

The Role of Allergens in Asthma

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The National Asthma Education and Prevention Program Expert Panel guidelines for the management of asthma recommend that patients who require daily asthma medications have allergy testing for perennial indoor allergens and that, when triggers are found, exposure to allergens and pollutants be controlled through avoidance and abatement. For patients whose symptoms are not controlled adequately with these interventions and who are candidates for immunotherapy, the guidelines recommend referral to an allergist. However, the data supporting these recommendations are not consistent. Although there is evidence that simple allergen avoidance measures are ineffective, there is good evidence for the effectiveness of a comprehensive approach based on known sensitization. Thus, allergen avoidance may include removal of pets, use of high-efficiency particulate air filtration and vacuum cleaners, use of allergen-impermeable mattress and pillow covers, cockroach extermination, smoking cessation, and measures to control mold growth in the home. All allergen-specific treatment is dependent on defining sensitization. This can be achieved through serum assays of immunoglobulin E antibodies or skin tests with aeroallergens. Information on sensitization can be used to educate patients about the role of allergens in their symptoms, to provide avoidance advice, or to design immunotherapy. (*Am Fam Physician* 2007;76:675-80. Copyright © 2007 American Academy of Family Physicians.)

Patient information:
Handouts on allergies and asthma are available at <http://familydoctor.org/x2445.xml>.

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Allergen exposure is a significant trigger of exacerbations for many patients with asthma. Standard first-line treatment for asthma includes short-acting beta₂ agonists and inhaled steroids titrated to asthma severity. Other daily maintenance medications include long-acting beta₂ agonists, cromolyn (Intal), leukotriene modifiers, nedocromil (Tilade), and theophylline.^{1,2} For patients whose asthma symptoms are persistent and who require daily medication, consideration should be given to identifying and treating allergic responses that may contribute to acute symptoms, chronic inflammation, and nonspecific bronchial hyperreactivity.^{1,2} This article discusses the evaluation and sensitization of patients with asthma and the benefits and limitations of allergen-specific therapy and immunotherapy.

Background

The form of hypersensitivity associated with asthma is described as immunoglobulin E (IgE)-mediated, or immediate. This is because histamine release from mast cells

or a wheal response to a skin test can occur within 10 minutes, and a bronchial challenge with allergens can cause rapid onset of bronchospasm. However, this immediate response is no longer considered to be a good model for the way in which allergens contribute to asthma pathogenesis. After a positive skin test or bronchial challenge, there is often a late reaction (at six to 12 hours) that includes an inflammatory response with mediators other than histamine and a cellular infiltrate. Allergen avoidance studies have provided further evidence for the chronicity of the response in the lungs. When allergic patients are completely removed from exposure (e.g., in a hospital room or institution), recovery from symptoms takes several weeks and reversal of hyperactivity in the lungs takes several months.^{3,4}

The effect of allergen exposure may be obvious; for example, experiencing an exacerbation of asthma within minutes of entering a house containing a domestic animal. Asthma symptoms may also coincide with the pollination season of a tree, grass, or weed.^{5,6} However, for most allergic patients,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Allergy testing for aeroallergens including perennial indoor allergens is recommended for persons with persistent asthma who are taking daily medications.	A	1, 2
An intensive indoor environmental control program is recommended for patients with allergy-mediated asthma.	A	2, 26, 30
Patients who require daily asthma medication and are candidates for immunotherapy should be referred to an allergy subspecialist.	A	2, 35, 37

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 612 or <http://www.aafp.org/afpsort.xml>.

exposure and symptoms are perennial. Consequently, many patients who are allergic to common indoor allergens are not aware of the role of allergen exposure in their disease. The most common perennial allergens come from dust mites, cats, dogs, and the German cockroach.^{3,7,8} However, less well-known allergens that have a long season (e.g., the fungus *Alternaria*) can also contribute to asthma.⁹

History of Symptoms

Evaluation of patients with asthma should include a history with questions about seasonal increases in pulmonary symptoms; other allergic symptoms; exposure to tobacco; and exposure to allergens at home, at work, or outdoors. Symptomatic rhinitis and rhinosinusitis occur in a large proportion of patients with asthma and are often perennial, whereas conjunctivitis is more common in patients who are allergic to pollen. Seasonal eye symptoms may be present in patients who have perennial nasal and pulmonary symptoms.

The history typically is not useful for identifying allergies to dust mite or cockroach allergens. Consistent with the theory for a delayed and persistent response, patients who are allergic to dust mites or cockroaches often are unaware of the effects of perennial exposure on their lungs. Another complicating factor in the identification of allergens is that many patients become allergic to domestic animals without having shared a house

with one,¹⁰ reflecting the fact that measurable airborne cat allergen is present in homes without a cat and in schools.¹¹⁻¹³ Conversely, many children who live in a house with a cat become tolerant to cat allergens.^{14,15}

The National Asthma Education and Prevention Program (NAEPP) Expert Panel guidelines for the management of asthma recommend that patients who require daily asthma medications have allergy testing for aeroallergens, including perennial indoor allergens.²

Defining Sensitization

In patients with perennial symptoms, evidence about sensitization can be used to educate the patient about the role of exposure to specific foreign proteins or allergens, and to determine treatment (e.g., measures to decrease exposure). For patients with allergies whose symptoms are inadequately controlled by medication or avoidance, particularly those with rhinoconjunctivitis, allergen immunotherapy can be beneficial.

Immediate (IgE-mediated) hypersensitivity can be demonstrated by skin testing with aeroallergens or by serum assay for specific IgE antibodies. The assays used are solid phase fluorescent tests (e.g., Immucap) derived from the original radioallergosorbent test. There are advantages and problems with each approach. Skin testing is favored by most allergy clinics because results are available in about 20 to 30 minutes, so decisions about management and further testing

can be made during one office visit. In addition, there is a substantial educational impact from showing patients the positive or negative results on their own skin.^{16,17} The disadvantage of skin tests is that they are slightly painful and may be uncomfortable if strongly positive. The risk of a systemic reaction is remote provided that prick tests are used before intradermal tests.

Blood tests have improved steadily in sensitivity and specificity since their introduction more than 20 years ago.¹⁸ The advantages of blood tests are that they are not influenced by dermatitis, dermatographism, or the drugs that suppress skin tests (e.g., antihistamines, tricyclic antidepressants). In theory, once serum has been obtained, it is also possible to repeat a test or to test for other specific IgE antibodies (although most commercial laboratories do not store serum).

Serum tests provide not only a positive or negative result, but also the titer (often expressed as a class from 1 to 6) of the IgE antibody response.^{14,19,20} For food allergy in childhood, low titers of IgE antibody (i.e., 0.7 to 6 IU per mL [0.7 to 6 kIU per L]) may be diagnostic.^{19,20} In contrast, patients with allergy-mediated asthma who present with an acute episode often have an IgE antibody titer of 10 IU per mL [10 kIU per L] or greater.^{14,21-24} Measuring total serum IgE is often helpful in interpreting a negative result. A high total IgE level (i.e., 400 IU per mL [400 kIU per L] or greater) may indicate the need for more tests or suggest the possibility of allergic bronchopulmonary aspergillosis, whereas a low level (i.e., 30 IU per mL [30 kIU per L] or less) may help confirm that allergy is not involved.

Expert opinions differ on the number of allergens that should be tested; however, 25 to 30 is a reasonable number for routine testing for inhaled allergens.^{16,17,25} For serum assays, it is not unusual to use a panel of 12 to 20 inhalant allergens.

Allergen-Specific Treatment

Treatment focused on controlling the allergic component depends on definition of sensitization and includes education about the role of allergens in the disease and advice about

avoiding allergen exposure. Allergen avoidance options require significant time for the physician to explain and may entail considerable effort and expense for patients, involving the use of an established protocol in the home (*Table 1*^{1,2,26-28}). Physicians should consider the potential benefits and the ability of the patient to comply when deciding whether to recommend this approach. Interventions in several studies that tested only a single measure or that did not establish the sensitivity of the patients were not successful.²⁹ In contrast, studies of a regimen of allergen-specific avoidance measures based on the sensitivity of the patients using multifaceted environmental control interventions have demonstrated clinical benefits.^{3,26-28,30-33}

There are several basic rules about avoidance measures: (1) measures are allergen-specific—it must first be established that the

Table 1. Measures for Avoidance of Dust Mite and Other Indoor Allergens

Dust mite allergen

Priorities

- Encase mattress and all pillows in allergen-proof covers
- Wash bed linens weekly in hot water (> 130°F [54°C])
- Encase box spring in vinyl or plastic
- Reduce clutter (e.g., soft toys) in bedroom
- Vacuum weekly using a cleaner that has a double-thickness bag, high-efficiency particulate air (HEPA) filter, or other technique for controlling leakage
- Place soft toys in freezer overnight or hot wash regularly
- Hang comforters or other bedding outside in sun or freezing weather
- Clean and replace central air filters

Longer-term

- Reduce indoor relative humidity with air conditioning or dehumidifier
- Replace carpet with polished flooring
- Replace upholstered furniture with leather or wooden furniture where possible
- Replace drapes with wipeable shades or washable curtains
- Avoid living in rooms below ground level

Other allergens

- Find a new home for pets
- Use integrated pest management for cockroach-infested homes
- Wash moldy surfaces with weak bleach solution
- Stop smoking and do not allow smokers to be near persons with asthma

Information from references 1, 2, and 26 through 28.

patient is allergic for advice about avoidance to be useful; (2) success of avoidance is dependent on effective education—at minimum, providing a sheet of proposed measures with a verbal explanation (*Table 1*^{1,2,26-28}). It is often more effective to persuade the patient to agree to a timetable of changes; and (3) it is important not to create an expectation of rapid improvement—the disease is chronic, and removing the allergen accumulated in the house will take time.^{3,34}

Immunotherapy

Immunotherapy for asthma has been a part of allergy practice for many years, and results from controlled trials have supported its role in easing symptoms of perennial asthma.³⁵ However, immunotherapy involves injections of allergen extract into allergic patients, with the potential risk of a rapid adverse allergic reaction. Thus, initiation of immunotherapy is generally considered to be a specialist activity, and clinics giving allergy injections should understand the safety measures necessary to prevent and treat adverse allergic reactions. Serious adverse events have resulted from use of immunotherapy based solely on serum results (i.e., where the extract

is designed by a nurse working for an in vitro laboratory rather than by a subspecialist in direct contact with the patient).

Immunotherapy is recommended only for a minority of children with asthma. It is most beneficial for patients who have persistent allergic rhinitis and asthma; in these patients, analysis of cost and overall symptom scores favors treatment.³⁶ Immunotherapy is not indicated in patients whose symptoms can be easily controlled with intermittent pharmacologic management and allergen avoidance, and it is not recommended for patients who are unable to comply with treatment, have brittle asthma, or are not allergic.

Indications for Referral

The availability of inhaled steroids, oral leukotriene antagonists, and long-acting beta₂ agonists, as well as nasal steroids and non-sedating antihistamines, makes it possible to treat many patients with mild allergic asthma empirically. The NAEPP guidelines recommend that patients who require daily asthma medications and who are candidates for immunotherapy be referred to an allergist. Other NAEPP indications for referral are listed in *Table 2*.^{1,2,37}

Table 2. Indications for Referral to a Subspecialist in Patients with Asthma

Single life-threatening asthma exacerbation occurs
Initial diagnosis is severe, persistent asthma
Patient is younger than three years and has moderate or severe persistent asthma
Patient history suggests asthma is being provoked by occupational factors, an environmental inhalant, or an ingested substance
Atypical signs and symptoms make asthma diagnosis unclear, or other conditions are complicating asthma or its diagnosis
Additional diagnostic testing is indicated
Treatment goals are not being met after three weeks to six months of treatment, or asthma is not responding to current therapy
Patient requires continuous oral steroid therapy or high-dose inhaled steroids, or has required more than two courses of oral steroids in one year
Patient or family requires additional education or guidance in managing asthma complications or therapy, following the treatment plan, or avoiding asthma triggers
Patient is a candidate for immunotherapy

Information from references 1, 2, and 37.

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