

PATIENT SELECTION AND ADMINISTRATION OF AEROALLERGEN VACCINES

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Allergic rhinitis and asthma are common throughout the world and continue to increase in prevalence. These disorders continue to have significant morbidity and mortality despite increased understanding of disease pathogenesis and development of new effective medications for treatment. Immunotherapy is indicated for many of these patients, but risk-benefit ratios should be considered during patient selection. The World Health Organization published a 1998 position paper summarizing the current status and future directions of immunotherapy.⁷¹ Still, among physicians, "opinions vary from complete rejection of the method for any purpose (a view held by many who are not allergists) to almost ritual use in any patient with upper or lower respiratory tract symptoms that are even vaguely allergic."⁴³ For conditions such as allergic rhinitis and asthma, immunotherapy is adjunctive to proper medical therapy, unlike in persons who have experienced a life-threatening stinging insect reaction where immunotherapy is curative. When aeroallergen immunotherapy in asthma was reviewed in a meta-analysis of 20 randomized, double-blind, placebo-controlled trials, there was significant improvement in asthmatic symptoms and a reduction in medication requirements, but only modest improvements in lung function for treated patients.¹ This analysis, however, included only two studies of children, and most studies did not use standardized vaccines.

The limited number of double-blind, placebo-controlled trials of

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specific allergen immunotherapy involving large numbers of patients has limited its widespread acceptance; however, numerous studies have shown that immunotherapy for allergic respiratory disease significantly lessens the severity of symptoms and medication requirements. There are no controlled trials demonstrating benefit in subjects treated with immunotherapy for atopic dermatitis.

The benefits of immunotherapy are specific for the antigen used for treatment. It is difficult to study large numbers of patients who are allergic to a single allergen, as most patients have multiple allergen sensitivities. Most studies that employed symptom diaries to judge effi-

Box 1. Considerations in Initiating Immunotherapy

1. Presence of an IgE-mediated disease amenable to immunotherapy
 - a. Allergic rhinitis
 - b. Asthma with allergic triggers
 - c. Stinging insect anaphylaxis
2. Documentation of specific sensitivity
 - a. Exposure to putative allergen, related to appearance of symptoms
 - b. Presence of specific IgE antibody
 - i. Skin tests
 - ii. In vitro assays (radioallergosorbent test [RAST])
 - iii. Provocative challenge
3. Severity and duration of symptoms
 - a. Subjective symptoms
 - i. Two seasons of seasonal symptoms despite avoidance measures and pharmacologic therapy
 - ii. Perennial symptoms failing trials of avoidance measures and chronic pharmacologic therapy.
 - iii. Anaphylaxis after Hymenoptera sting except in children with cutaneous anaphylaxis only
 - b. Objective parameters: time lost from work, emergency room visits, pulmonary function tests
 - c. Response to allergen avoidance
 - d. Response to conventional medication
4. Availability of quality allergenic vaccines
5. Age of patient
6. Sociological and logistical factors
 - a. Ability of patient to comply
 - b. Cost
 - c. Discussion of risks versus benefits
 - d. Availability of facilities to treat adverse reactions
 - e. Occupation of candidate
7. Objective evidence of efficacy of immunotherapy (controlled trials)
8. Presence of underlying conditions and medications (see later in text)

Adapted from Parry DE, Bush RK: Patient selection for allergen immunotherapy: When to start and stop. In Lockey RF, Bukantz SC (eds): Allergens and Allergen Immunotherapy, ed 2. New York, Marcel Dekker, Inc., 1999; reprinted from reference 50, p 383, by courtesy of Marcel Dekker, Inc.

cacy have found that treatment with a single allergenic vaccine provides incomplete relief of symptoms.⁴³ This may be due either to the limitations of the treatment itself or to the failure to immunize with all relevant allergens. Clinical observations during a period of natural allergen exposure cannot distinguish between these two possibilities; however, a controlled trial of multiple allergen immunotherapy in asthmatic children failed to show treatment benefit.²

Allergen avoidance remains the primary treatment for allergic disease and is essential in most cases of animal allergen sensitivity or occupational exposure. Most common aeroallergens, however, cannot be avoided completely, and exposure is almost inevitable, especially for patients with multiple sensitivities. Studies suggest that specific immunotherapy may prevent new allergic sensitization¹⁶ or even the onset of asthma.³⁰ Currently, studies are underway in Europe to address the question of whether treatment of allergic rhinitis with immunotherapy can prevent the development of allergic asthma.

PATIENT SELECTION

Considerations for Initiating Immunotherapy

Criteria to be considered when initiating immunotherapy are outlined in Box 1.^{11, 13, 46, 50, 56} The diagnosis of an IgE-mediated disease potentially amenable to immunotherapy must be demonstrated, including allergic rhinoconjunctivitis, asthma with allergic triggers, or stinging insect anaphylaxis (which is discussed elsewhere in this issue) with positive allergen-specific skin-test results or demonstrable serum-specific IgE. Symptoms and signs of rhinitis, asthma, or anaphylaxis should correlate with exposure to the putative allergen. Examples of exposure histories include symptoms during certain seasons, while in moldy environments, or animal exposure. Patients with the highest degree of sensitivity are most likely to benefit from immunotherapy.⁴⁹

The decision to use immunotherapy should also be based on severity and duration of symptoms, including seasonal rhinitis symptoms during two or more consecutive seasons, with inadequate relief of symptoms using medication or allergen avoidance.⁵⁶ One season of rhinitis with unusually severe symptoms or intolerable side effects from medication is also an indication. Immunotherapy is indicated for patients with concomitant seasonal allergic rhinitis and asthma and in perennial rhinitis or asthma in which sensitivity to a variety of allergens are likely contributing to the perennial symptoms. An appropriate medical therapy trial is suggested before initiating immunotherapy. Exposure to animal allergen can be avoided by many persons, but animal-sensitive veterinarians, animal handlers, technicians, and persons with guide dogs may require treatment with animal epithelial vaccines.

Potent, well-characterized allergen vaccines are essential to successful immunotherapy. Standardized vaccines are the ideal. Standardized

aeroallergen vaccines are available in the United States for house dust mite (*Dermatophagoides farinae*, *D. pteronyssinus*), cat pelt, cat hair, short ragweed, and selected grass pollens. Other standardized vaccines should become available in the near future.^{5, 54}

Data on the efficacy of immunotherapy for aeroallergen-induced allergic diseases in children under 6 years of age are not available. The use of immunotherapy for respiratory allergy in children under 6 years old requires further investigation before it can be routinely recommended.⁷¹ In contrast, venom immunotherapy for venom-induced anaphylaxis is proven to be efficacious in children younger than 6 years old. Similarly, data on the efficacy of immunotherapy for respiratory allergy in adults older than 60 years old are lacking, and the decision to treat respiratory allergies in the elderly should be reviewed cautiously.

Patients receiving immunotherapy must adhere to the treatment program, including frequent visits to the physician's office. In a Harvard HMO model health plan, only 33% of patients initiating immunotherapy completed the intended duration of 61 immunotherapy injections.¹⁹ Patient relocation may impact the ease of ability to continue immunotherapy. Written consent to therapy after being fully informed of the relative risks and benefits of the treatment is a useful means of documenting information exchange. The physician must have available adequate personnel, facilities, equipment, and the experience required to treat adverse reactions, including anaphylaxis and asthma exacerbations.⁶

Contraindications for Initiating Immunotherapy

Potential contraindications for immunotherapy include the following:

1. β -blocker therapy
2. Pregnancy (a contraindication to increasing dosing, not to maintenance therapy)
3. Allergic bronchopulmonary aspergillosis/hypersensitivity pneumonitis
4. Immunologic/autoimmune disease
5. Other significant medical conditions

Adapted from Parry DE, Bush RK: Patient selection for allergen immunotherapy: When to start and stop. *In* Lockey RF, Bukantz SC (eds): *Allergens and Allergen Immunotherapy*, ed 2. New York, Marcel Dekker, Inc., 1999; reprinted from reference 50, p 383, by courtesy of Marcel Dekker, Inc.

Patients using β -blockers ideally should be switched to a different class of medication before receiving immunotherapy. Although the frequency of anaphylactic reactions are probably unaffected by β -blocker therapy, the reactions are more severe and response to treatment is reduced.³⁴ Anaphylaxis that is refractory to epinephrine resuscitation is of particular concern in patients with asthma. The American Academy of Allergy and Immunology published recommendations in their position

statement,³⁴ including that the concomitant use of β -blocking agents and allergen immunotherapy should be avoided when possible and that potential benefits and risk must be weighed carefully in patients who cannot substitute an alternative drug for their β -blockers. They also advised that a warning label should be placed on both β -blockers and allergen vaccines, addressing the potential severe reactions that may occur during concomitant use of these agents.

Pregnancy is not a contraindication for immunotherapy; however, caution should be used in administration and the dose should not be increased. A pregnant patient can safely continue maintenance therapy, although some physicians reduce the dose 20% to 30% for additional safety. During a build-up phase the dose should either not be increased or treatment postponed until after delivery. Initiating treatment in pregnant patients is of limited value, as the dosage would remain low until delivery, limiting the efficacy of immunotherapy during the pregnancy. There are no contraindications for breastfeeding mothers to initiate or continue immunotherapy.

Unstable asthma is a contraindication to immunotherapy. Most fatalities associated with immunotherapy involve patients with symptomatic asthma preceding or during allergen administration.⁵⁵ Patients experiencing significant asthma symptoms or an increase in symptoms compared with baseline should not receive immunotherapy until their asthma is adequately controlled. Some investigators do not recommend the administration of immunotherapy if pulmonary function is not greater than 70% of predicted values.¹⁰

Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis are characterized by high levels of specific IgE; however, the pathophysiology of these disorders is not exclusively dependent on IgE. Immunotherapy has not been proven effective in these conditions and therefore is not indicated.

Immune complex and autoimmune diseases are not a contraindication based on prospective studies, but some physicians view these as relative contraindications. One perception is that the immune dysfunction of autoimmune disease may be altered unpredictably by immunotherapy. Therefore, patients with systemic lupus erythematosus, rheumatoid arthritis, and other collagen vascular diseases generally do not receive treatment with immunotherapy. Vasculitis has been associated with immunotherapy, but these reports probably reflected coincidental occurrence.

Finally, cost may be a limiting factor for some patients. The total cost of care for asthma and allergic rhinitis has been estimated to be both increased and decreased by immunotherapy.¹⁹ Variability in compliance with immunotherapy and effectiveness of treatment likely are the explanations for discordant cost data.¹⁹ Potential modulation of disease progression, such as reducing the development of asthma in subjects with rhinitis or preventing the development of additional sensitivities, would enhance the cost-effectiveness of immunotherapy.^{16, 30}

AEROALLERGEN IMMUNOTHERAPY EFFICACY

The central and ultimate issue when selecting patients to receive immunotherapy is evidence that treatment will be effective. Aeroallergens that are important in allergic rhinitis and asthma include grass pollens, weed pollens, tree pollens, fungi, house dust mites, and animal dander. Several published articles review data that support the use of immunotherapy for allergic rhinitis or asthma.^{11, 13} Cockroaches are important aeroallergens in asthma and bear mentioning; however, there are no large studies of cockroach immunotherapy.³³ The following section provides a brief synopsis of immunotherapy efficacy of specific treatment of allergic rhinitis and asthma (summarized in Tables 1 and 2). For additional details of aeroallergen immunotherapy efficacy, see the article by Ledford elsewhere in this issue.

Collective evidence indicates that grass-pollen immunotherapy is effective with persistent symptom benefit for grass-pollen-induced allergic rhinitis. This benefit appears to last at least 3 years following immunotherapy completion.¹ The studies cited indicate that children and adults with grass-pollen-induced rhinitis (Table 1) or asthma (Table 2) are candidates for immunotherapy. Patients with seasonal symptoms due to grass-pollen sensitivity are likely to benefit from immunotherapy and will likely retain this benefit after immunotherapy is discontinued.²¹

Weed-pollen immunotherapy studies generally use ragweed antigens. Based on the available data, patients with ragweed-induced rhinitis (Table 1) are appropriate candidates for immunotherapy when they do not respond adequately to pharmacotherapy or have side effects from or wish to discontinue such therapy. Overall, sufficient data have been obtained to justify ragweed immunotherapy in the treatment of children and adults with allergic rhinitis due to ragweed-pollen sensitivity, as well as for children and adults with ragweed-induced asthma (Table 2).

Tree-pollen immunotherapy data come from studies primarily using birch and mountain-cedar allergens. There are data that indicate that tree-pollen immunotherapy is effective in treating allergic rhinitis (Table 1) and asthma (Table 2). Studies comparing birch monotherapy with combination therapy (alder, birch, hazel) showed efficacy in both groups^{45, 72}; however, more controlled studies with a wider variety of tree pollen allergens and standardized vaccines are needed.

There are few controlled studies of immunotherapy using fungal vaccines; however, such therapy is in widespread use.^{17, 58} Available data indicate that immunotherapy is useful for *cladosporium*- and *alternaria*-induced rhinitis and asthma.^{38, 63} Efforts to expand our knowledge of fungal allergy, including the variable and complex nature of fungal vaccines,^{12, 28} and to define the role of fungal allergen immunotherapy are sorely needed.

Assessment of the effectiveness of house dust mite immunotherapy is very difficult because patients have different home environments; however, most evidence supports the use of standardized house dust

Table 1. SELECTED PLACEBO-CONTROLLED STUDIES OF EFFICACY OF IMMUNOTHERAPY IN ALLERGIC RHINITIS

Reference	Allergen	Length of Study (y)	Age Group	Number Improved/ Number Treated		Significant Difference
				Extract	Placebo	
37	Mixed Mixed grass	1-3	Adult/pediatric Adult	20/63	9/59	Yes
70		1		Symptom-medication scores better in 17 treated patients than in 16 controls		Yes
18	Grass Grass Grass	3	Adult/pediatric Adult Adult	18/28	10/28	Yes
24		1		78/101	33/101	Yes
66, 68		4		Symptom-medication scores better in 21 treated patients than in 19 controls		Yes
22	Ragweed	2	Pediatric	17/35	15/35	No
36	Ragweed	3-5	Pediatric	11/25	11/26	No
44	Ragweed	1	Adult	7/19	2/21	Yes
57	Ragweed	1	Adult	10/13	1/13	No
			Pediatric	13/18 treated patients had lower symptom scores than any of 17 control patients		Yes
35	Amb a I Birch	1-2	Adult Adult	14/18	7/18	Yes
53*		1		Symptoms and medication scores better in 20 treated patients than in 20 controls		Yes
67	Birch	1	Adult	32/38	11/19	Yes
51	Mountain cedar	1	Adult	13/17	6/15	Yes
56*	<i>Alternaria</i>	1	Adult/pediatric	8/13	5/11	Yes

*Included patients with asthma symptoms.

Adapted from Norman PS: Immunotherapy for nasal allergy. *J Allergy Clin Immunol* 81:992-996, 1988; with permission.

Table 2. SELECTED PLACEBO-CONTROLLED STUDIES OF ALLERGEN IMMUNOTHERAPY IN ASTHMA

Antigen	Reference	Duration of Study (mo)	No. of Subjects		Age Group	Type of Study	Significant Difference
			Active	Placebo			
Mixed aeroallergens	2	>18	61	60	Pediatric	Double blinded	No
Mixed aeroallergens	31	168	67	63	Pediatric	Not blinded	Yes
Mixed grasses	24	4	31	26	Pediatric/adult	Single blinded	Yes
	39	2	27	8	Pediatric/adult	Double blinded	Yes
	48	10	8	7	Adult	Double blinded	Yes
Ryegrass	27	24	11	9	Pediatric	Not blinded	No
Ragweed	15	24	37	40	Adult	Double blinded	Improved 1st year
<i>Cladosporium herbarum</i>	20	10	16	14	Pediatric	Double blinded	Yes
<i>D. pteronyssinus</i>	7	12	171	44	Pediatric/adult	Not blinded	Yes
Animal							
Cat	47	4-5	9	8	Adult	Double blinded	Yes
	61	3-4	5	5	Adult	Double blinded	Yes
	65	12	11	11	Adult	Double blinded	Yes
Cat and dog	60	12	22	17	Pediatric/adult	Double blinded	Yes
Dog	64	12	15	12	Pediatric	Double blinded	Yes

Adapted from Ohman JL, Jr: Allergen immunotherapy in asthma: Evidence for efficacy. J Allergy Clin Immunol 84:133-140, 1989; with permission.

mite vaccines for the treatment of allergic rhinitis⁷ and asthma^{8, 23} in house dust mite sensitivity. Patients with mild to moderate disease who continue to experience symptoms despite house dust mite avoidance measures are most likely to improve with treatment.

Exposure to domestic animals is a significant cause of allergic reactions. Greater than 50% of children with asthma are allergic to at least one animal species, and 10% to 32% of persons regularly exposed to laboratory animals experience allergic symptoms.¹⁴ Immunotherapy with cat vaccines decreases asthma symptoms and lessens bronchial reactivity to antigen,^{3, 11, 26, 46} but comparable data on immunotherapy with dog dander and rodent vaccines are not available. Avoidance is the major modality of therapy, and premedication with cromolyn, beta-agonists, and antihistamines is indicated for persons intermittently exposed to animals. A trial of immunotherapy is warranted for those who are continuously exposed, such as laboratory assistants, veterinarians, or animal-allergic patients who will not eliminate animals from their homes.

DOSING SCHEDULES

Opinions differ on how to best administer aeroallergen vaccines. Perennial dosing schedules have been the most extensively studied and are recommended.⁴ Injections are administered every 5 to 10 days on a prescribed schedule (Tables 3–5). The immunotherapy schedule can be tailored to maintain doses that are large enough to be efficacious yet low enough to be safe. Initial doses should be well tolerated in most patients. The dose is progressively increased until a maintenance dose is reached. Maintenance doses are calculated to contain between 4 and 12 μ g of each major allergen being administered. Most schedules use a maintenance dose of about 2500 protein nitrogen units (PNU)/allergen or 1:100 weight/volume (wt/vol) as the final maintenance dose.⁴¹ Some schedules use “high-dose” immunotherapy with maintenance doses of 10,000 PNU. Such schedules should be used cautiously. To maintain safety while administering pollen immunotherapy, the schedule may be modified based on the size of skin test results (Table 3). Patients with a moderate-sized skin test response to pollen allergens can be prescribed the regular schedule. More sensitive individuals, with skin tests measured as 3+,⁴ should be considered for the sensitive schedule. Finally, patients with a large skin test response⁴ (e.g., a 4+ reaction with pseudo-pods) should be considered for the very sensitive schedule. For additional safety, some allergists recommend beginning with a ten-fold more dilute mixture (10 PNU/mL or 1:100,000 wt/vol) and introducing additional dosage steps during the build-up. Patients with dust mite allergy generally receive a sensitive schedule (Table 4) using standardized antigen. Cat allergen immunotherapy is well standardized and is administered at a particular schedule (Table 5). When a maintenance vial is replaced, from annual expiration or exposure to extreme temperature, the dose is usually reduced. Most allergy specialists suggest a new vial dosage reduction from 25% to 75% of the maintenance dose. The dose is in-

Table 3. THREE SUGGESTED SCHEDULES FOR POLLEN ALLERGEN IMMUNOTHERAPY BASED ON SKIN TEST SENSITIVITY

Vial/Concentration	Dosage (mL)			Date	Reactions
	Regular Schedule	Sensitive Schedule	Very Sensitive Schedule†		
Vial #1—100 PNU/mL or 1:10,000 wt/vol	0.25	0.10	0.05		
	0.50	0.20	0.10		
	1.00	0.40	0.15		
		0.80	0.20		
Vial #2—1000 PNU/mL or 1:1000 wt/vol			0.30		
	0.15	0.15	0.40		
	0.25	0.20	0.50		
	0.35	0.30	0.60		
	0.50	0.40	0.70		
	0.65	0.50	0.05		
	0.80	0.60	0.10		
		0.80	0.15		
Vial #3—10,000 PNU/mL or 1:100 wt/vol			0.15		
	0.05	0.05	0.20		
	0.10	0.10	0.30		
	0.15	0.15	0.40		
	0.20	0.20	0.50		
	0.30	0.30	0.60		
	0.40	0.40	0.70		
	0.50	0.50	0.05		
	0.60	0.60	0.10		
	0.70	0.70	0.15		
	0.80	0.80	0.20		
	0.90	0.90	0.25		
	1.00	1.00	Maintenance*		
	Maintenance*	Maintenance*	Maintenance*		

*Continue injections at final volume from vial #3 every 21–28 days.

†Consideration should be given to initiating treatment at 10 PNU/mL or 1:100,000 wt/vol, particularly if the treated subject has asthma.

Table 4. SUGGESTED SCHEDULE FOR AEROALLERGEN IMMUNOTHERAPY: DUST MITE

Vial/Concentration	Dosage (mL)	Date	Reactions
Vial #1—100 AU/mL	0.10		
or	0.20		
1:10,000 wt/vol	0.40		
	0.80		
Vial #2—1000 AU/mL	0.15		
or	0.20		
1:1000 wt/vol	0.30		
	0.40		
	0.50		
	0.60		
	0.80		
Vial #3—10,000 AU/mL	0.05		
or	0.10		
1:100 wt/vol	0.15		
	0.20		
	0.30		
	0.40		
	0.50		
	Maintenance*		

*Continue injections at 0.50 mL from vial #3 every 21–28 days.

AU = allergy unit

Table 5. SUGGESTED SCHEDULE FOR AEROALLERGEN IMMUNOTHERAPY: CAT DANDER

Vial/Concentration	Dosage (mL)	Date	Reactions
Vial #1—1 BAU/mL	0.20		
	0.50		
	0.80		
Vial #2—10 BAU/mL	0.10		
	0.20		
	0.35		
	0.50		
	0.65		
	0.80		
Vial #3—100 BAU/mL	0.10		
	0.20		
	0.40		
	0.60		
	0.80		
Vial #4—1000 BAU/mL	0.10		
	0.20		
	0.40		
	0.60		
	0.80		
Vial #5—10,000 BAU/mL	0.10		
	Maintenance*		

*Continue injections at 0.10 mL from vial #5 every 21–28 days.

BAU = bioequivalent allergy unit.

creased weekly over several weeks until the full monthly maintenance dose is resumed.

Schedules for rush immunotherapy entail administering multiple injections on one day or, frequently, on multiple days in a row. Schedules using eight injections over 3 days⁹ or 8 injections in a single day⁵⁹ have been published. Adverse reactions are more common with rush immunotherapy, and there is greater risk of systemic reactions.²⁵ Pre-medication using H₁-blockers, H₂-blockers, and corticosteroids may reduce the frequency and intensity of adverse reactions.²⁵ A more conservative rush immunotherapy schedule administering 2 to 6 injections per day using traditional perennial schedule doses was completed in 5 to 8 days, with adverse effects approximating weekly dosing schedules.⁴⁰ There are no trials comparing the efficacy of rush immunotherapy and traditionally scheduled immunotherapy.

CONSENT FORMS

Prior to initiating immunotherapy, it is very important to obtain informed consent from the patient. Documentation of what immunotherapy entails and the risks involved is essential in providing informed consent. The consent form should be reviewed with the patient by the physician, signed, and placed in the medical record. A representative sample is included Box 2.

TECHNIQUES FOR ADMINISTRATION

1. Technique: Use a 1-mL disposable syringe, graduated to 0.01 mL, and a 26- to 27-gauge, 3/8-inch needle. Carefully withdraw the proper amount of antigen from the appropriate vial. Cleanse the area with an alcohol swab before injecting. Give the injection subcutaneously in the posterior aspect of the middle third of the arm. Gently draw back the plunger, and if blood appears, withdraw the needle and select a new site. Slowly inject the antigen, withdraw the needle, and apply pressure over the injection site for 15 to 20 seconds. Do not massage the area. Either arm may be used or the arms may be alternated. Allergy extracts should be refrigerated at 4°C. Avoid exposure to sunlight, extreme heat, or freezing. Do not administer expired allergy extracts.
2. A 30-minute wait: Each patient is expected to wait at least 30 minutes in a medical facility after receiving allergy injection treatment so that he or she can be checked for local and systemic reactions. A physician should be present during the 30-minute waiting period.
3. Management of local reactions: A lump or swelling with erythema is not as significant as a lump with a wheal. The wheal is the most significant part of the local reaction. If the wheal has pseudopods or is surrounded by hives, consult the prescribing physician. Size of

Box 2. A Representative Consent Form**IMMUNOTHERAPY**

Immunotherapy (allergy shots) is a form of therapy for allergic rhinitis (hay fever or cedar fever), for stinging insect allergy, and in some instances, for allergic asthma. When these injections are repeated, the body builds resistance or "immunity" to the allergen. Many carefully performed studies have shown that immunotherapy decreases allergic symptoms.

Who should be treated with immunotherapy? First, the patient must have one of the problems listed in the first paragraph. Second, the patient must have a positive skin test to the allergen to be used in immunotherapy. Third, the patient must have a history of symptoms occurring during exposure to the allergen. The duration of the season in which symptoms occur should be more than a few weeks and should be resistant to therapy with medication.

How is immunotherapy administered? In the course of immunotherapy very small doses of allergen are given to the patient and are gradually increased each week. This gradual build-up of the allergen decreases the possibility of the injection itself, causing an allergic reaction. Considerable dedication is required of the patient who must continue the weekly injections until a high dose of allergen is reached. Only after a high or "maintenance dose" is reached will the full benefit of the injections be appreciated. It may take up to 1 year for symptom relief to occur. Following the weekly build-up phase, which generally occurs over 4 to 5 months, maintenance injections are given monthly. Missed shots or reactions to shots can delay reaching maintenance dosing. The mixture of allergens given consists of those allergens to which the patient has positive skin tests and an appropriate history. Mixtures are "tailor made" for each patient.

How long should a patient be treated with immunotherapy? If a patient is so improved that symptoms do not occur during the allergy season, then after 3 to 5 years the injections may be stopped. In this time it is natural for about 30% of patients to improve to the point that immunotherapy is no longer needed. Unfortunately, we cannot identify those individuals who will relapse and subsequently need to go through the weekly injections again. Everything considered, we recommend that all patients discontinue therapy after 5 years to determine if continued therapy is necessary. Immunotherapy for insect-induced anaphylaxis is an exception to these general rules.

Remember, avoidance of all allergen when possible is the first and most important form of therapy. Second, medications, when effective, are safe and are the second form of therapy and are often used in conjunction with other forms of therapy. Finally, immunotherapy is an effective form of therapy in properly selected patients.

Box continued on following page

Box 2. A Representative Consent Form (Continued)

There are two types of **reactions** that may occur after an allergy injection. The most common type is the local reaction. These vary from a dime-sized itchy spot to a large lemon-sized swelling. They require no medical treatment and are generally managed by altering the injection schedule.

The second type of **reaction** is the generalized, systemic, or "anaphylactic" reaction. Less than 0.1% of all patients receiving shots have had a generalized reaction; however, they may be life threatening and should be treated immediately. Most generalized reactions are a reproduction-in-miniature of the patient's symptoms (e.g., sneezing, runny nose, itching, or shortness of breath). A shot of epinephrine (adrenaline) usually promptly relieves the symptoms. The most severe reaction is the swelling or allergic shock that requires immediate treatment and is the reaction that is life threatening. Approximately one death occurs in the United States per year due to allergy shots.

As we mentioned before, generalized **reactions** are rare but may occur at any time. They could occur with the first injection or after a long series of shots. They are not necessarily related to the dose of extract given. Because 99% of the more severe generalized reactions occur within 30 minutes after the injection, we ask that all patients remain in the doctor's office for 30 minutes of observation after receiving a shot. In the event that a reaction occurs after leaving the clinic, you will also be given a self-administered form of epinephrine.

This explanation of the way allergy shots help your allergic symptoms and of the benefits and risks associated with allergy shots is meant to increase your understanding of the treatment plan that we may recommend for your allergy symptoms.

I have read the explanation of allergy shots and agree to my/my child receiving allergy shots. I also agree to any additional therapy for reactions that is required.

SIGNATURE: _____

DATE: _____

the local reaction can affect advancement of the injection schedule. General guidelines include:

- (A) Negative or swelling to 15 mm (dime size)—progress according to schedule.
- (B) Swelling 15 to 20 mm (not redness) (dime to nickel size)—repeat same dosage.
- (C) Swelling 20 to 25 mm (nickel to quarter size)—return to the last dosage that caused no reaction.

- (D) Swelling persisting more than 12 hours or over 25 mm (quarter size or larger)—decrease dosage by 50%. If the reduced dose is tolerated, increase dose by 0.05 to 0.1 mL weekly and resume the previous schedule. If a local reaction occurs again, the patient should be seen in the office with their dosage sheet.

EMERGENCY EQUIPMENT

Systemic reactions resulting from injections occur occasionally in the course of treating allergic patients. Almost all reactions occur within 30 minutes after an injection.^{4, 52} Symptoms may include itching of the palms of the hands or other parts of the body, sneezing, coughing, urticaria, angioedema, and dyspnea. With anaphylaxis, acute asthma or hypotension may occur. At the first sign of a systemic reaction a tourniquet may be applied above the injection site and epinephrine administered. Specific emergency equipment used in anaphylaxis treatment should be on site at any office administering immunotherapy (Box 3).⁵² Personnel must be trained in the use of equipment, and the equipment must be maintained or replaced as components expire or are used.

DISCONTINUING AEROALLERGEN IMMUNOTHERAPY

The duration of immunotherapy required to maintain reductions in clinical symptoms is still unknown. Patients who do not respond after receiving maintenance doses of appropriate allergens for at least 1 year are unlikely to improve with continued treatment. Therefore, immunotherapy should be discontinued if no appreciable benefit occurs after 1 year of adequate dosing. For those patients who respond to treatment, many clinicians advise a 3- to 5-year course of therapy.⁷¹ In the study by Warner et al.,⁶⁹ most children who were switched to placebo after receiving 1 year of active treatment with dust mite vaccines relapsed within months, whereas those who continued on active treatment had ongoing improvement. Studies with cat dander immunotherapy²⁶ showed that at least one third of subjects continued to have increased tolerance to cat exposure up to 5 years after completing a 3-year course of immunotherapy. Grass-pollen immunotherapy has been shown to impart benefits that last at least 3 years after 3 to 4 years of treatment.²¹ For most patients, a 3- to 5-year course of treatment will be sufficient; however, a decision on when to discontinue allergen immunotherapy must be individualized.⁷¹ When patients who have completed a course of treatment relapse, they are candidates for another course of treatment.

REMOTE PRACTICE OF ALLERGY

Given the complexity of diagnosing specific allergic diseases, determining the efficacy of specific immunotherapy, and the prescribing of

Box 3. Equipment for the Treatment of Anaphylaxis

1. IM or SC epinephrine
 Adults—0.2 mL (0.2 mg) to 0.5 mL (0.5 mg) of a 1:1000 (1 mg/mL) w/v dilution every 10 to 15 minutes, up to a maximum of 1 mL (1 mg) per dose.
 Pediatrics—0.01 mL/kg (0.01 mg/kg) up to a maximum of 0.5 mL (0.5 mg) per dose of 1:1000 (1 mg/mL) w/v dilution, repeated every 15 minutes for 2 doses, then every 4 hours as needed.
 Establish an IV line if the patient is not responding to epinephrine.
2. IV epinephrine
 1:10,000 (0.1 mg/mL) or 1:100,000 (0.01 mg/mL) w/v dilution initially titrated at 1 μ g/min, which can be increased to 2 to 10 μ g/min as needed
3. Diphenhydramine
 1 to 2 mg/kg or 25 to 50 mg per dose given IM, PO, or IV
4. Corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone)
 Recommended, but efficacy not clearly delineated. Hydrocortisone 5 mg/kg or 250 mg IV or prednisone 1 to 2 mg/kg or 20 mg PO
5. IV fluid (e.g., normal saline) and vasopressors (e.g., dopamine) to treat hypotension
6. Inhaled β -adrenergic bronchodilator (e.g., albuterol) to treat bronchospasm
7. H_2 receptor blocker (e.g., ranitidine) for epinephrine-resistant hypotension
8. Oxygen
 Flow of 8 to 10 L/min
9. The ability to provide cardiopulmonary resuscitation (CPR) as needed to restore circulation and respiration
 Equipment includes oral airway, bag and mask, trained personnel
10. The ability to provide constant monitoring of cardiac, respiratory, and circulatory systems. Note: Beta-blockers and possibly angiotensin-converting enzyme (ACE) inhibitors may increase the difficulty of treating anaphylaxis. If a patient on this type of medication does not respond to epinephrine, consider glucagon 1 mg IV as a bolus, with continuous infusion of 1 to 5 mg/h.

From Practice parameters for the diagnosis and management of anaphylaxis. J Allergy Clin Immunol 101:S465-S528, 1998; with permission.

aeroallergens for use in immunotherapy, only trained allergists should prescribe aeroallergen immunotherapy. Ordering of immunotherapy by nonallergists has been shown to result in unnecessary costs and inappropriate immunotherapy.⁴² Because of inherent risk of systemic reactions, immunotherapy should only be administered in a facility with personnel trained in the treatment of anaphylaxis with appropriate equipment to treat anaphylaxis present. Therefore, patients should never receive immunotherapy at home administered by themselves or others. The risk of fatality resulting from immunotherapy has been associated with

receiving home immunotherapy.⁵⁵ Patients with long travel distances to an allergist's office may wish to receive immunotherapy injections at their primary care physician's office. This can be accomplished when a primary physician is comfortable administering or supervising administration of immunotherapy and the resources are available to treat anaphylaxis. However, patients receiving immunotherapy through an allergist's office were more likely to remain adherent to immunotherapy schedules (89%) than those receiving immunotherapy through another physician's office (65%).⁶²

GENERAL CONCLUSIONS REGARDING PATIENT SELECTION AND AEROALLERGEN IMMUNOTHERAPY

1. When properly instituted, aeroallergen immunotherapy is an effective treatment for allergic diseases.³²
2. Immunotherapy is indicated for allergic patients whose symptoms have been inadequately controlled with appropriate allergen avoidance and medications during at least one allergy season or who have experienced significant side effects from medications.
3. Patients with asthma should have their disease stabilized with appropriate medication before instituting immunotherapy.
4. Efficacy of immunotherapy for a variety of allergens has been demonstrated, but further double-blind, placebo-controlled studies of tree pollen and fungal sensitivity are needed.
5. Standardized vaccines of tree pollens and fungal allergens are needed.
6. Once patients have achieved maintenance doses of immunotherapy, treatment should be continued for a period of 3 to 5 years. Patients who relapse after discontinuation may need repeated treatment.
7. It is important for patients, or the parents of children, to fully understand the potential risks and benefits of immunotherapy, along with the time, effort, and expense involved in a full course of treatment.
8. The treating physician must have adequate personnel, facilities, equipment, and necessary expertise to treat adverse reactions to immunotherapy.

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