2 Diagnosing Allergic Asthma

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CONTENTS

KEY POINTS

- Most patients with asthma have allergic asthma, and, therefore, allergies may exacerbate their symptoms.
- The optimum treatment of allergic asthma requires identifying the offending allergens so they can be eliminated, avoided, or treated.
- The essential elements of this diagnosis require a careful allergy history, physical examination, and diagnostic allergy tests, such as skin tests, radioallergosorbent (RAST) tests, and/or challenge tests.
- The major categories of allergens affecting bronchial asthma consist of pollens, environmentals, food, and animals.

INTRODUCTION

The incidence and severity of allergy, asthma, and allergic asthma has been increasing *(1)*, and this makes diagnosing allergic asthma even more important. It is not sufficient to make the diagnosis of bronchial asthma without determining whether the patient is atopic, and if so, to what allergens. These allergens can be classified into the following broad categories:

- Pollens.
- Environmental.
- Animals.
- Foods.

When specific allergens have been identified as eliciting symptoms, they can frequently be eliminated, avoided, or decreased. Antimite avoidance measures, such as the

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use of mattress encasings *(2)*, HEPA filters *(3)*, and frequent dusting and vacuuming, may significantly improve the symptoms of the patient with asthmas who is mite sensitive. Allergen-specific therapy, such as allergy immunotherapy, may be undertaken as part of the patient's overall therapeutic regimen. This may prevent the seasonal exacerbations of asthma that plague many patients who have allergic asthma.

Allergic asthma manifests itself in the form of food allergy in many infants and young children. Although it may be somewhat difficult to diagnose the offending food, the removal of the offending food from the child's diet may be critical to the child's health.

Another important group of allergens that significantly affects children, as well as adults, is animals. Exposure to pets or animal parts can either cause acute exacerbations are be an underlying cause of chronic symptoms. This exposure can occur at both work (some occupations have large exposures to animal allergens) and home, even if there are no pets in the home. Studies have shown that because of the large number of dogs and cats, more than 1 million *(4)*, present in the United States *(5)*, almost everyone has animal allergens in his or her home, regardless of whether they have pets *(6,7)*. The animal hair and dander are transferred from pet owners to non-pet owners. These allergens are then brought into the nonsuspecting person's home from their clothes, so the diagnosis and subsequent cleaning and avoidance of offending animal allergens should be part of all optimum treatment plans for patients with allergic asthma *(8)*.

The importance of identification and avoidance of culpable allergens is often critical in preventing allergic asthma symptoms, exacerbations, and hyperactive airways.

ALLERGENS

The self-reported prevalence of bronchial asthma by individuals at least 18 yr old in the United States is 11% *(9)*, reported by the Behavioral Risk Factor Surveillance System in 2001. The mean prevalence for asthma had been estimated at 7.2%, with a range of 5.3–9.5% *(10)*. The survey also found that 78% of these patients with asthma had symptoms within the last 30 d. The role of allergy in the pathology, epidemiology, prevention, and treatment of bronchial asthma has gained in significance in the last decade. It is understood now that most people who develop asthma are believed to be extrinsic or have an underlying allergic diathesis *(11)*.

Allergic asthma triggers can be divided into four categories—pollens, environmental, food, and animal—which consist of the allergens cited in Table 1.

Pollens

The symptoms of pollen-induced allergic asthma tend to exacerbate seasonally, usually in the spring (grass and trees) and fall (weeds) when the pollen counts are the highest *(12)*. This effect varies greatly depending not only on pollen counts but also on microclimate, geography, and individual sensitivities *(13)*. These patients have the following signs and symptoms associated with pollen-induced asthma:

- Genetic predisposition.
- Family members usually have allergic asthma and other allergic diseases.
- Allergic asthma that most often begins in childhood.
- Usually accompanied by allergic rhinitis.
  - May have had atopic dermatitis in childhood.

Table 1
Allergic Asthma Triggers

Pollens	*Environmental*	*Food*	*Animals*
Grass	Dust mite	Milk	Dogs
Weeds	Cockroach	Eggs	Cats
Trees	Miscellaneous insects	Wheat	Birds
	Mold	Peanut	Horses
		Corn	Rabbits
		Pork	Mice and rats
		Shellfish	Hamsters and gerbils
		Fish	Guinea pigs

- Asthma is frequently also exacerbated by other allergens, mite, mold, etc.
- Positive skin and radioallergosorbent (RAST) tests to pollen.
  - Positive inhalation allergen test (not frequently performed).
- Seasonal exacerbations.
- Allergy immunotherapy may improve symptoms.
- Exercise-induced asthma worse during exposure to pollen.
  - Running outside during increased pollen counts (e.g., during football practice).
- Increased bronchial reactivity to irritants.
- Methacholine.
- Smoke.
  - Noxious aerosols.

Environmental Allergens

Patients who are allergic to the indoor environmental allergens (Tables 2–4) will have a yearlong or perennial symptoms but not seasonal exacerbations *(14)*. However, many patients are allergic to both pollen and indoor environmentals. House dust mites increase during periods of high humidity *(15)*. They thrive at sea level and do not survive in high altitudes *(16)*. Mites are primarily found in bedding, carpets, rugs, and furniture *(14)*. They are not usually airborne unless the air currents are disturbed by such events as opening or closing doors *(17,18)*. House dust mites are one of the most common allergens and may cause significant morbidity. The mites most likely to cause allergic asthma and rhinitis are *Dermatophagoides pteronyssinus (19)* and *Dermatophagoides farinae (20)*. Patients who are allergic to these allergens frequently have symptoms associated with exposure to vacuuming and dusting.

Cockroaches are commonly found in the inner cities *(21)*. The German cockroach, *Blattella germanica,* is the most common roach found in the United States *(22)*. Cockroaches increase in the warm, humid periods. They are believed to be one of the reasons for the high incidence and high morbidity of asthma in the urban areas.

Mold thrives in damp *(23)* and dark locations, contaminated food, and humid climates (*see* Table 3). The effect of mold is controversial. Mold is known to cause allergic reactions. Alternaria has caused severe bouts of allergic asthma *(24)*. It is debatable regardless of whether mold releases a toxin that causes allergic or other medical complications *(25,26)*.

Table 2
Common Pollen Allergens

Grass pollen	
Common name	*Genus and species*
Johnson grass	*Sorghum halepense*
Berumda grass	*Cynodon dactylon*
Orchard grass	*Cactylis glomerata*
Meadow fescue	*Festuca elatior*
Perennial rye	*Lolium perenne*
Kentucky bluegrass	*Poa pratensis*
Redtop grass	*Agrostis alba*
Sweet vernal	*Anthoxanthum odoratum*
Timothy grass	*Phleum pratense*
Weed pollen	
Common name	*Genus and species*
Short ragweed	*Ambrosia artemisiifolia*
Giant ragweed	*Ambrosisa trifida*
Mugwort	*Artemsia vulgaris*
English plantain	*Plantago lanceolata*
Lambs quarters	*Chenopodium album*
Russinan thistle	*Salsola kali*
False ragweed	*Franseria acanthicarpa*
Tree pollen	
Common name	*Genus*
Elm	*Ulmus*
White oak	*Quercus*
Beech	*Fagus*
Birch	*Betula*
Chestnut	*Castanea*
Cypress	*Cupressus*
Cedar	*Juniperus*
Pine	*Pinus*
Pine	*Fraxinus*
Olive	*Olea*
Maple	*Acer*
Walnut	*Juglans*
Hickory	*Carya*
Cottonwood	*Populus*
Willow	*Salix*
Mesquite	*Prosopis*
Privet	*Ligustrum*
Common molds	
Penicillium	Fusarium
Cladosporium	Claviceps
Cladosporium	Rhizopus
Alternaria	Epicoccum
Aspergillus	Helminthosporium

Modified from ref. *27*.

Table 3
High Indoor Mold Concentrations

Mold	*Characteristic*
Total mold	Temperature in child's bedroom (5°F above the rest of the home)
	Forced air heating
	Reported water, dampness, or leaks in any room in past 12 mo
	Observed evidence of moisture or leaks in child's bedroom
	Reported cat living in home within past 6 mo
Alternaria	Reported water, dampness, or leaks in any room in past 12 mo
Aspergillus	Season (winter)
	Forced air heating
	Observed evidence of cockroaches in child's bedroom
	Reported cat living in home within past 6 mo
Cladosporium	Observed evidence of moisture or leaks in child's bedroom
Penicillium	Season (winter vs other)
	Observed musty smell in child's bedroom

Modified from ref. *27a*.

Table 4
Environmental Allergens

Allergen	*Location*
Cockroaches	Inner city
Mold	Dark, damp, humid locations
Miscellaneous insects	Ubiquitous
House dust mites	Lower elevations, bedding, and mattress

Animal Allergy

Allergies to pets and other animals are common and often denied by patients and family members *(28)*. Cats cause severe bouts of asthma and allergy symptoms *(29)*. The allergens from pets can come from their hair, skin, fur, saliva, urine, or feces *(4),* so people can be exposed in a diverse manner. The most common pets causing allergy are dogs, cats, birds, mice, rabbits, gerbils, guinea pigs, and ferrets.

In the United States, it has been estimated that there are 105 million dogs and cats *(30)*. Studies have shown that almost everyone has cat hair and dander in his or her home *(31)*. This occurs even if a cat has never been in the home. The large number of these animals causes the almost ubiquitous nature of this allergen that is probably transferred from one person's clothes to another and they are into their home or office *(32,33)*.

Allergy to pets is frequently denied, making the diagnosis more difficult *(3)*. Many pet owners claim that they would rather give up their allergic spouse rather than parting with their pet. Pets can not only cause an acute exacerbation but also add to the total cumulative allergy load. This exposure has been compared with a glass of water. If some

pollen is put into a glass followed by mite allergen, mold allergen, and then when you add pet allergens, the glass begins to overflow (as do patients' symptoms).

Food Allergy

Food allergy is common and has a more important role in infancy and early childhood *(34)*. Sicherer and Furlong studies have shown that approximately 4% of the US population and 6% of children under the age of 3 yr have food-induced hypersensitivity *(35)*. Allergic reactions to foods occur immediately or several hours later, making it difficult to determine the cause and effect of the child's wheezing *(36)*. This makes it is more complicated to ascertain if specific food is a factor in allergic asthma in this age group. The most common foods that cause allergy in childhood are as follows *(37)*:

Milk	Egg albumin
Casein	Yolk
β-lactaglobin	Pork
α-lactaglobin	Corn
Whey	Peanuts
Albumin	Fish
Eggs	Wheat

Food allergy should be suspected in adults who have persistent asthma or who have intermittent exacerbations with no apparent trigger. They may also have the following signs and symptoms *(38)*:

- History of atopic dermatitis in childhood.
- Family history of food allergy.
- History of colic or feeding difficulties.
- Persistent or refractory asthma.
- No known triggers to explain exacerbations.
- History of positive skin or RAST test to a food.

Food allergy can cause severe bouts of bronchial asthma *(39)*. In one study, 50% of adults with difficult-to-treat asthma had food allergy *(40)*. Allergic reactions are sometimes, but not commonly, caused by inhalation of the vapor of the food being cooked *(41)*. The inhalation of peanut dust on an airplane causing anaphylaxis is an example of this *(42)*.

Children have a higher incidence of food allergy than adults. The overall incidence is increasing, but it is difficult to detect the exact number of people who are plagued with this problem *(35)*. Table 5 lists the estimated incidence of food allergy *(34)* to common foods in both children and adults.

Food allergy in childhood has been well established to cause symptoms of allergic rhinitis *(43)*, atopic dermatitis *(44)*, asthma *(45)*, urticaria *(46)*, and pruritus *(47)*. This type of allergy also causes the following gastrointestinal symptoms *(48)*:

- Bloating.
- Nausea and vomiting.
- Gas and flatulence.
- Abdominal pain.
- Colic and cramps.
- Diarrhea.
- Bloody diarrhea.
- Heartburn.

Table 5
Prevalence of Food Allergies in the United States

Food	*Young children, %*	*Adults, %*
Milk	2.5	0.3
Egg	1.3	0.2
Peanuts	0.8	0.6
Tree nuts	0.2	0.5
Fish	0.1	0.4
Shellfish	0.1	2.0
Overall	6	3.7
Food-induced wheezing	7	
Atopic dermatitis	35	

Table 6
Commonly Used Allergy Tests

Test	*Problems*	*Types of test*	*Conclusion*
Skin test	Inaccurate results May be dangerous	Prick test Intradermal	Not definitive, a guide Not routinely performed
RAST	Not accurate	Cap-RAST	Good as a guide, especially if a severe reaction was suspected
DBFCT	Difficult to perform May be dangerous, expensive	Food challenge	Most accurate
Single-blind food challenge test	Difficult to perform and interpret	Food challenge	Not as accurate as DBFCT
Basic diet and challenge	Time consuming and difficult	Diet manipulation	Requires families to cooperate
Elimination diet and challenge	Diet manipulation	Diet manipulation	Easier for families to follow

RAST, radioallergosorbent test; DBFCT, double-blind food challenge test.

The diagnosis of food allergy is made by a careful history, physical examination, and diagnostic tests *(49)*. Food allergy skin tests and RAST tests, unlike other allergy tests, such as pollen or hymenoptera, are used as more of a guide than as a definitive test *(50)*. Food allergy testing has a higher rate of false-positive and false-negative test results *(36)*. Table 6 lists the commonly used tests for food allergy *(51,52)*.

There are many false-positive and false-negative food allergy tests *(53)*. Many patients (and physicians) have difficult understanding that a "positive skin" test to a food does not equate to a food allergy. Food allergy skin testing can be dangerous and difficult to interpret *(54)*. It is usually not advisable to perform this type of testing on patients who have a history of an anaphylactic reaction to the suspected food *(55)*. Food allergy skin tests should always begin with a prick test (1/100) and only proceed by dilution (1/1000) intradermal testing by experienced allergists who is prepared to treat anaphylactic reactions *(56)*. Food allergy testing is usually done both as a screening procedure during

routine skin testing and for specific food allergies that were elicited during the allergy history. RAST tests can also be used instead of skin testing, but they are not as accurate as a properly applied and interpreted skin test *(57)*. However, if a severe food allergy is suspected, a RAST test is safer than a skin test.

Once a food is suspected by history and skin or RAST test, a diagnostic challenge should occur, except for when severe food allergy reactions have occurred or are suspected by previous testing. The gold standard in this type of testing is the double-blind food challenge test (DBFCT) *(58)*. In the DBFCT, both the suspected food allergen and a placebo are usually lyophilized and disguised in either capsules, "shakes," or other vehicles, so that it is impossible to tell them apart *(59)*. This eliminates bias so that it is the most objective way of food challenge testing. The DBFCT has some drawbacks in that it is expensive and time consuming, no Food and Drug Administration-approved product for testing is available, and it also has the possibility of causing anaphylactic reactions in extremely sensitive patients *(52)*. People who are experienced and prepared to treat anaphylaxis should, therefore, only conduct this test. Like any test, the DBFCT is not 100% foolproof and can have some false-positive and false-negative results, but it is the most accurate test of food allergy. Antihistamines must be discontinued at least 48 h before the challenge. The suspected food should be removed from the child's diet for at least 1 wk before the food challenge test is undertaken. The initial challenge usually begins with 125–500 mg of the suspected food and then doubled every 20–60 min, until 10 g of food have been eaten *(60)*. If the food allergy tests are negative, the food is given to the patient in the office, in an open challenge.

Children frequently outgrow their food allergy, so that in the nonanaphylactic forms of food allergy, elimination diet and challenge testing may be performed every 6 mo.

In the single-blind placebo controlled food challenge test (SBFCT), it is not possible to blind the investigator; only the patient can be blinded. The results, therefore, have some investigator bias, and the test is not as objective as the DBFCT.

Like the SBFCT, elimination diets are not as objective as the DBFCT, but they are much easier and cheaper to undertake *(49)*. Elimination diets consist of two types, a so-called basic diet and a regular diet that systematically eliminates and then challenges patients with the eliminated food. Basic diets consist of foods that are believed to have a low risk of causing food allergy, such as lamb, rice, potato, carrot, sweet potato, and pear. After 1 wk of eating such a diet, a new food is introduced every 3 d. If the new food causes a suspected allergic reaction, that food is removed from the diet and then subsequently reintroduced (unless a dangerous reaction may occur) or challenged into the diet. In this manner, elimination diets and challenge may detect the food allergen. Elemental basic diets are mainly used in infants and toddlers.

SKIN TESTS

Allergy skin tests are probably the most important diagnostic test in identifying allergic asthma but RAST is equally reliable (*see* Tables 7 and 8). Skin tests are accurate and reproducible *(61)*. A positive, histamine, and negative saline test must always be used to compare the test allergens. If the histamine test does not elicit a classic positive test, then the testing is not valid. This usually occurs when patients have not stopped taking antihistamines within the prior allotted time period. Patients should return in 48–72 h for repeat skin tests and be instructed to stop taking all antihistamines. An abnormal positive saline test is found when a patient has dermatographism, as a result of the device or technique, or when the saline test material was contaminated by either a histamine or an allergen *(62)*.

Table 7
Allergy Skin Testing

Pros	*Cons*
Easy to perform	Skin must be intact and no dermatographism
Rapid results	Experience needed in interpretation
High sensitivity	Somewhat dependent on methodology and technician
Reproducible	
Inexpensive	Medication must be withheld (antihistamines, systemic steroids, and tricyclics)
Many allergens available	Remote possibility of systemic reaction
Accurate for pollens and environmentals	Results not as exact for foods

Note. Infants as well as adults can be tested. Some patients are reluctant to undergo testing owing to fear of needles.

The two types of skin tests performed today are the prick-puncture test and the intradermal or intracutaneous test. The skin-prick test is the most accurate way to perform this type of testing *(63)*. In this method, a small drop of allergen is placed on the skin and a needle is used to inject the material in the skin by lifting or "pricking" the skin. The allergens should be placed at least 2 cm apart so the individual tests do not run into each other and accurate results can be measured. The puncture has to be done carefully so that the skin is sufficiently punctured but that bleeding does not occur. Insufficient puncture can result in a false-negative test, and bleeding can lead to false-positive tests. The results consist of the swelling or "wheal" and the erythema or "flare." A positive test is considered if the wheal is 3 mm larger than a saline control *(64)*. If a patient has a negative reaction to both the histamine and the saline, he or she probably has not stopped taking antihistamines. This type of patient may have to return in 48 h for repeat skin testing. In general, antihistamines should be withheld for 48 h and hydroxyzine for 72 h.

These prick tests are either measured or graded on a scale from 0 to 4. Intradermal tests are usually injected with a 25- or 26-gage needles and disposable 1-mL syringe. The allergens are more dilute than the solutions used for the prick tests (1:1000 or 1:5000). When using this methodology approx 0.02 mL of the allergen is injected in the epidermis so that a small bleb forms similar to a purified protein derivative test for tuberculosis *(65)*. These tests are less sensitive but more specific than the prick test, and more false-positive tests result from this type of testing *(66)*. Intradermal testing causes more systemic reactions than the prick test, so the prick test should be used initially *(67)*. Therefore, only patients with a negative prick test should undergo an intradermal test. Intradermal tests are usually reserved for hymenoptera, pollen, mite, and, occasionally, mold. Food intradermal tests are avoided because of the difficulty in interpreting the results and the increased chance of a systemic reaction.

PREVENTING ERRORS WITH ALLERGY SKIN TESTING

General (68)

1. Instruct patient not to use any antihistamines or tricyclics for 48–72 before testing.
2. Use caution in testing an extremely allergic patient, especially during his or her susceptible "season" with too many allergens in one setting.
3. Have epinephrine readily available to treat a systemic reaction.

Table 8
Laboratory Measurement of Allergic Disease *(69)*

Allergen specific	*RAST testing*
Screen for allergy	Multiallergen screen (adult and pediatric forms)
Other non-RAST test	
General screen	
Marker for mast cell degranulation	Tryptase, useful in anaphylaxis
Sputum screen	Eosinophils
Complete blood count	Percentage of eosinophils

4. Perform tests on normal skin.
5. Do not allow bleeding to occur.
6. Do not place tests closer than 2 cm for proper reading of results.
7. Do not skin test a patient during an asthma exacerbation.
8. Record results in approx 15 min after the tests are applied.

Prick-Puncture

1. Penetrate the skin sufficiently to prevent false-negative results.
2. Perform prick test before intradermal testing to prevent systemic reactions.
3. Do not contaminate the needles with other allergens.
4. Avoid spreading the allergen solution during testing.
5. Use to test foods that are not suspected of causing severe allergic reactions.

Intradermal Testing

1. Starting dose with a previous negative prick test should be 1000 times weaker than the concentrated dilution used for prick-puncture (or roughly 10 AU for standardized allergy extracts).
2. In general, should not be used to test foods.
3. If no bleb occurs, then a subcutaneous injection has occurred, which may lead to false-negative test.
4. Inject 0.01–0.03 mL, otherwise irritant reaction may occur.
5. One intradermal syringe per allergen per patient should be used to prevent infectious contamination.

RAST TESTING

The Phadebas RAST test was the first important and accurate in vitro test developed for the laboratory detection of allergen-specific IgE antibody *(70)*. This type of RAST test used an allergen that was coupled to a cellulose paper disk (radioallergosorbent). Human sera would then be added, so that if there was specific IgE in the sera against the coupled allergen, they would bind together. The addition of human radiolabeled antihuman IgE antibody would then bind with the bound IgE, which are detected and quantified via calibration curves. New tests, such as the Pharmacia CAP RAST, have increased the accuracy in both specificity and sensitivity of RAST testing *(71)*.

Table 9
Pros and Cons of RAST Testing

Pro	*Con*
In vitro test	Expensive
No patient risk	Results not immediately available
Screening test available	Fewer allergens available than for skin tests
Not affected by medication, so patients do not have to stop them	Skin tests more accurate than RAST tests

RAST, radioallergosorbent.

Table 10
Allergy History

Seasonal affects	Pollen
Worsening of symptoms at home	Environmental
Increased symptoms with exposure to pets	Animals
Children with frequent symptoms	Food

The Multiallergen IgE E screen is a qualitative RAST test that consists of 15 indoor and outdoor allergens *(57,72)*. The specific allergens vary from company to company and are not listed. In general, they consist of allergens from grass, weeds, trees, molds, mites, dog, and cats *(66)*. They are meant to be a general screening test when a patient's history conforms to any type of aeroallergen. This is designed to detect common allergens that affect adults. A pediatric multiallergen is also available that consists of common food allergens.

Despite the improvement in this in vitro allergy testing, which is now closer to the diagnostic importance of allergy skin testing, RAST testing still suffers from what is shown in Table 9 *(30)*.

CONCLUSION

All patients who are diagnosed with bronchial asthma should be diagnosed for allergy. This should consist of a detailed history (*see* Table 10).

It is critical to make this detailed diagnosis so that the proper therapeutic interventions can be instituted, such as allergen avoidance, allergy environmental control, allergy immunotherapy, and omalizumab (Xolair®) *(73)*. Referral to an allergist can assist in this diagnosis.

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