

ALLERGEN IMMUNOTHERAPY

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The scientific basis of allergen immunotherapy stems from the initial report by Noon and Freeman³² in 1911 describing preparation of grass pollen extracts and injections of increasing quantities of pollen into patients with allergic rhinitis. Pollens were considered to be toxins, and injections were thought to induce antitoxins.

The evolving concept of anaphylaxis, beginning with Portier and Richet in 1902,²¹ and astute clinical observation of human allergic disease directed investigators to conclude that the mechanism responsible for clinical allergy is a hypersensitivity reaction and not exposure to toxins. Immunotherapy is a form of immunomodulation that decreases allergen hypersensitivity.¹⁵

IMMUNOLOGICAL EFFECTS

Allergen immunotherapy is the administration of increasing quantities of allergens to patients with IgE-mediated allergic rhinitis, asthma, or stinging or biting insect anaphylaxis. Immunotherapy is distinguished from desensitization, which refers to more rapid administration of an antigen that combines with and neutralizes IgE antibodies such as occurs during a course of penicillin in a penicillin-allergic patient.

During succeeding decades, the clinical experience and majority of clinical trials have been unable to define one mechanism by which immunotherapy is effective in allergic disorders. The following hypotheses are partially supported by clinical and scientific data:

1. Blocking antibody. Immunotherapy induces allergen-specific IgG, or "blocking antibody," which competes with IgE for allergen

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binding.^{23, 29, 52} There are a few studies demonstrating clinical improvement in the absence of an increase in allergen-specific IgG, but the bulk of evidence shows a correlation between reduced symptom and medication scores and serum levels of specific IgG.¹⁰ The role of IgG in affecting allergic symptoms has been more clearly established in insect venom sensitivity than in inhalant allergy.¹³

2. Decrease in IgE. Immunotherapy results in a reduction of allergen-specific IgE.¹¹ The decrease in specific IgE is gradual, although IgE levels increase initially in response to treatment.¹² Studies on ragweed immunotherapy also show a decrease in the postseasonal rise in IgE.⁵³
3. Modulation of mast cells and basophils. Immunotherapy modulates target cell function and thereby reduces mediator release from mast cells and basophils in spite of the presence of specific IgE on their surfaces.²⁸ This effect has been demonstrated by a postimmunotherapy decrease in histamine release from peripheral blood basophils following in vitro allergen challenge, which preceded a decrease in specific IgE or an increase in specific IgG.
4. Increase in suppressor lymphocyte activity and modulation of other regulatory cells. Immunotherapy alters regulatory cellular networks by increasing T-lymphocyte suppressor activity.⁴⁴ IgE production, maturation of select mast cell populations, macrophage activation, mediator release from mast cells and basophils, and bone marrow cellular response are all regulated by T lymphocytes.⁴⁴ Therefore, alteration in T-cell function affects allergic mechanisms.

ALLERGEN EXTRACTS

The methods used to manufacture aqueous allergen extracts have not changed appreciably since the initial report on the efficacy of "hypodermic inoculation of pollen vaccine" in 1911.³² A certain mass of source material, for example, a pure pollen, is mixed with a given volume of a buffered solution. The extractable proteins are dissolved, the insoluble material is removed, and a preservative is added to maintain allergen stability.⁵¹ The need for standardized extracts for immunotherapy has been recognized for years. Recently, the US Food and Drug Administration has initiated a program to ensure that extracts are of consistent allergenic potency made as standardized extracts.

Storage of Extracts

Allergen extracts should be maintained near labeled potency until used for diagnostic tests or immunotherapy. Because standard extracts lose their potency when stored at room temperature and with freezing

and thawing, specific steps must be taken to preserve their potency. Allergen extracts should be kept at about 4°C in a standard refrigerator. Dilutions of concentrated extracts lose their potency more rapidly than concentrated extract.^{20, 53}

EFFICACY OF IMMUNOTHERAPY

Immunotherapy has been used on an empirical basis for the treatment of aeroallergen-induced rhinitis and asthma since the early twentieth century. Nevertheless, controlled trials clearly demonstrating the effectiveness of immunotherapy and methods necessary for effective immunotherapy have only been performed since the early 1950s.

Immunotherapy for Allergic Rhinitis

It has become increasingly clear that immunotherapy with specific aeroallergen extracts is an effective treatment for allergic rhinitis. From the pioneering work of Frankland and Augustin¹⁵ in London; Lowell and Franklin²² in Boston; and Norman, Lichtenstein, Winkenwerder, and their colleagues^{24, 33, 34, 45} in Baltimore, the proper design for appropriate controlled trials has emerged. Ragweed was studied as a cause for seasonal allergic rhinitis. Such rigorous studies clearly demonstrated that ragweed extract was more effective than placebo for reducing symptom-medication scores.²² The effect was dose related, and an effective dose produced definite immunological changes that were not produced by placebo or by inadequate doses.¹² Immunological changes included (1) a rise in serum levels of ragweed IgG to a plateau well above pretreatment levels, (2) an initial rise of serum levels of ragweed IgE followed by a failure of the customary rise during the ragweed season and ultimately by a decline to pretreatment levels usually achieved by 18 to 24 months, and (3) a decrease in skin sensitivity to the treatment ragweed extract.⁵³ Other controlled trials have demonstrated efficacy for grass,^{15, 37} mountain cedar,³⁸ and birch pollen⁵⁴ extracts as well as for house dust mite (*Dermatophagoides pteronyssinus*) extract.²⁷ When given for treatment of allergic rhinitis, *Alternaria* extract²⁰ immunotherapy produced significant decreases in symptom-medication scores.

Immunotherapy for Allergic Asthma

The evidence for effectiveness of immunotherapy for asthma caused by exposure to an aeroallergen is by no means as extensive as that for hay fever but, in general, tells the same story. Ragweed, grass and birch pollen, cat,^{23, 49} dog,^{23, 49} house dust,⁷ house dust mite,⁵⁵ and molds²⁵ have been studied. The majority of controlled trials demonstrated beneficial effects of immunotherapy in both seasonal and perennial allergic asthma.

Immunotherapy for Venom Sensitivity

Anaphylaxis caused by insect stings has been recognized for many years as a serious medical problem. In the United States, at least 40 deaths per year are the result of allergic reactions from insect stings.⁴¹ Stinging insects are members of the Hymenoptera order, which contains apids (honey bees), vespids (yellow jacket, yellow hornet, white-faced hornet and wasp), and formicids (imported fire ants). The availability of purified venoms and subsequent commercial distribution provided a major breakthrough in treatment of insect-allergic individuals. Initial studies documented the almost 100% effectiveness of venom immunotherapy in preventing resting anaphylaxis.⁴² The goal of venom immunotherapy is to provide protection from subsequent stings in individuals considered to be at risk as defined by a history of insect sting anaphylaxis and the presence of venom-specific IgE (positive skin test). Venoms are available for the honey bee, yellow jacket, yellow hornet, white-faced hornet, wasp, and fire ant. The testing for imported fire ant sensitivity is indicated in a clinical situation that usually differs from those of the other Hymenoptera.⁴⁷

Immunotherapy for Adverse Reactions to Foods

There are no clinical studies to indicate that food immunotherapy, either oral or by injection, has a role in the management of allergic individuals. One group of investigators demonstrated efficacy with immunotherapy in peanut-sensitive subjects; however, more data are needed before such therapy can be recommended for routine clinical use. Food immunotherapy in highly allergic individuals may have a greater risk for severe life-threatening reactions than inhalant immunotherapy.³⁶

Ineffective Methods of Immunotherapy

Low-Dose Immunotherapy

Various low-dose regimens have been employed since the late 1920s. Coseasonal low-dose immunotherapy was introduced to permit the immediate treatment of aeroallergen-induced hay fever and asthma.¹⁸ Rinke⁴³ popularized the concept that a specific therapeutic dose could be determined by an intradermal skin test end point. Several placebo-controlled studies have shown that this low-dose method is no more effective than a placebo and is less effective than the standard high-dose method for relieving symptoms of ragweed hay fever.

Immunotherapy Based on Provocation-Neutralization Testing

Intracutaneous and subcutaneous provocations have been employed for the diagnosis and immunotherapy of aeroallergen allergy since at least 1961.¹ Subsequently, small amounts of successive fivefold dilutions of the aeroallergen extract previously used for provocation are injected or given sublingually until the so-called "neutralizing dose" is found that relieves or neutralizes the patient's symptoms. Many investigators have attempted to perform controlled trials of these provocation-neutralization procedures for diagnosis and immunotherapy of both food and aeroallergen allergy but have not produced proof of effectiveness.¹

Dose Dependence of Immunotherapy

Larger amounts of administered allergen generally result in greater clinical and immunological improvement. A comparison of two doses of allergen extract for the treatment of ragweed hay fever demonstrated improvement only with the higher dose.¹² Increasing the dose of immunotherapy beyond a certain level does not result in further improvement.¹⁰ For example, improvement with immunotherapy in asthma due to cat allergen correlates with the dose of allergen administered.³⁵ The improvement was assessed both by clinical symptoms and bronchial challenge with cat antigen. A comparison of several studies with venom immunotherapy has demonstrated that a 100- μ g maintenance dose is 96% to 100% effective following sting challenge, whereas a 50- μ g maintenance dose is 79% effective.¹⁶

CLINICAL APPLICATIONS OF IMMUNOTHERAPY

Indications and Considerations

The symptoms or disease process should be consistent with known immunological mechanisms such as allergic asthma, allergic rhinitis, or insect sting anaphylaxis (Table 1). Chronic urticaria, eczema, and food allergy have not been consistently benefited by immunotherapy, but treatment of severe atopic dermatitis with immunotherapy is a consideration in selected cases. Specific IgE for appropriate allergens must be documented, and symptoms should correlate with exposure to those specific allergens selected for immunotherapy. The correlation of symptoms with allergen exposure and sensitivity requires a knowledge of the environment of the patient as well as a familiarity with the quality and reliability of allergen testing materials used to document sensitivity. Quality allergen extracts are a prerequisite for testing and treatment. Standardized extracts should be used if available. The age of the patient is a factor in that studies showing benefits with immunotherapy have

Table 1. CONSIDERATIONS FOR INITIATING IMMUNOTHERAPY

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1. Presence of IgE-mediated disease proven to benefit from immunotherapy
 - a. Allergic rhinitis
 - b. Allergic asthma
 - c. Anaphylaxis following Hymenoptera stings
 2. Documentation of sensitivity to allergens associated with symptoms
 3. Symptoms of sufficient duration and severity
 - a. Two seasons of seasonal symptoms despite avoidance measures and pharmacologic therapy
 - b. Perennial symptoms failing trials of avoidance measures and chronic pharmacologic therapy
 - c. Anaphylaxis following Hymenoptera sting except children with cutaneous anaphylaxis only
 4. Availability of allergenic extract of allergen responsible for sensitivity
 5. Other considerations
 - a. Discussion of long-term nature of treatment and need for compliance
 - b. Discussion of risk versus benefit of treatment
 - c. Accessibility of facilities and personnel capable of administering treatment and treating anaphylaxis
 - d. Emphasis of avoidance as treatment of choice
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Adapted from Bush RD, Huftel MA, Busse WW: Patient selection. In Lockey RF, Bukantz SC (eds): Allergen Immunotherapy. New York, Marcel Dekker, 1991, p 27; with permission.

been limited, for the most part, to children older than 6 years of age and to adults younger than 50 years of age.⁹

The association of symptoms with exposure may be difficult to document with perennial asthma and rhinitis. The severity and duration of symptoms should be of a degree to justify immunotherapy. Perennial symptoms should be associated with a high degree of allergic sensitivity coupled with a failure of avoidance measures and chronic pharmacological therapy. Significant seasonal symptoms should be present for at least two seasons, despite the appropriate use of pharmacological therapy and avoidance measures. Occasionally, immunotherapy should be considered earlier if symptoms are particularly severe.²¹

Allergen Selection

Allergens are selected for immunotherapy when exposure results in significant symptoms and when significant sensitivity has been demonstrated by a skin or in vitro test (radioallergosorbent test or similar test). This information should be combined with a thorough patient history with regard to patient environment and timing of symptoms. Allergens selected for immunotherapy should not be based on a positive skin or in vitro test alone.²¹

Relative Contraindications to Immunotherapy

The following clinical circumstances may dissuade the physician from using immunotherapy; at the least, they are indications of the

necessity for additional caution due to the potential for increased adverse events.

β -Blocker Treatment

There are numerous case reports and studies indicating that patients receiving immunotherapy while using β -adrenergic receptor antagonists (β -blockers) can sustain more severe and protracted anaphylactic reactions resistant to conventional therapy compared with patients not receiving β -blockers. β -blockers used at physiological doses for the treatment of hypertension and cardiac disease normally have the effect of decreasing the heart rate, cardiac output, and mean arterial blood pressure. These effects may potentially exacerbate anaphylaxis induced by immunotherapy.²

Allied health personnel administering allergen immunotherapy should regularly ask the patient to update current medications. This practice screens patients regarding concomitant therapy that may lead to an increased risk of protracted anaphylaxis.

Pregnancy

Immunotherapy has been given to pregnant patients for more than 50 years; however, only recently have there been attempts to validate its safety.⁴⁶ Early case reports were principally concerned with the risk of spontaneous abortion due to severe anaphylactic reactions.

In a retrospective study of 121 pregnancies in 90 atopic mothers who received high-dose inhalant allergen immunotherapy during pregnancy compared with the pregnancies of 147 untreated atopic mothers studied in parallel as a control group, the incidence of prematurity, toxemia, spontaneous abortion, neonatal death, and congenital malformation was found to be no greater in the control group than in the pregnant atopic mothers who received allergen treatment.⁴⁶

Current recommendations suggest that untreated patients who become pregnant should not be started on immunotherapy until after delivery because of the incidence of systemic reactions when beginning immunotherapy. If immunotherapy has already been started, it should be carefully increased in slow but progressive increments in those patients deriving benefit who are not experiencing systemic reactions. If the patient has a history of previous systemic reactions to immunotherapy at any dose, the possibility of discontinuing immunotherapy until after delivery should be considered, because the risk of anaphylaxis during pregnancy may outweigh the potential clinical benefits.

Underlying Cardiac Disease

Patients with underlying cardiac disease are at greater risk for morbidity and mortality after anaphylactic reactions to immunotherapy. This is due to the effects of anaphylaxis on the myocardium. Hypoten-

sion and pulmonary vasoconstriction serve to increase the load on the heart while impairing myocardial perfusion at the same time. In many studies, it has been difficult to distinguish events directly induced by anaphylaxis from those secondary to hypotension or therapy for anaphylaxis such as epinephrine injection.¹⁴

Hypersensitivity Conditions Not Exclusively Dependent on IgE Mechanisms

Examples of hypersensitivity disorders in which an IgE mechanism is not essential include allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. Despite the presence of significant quantities of specific IgE, immunotherapy has no beneficial effect and is relatively contraindicated.¹⁴

Immune Complex and Autoimmune Disease

There are no prospective studies to demonstrate that immunotherapy causes or aggravates immune complex disease, vasculitis, or autoimmune disease. Likewise, there is no evidence that immunotherapy adversely affects autoimmune disease, but the common perception is that the immune dysregulation characteristic of autoimmune disease should not be disturbed by immunotherapy.¹⁴ Therefore, allergic diseases occurring in subjects with systemic lupus erythematosus, rheumatoid arthritis, and other collagen vascular diseases are usually not treated with immunotherapy.

ADMINISTRATION OF IMMUNOTHERAPY

Nursing personnel must be focused when preparing or administering immunotherapy. As outlined in the following list, antigen preparation should be accomplished using strict protocols to ensure accuracy and continuity:

- Strict protocols
 - Accurate
 - Continuity
 - Focused
 - Uninterrupted
 - Organized
- Extract continuity
- Labeling
 - Clear, concise
 - Color-coded
 - Dated
- Record keeping
 - Clear instructions
 - Legible, up to date charting

"Conscientious compulsiveness" would best describe the conditions surrounding both antigen preparation and administration. The guidelines for antigen administration are as follows:

- Identify patient
 - Sign in
 - Call by first and last name
 - Verify birth date or patient number
- Ask patient if symptoms are controlled
- Ask patient if reaction after last injection
- "Three rights"
 - Right chart
 - Right antigen
 - Right patient
- Triple check antigen
 - Label, patient name
 - Contents
 - Dilution
 - Expiration date
 - Date of last injection

The antigen should be labeled and dated using clear and concise methods. Record keeping should be well organized, clear, and up to date.

Inhalant Extracts

Immunotherapy is given by subcutaneous injection in the deltoid region of the arm. The site should be alternated with each injection. A 0.5- or 1.0-mL allergy treatment syringe should be used to facilitate accurate measurement of the volume of extract administered. A 0.375- to 0.5-in 27-gauge needle provides the most patient comfort. The plunger of the syringe should be withdrawn after the needle is inserted in the subcutaneous position before the extract is injected to ensure that the extract is not given intravenously. If blood is aspirated into the syringe, the syringe and antigen should be discarded and the procedure should be restarted from the beginning. A separate disposable needle and syringe should be used for each patient to prevent transmission of infectious agents from one person to another. The patient should be asked to wait in the clinic for 20 to 30 minutes following the injection, because the majority of systemic reactions occur within this time period.^{3, 5, 40} Patients at higher risk, for example, asthmatics who are having an exacerbation, patients with a higher degree of sensitivity, or individuals receiving β -blockers, should be observed for 30 minutes or longer.⁸ The number of injections administered should be determined by the physician and should be based on the number of sensitivities. Increasing the number of allergens in a given vial of extract dilutes the amount of any single allergen given with each injection. This could jeopardize a benefi-

cial response to treatment, as improvement is associated with larger amounts of each selected allergen administered.⁵¹ Allergen extracts are generally mixed in variable combinations dictated by the pattern of patient sensitivity.

Dosing Schedule

Immunotherapy may be given intermittently during the year (a preseasonal or coseasonal schedule) or throughout the year (a perennial schedule).⁵² The perennial schedule has been the best studied and is the generally recommended regimen. Immunotherapy is administered on a weekly or twice-weekly schedule (Table 2). The starting dose is chosen to be well tolerated by most sensitive patients, and the dose may be adjusted on the basis of patient history and skin testing results. The dose is increased with each injection until a maintenance dose is reached. The optimal maintenance dose is determined by the tolerance and sensitivity of the patient. The dose should be large enough to be effective and low enough to be safe.

The maintenance dose is usually administered at 2- to 4-week intervals provided that the injections are well tolerated and symptoms improve. If systemic reactions or anaphylaxis occurs, the physician should review the patient's immunotherapy history and adjust the dose of immunotherapy accordingly. Subsequently, the dose is increased as tolerated at weekly or twice-weekly intervals. The maintenance vial is replaced with a newly prepared vial every 6 to 12 months, and the dose of the next injection is reduced by one third to one half with the first injection of the new vial. The dose is subsequently increased weekly or twice weekly to the routine maintenance dose. Large local reactions, for example, erythema and induration of 2 cm or less, may be treated symptomatically or may necessitate dose modification to facilitate tolerance. Reactions greater than 2 cm in diameter should be treated with topical application of ice to reduce local blood flow; oral antihistamine therapy, topical corticosteroid therapy, or even systemic corticosteroid therapy may occasionally be necessary. There are no data to indicate that large local reactions are harbingers of systemic anaphylactic reactions.⁸ It is advisable to educate the patient to avoid vigorous exercise for a period of 2 to 4 hours following immunotherapy administration. The dose of maintenance immunotherapy during the major pollen season may be reduced if the patient is sensitive to the pollen and is receiving the allergen in the treatment extract.

Duration of Aeroallergen Immunotherapy

Data do not exist to identify the optimal duration of inhalant immunotherapy. Maintenance immunotherapy is usually administered until symptoms have improved to a satisfactory level for 1 year, until symptom improvement is noted in three consecutive annual seasons, or until 3 to 5 years of maintenance immunotherapy have been completed.¹⁷

Table 2. EXAMPLE OF AN IMMUNOTHERAPY TREATMENT SCHEDULE FOR INHALANT ALLERGY

Date	Extract Concentration (wt/vol)	Extract Concentration (PNU/mL)	Volume	Remarks
	1:10,000	100 PNU/mL	0.05	
			0.10	
			0.15	
			0.20	
			0.30	
			0.40	
			0.50	
	1:1000	1000 PNU/mL	0.05	
			0.10	
			0.15	
			0.20	
			0.30	
			0.40	
			0.50	
	1:100	10,000 PNU/mL	0.05	
			0.10	
			0.15	
			0.20	
			0.30	
			0.40	
			0.50	

From Grammer IC, Shaughnessy MA: Principles of immunologic management of allergic diseases due to extrinsic antigens. In Patterson R, Grammer LC, Greenberger PA, et al (eds): Allergic Diseases: Diagnosis and Management, ed 4. Philadelphia, JB Lippincott, 1993, p 264; with permission.

Venom and Fire Ant Immunotherapy

Patients treated with pure venom extracts are usually given each venom to which sensitivity has been documented, regardless of the insect suspected to have caused the reaction.⁵⁷ White-faced hornet, yellow hornet, and yellow jacket venoms cross react immunologically and are available commercially in a mixed vespid preparation for administration. Each of these venoms is also available in individual preparations. Honey bee venom does not cross react with the above venoms and is

given in a separate venom preparation when indicated. The techniques of administration are the same as those for inhalant extracts.

Testing for imported fire ant sensitivity is indicated in a clinical situation that usually differs from those of the other Hymenoptera. It is not advisable to test for imported fire ant sensitivity when evaluating for venom sensitivity unless there is a historical reason to suspect sensitivity to the imported fire ant.

Dosage Schedule

Various schedules have been suggested for the administration of venom immunotherapy (Table 3). Due to the unpredictability of life-threatening reactions to Hymenoptera stings, an accelerated immunotherapy schedule is often used. Using this accelerated schedule, giving several injections each day, expedites reaching a maintenance dose of each venom employed. One hundred micrograms of each venom provides the equivalent of two or more natural stings. Some investigators have reported that 50 μg of each venom may be adequate. The maintenance dose is administered at 4- to 6-week intervals. Imported fire ant immunotherapy is usually administered following a schedule similar to that of inhalant immunotherapy.⁴⁷

Duration of Venom or Imported Fire Ant Immunotherapy

There is no consensus to define guidelines concerning the optimal duration of immunotherapy for Hymenoptera hypersensitivity. Various investigators have proposed and presented data supporting three approaches: (1) measure the specific IgG to the venom used and discontinue immunotherapy when a concentration of 5 $\mu\text{g}/\text{mL}$ or more is reached,¹⁶ (2) repeat the measurement of specific IgE by either in vitro or skin testing and discontinue when the level decreases from the initial value or disappears,³⁹ and (3) discontinue without testing after immunotherapy has been given for a time period of 3 to 5 years.⁴² It is possible that all of these approaches have clinical use. Application of clinical judgment with use of some of the aforementioned guidelines is generally the best course of action.

Other Forms of Immunotherapy

Local Nasal Aeroallergen Immunotherapy

Local nasal aeroallergen immunotherapy is an alternative form of immunotherapy using an aqueous solution of allergen to spray on the nasal mucoia at specified time intervals.⁵¹ The primary side effects (pruritus, congestion and sneezing) are of sufficient severity in some subjects to result in discontinuation. Sufficient long-term trials are not yet available to permit recommendation of this form of immunotherapy.

Table 3. SELECTED DOSAGE REGIMENS FOR VENOM IMMUNOTHERAPY

Day	Week	Slow	Step	Moderate Rush	Rush	Rapid
1	0	0.01	1	1	0.001	0.05
			5	5	0.01	0.10
			10	10	0.1	0.20
						0.40
						0.80
						2
						5
						10
						20
						20
2		—	—	—	1	—
					5	
3		—	—		10	60
					20	
7		—	—	—	—	70
8	1	0.03	25	—	20	—
					30	
9	—	—	—		50	—
			—		50	
15	2	0.1	—	30	100	—
21	3	0.25	25	—	—	80
28	4	0.5	—	60	100	—
35	5	1.0	25	—	200*	100*
42	6	2.5	50	100		
49	7	5	—	—		
56	8	10	50	100		
63	9	20	—	—		
70	10	30	50	—		
77	11	40	100	100		
84	12	60	—	—		
91	13	80	100	—		
98	14	100	—	—		
105	15	100	100	100*		
112	16	—	—			
119	17	100	—			
126	18	—	100*			
133	19	—				
140	20	100*				

*Data from Golden DK, Valentine MD, Kagey-Sobotoka A, et al: Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 92:621, 1980; Bousquet J, Knani J, Velasquez G, et al: Evolution of sensitivity to Hymenoptera venom in 200 allergic patients followed for up to 3 years. *J Allergy Clin Immunol* 84:94, 1989; and Bernstein DI, Mittman RJ, Kagen SL, et al: Clinical and immunologic studies of rapid venom immunotherapy in Hymenoptera-sensitive patients. *J Allergy Clin Immunol* 84:952, 1989.

Oral aeroallergen immunotherapy with birch pollen extract has been shown to be efficacious.⁶ A double-blind placebo-controlled trial of sublingual standardized cat immunotherapy for the treatment of asthma demonstrated no benefit.³¹ Oral immunotherapy is of uncertain efficacy, and additional studies are needed.

Alum-Precipitated Allergen Extracts

Modification of aqueous extracts by precipitation of proteins with aluminum hydroxide results in a product that produces fewer systemic reactions than aqueous allergen extracts.¹⁸ This modification permits a more rapid increase in the dosage of the treatment, and fewer total injections are required before benefits are realized. Ragweed, cat, and grass alum-precipitated extracts have been studied and found to have the equivalent efficacy of aqueous extracts. Systemic reactions are decreased; rarely, some patients experience a prolonged local reaction following administration of alum-precipitated extracts.⁵¹

Prior to alum precipitation, allergens can be extracted with pyridine to further reduce the potential for systemic reactions following administration. Alum-precipitated pyridine grass extracts have been shown to be efficacious, but other allergens such as ragweed are denatured by the pyridine treatment and rendered ineffective.⁵¹ The use of alum-precipitated pyridine extracts is limited and largely unproven.

Modified Aeroallergen Extracts

Aggregation of the proteins of an aqueous extract reduces the allergenicity while preserving the immunogenicity of the product. Two methods of modification have accomplished this goal: formalin-treated allergens (allergoids) and glutaraldehyde-treated allergens (polymerized allergen extracts).²⁶ Regimens using these extracts permit completion of an immunotherapy program with 10 to 15 injections with a less than 1% occurrence of systemic reactions.¹⁷ One trial of immunotherapy with polymerized extracts demonstrated clinical improvement lasting at least 4 years following a course of treatment.¹⁴ The possibility of long-term side effects has hindered commercial development of this form of antigen.

Adverse Effects of Immunotherapy

Because the substance administered to the patient during immunotherapy has been proven to cause sensitivity to that patient, there is a risk that an adverse reaction can occur. The risk of significant adverse reactions is low, ranging from 0.05% to 3.5% per injection.⁴⁸ Most of these adverse events are systemic manifestations of hypersensitivity such as asthma, urticaria, laryngospasm, hypotension, and angioedema. The American Academy of Asthma, Allergy, and Immunology has collected and published retrospective data on deaths following immunotherapy

in the United States.⁴⁰ Data were obtained for 24 fatalities following immunotherapy between 1945 and 1984, for 17 between 1985 and 1989, and for 10 from 1990 through most of 1991. The majority of these patients were "highly sensitive," and most had asthma. The cause of death in almost all of the subjects with asthma was respiratory with or without anaphylactic shock. Neither the initial signs and symptoms of the systemic reaction nor the history of previous reactions to immunotherapy was predictive of fatality.

The Executive Committee of the Academy has issued a position statement stating that immunotherapy must be administered in a medical facility by carefully trained personnel who are able to recognize, assess, and treat anaphylaxis.⁵

Recognition of Reactions

Local Reactions

Most patients receiving immunotherapy with extracts of aeroallergens at some time have small areas of redness and swelling at the site of the injection that produce little discomfort and are of no concern. These reactions are to be distinguished from large local reactions 4 cm or greater in diameter that may cause considerable discomfort, may persist for 24 hours or longer, and may be associated either with a systemic reaction or create concern that a further increase in dosage may cause a systemic reaction.⁵¹ Treatment consists of applying cold compresses, giving oral antihistamine, and reduction of the immunotherapy dose.

Vasovagal Reactions

These must be differentiated from anaphylactic reactions. With vasovagal reactions, low blood pressure is associated with an abnormally slow pulse rather than with an abnormally fast pulse. Cold or warm skin and perspiration may be present. There is no urticaria or angioedema. No medication is indicated for treatment. The patient usually responds promptly once in a recumbent position. No dose modifications are indicated.

Systemic Reactions

The manifestations range in severity from a few hives to severe anaphylaxis and include the following systemic reactions:

- Flushing, sensation of warmth, diaphoresis
- Urticaria; intense itching of palms, soles of feet, or scalp
- Fullness or "lump" in throat
- Chest tightness, wheezing, dyspnea
- Feeling of impending doom

- Rhinitis, sneezing
- Paroxysmal coughing, stridor, dysphonia
- Nausea, vomiting, dizziness, fainting
- Tachycardia, hypotension
- Angioedema, conjunctivitis
- Metallic taste in mouth
- Uterine cramping

Generally, urticaria or angioedema may occur. Swelling of the tongue, throat, or lower airway can impair breathing and swallowing. Typical manifestations of hypovolemic shock may occur, including cold damp skin, rapid pulse, and low blood pressure. Eye itching and tearing, nasal congestion and discharge, sneezing, coughing, wheezing, and dyspnea may occur. The reaction usually begins within 15 minutes of the injection; however, the reaction may be delayed from 30 minutes to 6 hours after the injection.³⁻⁵

Treatment includes:

1. Putting patient in a recumbent position to maintain blood flow to the head.
2. Injecting aqueous epinephrine at a 1:1000 ratio subcutaneously (0.3–0.5 mL for adults, 0.01 mL/kg of body weight or 0.3 mL/m² of body surface area for children).
3. Providing reassurance.

These three maneuvers should be accomplished nearly simultaneously and as rapidly as possible. Improvement usually begins promptly. The availability of intravenous fluids, oxygen, corticosteroids, and cardiopulmonary resuscitation and tracheal intubation equipment is important for further treatment. The American Academy of Asthma, Allergy, and Immunology has published the following recommendations³⁻⁵:

1. The patient should be observed for at least 20 minutes after the injection.
2. Office or clinical personnel should be familiar with adjustment of the dose of allergenic extract so as to minimize reactions, recognition and treatment of local reactions, recognition and treatment of systemic reactions, and basic cardiopulmonary resuscitation.
3. Available equipment and reagents should include a stethoscope and sphygmomanometer, tourniquets, syringes, hypodermic needles, aqueous epinephrine hydrogen chloride at a 1:1000 ratio, equipment for administering oxygen by mask, an oral airway large-bore needle (14-gauge) for tracheotomy, equipment for administering intravenous fluids, diphenhydramine or a similar antihistamine, aminophylline for intravenous injection, and corticosteroids for intravenous injection.

The prompt recognition of systemic reactions and the immediate use of epinephrine are considered by the Academy to be the mainstays of therapy.

Table 4. CIRCUMSTANCES UNDER WHICH THE FREQUENCY AND SEVERITY OF SYSTEMIC REACTIONS MAY INCREASE

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1. Early months of immunotherapy when doses are being increased
 - a. Effective dose near highest tolerated dose
 - b. Large local reactions indicate need to reduce dose
 2. Errors in magnitude of dose
 - a. Patient incorrectly identified
 - b. Extract incorrectly identified
 - c. Dilution incorrectly identified
 - d. Dose incorrectly identified
 3. Intravenous administration of dose
 4. History of previous systemic reaction
 5. Patient highly sensitive
 6. Vigorous exercise just before/after injection
 7. New extract substituted
 8. Concomitant use of drugs that block β -adrenergic receptors
 - a. Increased incidence of systemic reactions
 - b. Interference with treatment of systemic reactions with epinephrine
 - c. Interference with decisions about need for immunotherapy
 9. Presence of the start of a new illness or of fever
 10. Presence of uncontrolled asthma
 11. Natural exposure to a component allergen in the extract (e.g., grass pollen exposure in a patient receiving grass extract)
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Adapted from Van Metre Jr TE: Immunotherapy for aeroallergen disease: Circumstances under which the frequency and severity of systemic reactions may increase. In Middleton E, Reed CE, Ellis EF, et al (eds): Allergy: Principles and Practice, vol 2, ed 4. St. Louis, Mosby-Year Book, 1993, p 1501; with permission.

Personnel who administer immunotherapy should be aware of the circumstances under which the frequency and severity of systemic reactions may increase (Table 4) and of methods to exercise caution and prevent reactions from immunotherapy.

SUMMARY

Allergen immunotherapy is an effective modality for patients with allergic rhinitis, allergic asthma, and stinging and biting insect hypersensitivity. An effective dose of allergen is necessary to achieve the desired reduction of symptoms, but it is essential to balance the risk of anaphylaxis with the need to relieve symptoms. The allied health caregiver plays an important role in the "hands on" administration of immunotherapy and in the prevention and recognition of symptoms of adverse reactions as well as the knowledge of how to initiate expedient treatment of adverse reactions.

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