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Risk management in allergen immunotherapy

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The major risk of allergen immunotherapy is the development of systemic anaphylactic reactions. The reported frequency of systemic reactions after allergen immunotherapy varies from <1% in patients receiving conventional immunotherapy to >36% in patients receiving rush immunotherapy. Fatal and systemic reactions to allergen immunotherapy have similar characteristics. The onset of both types of reaction occurs <30 minutes after injection in approximately 70% of patients. The most common risk factors for fatal and systemic reactions to allergen immunotherapy include a history of asthma, increasing allergen dose, high allergen sensitivity, previous systemic reaction, and injection during an active allergen season. On the basis

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of findings from several studies, precautions during allergen immunotherapy have been recommended. In addition, several interventions, including premedication with antihistamines or corticosteroids, measurement of peak flow before injection, and access to an antihistamine or injectable epinephrine after an allergen injection, have been suggested as measures to prevent reactions to and improve the safety of allergen immunotherapy. However, additional studies are necessary before these regimens are implemented routinely in allergen immunotherapy protocols. (J Allergy Clin Immunol 1996;98:S330-4)

Key words: Allergen immunotherapy, fatal reaction, precautions, risk factors, risk management, systemic reaction

Allergen immunotherapy has been used for years to treat selected patients who have allergic rhinitis, asthma, and sensitivity to hymenoptera. Clinical improvement can be expected in the majority of patients with proper selection.¹ The major risk of allergen immunotherapy is the development of systemic anaphylactic reactions.² In a retrospective analysis of the incidence of constitutional reactions in 8706 patients who had received 1.25 million allergen injections between 1935 and 1955, VanArsdel and Sherman³ found that 663 (7.8%) patients had a total of 1774 reactions, an incidence of 0.14%. A more recent study found that 144 (4.5%) of 3178 patients had systemic reactions in the course of 166 visits and 56,106 allergen injections, an incidence of 0.3%.⁴ Overall, the reported frequency of systemic reactions after allergen immunotherapy varies considerably, from <1% in patients receiving conventional immunotherapy to >36% in patients receiving rush immunotherapy.⁵⁻¹⁵ Several factors influence the frequency of reactions, including type of allergen, patients selected, treatment schedule, and use of pretreatment procedures.

In addition to allergic, presumably IgE-mediated, reactions, other types of adverse reactions to allergen immunotherapy may occur. Bukantz and Lockey⁵ concluded that the incidence of type III immune-complex reactions, brachial plexus neuropathy, positive rheumatoid factor, pemphigus vulgaris, and polyarteritis nodosa was not significant in patients undergoing allergen immunotherapy. These possible adverse reactions to allergen immunotherapy are not considered further in this article.

FATAL REACTIONS TO ALLERGEN IMMUNOTHERAPY

Although most reactions to allergen immunotherapy are relatively mild and easily treated, fatal reactions represent the catastrophic outcome that must be prevented. Lamson^{16, 17} first described sudden death from anaphylaxis after injection of foreign substances and allergen immunotherapy in the 1920s. Subsequent reports confirmed the occasionally fatal hazards of injection of antigenic material.^{18, 19} After a report of a death after allergen immunotherapy,²⁰ the Committee on Safety of Medicine²¹ in the United Kingdom issued a report in 1986 describing 26 fatalities after allergen

immunotherapy, including two that occurred >30 minutes after injection. Consequently, the Committee recommended that the observation period after injection be increased to 2 hours, which led to the virtual abandonment of allergen immunotherapy in the United Kingdom. In response to this recommendation, a Working Group Report by the World Health Organization international Union of Immunologic Societies²² concluded that a 30-minute waiting period was adequate, because the majority of fatalities had occurred in patients who were at increased risk or in cases in which injections had been administered by inexperienced physicians.

Lockey et al.² and Reid et al.²³ summarized the data on the risk of fatal reactions to allergen immunotherapy and allergen skin testing in the United States. Allergen skin-testing data showed that 13 (87%) of 15 fatalities between 1928 and 1984 occurred when epicutaneous (prick or scratch) testing had not preceded intradermal skin testing.² There were no fatalities from skin testing in the 5-year period from 1985 to 1989, possibly because of the widespread use of epicutaneous methods of skin testing beginning at that time. On the basis of these observations, it has been concluded that in allergen skin testing, epicutaneous methods should be used before intradermal testing (if required) to reduce the risk of fatal reactions.^{5, 15}

Fatal reactions to allergen immunotherapy have not been as easy to prevent. In a retrospective review of allergen immunotherapy in the United States, 24 cases of fatal reactions were identified in the period between 1945 and 1984.² A later prospective report identified 16 fatal reactions to allergen immunotherapy in the period between 1985 and 1989.²³ Bukantz and Lockey⁵ reviewed and summarized several important characteristics from the 74 reported fatal reactions to allergen immunotherapy, which included the 26 described in the report of the Committee on the Safety of Medicine in the United Kingdom. The time of onset for the 74 fatal reactions was <20 minutes after injection in 41 (55%) reactions and <30 minutes after injection in 52 (70%). Only 6 (8%) reactions occurred >30 minutes after injection, and no time of onset was reported for 15 (20%) reactions. The most common risk factors for fatal reactions associated with allergen immunotherapy were history of asthma (74%), increasing allergen dose (70%), and high allergen sensitivity (62%) (Table I).

TABLE I. Risk factors for fatal and systemic reactions to allergen immunotherapy

Risk factor	Reactions (%)	
	Fatal ⁵ (n = 74)	Systemic ²⁴ (n = 143)
History of asthma	74	50
Increasing allergen dose	70	—
High allergen sensitivity	62	—
History of systemic reaction	—	45
Injection during active allergen season	34	36
Late injections	—	14
New (fresh) extracts	—	7
β-Blocker therapy	5	0

—, Not reported.

Although it is not practical to eliminate all risk factors in patients requiring allergen immunotherapy, several conclusions can be drawn from these studies: patients with asthma should not receive allergen immunotherapy during periods of unstable asthma; increasing doses of allergen should be administered on a regular schedule, with close monitoring of patients; immunotherapy in patients with high allergen sensitivity as determined by skin testing, RAST, or history should be started with very low allergen doses, with careful surveillance for adverse reactions to immunotherapy; allergen doses should not be increased during an active allergy season in patients with enhanced allergy symptoms; and patients receiving β-blockers should not be given allergen immunotherapy unless the benefits of combined therapy outweigh the risks.

SYSTEMIC REACTIONS TO ALLERGEN IMMUNOTHERAPY

Several studies have investigated the risks of systemic reactions to allergen immunotherapy.⁶⁻¹⁴ The results of our study of systemic reactions to allergen immunotherapy in an ambulatory population enrolled in a health maintenance organization²⁴ are in agreement with those of other studies and, not unexpectedly, reflect some of the same observations made in studies of fatal reactions.^{2, 5, 23}

In our study of 27,806 injection visits (1 to 5 injections of inhalant or venom allergens per visit), 143 systemic reactions, an incidence of 0.51%, occurred.²⁴ Symptoms associated with the reactions are summarized in Table II. The occurrence of subjective symptoms, including itching, anxiety, light-headedness, dizziness, and a feeling of being hot, did not necessarily correspond with the presence of objective signs or abnormal vital signs. Patients having only subjective symptoms may not have had true reactions, but their symptoms were tabulated to ensure that all reactions were recorded. Most (61%) patients had only one of the symptoms, including subjective symptoms, listed in Table I; 24% had two symptoms; and 16% had three or more symptoms. The time of onset of systemic reactions (Fig. 1)

TABLE II. Signs and symptoms of 143 systemic reactions to allergen immunotherapy in patients enrolled in a health maintenance organization

Symptom	No. of reactions
Subjective	56 (39)
Rhinoconjunctivitis	42 (29)
Urticaria or angioedema	35 (24)
Cough	27 (19)
Wheezing or stridor	15 (10)
Abdominal pain	5 (4)
Hypotension	2 (1)

Data from Matloff et al. Allergy Proc 1993;14:347-50.

was similar to that reported in studies of fatal reactions to allergen immunotherapy: systemic reactions began <30 minutes after injection in 72% of patients and 2 to 24 hours after injection in 8%. Although an accurate time of onset was not recorded for 10% of patients with reactions, most of these reactions probably occurred in the office within the first 30 minutes after injection.

Symptoms experienced by patients with late reactions (2 to 24 hours after injection) were similar to those experienced by all patients having reactions: rhinoconjunctivitis (25%), wheezing (16%), cough (16%), nonurticarial rash (16%), and urticaria (8%). This finding demonstrates that persons with late-phase reactions probably represent a homogeneous subgroup of all people with reactions rather than a distinct population with a different makeup of or cause for their reactions. Risk factors associated with systemic reactions were similar to those reported for fatal reactions (Table I). Although doses of active pollens were reduced by 50%, 36% of patients had reactions to pollens for which they were receiving injections during active pollen seasons. Very few patients were receiving β-blocker therapy, because it is not permitted at our institution for patients receiving allergen immunotherapy unless there are compelling reasons; no reactions to allergen immunotherapy occurred in these patients.

From these observations of systemic reactions and the data on fatal reactions to allergen immunotherapy, it is possible to identify several factors that may increase risk (Table I) and to recommend precautions to observe in the treatment of patients who require allergen skin testing or immunotherapy (Table III). These include (1) performing percutaneous skin tests before intradermal testing; (2) informing patients of the signs and symptoms of systemic reactions so that they can report problems if they develop; (3) administering allergen immunotherapy only when a physician skilled in managing allergic reactions is present; (4) administering immunotherapy in facilities equipped to treat systemic reactions; (5) observing patients for 20 to 30 minutes after the allergy

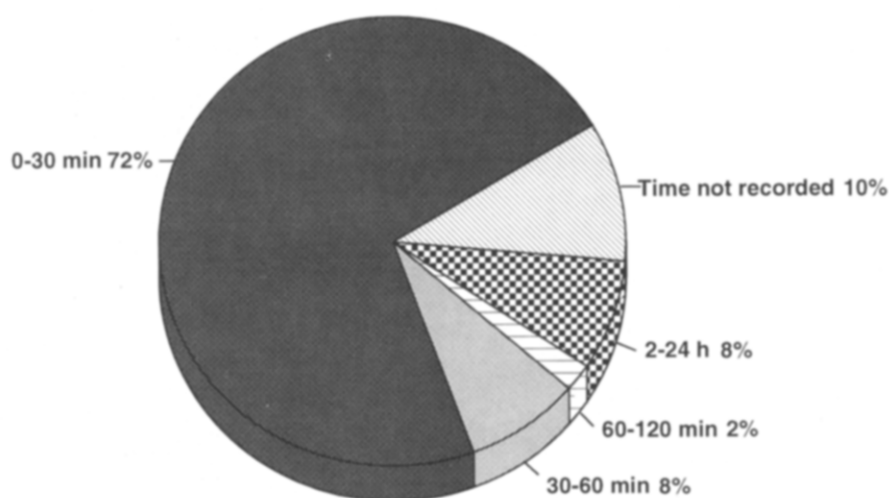


FIG. 1. Time of onset of systemic reactions. (Data from Matloff et al. *Allergy Proc* 1993;14:347-50.)

injection; and (6) whenever possible, avoiding allergen immunotherapy in patients who have unstable asthma or who are receiving a β -blocker.

PREVENTING REACTIONS TO ALLERGEN IMMUNOTHERAPY

Too few data are available to establish a role for any of several interventions aimed at preventing reactions to or improving the safety of allergen immunotherapy. One approach is to administer antihistamine premedication to patients before they receive allergy injections; however, some physicians have hypothesized that mild reactions may be masked by the antihistamines, leading to increases in allergen doses, which might cause severe reactions. In patients undergoing rush immunotherapy, in which allergen doses are increased deliberately with only short waiting times, there is a much greater acceptance of risk. Data from rush immunotherapy seem to indicate that these patients have fewer reactions when antihistamine and corticosteroid premedications are given. Pretreatment with corticosteroids for conventional allergen therapy is not practical. The data based on rush immunotherapy are not transferable to conventional allergen immunotherapy, and additional studies are necessary. We are conducting a premedication study in our patient population and expect to have data in approximately 1 year.

It has not yet been determined whether routine monitoring of peak flow in patients with asthma before administration of immunotherapy should be recommended in all cases. Although data supporting this approach are lacking, peak-flow monitoring is believed by some clinicians to be a practical and inexpensive method of reducing the risk associated with unstable asthma. Another potential intervention for which there are too few data to establish a policy is that of access to an antihistamine or injectable epinephrine for use if necessary after an allergy injection. Further work is

TABLE III. Precautions for skin testing or immunotherapy

- Start with percutaneous skin testing
- Inform patient of potential risks of immunotherapy
- Inform patient of signs and symptoms of systemic reactions
- Avoid use of β -blockers
- Administer immunotherapy with physician present in facilities equipped to treat systemic reactions
- Observe patient for 20 to 30 minutes after injection

necessary also to determine whether improved quality and reproducibility of allergen extracts and greater standardization of injection schedules will reduce the incidence of systemic reactions. Although it is clear that standardized extracts are more predictable than older, unstandardized extracts, some clinicians believe that the increased potency of some standardized extracts may actually increase the risk of systemic reactions.

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Legal issues in allergy and clinical immunology

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Clinical risk management for the allergist focuses primarily on concerns regarding adverse occurrences and the possibility of civil litigation as a result of negligence or professional liability. Risk is substantially reduced with an understanding of such predictable drug reactions as overdosage, side effects, secondary effects, and drug interactions. In addition, all clinicians who prescribe have a duty to disclose to their patients the possibility of unpredictable reactions, including intolerance, idiosyncrasy, and allergy or hypersensitivity. This disclosure should be part of a comprehensive discussion of the risks and benefits of, and alternatives to, therapeutic agents and procedures they recommend. The process of informed consent becomes even more critical with the increasing influence of hospital and managed care formularies on prescribing decisions. Although cost effectiveness is an important factor in prescribing

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