitating factors may help to distinguish allergic from nonallergic rhinitis (Figure 1). Patients should be asked for a list of past medications that were directed at their symptoms, from which a list of effective and ineffective medications can be compiled.

The impact of symptoms on quality of life also should be assessed. Patients with rhinitis may complain of fatigue due to sleep loss, headaches, poor concentration, repeated nose blowing, itchy and watery eyes, and general irritability. All of these things can have a negative impact on their ability to complete home and work responsibilities.

The physical should include examination of the nasal passageways, secretions, turbinates, and septum. Also, the presence of nasal polyps should be determined (Table 1). Pale, swollen nasal mucosa is typical in patients with rhinitis; bluish-gray mucosa may be seen in patients with severe mucosal edema. Unfortunately, dis-

TABLE 1

Possible rhinitis: Elements of the physical examination

General

- Allergic salute (pushing nose up with palm of hand)
- Allergic shiners (infraorbital dark skin)
- Facial pallor
- Nasal crease (across bridge of nose, caused by rubbing)
- Mouth breathing

Skin

- Dryness
- Dermographism
- Eczema

Eyes

- Evidence of conjunctivitis (watery discharge, puffy eyelids)
- Dennie-Morgan lines (lines or folds below margin of lower eyelid)

Ears

- Evidence of middle ear disease

Nose

- Secretions (amount, color, consistency)
- Mucosal swelling
- Polyps
- Septal abnormalities (perforated, deviated)
- Blood

Mouth

- Elevated upper lip
- Overbite
- High arched palate
- Tonsillar hypertrophy
- Lymphoid streaking
- Postnasal discharge
- Halitosis

Neck

- Lymphadenopathy
- Enlarged thyroid

Lungs

- Evidence of asthma

Adapted from Dykewicz et al.¹

tinguishing between allergic and nonallergic rhinitis can be difficult based on mucosal appearance because both may present with mucosal pallor, edema, or hyperemia.¹

■ MANAGEMENT

A working diagnosis of allergic rhinitis was made, and blood was drawn for specific IgE testing. The patient was given a prescription for cetirizine (10 mg/d).

Results of the blood test, which included 12 inhalant allergens endemic to the area, showed no significant IgE elevations. Therefore, the diagnosis was revised to nonallergic rhinitis and earlier plans to suggest allergen avoidance measures were aborted. The symptomatic benefit obtained from cetirizine was judged to be insignificant and attributed to a possible placebo effect; therefore, the drug was discontinued.

The patient was told that her smoking probably aggravated her congestion and was advised to quit.

She declined a prescription for nasal steroids, saying that she did not want a medication that had to be used every day. Over-the-counter pseudoephedrine, taken as needed, was suggested as an alternative to nasal steroids.

In this case, results of specific IgE blood testing contradicted the diagnostic assumptions made on the basis of the clinical history and physical examination, resulting in a revised diagnosis of nonallergic rhinitis. The benefits of having performed specific IgE blood testing in this patient are readily apparent. She does not have to struggle with difficult avoidance measures, including the possibility that she will again be told to get rid of her cat. She now has a good reason to give up cigarettes. Needless drug therapy and potential referral to an allergy specialist have been avoided.

TABLE 2

Allergic and nonallergic rhinitis

Allergic	Nonallergic	Symptom-mimicking conditions
<ul style="list-style-type: none"> • Seasonal • Perennial • Episodic • Occupational 	<ul style="list-style-type: none"> • Idiopathic (vasomotor) • Infectious • Atrophic • Drug induced • Reflex induced (eg, gustatory) • Exercise induced • Hormonally induced (eg, in pregnancy) • Occupational • NARES (nonallergic rhinitis with eosinophilia syndrome) • Ciliary dyskinesia syndrome 	<ul style="list-style-type: none"> • Structural/mechanical <ul style="list-style-type: none"> – Foreign bodies – Tumors – Septal anomalies – Hypertrophic turbinates – Adenoidal hypertrophy – Choanal atresia • Inflammatory/immunologic <ul style="list-style-type: none"> – Wegener's granulomatosis – Sarcoidosis – Midline granuloma – Systemic lupus erythematosus – Sjögren's syndrome – Nasal polyposis • Cerebrospinal fluid rhinorrhea

Adapted from Dykewicz et al.¹

Seeing that this patient obtained partial relief from cetirizine, a clinician might be inclined to simply prescribe a second medication or switch to another, hopefully more efficacious, antihistamine. In hindsight, after IgE testing, such an approach would have been misguided and possibly ineffective.

The differential diagnosis of nonallergic rhinitis is extensive (Table 2); of these, vasomotor rhinitis is by far the most common. The etiology of vasomotor rhinitis is unclear, which accounts for its other name, idiopathic nonallergic rhinitis. The diagnosis for vasomotor rhinitis is one of exclusion: normal total IgE levels, negative specific IgE tests, and a lack of identifiable inflammation on nasal cytology.²

Patients tend to present in 2 different ways, either with rhinorrhea as the main complaint or with nasal congestion, blocked airflow, and minimal rhinorrhea.¹ Symptoms may be provoked by nonspecific stimuli such as cold dry air, perfume, paint fumes, and cigarette smoke.¹

Blood testing for specific IgE, in addition to

convenience, has several other advantages (Table 3).³⁻⁵ The procedure does not produce potentially irritating skin reactions, and its outcome is not influenced by concomitant medications (eg, antihistamines). Thus, blood testing is an option for patients who refuse or cannot cooperate with skin testing. Moreover, blood testing can be performed in patients with contraindications to skin testing, such as a chronic skin condition, poorly controlled asthma, or increased risk of anaphylaxis to the skin-test allergen.

Blood or skin testing for specific IgE can confirm hypersensitivity to a wide variety of allergens; however, test results alone are not diagnostic (Table 4). Results must correlate with the patient's symptoms and history—the amount of specific IgE in the serum or the size of a skin test wheal is not necessarily related to its clinical significance.

■ FOLLOW-UP

Several months later, the patient had quit smoking. She was using pseudoephedrine once or twice a week

TABLE 3

Skin or blood testing: Which to choose?

Advantages of skin testing

- May be more sensitive than blood testing
- Results are immediate
- Patients can see erythema and feel itching, which reinforces avoidance compliance

Advantages of blood testing

- Easy to perform; 1 simple blood draw
- No risk of anaphylaxis
- No irritating skin reactions
- Not affected by patient's medications
- Diagnostic performance similar to that of skin test
- Convenient method for monitoring changes in sensitization in response to allergen avoidance
- Convenient method for following development of sensitization in childhood
- Readily available to primary care physicians

Blood testing may be preferable to skin testing in patients

- With severe dermatographism or other chronic, widespread skin condition
- With very young skin or atrophic skin
- With poorly controlled asthma ($FEV_1 < 70\%$ personal best effort)
- With a history of anaphylaxis (eg, to a food or drug)
- With a history of hymenoptera sensitivity
- Who are being tested for allergens (eg, venom, latex) that require precaution or titration with skin testing
- Who are taking medications that can alter skin test results (eg, antihistamines, β -blockers, angiotensin-converting enzyme inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, steroid/immunomodulating agents)
- Who are pregnant (many allergy clinics do not recommend skin testing during pregnancy)

Adapted from AAAAI,³ Hedges and Pollart,⁴ Selner et al,⁵ Høst et al,⁶ Gendo and Larson.⁷

TABLE 4

Placing specific IgE test results into context

- Specific IgE test results cannot be the sole basis for clinical diagnosis.
- Positive skin or blood test results should correlate to symptoms and history of exposure. A positive test indicates that the patient has antigen-specific IgE but does not prove that exposure to the allergen in question causes significant allergic symptoms.
- In case of disagreement between clinical history and results of a skin or blood test, a supplementary skin or blood test should be performed.
- Skin and blood tests have been compared with each other but not with a gold standard. In fact, no gold standard for assessing sensitivity and specificity of either test has been found.
- Studies have shown significant variations in the quality (ie, reproducible, standardized results) of both skin and blood tests; therefore, a test for office use should be chosen very carefully.

Adapted from Selner et al,⁵ Høst et al.⁶

for congestion and felt that her symptoms were under control.

Eliminating allergies as the cause of this patient's rhinitis motivated her to quit smoking; she could no longer blame her symptoms on allergies and realized that her rhinitis symptoms were probably being caused by something she could control, her smoking habit. Smoking cessation and treatment of remaining symptoms with pseudoephedrine provided adequate relief.

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Case 2: An elderly woman with nasal congestion, sneezing, and asthma

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■ PRESENTATION

A 70-year-old, obese woman with a long history of nasal congestion, sneezing, and asthma presented for evaluation.

■ HISTORY

The patient's nasal congestion and sneezing had occurred intermittently during the last 50 years and were usually most severe in the spring and fall. Loratadine (10 mg/d prn) provided partial relief. The severity and frequency of her nasal symptoms had been increasing over the years, and she now asked that they be specifically addressed.

Her medical history was significant for asthma, controlled with inhaled fluticasone (44 µg, 2 puffs twice a day) and albuterol (2 puffs 4 times a day, prn). The

patient also had stable angina pectoris. She was allergic to sulfa drugs, which caused a rash. She did not drink alcohol or smoke. She owned a cat and a dog, and neither animal slept in her bedroom, which was carpeted. She did her own vacuuming with a machine that did not have a high-efficiency particulate air (HEPA) filter. Her family history included a brother with asthma.

This case is interesting because of the patient's age at presentation and the progressive nature of her nasal symptoms. Moreover, allergies are not the most common cause of rhinitis in patients older than age 65. More likely causes of rhinitis in this age-group include cholinergic hyperactivity, α -adrenergic hyperactivity, or sinusitis.¹

■ EXAMINATION

A review of systems and the physical examination were unrevealing. The patient's nasal mucosa was inflamed; lungs showed fair air movement and a mild expiratory wheeze. Peak expiratory flow was 74% of predicted value.

■ MANAGEMENT

The patient received a working diagnosis of allergic

rhinitis in addition to her asthma. Specific IgE blood testing was performed. Results showed varying degrees of reactivity: a strong reaction to dust mite and grass and tree pollens, a moderate reaction to cat and dog dander, and a mild reaction to mold.

The results of the blood test prompted a switch from loratadine to cetirizine (10 mg/d) with the hopes that the latter agent would induce a more robust response. Intranasal fluticasone (2 sprays twice a day) was added to her regimen, and the inhaled fluticasone dosage was increased to 110 µg. The patient also received counseling on the avoidance of allergens, including house-dust mites and animal dander.

In this case, blood testing confirmed that this asthmatic patient also had allergic rhinitis. Test results also helped to redirect pharmacologic therapy and provided renewed motivation to institute allergen avoidance measures. In fact, specific avoidance therapy would not have been possible without knowing to which allergens the patient was sensitized. Finally, the use of blood, instead of skin, testing allowed the patient to continue taking her antihistamines without interruption.

The second-generation (ie, non-sedating) H₁-receptor blocking antihistamines are a mainstay of treatment for allergic rhinitis. This patient reported some symptomatic improvement with loratadine. However, it was decided to switch her from loratadine to cetirizine. *The Medical Letter*, in an assessment of cetirizine, fexofenadine, and loratadine, noted that the data indicate, although not conclusively, that the 3 agents may vary in efficacy and degree of associated sedation.²

The patient also started therapy with an intranasal corticosteroid, which is the most effective pharmacologic agent for treating allergic rhinitis; it addresses the inflammatory component of the disease.³ Intranasal steroids take longer to exert their effect than do oral antihistamines. Moreover, intranasal steroids must be administered regularly, even in the absence of

symptoms, to maintain effectiveness. For patients with seasonal allergic rhinitis, treatment with these agents should start approximately 2 weeks before the anticipated pollen season or at symptom onset. Treatment should continue for 2 to 3 weeks after pollen season ends to decrease nasal hyperreactivity that may persist after pollen exposure.

Oral sympathomimetic agents should be avoided when choosing allergy therapy for elderly patients, especially for those with coronary artery disease.

Allergen avoidance. When counseling patients on allergen avoidance (**Table 1**), compliance is best accomplished by assigning priorities, tailoring preventive measures to fit the patient's lifestyle, and avoiding scare tactics. Total avoidance is not always practical. The cost of avoidance can be substantial; when possible, cheaper alternatives should be provided.

The 5 main categories of IgE-dependent triggers for allergic rhinitis are pollens, molds, house-dust mites, animals, and insect allergens. Outdoor allergens, primarily pollens, play a major role in seasonal allergy symptoms. Indoor allergens, such as dust mites, molds, and animal and insect allergens, play a major role in perennial allergic rhinitis and allergic asthma. Potential triggers can be sought by careful questioning of the patient to associate symptom onset with allergen exposure and then may be confirmed with specific IgE testing.

■ FOLLOW-UP

Two months later, the patient's hay fever and asthma symptoms had resolved by 50% to 75%, yet she felt her symptoms were inadequately controlled. She was referred to an allergist for possible immunotherapy. Six months after beginning immunotherapy, the patient's symptoms showed marked and progressive improvement.

The patient is the final judge of his/her response to allergy drug therapy. This patient deemed her response to be suboptimal, and

TABLE 1

Allergen avoidance tips

Pollen

- Avoid, if you can, going outside when the pollen count is high (eg, early morning, late evening, and dry windy days).
- Check forecasts on local pollen counts (eg, on the Weather Network or in a newspaper).
- Keep windows closed; use air conditioning when possible. Air conditioning decreases indoor pollen counts by recirculating indoor air instead of outside air, which carries pollen.
- Have someone kill weeds around the house either by cutting them or using weed killers.
- Avoid plants related to ragweed (eg, zinnias, chrysanthemums, marigolds, dahlias, and sunflowers).
- Consider using a high-efficiency particulate air (HEPA) filter in the home and on the vacuum cleaner in particular. HEPA filters are designed to absorb most particles floating in the air; they keep vacuumed dust from escaping back into the air. HEPA filters and vacuum cleaners are available at Home Depot, Target, and other department stores.

Mold

- Reducing excess dampness in the house is the best way to control mold.
- Reduce house dust; it may contain mold.
- Wash window ledges and shower stalls with chlorine bleach or similar cleanser at least once every 3 months.
- Apply mold-resistant paints to the walls of unfinished basements.
- Keep houseplants to a minimum or use solutions (available at nurseries) that, when mixed with potting soil, inhibit the growth of mold.
- Clean furnace filters, air conditioners, dehumidifiers, and vaporizers frequently to prevent mold build-up.
- Wallpaper, especially in the bathroom, is a prime spot for mold growth. When hanging wallpaper, add borax or boric acid to the paste to slow down mold growth.
- Dry damp clothes promptly.
- Vent clothes dryers to outside of the home to prevent moisture build-up inside.
- Spread out towels and shower curtains as often as possible so that they will dry promptly.
- Discard damp piles of papers, carpeting, and old furniture.
- Replace old pillows and bedding. Use Dacron-filled pillows and comforters instead of foam rubber, which encourages mold growth.
- Check attics and crawl spaces for moisture and mold.

House-dust mites

- Keep the bedroom clean. You spend up to a third of your life in the bedroom, so efforts to improve this environment are a priority. Use wood or linoleum flooring, if possible. Keep your bed away from air vents.

Everything in the bedroom should be washable, including bedding, rugs, and foam mattresses. Use pillows filled with Dacron or foam instead of feathers. Vacuum mattresses and enclose them in a protective dust-mite cover. Use synthetic blankets.

- Avoid being present during house cleaning, if possible, or wear an appropriate mask if you clean the house. Clean rooms with a damp dust cloth twice a week.
- Avoid overstuffed furniture; if you have it don't sit on it.
- Eliminate dust catchers and avoid clutter.
- Replace old carpets and rugs, if possible. If you keep your carpet or if it is new, you can reduce its allergen content by applying a solution that helps to minimize dust formation. Use a low-emission vacuum cleaner.
- Use only washable curtains made of cotton or polyester. Venetian blinds are not recommended because they catch too much dust.
- Have furnace ducts cleaned and its filters replaced regularly.

Animal dander

- Never let a pet into your bedroom.
- Keep your pet outside as much as possible, and ask someone who's not allergic to bathe your pet.
- Professional cleaning of carpets and air ducts is usually required to remove animal dander, even after the pet has been removed from the home.
- If you are going to visit someone who keeps a pet in the home, consider taking a nonsedating antihistamine (as recommended by your doctor) before visiting.
- Live animals are not the only source of allergies. Clothing made of cashmere, animal hair, or mohair can trigger an allergic reaction, as well as animal hair-stuffed chairs, sofas, toys, and down-stuffed pillows. Use Dacron-filled pillows and comforters instead of foam rubber, which encourages mold growth.
- Consider HEPA filters (see pollen tips).

Cockroaches*Reduce their food supply.*

- Vacuum or sweep after every meal.
- Wash dishes in soapy hot water to eliminate grease.
- Keep trash in a tightly closed container.
- Store uneaten food in a tightly sealed container.

Dry up their water supply.

- Fix dripping faucets.
- Do not overwater houseplants; cockroaches are attracted to damp soil.
- Keep sink plugs over drains.

Make it difficult for them to hide.

- Move woodpiles away from outside walls.
- Do not save food cans.
- Do not let newspapers pile up.



she was referred for possible immunotherapy.

In addition to inadequate response to avoidance and pharmacologic therapy, immunotherapy may be considered in patients who have intolerable drug side effects, require drug therapy for more than 3 to 4 months a year, have coexisting allergic rhinitis and asthma, or want long-lasting control without drug therapy.^{4,5} The treatment is not recommended in patients with poorly controlled asthma (FEV₁ <70% of best effort) or a febrile illness and during β -blocker therapy or pregnancy.^{4,5}

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Case 3: A man with persistent bronchitis

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■ PRESENTATION

A 34-year-old man presented to his family physician for follow-up of bronchitis. One month earlier, the patient had been diagnosed with a viral upper respiratory infection, and symptomatic treatment had been prescribed. He returned 3 days later with a severe cough and wheezing for which a 5-day course of azithromycin and a cough suppressant with hydrocodone were prescribed. The cough suppressant prescription was refilled once.

At the follow-up visit, the patient said that he had not had any rest, and was not getting better. He described his cough as dry and worse at night. At work, he would go into “fits of coughing” while talking on the phone. He had been afebrile throughout this illness.

■ HISTORY

The patient had consulted his family physician many times over the years for recurrent respiratory symptoms. Every November, he would have his “yearly

infection.” He worked in an office that had circulated and presumably filtered air. He did not smoke or drink. He had been tested for allergies many years earlier and said that he was allergic to “everything.” He had a short-acting, α -adrenergic bronchodilator that he used intermittently for “a little asthma,” as well as a prescription for fexofenadine (180 mg/d) that he used in the spring and summer for “hay fever.” He did not use environmental avoidance measures in his home “because they never did any good.”

■ EXAMINATION

Physical examination revealed an afebrile, mildly overweight man in no apparent distress. His intermittent coughs during the examination were associated with wheezing (prolonged expiratory phase); however, no wheezing was noted on auscultation of the lungs. Peak expiratory flow was 72% of his predicted value. The tympanic membranes appeared normal. The nasal mucosa was pale pink and swollen; there was no nasal discharge. Mild injection and lymphoid hyperplasia were noted in the posterior pharynx.

Viral respiratory infection is the most common cause of asthma symptoms. Exacerbation of asthma symptoms by a viral respiratory infection may be intermittent yet severe.¹ Despite the intermittent nature of this patient’s symptoms, they are moderately severe. Baseline

peak flow measurements might provide evidence of at least mild persistent asthma.

The history suggests that this patient's asthma has an allergic component. Asthma symptoms are commonly associated with both seasonal and perennial allergic rhinitis. In fact, as many as 38% of patients with allergic rhinitis have asthma, and up to 78% of those with asthma have nasal symptoms.¹

The patient had been given an annual diagnosis of acute bronchitis primarily, one supposes, because of his strong belief that this was his "yearly infection." At the time of these episodes, an adequate history of allergies or asthma had not been obtained. Nevertheless, their frequent occurrence in a nonsmoker should have been the clue to prompt a more thorough workup.

■ MANAGEMENT

The patient was treated with combined fluticasone and salmeterol (250 µg/50 µg, 1 inhalation twice a day) and benzonatate (100 mg, 3 times a day) for cough suppression. He was told to increase his fluid intake, get as much rest as possible, call if fever developed, and return in a week.

The National Asthma Education and Prevention Program (NAEPP) recommends that patients with mild persistent asthma be treated with low-dose inhaled corticosteroids.² For moderate persistent asthma, the preferred treatment is a low-to-medium dose of inhaled corticosteroid plus a long-acting, inhaled β-adrenergic bronchodilator. According to the NAEPP, there is strong evidence from clinical studies indicating this combination alleviates symptoms, improves lung function, and reduces the need for short-acting, β-adrenergic bronchodilators. An alternative approach for which the evidence is not as substantial is to add a leukotriene modifier or theophylline to the inhaled corticosteroid or to double the dosage of the inhaled steroid.

In addition to pharmacotherapy, an important component in controlling asthma symp-

TABLE 1

Amelioration of nonenvironmental asthma triggers

Rhinitis/rhinosinusitis

- Optimize treatment of chronic allergic and nonallergic rhinitis and rhinosinusitis

Respiratory infection

- Give annual flu shots to patients who do not have a severe sensitivity to egg

Gastroesophageal reflux (frequent heartburn or possible GERD)

- Advise patients to
 - Avoid caffeine, alcohol, and chocolate
 - Not eat or drink 3 hours before retiring
 - Elevate head of bed 6 to 8 inches
- Consider antireflux therapy

Obstructive sleep apnea

- Advise patients to reduce weight
- Optimize treatment of rhinitis
- Consider intervention (eg, continuous positive airway pressure)

Aspirin sensitivity

- Advise patients to avoid aspirin and other NSAIDs
- Consider aspirin desensitization

β-Blocker therapy

- Avoid β-blockers (including eye drops); consider alternative agents

Sulfite sensitivity

- Advise patients to avoid foods with sulfite preservatives (eg, dried fruit, shrimp, processed potatoes, wine, beer)

Adapted from AAAAI.¹

toms is limiting exposure to factors that may contribute to an asthma exacerbation (Table 1, also see avoidance tips on page S22). As mentioned in the discussion of previous cases, skin or blood testing for specific IgE can help identify triggering allergens.

■ FOLLOW-UP

When seen 10 days later, the patient was significantly improved. He had been able to sleep more com-

fortably and no longer had coughing spasms at work. After a discussion of his diagnosis and its possible causes, the patient was offered specific IgE blood testing at the office or referral to an allergist. He declined referral; serologic testing revealed elevated IgE to 13 allergens in the 15-allergen panel.

IgE blood testing confirmed that this patient had allergic disease. His treatment should be reviewed every 1 to 6 months. If symptoms improve, his drug therapy can be gradually reduced; for example, the dosage of the combined fluticasone and salmeterol can be decreased to 100 µg/50 µg (1 inhalation twice a day). On the other hand, his medication may need to be increased in the fall or with the onset of another viral upper respiratory infection. Anticipating the need for additional treatment and, if possible, starting those treatments prior to symptom onset, may decrease the severity of his symptoms.

Efficacy of avoidance. The patient had limited interest in environmental control measures because in the past these methods “never did any good.” There is some evidence to support his claim. The conventional wisdom on environmental control has been challenged recently. Some studies have supported environmental control, while others have concluded that it has no benefit, especially when it is directed at single allergens. It is unclear which patients will benefit and by how much, and whether allergen avoidance is cost-effective.³

Impermeable bed covers. Two recent studies found that bed covers impermeable to house-dust mites were clinically ineffective in patients with asthma and allergic rhinitis. The asthma study, which enrolled 1,122 adults, of whom 65% were sensitized to dust-mite allergen, provided permeable or impermeable mattress, pillow, and quilt covers but no information on allergen avoidance.⁴ At 6 months (965 patients remaining), the peak expiratory flow rate in the intervention and control groups was not significantly different. At 12 months (882 patients remaining), 17% of

patients in each group had stopped taking their inhaled corticosteroids and mean steroid-dose reduction in subjects who had begun the weaning process was 47% in the intervention group and 48% in the control group.

All 232 patients who completed the allergic rhinitis study were sensitized to dust-mite allergen (175 had high sensitivity, 75 had low sensitivity).⁵ In addition to permeable or impermeable mattress, pillow, and quilt covers, patients received general information on allergen control. After 1 year, there was no significant difference in the primary endpoint, the rhinitis-specific visual-analogue score. The mean score decreased by 10 points in the intervention group and by 11 points in the control group.

Air filters. Another 2 studies reported similar findings on the efficacy of in-home air filters. Wood et al examined the effect of a high-efficiency particulate air (HEPA) cleaner on asthma and rhinitis in 35 cat-allergic subjects who were living with one or more cats.⁶ Subjects' bedrooms were equipped with a HEPA or control filter system. After 3 months, airborne allergen levels were reduced significantly in the bedrooms with HEPA filters, compared with control bedrooms ($P=.045$). However, there were no differences in settled-dust allergen levels, nasal- or chest-symptom scores, sleep disturbance, peak-flow rates, or use of rescue medications. Moreover, the addition of impermeable bed covers and banning cats from the bedroom did not have a significant effect on disease activity.

In a study reported by Warner et al, the homes of 40 subjects with asthma and sensitivity to dust-mite allergen received mechanical ventilation and a high-efficiency vacuum cleaner (HEVC), mechanical ventilation alone, HEVC alone, or no intervention.⁷ Twelve months later, homes with mechanical ventilation had significant reductions in humidity levels ($P<.001$), dust-mite numbers ($P<.05$), and dust-mite allergen concentrations (mg/m^3 , $P=.006$). The addition of an HEVC enhanced this effect. However, these environmental effects were not associated

with improvements in lung function, bronchial hyperresponsiveness, or symptom scores.

Cochrane reviews. Reviews of multiple studies on allergen avoidance also arrive at equivocal conclusions. Gotzsche et al reviewed 29 trials (939 patients) that examined the effects of chemical and physical methods to control dust-mite allergens on patients with asthma and dust-mite sensitivity.⁸ The allergen control measures had no statistically significant effect on asthma improvement (relative risk, 1.04; 95% confidence interval [CI], 0.83-1.31), asthma symptom scores (standardized mean difference [SMD], -0.07; 95% CI, -0.35-0.22), medication requirements (SMD, -0.14; 95% CI, -0.43-0.15), or morning peak flow (SMD, 0.04, 95% CI, -0.13-0.21). The reviewers concluded that these studies do not provide “a secure basis for advice and policy.”

In combination with drug therapy, allergen avoidance measures may have an added impact on symptoms.

In a review of dust-mite avoidance in patients with perennial allergic rhinitis and confirmed sensitivity to dust-mite allergen, only 4 studies met inclusion criteria and these were small and “of poor quality.”⁹ Data analysis suggested that reducing exposure to dust-mite allergen may provide some symptomatic benefit, but the reviewers could not estimate the magnitude of the benefit. In addition, the small size and poor methodologic quality of the trials reported to date made it difficult to offer definitive recommendations on the role, if any, of dust-mite avoidance in sensitive patients with perennial allergic rhinitis.

Conclusion. The conflicting evidence on the efficacy of environmental allergen control does not mean that it should be abandoned. Granted, avoidance measures are unlikely to be successful as monotherapy, but in combination with drug therapy, avoidance may have an added impact on symptoms. In an editorial that

accompanied the 2 studies^{4,5} cited above on impermeable bed covers and dust-mite allergy, Platts-Mills stated that “the correct conclusion is that treatment by means of allergen avoidance requires the definition of what patients are allergic to, additional measures beyond the use of mattress covers, and education.”¹⁰

Dr Fromer described the concept of the allergic threshold (see Figure 2 on page S6), which suggests that removal of 1 antigen may reduce the patient’s accumulated allergen load to below the symptom threshold, thereby reducing the need for drug therapy or at least adding a degree of symptomatic improvement to established drug therapy. Comprehensive avoidance of multiple allergens to which the patient is sensitized should have a greater impact than avoidance measures directed at a single allergen.

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Case 4: A child with acute bronchospasm

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■ PRESENTATION

A 7-year-old girl presented to her family physician for follow-up of an emergency room visit where she had been diagnosed with bronchospasm. Signs and symptoms in the emergency room included wheezing, use of accessory respiratory muscles, decreased peak expiratory flow (PEF) to 65% of her predicted value, and an oxygen saturation of 88%. All of these parameters improved following treatment with an inhaled, short-acting β -adrenergic bronchodilator. The patient was discharged with prescriptions for an oral corticosteroid and an inhaled, short-acting β -adrenergic bronchodilator (albuterol).

■ HISTORY

The patient's medical history was significant for eczema as an infant and seasonal rhinitis, which occurred each spring. Last April, she had had both rhinitis and conjunctivitis. Her mother was allergic to cat dander and house-dust mites; currently, her allergy symptoms were minimal. Her father had no allergies. One sibling had seasonal allergic rhinoconjunctivitis that previously had been treated with an over-the-counter medication. Both parents were nonsmokers.

Allergen avoidance measures had been instituted in the home. All beds and pillows were covered with allergen-impermeable covers. Floors were hardwood; the playroom floor, located in the basement, consisted of a concrete slab covered with hardwood and ceramic tile. There were no pets in the house.

■ EXAMINATION

On examination, the patient appeared to be comfortable. Her respiratory rate was 22 breaths per minute, PEF was 80% of her predicted value, and oxygen saturation was 94%. Her lungs were clear. Nasal examination

showed erythematous mucosa and a clear discharge. The conjunctiva were injected and had a clear discharge.

Two factors stand out in this patient: her family history of allergic disease and her own history of seasonal rhinitis and infantile eczema. The development of allergic disease is influenced by many factors, but the single most important risk factor in children is a family history of allergy. The risk of a child developing allergies is 50% if 1 parent is atopic and 66% if both parents are atopic.¹

The patient's history of eczema is consistent with the concept of the allergy march, described by Leonard M. Fromer on page S4. Eczema or exudative dermatitis is typical in patients with allergic dermatitis and is often the first symptom of allergic disease. Allergic dermatitis affects 10% to 15% of the population; the condition presents before age 1 year in 50% of those affected and between ages 1 and 5 in another 30%.² Food allergies are frequent in children with allergic dermatitis, and asthma develops in about 50% of them.³

This patient also had seasonal rhinitis, which each year affects about 40% of children in the United States.⁴ Allergic rhinitis has been associated with the development of other diseases, including allergic conjunctivitis, asthma, otitis media, and rhinosinusitis.

The history suggests that this patient's rhinitis and asthma stem from a common cause. The asthma presented during the pollen season; in previous years, she had had other allergic manifestations during the same season. However, it is possible the new-onset asthma is an example of the allergy threshold, also described by Dr Fromer. The patient may be sensitized to numerous allergens in her environment and her exposure to pollen, on top of her other allergies, may have tipped her over the edge into an asthma attack.

■ MANAGEMENT

The patient was treated with rescue medication

(inhaled albuterol, prn) and prophylactic therapy with an intranasal and an inhaled corticosteroid. Skin testing showed a strongly positive reaction to local tree pollen, moderately positive reactions to house-dust mites and cat dander, and negative reactions to local grass and weed pollens.

The skin test results corroborated the clinical suspicion raised by the history and physical examination—this patient probably has allergic asthma in addition to allergic rhinitis and conjunctivitis. Moreover, skin testing showed that she was most sensitized (ie, most allergic) to tree pollen (followed by dust mites and cats), and this knowledge helped to direct management of all 3 conditions. Avoidance measures already have been instituted in the home, so she probably is exposed to only low levels of dust-mite and cat allergens. That she is allergic to tree pollen but not to grass or weed pollen helps to define the duration of both outdoor allergen avoidance (**Figure 1**) and prophylactic therapy.

It is important to know which allergens are included in the allergy panels of skin and blood tests. Most panels include allergens that are common to patients in a geographic area and typically include tree, grass, and weed pollen, mold, animal allergens, and house dust mites. However, panels may not include all desired allergens. For example, the panel just described did not test for hypersensitivity to cockroaches, which is a fairly common allergy in some parts of the United States. Ideally, allergy panels should be developed in conjunction with allergy experts familiar with allergens common to their geographical area.

Skin testing should be done only in a medical facility staffed with personnel available to treat any reaction that may occur, including severe, life-threatening reactions. In general, skin tests can be performed on most patients regardless of age.^{2,5,6} Contraindications fall into 4 broad categories: chronic and widespread skin conditions, poorly controlled asthma, certain medica-

tions, and increased risk of anaphylaxis. Although this patient presumably had allergic asthma, its presentation during pollen season in association with seasonal rhinitis did not obviate skin testing. Patients on a contraindicated medication may be able to stop taking the drug before skin testing (eg, at least 3 days for antihistamines and at least 7 days for antidepressants); if not, they as well as patients in the other 3 categories should be considered for specific IgE blood testing.

Treatment of allergic rhinitis. This patient's rhinitis was managed with allergen avoidance and an intranasal corticosteroid. Avoidance measures to house-dust mites had been instituted well before the patient presented. Skin test results indicated that decreased exposure to tree pollen was a priority.

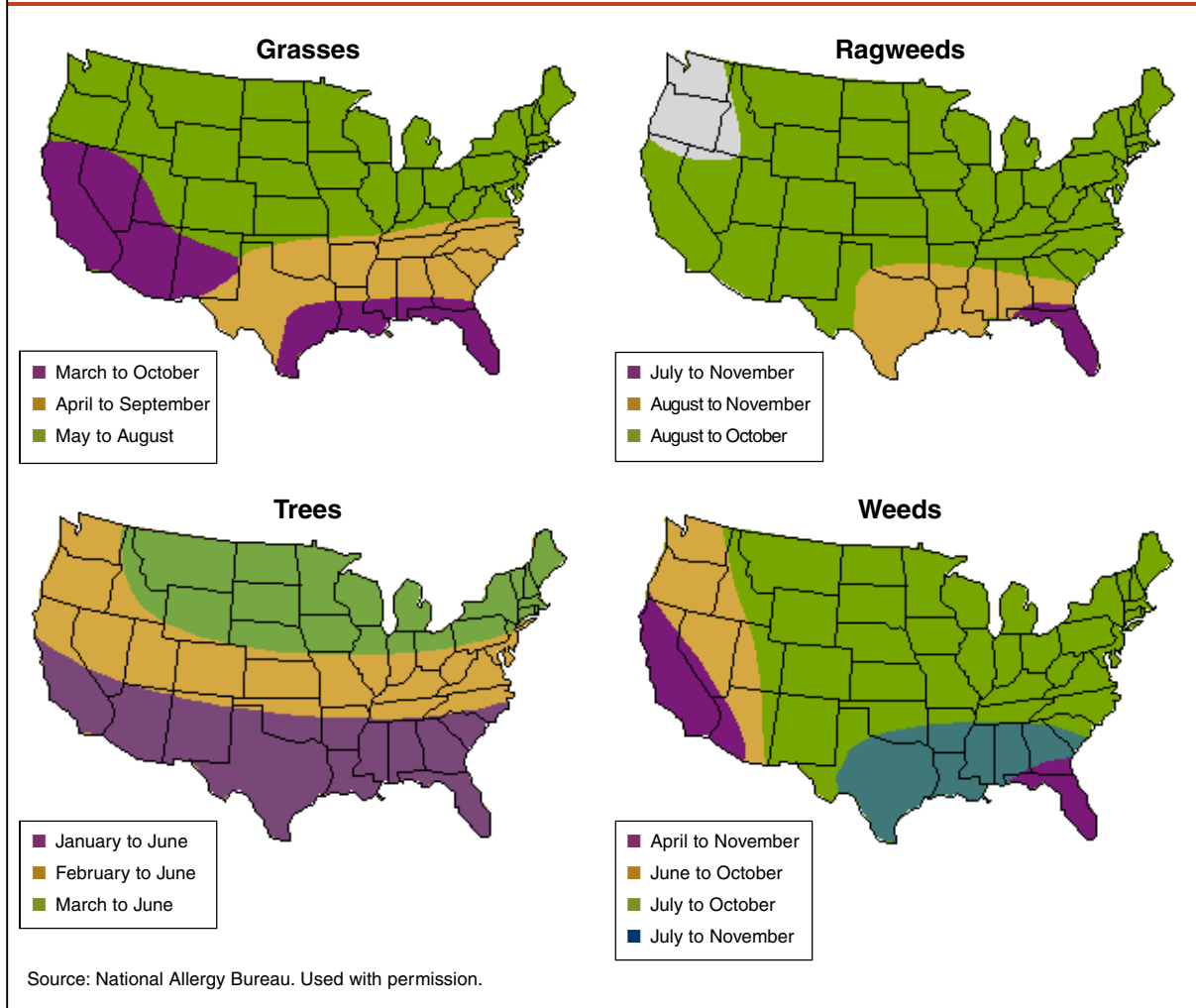
As mentioned in case 2, intranasal corticosteroids address underlying inflammation in allergic rhinitis, and studies have shown that they are the most effective treatment for this condition.^{7,8} In this patient, an intranasal steroid also may help to control asthma symptoms; control of allergic rhinitis is often essential for the control of asthma.⁹⁻¹²

Treatment of asthma. This patient's asthma was treated with an inhaled corticosteroid (for long-term control) and an inhaled, short-acting β -adrenergic bronchodilator (for acute exacerbations). Inhaled corticosteroids are, according to the American Academy of Allergy, Asthma, and Immunology, the most potent and effective long-term anti-inflammatory medications currently available for improving both asthma symptoms and pulmonary function.² They decrease the need for rescue medications and have fewer adverse effects than oral corticosteroids.

Short-term studies have shown that inhaled corticosteroids decrease growth velocity in some children (0.5-1.5 cm on average during the first year of treatment). In 2002, the NAEPP published a Systematic Review of Evidence, which found that in children receiv-

FIGURE 1

Pollen seasons in the United States



ing low-to-medium doses of inhaled steroids, this effect “is not sustained ..., is not progressive, and may be reversible.”¹³ Children followed for 10 or more years attained final predicted growth. Even so, the NAEPP advises that height be checked every 3 to 4 months regardless of the route of administration.

Alternatives to inhaled corticosteroids in this patient include montelukast, cromolyn, and nedocromil. Montelukast and zafirlukast are leukotriene modifiers approved for the treatment of asthma. Montelukast also is approved for treatment of allergic rhinitis and would therefore have been a reasonable first-

choice agent in this patient.

The nonsteroidal anti-inflammatory agents cromolyn and nedocromil are no longer considered to be first-choice asthma therapies in children; in fact, treatment with nedocromil is no longer recommended before age 5 because of uncertainty about its safety and effectiveness in this age-group.¹³ However, either agent could have been used in this patient, had there been a reason not to use an inhaled corticosteroid.

FOLLOW-UP

Four weeks after the patient’s initial evaluation, she was asymptomatic. Her examination was normal; the

PEF was 101% of her predicted value. Local pollen counts indicated that the tree pollen season had ended. She was weaned from all her medications, although inhaled albuterol was kept available should respiratory symptoms recur.

She continued to do well; the PEF remained at about 100% of her predicted value. She was advised to get an annual flu shot and scheduled for routine follow-up, including an anticipatory visit in March of the following year.

The patient was asymptomatic when she returned the following March. Prophylactic treatment with intranasal and inhaled corticosteroids was started. Her mother was given information on how to reduce pollen influx into the home and the car. Use of her inhaled bronchodilator was reviewed.

The patient did well during the tree pollen season, although she occasionally complained of minor eye symptoms. Olopatadine, a topical mast-cell stabilizer, was prescribed for allergic conjunctivitis. As in the previous year, she was weaned from the inhaled and nasal corticosteroids at the end of tree pollen season, and the inhaled bronchodilator was kept available as rescue medication.

Prophylactic treatment of seasonal allergic rhinitis should be started approximately 2 weeks prior to the start of the pollen season or at the onset of symptoms. Treatment should continue for 2 to 3 weeks after the pollen season ends to control persistent nasal and airway hyperactivity. In general, tree pollen is highest in early spring to midspring, grass pollens in late spring to early summer, and weed pollens in late summer to early fall. Pollination may occur year round in the southern United States.

As in this case, patients with allergic rhinitis often have allergic conjunctivitis as well. Seasonal allergic conjunctivitis is the most common form. Its clinical manifestations, which are usually bilateral, include ocular and periocular pruritus, tearing, burning, stinging, and pinkish or milky conjunctiva. Symptoms may be episodic or persist throughout the allergy season.

The treatment of allergic conjunctivitis

includes both allergen avoidance and medication. Irrigation with a saline solution or artificial tears may remove offending antigens from the eye and provide temporary relief. Drug therapy can include both oral and ocular agents. In this case, a topical mast-cell stabilizer—chosen for its efficacy and lack of side effects—provided symptomatic relief. Other options include oral or topical antihistamines, topical vasoconstrictors, nonsteroidal anti-inflammatory agents, and corticosteroids.

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Respiratory disease:

Addressing the
underlying cause

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