

ADVERSE EFFECTS OF ALLERGEN IMMUNOTHERAPY

Assessment and Treatment

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Allergen vaccines modify or down-regulate the immune response to specific allergic stimuli and complement environmental control measures and medications in the management of allergic respiratory disease. Effectiveness depends on the administration of appropriate doses of clinically relevant allergens. Low-dose immunotherapy is generally ineffective, whereas excessive doses may produce an unacceptably high frequency of local or systemic reactions.

Subcutaneous injection of allergen vaccines is the primary method of administering immunotherapy for the treatment of allergic respiratory diseases. The inconvenience of frequent injection visits, injection-associated discomfort, and the possibility of adverse reactions, however, have prompted the exploration of local immunotherapy for delivering allergen vaccines sublingually, orally, nasally, and bronchially (Table 1). A potential advantage of administering allergens topically is the possibility of directly modifying the immune system in the allergic target organ while simultaneously exerting a systemic effect.⁸⁴

This article reviews local and systemic reactions associated with immunotherapy (i.e., subcutaneous injection and local application), including risk factors, appropriate treatment, and preventive strategies.

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Table 1. LOCAL ALLERGEN IMMUNOTHERAPY*

Route	Description
Oral	Patient immediately swallows vaccine (prepared as drops, capsules, or tablets).
Sublingual-swallow	Patient holds the vaccine sublingually for 1–2 min and then swallows it.
Sublingual-spit	Patient holds the vaccine sublingually for 1–2 min and then spits it out.
Nasal	Appropriate devices deliver the vaccine (aqueous or powdered) into the nose.
Bronchial	Appropriate devices deliver the vaccine (aqueous or powdered) into the bronchi.

*Noninfective routes of specific immunotherapy that have been evaluated in double-blind, placebo-controlled studies.

From Bousquet J, Lockey RF, Malling H-J (eds): World Health Organization Position Paper: Allergen immunotherapy: Therapeutic vaccines for allergic diseases. *Allergy* 53(suppl):1–42, © 1998 Munksgaard International Publishers Ltd. Copenhagen, Denmark; with permission.

ADVERSE REACTIONS

IgE-Mediated Reactions

The interaction of specific IgE antibody with the allergen(s) contained in immunotherapy vaccine may induce the release of chemical mediators, thereby causing local or systemic reactions. Most reactions occur in 15 to 30 minutes, but some reactions may occur after 30 minutes. *Local reactions* occur at the injection site and may be divided into those that develop within 15 to 30 minutes and those that develop more than 30 minutes after an injection. Erythema, pruritus, localized edema, and discomfort are typical. Such reactions may necessitate adjustments in vaccine dosage before subsequent injections.

Subcutaneous nodules, which occur at the site of injection, are more commonly associated with aluminium-precipitated vaccines.²⁶ These nodules generally disappear and do not necessitate an adjustment in the immunotherapy dosage. Aluminum-free preparations should be used in individuals who develop persistent nodules.²⁷

Local reactions to local/topical immunotherapy occur in the region where the allergen contacts the mucosal surface. For example, oral immunotherapy may cause mouth itching, abdominal cramps, or diarrhea, and nasal immunotherapy may cause rhinitis or nasopharyngeal irritation.

In his initial description of immunotherapy in 1911,⁵² Leonard Noon wrote, "In the early stages of immunization it is possible, by an overdose, to induce a severe attack of hay fever lasting nearly 24 hours. . ." He described a systemic reaction. *Systemic reactions* (including anaphylaxis) usually begin within a few minutes after an immunotherapy injection, and are characterized by the following signs and symptoms, alone or in combination: diffuse erythema, pruritus, urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, laryngeal edema, hyperperistalsis, hypo-

tension, and cardiac arrhythmias.³⁸ These reactions rarely may develop more than 30 minutes after an injection. Systemic reactions necessitate the re-evaluation of an individual's immunotherapy regimen.

IgE-Independent Adverse Reactions

IgE-independent reactions associated with immunotherapy injections also have been reported and many are controversial. Immune complex disease,^{11, 13, 39, 54, 69} serum sickness,⁸¹ contact dermatitis,¹⁴ brachial plexus neuropathy⁸⁵ and "nonorganic" disease⁶⁵ have been investigated.

Phanuphak and Kohler⁵⁴ reported that 6 of 20 consecutive patients with polyarteritis nodosa (PAN) were receiving allergen immunotherapy at the time of the onset of their vasculitic symptoms, suggesting immune complex disease. When compared with the 14 other patients with PAN, the six receiving immunotherapy had statistically significant increases in cutaneous disease and peripheral eosinophilia. Evidence of circulating immune complexes with decreased hemolytic complement, increased cryoglobulins, or increased C1q-binding was present in all 20 patients. The authors, however, reported that no antiallergen precipitating antibodies were detected in the six patients receiving immunotherapy and less than 16 mg of allergen had been injected in five of these six patients.

Stein and others reported that 50 patients receiving maintenance dosages of immunotherapy for allergic rhinitis had no statistically significant increases in C1q-binding immune complexes, complement consumption, rheumatoid factor, or cryoglobulinemia compared with two control groups (one group was nonallergic volunteers and another consisted of patients with allergic rhinitis not receiving immunotherapy).⁶⁹ Similarly, 41 patients between 18 and 50 years of age who received immunotherapy for 5 or more years as treatment of allergic rhinitis or asthma had no increase in C1q-binding immune complexes, complement consumption, or rheumatoid factor compared with an age- and gender-matched control group.³⁹

Busse and colleagues¹¹ addressed the possible role of allergen-precipitating antibodies (precipitins) in a prospective study of adverse reactions associated with immunotherapy. Of 23 *Alternaria*-sensitive patients, five had IgG precipitins before immunotherapy and another six developed them during therapy. Only one of the 23 patients experienced an adverse reaction 4 to 6 hours after an injection of *Alternaria* vaccine. The investigators concluded that precipitins to *Alternaria* are common, do not appear to cause late-phase allergic reactions, and do not contraindicate immunotherapy.

Another study evaluated immune complex disease during venom immunotherapy. Clausen and Yanari¹³ prospectively evaluated 30 adult and 15 pediatric patients receiving monthly maintenance doses of Hymenoptera venom (100 µg of venom) for 9 to 12 months. No patients developed manifestations of immune complex disease, and four of the 45 patients had elevated Raji cell assays, suggesting the presence of

immune complexes prior to venom administration. There was no change in Raji cell determinations 12 hours after injection. The investigators concluded that maintenance venom immunotherapy does not seem to be associated with immune complex disease.

Umetsu and colleagues⁸¹ described an 8-year-old boy who developed serum sickness as a complication of anaphylaxis associated with immunotherapy to inhalant allergens (i.e., pollens, molds, and dust). He had previously tolerated his immunotherapy for 2 years with only minor local reactions. One hour after injection, he developed puffy eyes that progressed over 3 hours to urticaria and tightness of the throat and chest. He had biphasic anaphylaxis with a recurrence of anaphylaxis 5 hours after discharge. The systemic reaction progressed to generalized urticaria followed by a hemorrhagic, palpable rash, angioedema, bronchospasm, fever, arthralgias, cervical lymphadenopathy, splenomegaly, leukocytosis, hyponatremia, proteinuria, and delirium. A skin biopsy revealed perivascular infiltrates of lymphocytes and a few neutrophils. The authors hypothesized that the enhanced vascular permeability accompanying the systemic reaction may have permitted the intravascular deposition of pre-existing immune complexes. Tests for these immune complexes were negative and complement determinations were normal. Acute phase reactants, such as haptoglobin, however, were elevated and the authors speculated that normal complement concentration was the result of an increase, owing to the acute phase response, followed by consumption from the presumed immune complexes.

Clemmensen and Knudsen¹⁴ described a patient with eczema, who apparently developed contact sensitivity to aluminium while receiving allergen immunotherapy with aluminium-precipitated grass allergen. Patch testing revealed a positive test to aluminium disks and negative tests in 53 controls. Intradermal testing with aluminium was positive in the subject and negative in nine controls. The dermatitis resolved after discontinuation of immunotherapy injections.

Wolpow⁸⁵ described two patients that developed acute, transient, unilateral brachial plexus neuropathy in association with dust and mold immunotherapy. The author also discussed previous cases of injection-associated neuropathy, some of which followed injection of foreign proteins or *nonproteinaceous* agents, such as penicillin or heroin.

Schatz and colleagues⁶⁵ described 10 patients who developed adverse reactions after immunotherapy that resembled immune reactions but were thought to be "nonorganic" in origin. Six of these patients had coexisting psychiatric illnesses, particularly "hysterical or hypochondriacal personality traits," and the remaining four patients were considered likely to have psychiatric illness. These reactions occurred in younger patients (mean age, 33 years), at relatively low-allergen dosages, and with minimal or no objective findings. Some patients were able to resume and tolerate their injections after the investigators explained the nature of the reactions.

FREQUENCY OF SYSTEMIC REACTIONS

Injection Immunotherapy

The incidence of adverse reactions during allergen immunotherapy reported retrospectively and prospectively vary considerably depending on the type of vaccine preparation, the patients selected, the treatment schedule observed, the use or omission of premedication, and other factors. Stewart and Lockey⁷⁰ reviewed systemic reactions associated with immunotherapy in 38 studies. The percentage of patients experiencing one or more systemic reactions ranged from 0.8% to 46.7% for conventional dosage schedules (mean 12.92%, standard deviation [SD] 10.8%). Systemic reactions per injection during buildup occurred in 0.05% to 3.2% of patients (mean 0.5%, SD 0.87%). All but one study reported rates per injection of 0.6% or less. Twenty-three studies of rush or accelerated immunotherapy schedules also were reviewed. The percentage of patients experiencing one or more systemic reactions during the maintenance phase of immunotherapy ranged from 0% to 21.1% (mean 4.77%, SD 6.47%). The number of systemic reactions, however, was higher during buildup when the interval between injections was reduced (rush or semirush protocols). Patients experiencing one or more systemic reactions ranged from 0% to 66.7% with these accelerated schedules (mean 21.33%, SD 17.86%). These protocols were associated with rates of systemic reactions per injection ranging from 0% to 6.4% (mean 2.36%, SD 1.7%).

Two additional studies monitored nearly 10,000 patients during both buildup and maintenance allergen immunotherapy.^{40,76} Systemic reactions occurred in 2.1% of patients over 1 year,⁷⁶ and in 2.9% of patients over a 13-year observation period.⁴⁰ The usual maintenance dosage was 2,400 protein nitrogen units (PNU)/allergen⁴⁰ or 1:100 w/v of allergenic material.⁷⁶ Reactions were more frequent during the initial buildup.⁴⁰

Matloff and colleagues reported that 27,806 injection visits in a large health maintenance organization (HMO) resulted in 143 systemic reactions (0.51%).⁴⁵ Fifty-seven percent of these systemic reactions occurred at vaccine concentrations of 1000–10,000 PNU/mL.

In a similar analysis, Wells⁸³ reported that 22 systemic reactions (0.02%) occurred in 104,101 injection visits over 1 year. Reactions also were more common during buildup phase. The author attributed his low incidence of systemic reactions to a lower initial dose, more gradual buildup phase, more frequent maintenance injections, lower maintenance dosages or some combination of these factors.

Toubi and colleagues⁷⁸ reported that 37 (13%) of 280 patients receiving immunotherapy injections (pollens, mites, venoms) experienced systemic reactions during a 3-year prospective study in Israel. Twenty-six (70%) of the systemic reactions occurred during the buildup phase. The maintenance dosage for pollens, mites, and Hymenoptera venoms were 0.5 mL of a 1:100 or 1:200 w/v dilution, 300 to 600 allergen units (AU)/injection, and 50 to 100 µg/injection, respectively.

Local Immunotherapy

Two double-blind, placebo-controlled studies have reported urticaria in patients receiving oral immunotherapy with high doses of allergen vaccine.^{48, 75} Other controlled studies^{16, 28, 47, 53, 74} have observed no severe side effects and no significant differences in side effects compared with placebo. Some mild gastrointestinal side effects occurred in several studies, but discontinuation of oral immunotherapy was not necessary.

Doses of allergen used in controlled studies of sublingual immunotherapy (i.e., sublingual-swallow or sublingual-spit methods)* are usually at least 5 to 20 times greater than the doses required for efficacy with injection immunotherapy.⁶⁴ These studies have reported no side effects in adult patients, and most of these studies have observed no appreciable difference in side effects compared with placebo. Tari and colleagues,⁷² however, reported urticaria and/or asthma in some of their pediatric patients. Similarly, Di Rienzo and colleagues²⁰ reported mild systemic side effects (i.e., urticaria, rhinitis, conjunctivitis, and abdominal pain) in eight (3%) of 268 children treated with sublingual immunotherapy.

A high frequency of reactions (i.e., rhinitis) occurred in initial trials of nasal immunotherapy using aqueous allergen vaccines.⁵ Dry-powder vaccines are comparable to aqueous vaccines when used intranasally in efficacy and have fewer side effects. D'Amato and colleagues,¹⁹ however, reported asthma after the administration of nasal vaccines. Pretreatment with a nasal preparation of cromolyn sodium may reduce nasal side effects.³²

Two controlled clinical trials evaluated the efficacy of bronchial immunotherapy with vaccines of domestic (house dust) mites.^{18, 73} These studies reported that bronchospasm developed after allergen vaccine administration in most of the patients in the active treatment group.

FATALITIES ASSOCIATED WITH IMMUNOTHERAPY INJECTIONS

Three studies^{41, 59, 60} suggest that fatalities from allergen immunotherapy occur at an approximate rate of 1 per 2 million injections. The physicians in these surveys, however, included only members of the American Academy of Allergy, Asthma, and Immunology. Therefore, the prevalence of fatalities resulting from immunotherapy administered by physicians that are not specially trained in the practice of allergy and immunology remains unknown. These studies together evaluated 91 fatalities from immunotherapy and skin testing between 1945 and 1995. Most of the immunotherapy fatalities occurred from reactions that developed within 20 minutes of the injection. Patients with asthma or with high levels of allergen-specific IgE were more likely to die from anaphylaxis. Patients who were symptomatic, especially with asthma, at the

*References 9, 12, 20, 23, 24, 50, 57, 58, 61, 62, 64, 72, 79, and 82.

time of the injection or who were in their "allergy season" also were at increased risk. Errors in vial selection, especially when advancing to the next vial, and mistakes in dosage or administration were important causes of preventable anaphylaxis and subsequent fatality in these surveys. The most recent study in the series⁵⁹ observed no seasonal predilection for fatalities and no single, predictive risk-factor. Data were incomplete in nine (30%) of the 28 fatalities reviewed in this 1996 abstract. Twenty-seven of the 28 fatalities occurred after immunotherapy injections. The other fatality discussed in the report was associated with skin testing. Four of the immunotherapy-associated fatalities occurred when injections were administered at home or without a physician present, 19 occurred in asthmatic individuals, three were associated with an improper dosage, and five occurred despite emergency treatment for anaphylaxis. Data in this study are similar to previous reports.

The British Committee on the Safety of Medicines reported in 1986 that 26 fatalities from allergen immunotherapy had occurred in the United Kingdom since 1957.¹⁵ All died from immunotherapy vaccine-induced bronchospasm and/or anaphylaxis, five during the 18 months preceding the report. Two of the fatalities developed their first symptoms more than 30 minutes after injection.

Lüderitz-Püchel, May and Haustein⁴³ analyzed 28 of 48 immunotherapy-related fatalities reported to the Paul Ehrlich Institute by Germany and other European countries from 1977 to 1994. Three additional patients experienced hypoxic brain injury following anaphylaxis. In 23 of the 28 fatalities investigated, the authors could not exclude medical error and/or inadequate information provided to the patients as contributory factors to fatal anaphylaxis. Common errors included mistakes in dosage and administration of allergen vaccines and failure to adhere to the recommended 30-minute period of observation following injection.⁴³

RISK FACTORS FOR ADVERSE REACTIONS

Risk factors for allergen immunotherapy are summarized as follows:

- Errors in dosage
- Presence of symptomatic asthma, especially in children for whom bronchospasm may be more difficult to control
- High degree of hypersensitivity (by skin tests or specific in vitro IgE measurements)
- Use of β -blockers
- Accelerated or "rush" administration schedules (greater risk in children)³³
- Injections from new vials
- Injections made during periods of exacerbation of asthma or rhinitis

Risk Factors Based On Nonfatal Systemic Reactions

Most nonfatal systemic reactions associated with immunotherapy begin within 15 to 20 minutes, regardless of whether conventional or accelerated dosage schedules are followed.⁷⁰ Some systemic reactions, however, begin 30 to 60 minutes after the vaccine injection.³¹ Large local reactions do not predict subsequent systemic reactions.⁴⁹

Asthma appears to be a significant risk factor for both fatal and nonfatal systemic reactions.^{34, 71} Symptomatic asthma and a forced expiratory volume in one second (FEV₁) less than 70% of the predicted value are risk factors for developing bronchospasm following an immunotherapy injection. Asthmatic patients also tend to have more severe systemic reactions than individuals without asthma.^{7, 8, 17}

Medications may either prevent or potentiate systemic reactions. Some evidence suggests that there is a threefold greater incidence of systemic reactions in patients receiving allergen immunotherapy and β -adrenergic blocker therapy.⁴⁹ In contrast, a 1-year, prospective study of 3178 patients receiving allergen immunotherapy reported no statistical difference in the incidence of systemic reactions between patients who took β -blockers throughout the study period and those who did not. The authors, however, recommended alternatives to immunotherapy in patients taking β -blockers because of the risk of severe symptoms and the poor response to medications if a systemic reaction should occur following an injection.³⁵ Profound hypotension, severe bronchospasm, and paradoxical bradycardia that persist despite treatment with epinephrine may characterize these attacks. Dosage increases of β -agonists up to 80-fold are necessary experimentally to overcome β -receptor blockade.⁷⁷

The 2000 *Physicians' Desk Reference*⁵⁵ contains prescribing information for 10 ACE inhibitors. All warn of the potential for systemic reactions when prescribed to individuals receiving venom immunotherapy. Investigators have reported that angiotensin II levels increase as a compensatory physiologic response to intravascular volume shifts in anaphylaxis. Serum angiotensin II concentrations are low in patients allergic to Hymenoptera venom and increase following Hymenoptera venom immunotherapy (reviewed in reference).³⁷ Tunon-de-Lara and colleagues⁸⁰ reported two venom-allergic patients who experienced systemic reactions from venom immunotherapy injections while receiving the ACE inhibitor, enalapril. No systemic reactions were observed when ACE inhibitors were withheld before immunotherapy injections, but they recurred when enalapril was restarted. No systematic studies have been conducted to evaluate the potential risk of ACE inhibitors in patients receiving venom immunotherapy. Kemp and Lieberman³⁷ proposed further collection of epidemiologic data to prove or disprove the possible association between these agents and anaphylaxis. Clarification of the risk is particularly important because the usage of ACE inhibitors is increasing. Practice parameters for anaphylaxis recommend cautious administration of immunotherapy to patients receiving ACE-inhibitor therapy and the preference of changing the ACE inhibitor to an alternative medication.³⁶ However, again more data are

necessary to confirm that ACE inhibitors could be problematic with any form of immunotherapy.

Conversely, two studies have reported that premedication with methylprednisolone, ketotifen (an oral mast cell stabilizer not commercially available in the United States), and a long-acting theophylline preparation can decrease the incidence of systemic reactions following allergen immunotherapy injection.^{33, 34} Other studies have demonstrated that premedication with antihistamines (H_1 -antagonists with or without H_2 -antagonists) reduces the rate of systemic reactions.^{4, 10, 51} Portnoy and colleagues also have suggested that premedication with a combination of corticosteroids and H_1 - and H_2 -antagonists reduces the risk of systemic reactions during accelerated immunotherapy schedules.⁵⁶

The American Academy of Allergy, Asthma, and Immunology prospectively studied 1410 Hymenoptera-allergic patients for side effects of venom immunotherapy.⁴² Systemic reactions occurred in 12% of patients. The incidence of pruritus and urticaria/angioedema did not vary appreciably with the severity of the reaction. Moreover, severity of the systemic reaction had no correlation with the severity of previous insect sting reactions, the historic severity of a systemic reaction following venom skin testing, the total venom dose administered, or the degree of skin-test reactivity. Most systemic reactions occurred during buildup dosages between 1 and 50 μ g and at maintenance (100 μ g). Honeybee or *Polistes* (wasp) venoms were the most common cause. This survey did not include imported fire-ant immunotherapy.

Risk Factors Based On Fatal Reactions

Of the 46 fatalities associated with skin testing and immunotherapy injections between 1945 and 1984, Lockey and colleagues⁴¹ determined that 30 had sufficient data for analysis. Six of the 30 fatalities were associated with skin testing and the remaining 24 were associated with immunotherapy injections. Identified risk factors included uncontrolled asthma, greater allergen sensitivity, and concomitant use of β -blockers. The 24 patients ranged in age from 7 to 70 years (mean age, 34 years). Fifteen (62%) of the 24 patients developed symptoms within 20 minutes, three (12%) had symptoms within 20 to 30 minutes, and two patients (8%) had onset of symptoms more than 30 minutes after receiving their fatal immunotherapy injections. Data concerning the onset of symptoms were not available for the remaining four patients. Reid and colleagues⁶⁰ reported an additional 17 fatalities associated with immunotherapy injections from 1985 to 1989. Sixty-five percent of these patients were in the buildup phase of immunotherapy. These reports^{41, 60} identified additional risk factors for death. These risk factors included changing to a new vial of unstandardized allergen vaccine, mistakes in vaccine dosage, not waiting sufficient time under medical observation after injection, and home administration of vaccines. The cause of death in most patients was airway obstruction. Other reports of immunotherapy fatalities provide similar data^{15, 43, 59}

PRECAUTIONS AND PREVENTIVE STRATEGIES DURING IMMUNOTHERAPY

Several guidelines have been published in an effort to minimize the risk of anaphylaxis and death.^{1, 6, 8, 30, 44, 84} Each emphasizes the importance of thorough training of all individuals in the administration of immunotherapy vaccines, and the prompt recognition and appropriate treatment of systemic reactions. Use of standardized vaccines is strongly encouraged. Patients should be informed prior to receiving immunotherapy of the risk of potential adverse reactions (including death), and the factors that influence these reactions. No allergenic vaccine, regardless of the planned route of administration, should be considered absolutely safe for an individual allergic to its constituents. Therefore, immunotherapy injections should be administered only by trained personnel, who know how to adjust dosages properly and treat local and systemic reactions, in a setting properly equipped for the immediate management of such reactions.

No recommendations have been issued for local immunotherapy because of the relative lack of controlled safety data. Further data are needed. Bronchial immunotherapy, however, appears to be associated with a high incidence of bronchospasm and alternatives to this route of administration are likely advisable.

Conditions proposed as relative contraindications to injection immunotherapy include poor medical compliance, severe psychiatric disorders, serious concomitant immunopathologic conditions (e.g., vasculitis), malignancy, and treatment with β -blocking agents, regardless of the route of drug administration.^{8, 84}

The most severe adverse reactions tend to develop soon after an immunotherapy injection. All patients in one study⁷⁶ developed systemic reactions within 30 minutes, whereas another study reported that all severe reactions occurred within 60 minutes of injection.³¹ A third study, however, reported the occurrence of severe symptoms in some patients more than 2 hours after injection.⁴⁵

Patients whose FEV₁ is less than 80% of predicted are particularly susceptible to bronchospasm following immunotherapy. On this basis, Bousquet and others have recommended that immunotherapy injections should not be administered to patients whose FEV₁ is less than 70% of predicted.⁸ Therefore, measurement of peak expiratory flow rate (PEFR) may be appropriate in some patients before injection and before the injected patient's departure from medical observation.

Patients receiving immunotherapy should be required to wait 20 to 30 minutes after their injections because most fatal reactions begin within this period.^{41, 59, 60} A position statement of the American Academy of Allergy, Asthma, and Immunology has proposed a 20-minute waiting period with the additional recommendation that this waiting period "may be extended for high-risk patients."²² Longer waiting periods may be required for individuals receiving accelerated or "rush" immunotherapy injections, labile asthma, marked allergen hypersensitivity, high-

dose immunotherapy, a history of systemic reactions to immunotherapy, or another condition considered by the prescribing physician to increase the risk for systemic reactions.

The World Health Organization position paper on immunotherapy considers the 20-minute waiting period to be adequate for conventional immunotherapy schedules.⁸⁴ The European Academy of Allergology and Clinical Immunology recommends a 30-minute waiting period.⁴⁴ The British Society of Allergy and Immunology, however, has proposed a much longer waiting period of 60 minutes, with further extension of this period if a patient experiences any generalized symptoms, however mild, following an immunotherapy injection.¹ This British position paper updates the 1986 recommendations by the Committee on Safety of Medicines that medical observation after injections should last at least 2 hours.¹⁵ These recommendations essentially curtailed the use of immunotherapy in the United Kingdom.

Home administration of immunotherapy injections is discouraged because it removes patients from settings where trained medical personnel are available to treat potential systemic reactions. Additional precautions for the safe administration of immunotherapy injections include monitoring patients to ensure that they remain in the clinical area throughout the waiting period; questioning patients before each injection to verify that he/she has not initiated since the last visit any medications, such as β -blockers or drugs (e.g., monoamine oxidase inhibitors) that have harmful interactions with epinephrine, that will potentially increase the risk of immunotherapy; providing adequate instructions and guidance to physicians and their staffs who administer vaccines prescribed by the allergist-immunologist at another office or clinic; and requesting that female patients notify their physicians immediately if they become pregnant while receiving immunotherapy.

Two studies of 171 women evaluated the safety of immunotherapy during pregnancy.^{46, 66} These studies observed that the incidence of prematurity, abortion, perinatal mortality, congenital anomalies, and toxemia was no greater than in control groups of allergic women not receiving allergen immunotherapy.

Glovsky and others²⁹ studied the effects of specific allergen immunotherapy during pregnancy on 14 children (average age, 7 years), 3 to 12 years after parturition. Fourteen additional children from the same allergic mothers, who did not receive immunotherapy during the gestation periods of these children, served as controls. The control group had more positive skin tests than the group whose mothers had received immunotherapy, and the results were statistically significant for tests to grass-pollen vaccines.

Systemic reactions occurring during pregnancy can have dire consequences. Epinephrine has potentially harmful vasoconstricting effects on the uteroplacental circulation.² A report and accompanying discussion reviews the case of a 34-year-old woman who experienced an abortion following a systemic reaction that began 2 hours after receiving an injection of grass-pollen vaccine.⁶³ For these reasons, many allergist-

immunologists are cautious in pregnant patients, recommending reductions in maintenance immunotherapy dosages, avoiding any increases in dosage during buildup or delaying initiation of immunotherapy until the end of pregnancy.

TREATMENT OF LOCAL AND SYSTEMIC REACTIONS

Local reactions do not contraindicate further immunotherapy. Most require no specific therapy. Severe, uncomfortable local reactions that may persist for several days, however, usually respond to treatment with oral antihistamines, topical corticosteroids, or occasionally, bursts of oral corticosteroids. Local application of ice reduces edema, pain, and itching at the injection site. Topical antihistamine sprays (e.g., azelastine) or nasal cromolyn may reduce nasal symptoms after nasal immunotherapy.

Practice parameters concerning anaphylaxis (a potentially life-threatening systemic reaction) and its management have been published.³⁶ A sequential approach to management is outlined in Box 1 and Reference 38 provides a detailed discussion of anaphylaxis and its management.

Box 1. Treatment of Life-Threatening Systemic Reactions*

- I. Immediate intervention
 - a. Aqueous epinephrine 1:1000, 0.3–0.5 mL (1 mg/mL in children, max. 0.3 mg/dosage) subcutaneously or intramuscularly. Repeat as necessary every 15–20 minutes to control symptoms and sustain blood pressure.
 - b. Aqueous epinephrine 1:1000 0.1–0.3 mL in 10 mL of normal saline (1:100,000 to 1:33,000), intravenously over several minutes and repeat as necessary for severe, refractory reactions. A 1:10,000 dilution for intravenous infusion may be necessary.
- II. General intervention
 - a. Place patient in recumbent position and elevate lower extremities.
 - b. Secure and maintain airway (endotracheal intubation or cricothyrotomy may be required).
 - c. Administer oxygen.
 - d. Establish venous access with administration of normal saline intravenously for fluid replacement. If severe hypotension exists, rapid infusion of volume expanders is necessary (colloid-containing solutions or saline).
 - e. A venous tourniquet above the injection site may decrease absorption of the injected allergen.
- III. Specific intervention
 - a. Aqueous epinephrine 1:1000, 0.1–0.3 mL, at the reaction site may delay allergen absorption.

- b. Diphenhydramine, 5 mg/kg/d in divided doses orally or intravenously, with maximum daily dosage of 300 mg for children and 400 mg for adults.
- c. For bronchospasm, nebulized albuterol or metaproterenol, 1.25–2.5 mg (0.25–0.5 mL of 5% solution) in 3 mL of saline. Repeat as needed.
- d. Aminophylline, 5 mg/kg over 30 minutes intravenously if no response to inhaled β -agonist. Note: adjust dosage based on age, concurrent medications, or current use of theophylline.
- e. If hypotension persists, dopamine, 400 mg in 500 mL D5W, may be administered intravenously at 2–20 μ g/kg/min with the rate titrated to maintain adequate blood pressure.
- f. Cimetidine, 300 mg, or ranitidine, 150 mg, administered intravenously over 10–15 minutes may also be useful. Rapid intravenous administration of cimetidine may cause hypotension, but ranitidine may be diluted to 20 mL and administered over 5 minutes.
- g. Glucagon, 1–5 mg, administered intravenously over 5 minutes and followed by an infusion, 5–15 μ g/min, may be useful when a β -blocker complicates treatment. Aspiration precautions should be observed because glucagon may cause nausea and emesis.
- h. Systemic corticosteroids, such as methylprednisolone 1–2 mg/kg for 24 hours, are usually not helpful acutely but may prevent prolonged reactions or relapses.

**Modified from Kemp SF, deShazo RD: Anaphylaxis and anaphylactoid reactions. In Lockey, RF, Bukantz SC (eds): Allergens and Allergen Immunotherapy, ed 2. New York, Marcel Dekker, Inc., 1999; reprinted from reference 38, pp 533–555, by courtesy of Marcel Dekker, Inc.*

Office equipment recommended by the American Academy of Allergy, Asthma, and Immunology for the treatment of systemic reactions associated with immunotherapy includes the following:

1. Stethoscope and sphygmomanometer
2. Tourniquets, syringes, hypodermic needles, large-bore needles (14-gauge)
3. Injectable aqueous epinephrine 1:1000
4. Equipment for administering oxygen
5. Equipment for administering intravenous fluids
6. Oral airway
7. Diphenhydramine or similar injectable antihistamine
8. Aminophylline for intravenous administration
9. Corticosteroids for intravenous injection
10. Vasopressor (e.g., dopamine or norepinephrine)

From Board of Directors: American Academy of Allergy and Immunology: Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts [position statement]. J Allergy Clin Immunol 93:811–812, 1994; with permission.

Assessment and maintenance of the ABCs of basic life support (airway, breathing, and circulation) are necessary before proceeding to other management steps. The remaining treatment of a systemic reaction

depends on its severity because inappropriate treatment may potentially be as hazardous as the systemic reaction itself. Patients should be monitored continuously for any therapeutic complications.

Injectable epinephrine is used in all systemic reactions to restore vasomotor tone and to prevent further release of harmful chemical mediators, such as histamine and leukotrienes.² All subsequent therapeutic measures depend on the initial response to epinephrine. Three surveys of immunotherapy-related fatalities reported that most patients died from respiratory complications and some had failed to respond to epinephrine.^{41, 59, 60} These reports, however, provided no specific data concerning the time that elapsed from symptom onset until epinephrine administration.

Fatalities during witnessed anaphylaxis not related to immunotherapy usually result from delayed administration of epinephrine and from severe respiratory complications. In a retrospective review of six fatal and seven nonfatal episodes of food-induced anaphylaxis in children and adolescents, all patients who survived had received epinephrine before or within 5 minutes of developing severe respiratory symptoms. None of the patients who died received epinephrine before the onset of severe respiratory symptoms.⁶³

The recommended dosage of epinephrine for the treatment of systemic reactions in adults or adolescents without cardiovascular compromise is 0.3 to 0.5 mg of a 1:1000 dilution administered subcutaneously or intramuscularly and repeated every 15 to 20 minutes, as needed. Test doses of 0.1 mg may be appropriate and clinically sufficient in some circumstances. The suggested dosage for children is 0.01 mg/kg of a 1:1000 dilution, with a maximum dose of 0.3 mg, administered subcutaneously every 15 to 30 minutes, as needed.³ One study, however, has suggested that absorption is complete and more rapid in children who receive epinephrine intramuscularly.⁶⁸

The standard treatment of systemic reactions should include antihistamines (H_1 - ± H_2 -antagonists) and corticosteroids in addition to epinephrine. Even at maximum dosages, however, antihistamines cannot abort a systemic reaction if histamine already occupies its receptor. Thus, antihistamines should never be administered alone as treatment for systemic reactions. These agents, however, may attenuate urticaria or generalized pruritus, and they may prevent relapse. Systemic corticosteroids have no immediate effect, but they may potentially prevent prolonged episodes or recurrences.

Oxygen should be administered to patients with systemic reactions who require multiple doses of epinephrine, have protracted reactions, or have pre-existing hypoxemia or myocardial dysfunction. Continuous pulse oximetry or arterial blood gas determination may guide oxygen therapy. Inhaled β_2 -agonists (e.g., albuterol) may be administered for any bronchospasm refractory to epinephrine. Intravenous aminophylline may also be administered cautiously. Because it produces bronchodilation by a different mechanism, aminophylline may also be administered cautiously. Because it produces bronchodilation by a different mecha-

nism, aminophylline may potentiate the bronchodilatory effects of β_2 -agonists and may be lifesaving in patients who develop bronchoconstriction while taking β -blockers. The loading dose for aminophylline is 5.0 mg/kg administered over 20 to 30 minutes, with a 0.9 mg/kg/h maintenance infusion. Serum levels of 8 to 15 $\mu\text{g/mL}$ are recommended. Aminophylline may induce cardiac arrhythmias that are difficult to reverse in the presence of hypoxemia or myocardial dysfunction. The initial infusion of aminophylline preferably should be administered with cardiac monitoring and should be discontinued if nausea, vomiting, or arrhythmias occur.

Systemic reactions to immunotherapy injections in patients receiving β -blocker therapy may not respond to the usual doses of epinephrine, and higher doses of epinephrine may cause predominantly α -agonist effects. In such situations, both volume expansion with isotonic fluids and glucagon administration are recommended. Glucagon is an effective bronchodilator⁶⁷ and potentially may reverse refractory hypotension and bronchospasm during a systemic reaction.⁶⁶ Glucagon directly activates adenylyl cyclase and bypasses the β -adrenergic receptor, thus negating any influence of β -blockers on its actions. Protection of the airway is particularly important in obtunded patients who receive glucagon because this medication may cause emesis and place these patients at an increased risk for aspiration.

Some investigators have observed that patients experiencing hypotension during anaphylaxis caused by insect stings have elevated endogenous levels of norepinephrine, epinephrine, and angiotensin II.³⁷ These findings may explain why some individuals with hypotension during anaphylaxis do not respond to epinephrine injections. The patient whose hypotension persists despite subcutaneous epinephrine should receive intravenous crystalloid solutions and volume expanders, such as hetastarch. Vasopressors, such as dopamine or norepinephrine, should be administered if hypotension remains unresponsive to volume expansion. Central venous access may be needed to enable rapid administration of fluids and continuous assessment of intravascular fluid status.

FUTURE STRATEGIES FOR IMMUNOTHERAPY

Advances in clinical and laboratory immunology should lead to safer, more effective means of manipulating and modulating the human immune response to allergens. Some of the methods under investigation as potential alternatives to injection and local immunotherapy include the following⁸⁴:

- Therapeutic vaccines containing highly purified and defined allergens
- Novel delivery systems
- Nonanaphylactic allergens, allergen fragments, or peptides for active immunotherapy

- IgE-binding haptens of major allergens for passive saturation of effector cells and induction of blocking antibodies
- Immunization with plasmid DNA
- Allergen-specific antibodies and antibody fragments for passive immunotherapy in the allergic effector organs
- Immunotherapy with humanized anti-IgE monoclonal antibodies or IgE-mimotopes

The World Health Organization position paper on immunotherapy provides an overview of these strategies and representative references.⁸⁴ Discussion of these investigative methods is beyond the scope of this article (see article by Mohapatra elsewhere in this issue).

UNRESOLVED ISSUES IN IMMUNOTHERAPY SAFETY

Presently unresolved issues in allergen immunotherapy safety include:

1. Will premedication with antihistamines or other drugs administered alone or in combination reduce the incidence of systemic reactions and fatalities associated with immunotherapy?
2. Will local immunotherapy and/or alternative immunotherapy strategies (e.g., anti-IgE monoclonal antibodies) prove equally or more efficacious, safer, and more cost-effective than injection immunotherapy?
3. Does the risk of systemic reactions associated with immunotherapy decline after prolonged periods?
4. Some investigators have proposed that vaccine mixes containing allergens to which the patient is not sensitive may sensitize an individual to these allergens to which he/she previously had no detectable IgE response. Does this increase the risk for a systemic reaction?
5. Should immunotherapy be contraindicated in autoimmune disease or disease states of T-cell dysregulation (e.g., infection with human immunodeficiency virus)?
6. Because of the high risk of complications associated with asthma, should screening spirometry (FEV₁) be obtained for all individuals receiving immunotherapy injections?
7. Since some life-threatening systemic reactions have occurred more than 30 minutes after injection, are there circumstances in which epinephrine kits should be prescribed for self-administration after departure from the office or clinic?

SUMMARY

1. No allergenic vaccine should be considered completely safe for an individual allergic to its contents.

2. Physicians who prescribe allergen immunotherapy should administer injections in an office or clinic that has appropriate medical equipment and personnel trained to recognize and treat a systemic reaction promptly and efficiently if one occurs.
3. The risk of a fatal systemic reaction may be reduced by careful selection and monitoring of individuals placed on immunotherapy, the use of standardized allergen vaccines, the use of conventional administration schedules, and the prompt recognition and treatment of systemic reactions.
4. Injectable epinephrine is the treatment of choice for systemic reactions and all subsequent therapeutic measures depend on the initial response to epinephrine.
5. A 20-minute waiting period after an immunotherapy injection is generally adequate, but the period should be extended for patients considered high risks for systemic reactions.
6. Fatalities associated with allergen immunotherapy are rare with an estimated incidence of 1 per 2 million injections.
7. Individuals at greatest risk for a systemic reaction to immunotherapy are those with asthma, particularly poorly controlled asthma.
8. Other significant risk factors for anaphylaxis due to immunotherapy include accelerated ("rush") immunotherapy regimens, concurrent use of β -blocker medications, a seasonal exacerbation of asthma or rhinitis, and a high degree of allergic hypersensitivity.
9. More placebo-controlled studies are necessary to clarify the therapeutic role of local immunotherapy. While other modes of delivery may be effective and produce fewer side effects than injection immunotherapy, bronchial immunotherapy has produced bronchospasm in most patients.

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