Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001

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Background: Fatal reactions associated with skin testing and injection immunotherapy have not been surveyed in North America since 1989.
Objective: A survey of fatal reactions related to skin testing and immunotherapy and of near-fatal immunotherapy reactions that transpired from 1990 through 2001 was conducted among member practices of the American Academy of Allergy, Asthma and Immunology.
Methods: A short survey of fatal reactions was sent to all American Academy of Allergy, Asthma and Immunology physicians, and an 87-item follow-up detailed questionnaire was sent to those reporting fatal reactions.
Results: Of 2404 members, 646 (25%) responded to the short survey. There were 20 fatal immunotherapy reactions that were directly reported and 21 indirectly reported cases by local physicians. There were 273 (42% of the responding sample) reports of near-fatal reactions. It was estimated that fatal reactions occurred every 1 per 2.5 million injections, with an average of 3.4 deaths per year. One fatality was confirmed after skin prick testing with multiple food allergens. Of 17 fatal deaths described in long questionnaires, 15 were in asthmatic patients, the majority of whose symptoms were not optimally controlled. Three reactions occurred in a medically unsupervised setting. None were receiving β-blockers, and one was taking an angiotensin-converting enzyme inhibitor. Most fatal reactions (59%) occurred with maintenance allergen doses. The onset of 3 reactions began more than 30 minutes after injections, with a significant delay in starting epinephrine. Epinephrine was not administered in 3 other fatal reactors.
Conclusions: Fatal reactions to immunotherapy injections occurred at similar rates reported in previous surveys. Certain clinical practices have improved (ie, exclusion of β-blockers), and dosing errors were infrequent. Fatal reactions to immunotherapy often occur in settings inappropriate for optimal treatment of anaphylaxis. Strict adherence to practice guidelines might prevent or minimize future fatal reactions.
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Key words: *Immunotherapy, fatality, skin testing, near fatal, fatal, injection, epinephrine, allergen*

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Allergen immunotherapy has proved to be effective in reducing the symptoms of allergic rhinitis and asthma, provided that adequate maintenance doses are achieved.[1-4] Despite its clinical benefit, there is a small risk of fatal allergic reactions associated with subcutaneous administration of aeroallergens.[5]

In 1987, Lockey et al[6] reported the first survey of immunotherapy fatalities among members of the American Academy of Allergy, Asthma and Immunology (AAAAI). Twenty-four immunotherapy fatalities and 6 fatal reactions to skin testing from 1959 through 1984 were described. Dosing errors, concomitant use of β-blockers, previous systemic reactions to immunotherapy, and administration during peak seasonal allergen exposure were factors presumed to contribute to fatal outcomes. Reid et al[7] reported 15 immunotherapy-related and 2 skin test–related fatalities in a follow-up of fatal events that occurred between 1985 and 1989. In both of the latter and other surveys, moderate or severe asthma was present in the vast majority of patients.[6-8]

To conduct ongoing surveillance in North America of fatalities related to skin testing and immunotherapy and to form the basis for updating future guidelines pertaining to patient safety, the Immunotherapy Committee of the AAAAI conducted a 2-part survey to identify deaths that had occurred since 1990. The objectives of this survey were (1) to estimate the incidence of fatal and near-fatal reactions to immunotherapy injections from 1990 through 2001, (2) to identify fatal reactions related to allergen skin testing, and (3) to evaluate patient characteristics, as well as details of immunotherapy administration and treatment of anaphylactic reactions, associated with fatal outcomes.

METHODS

The survey was conducted in 2 stages. In phase 1 a short 6-question survey was distributed 3 to 4 times to all members of the AAAAI by fax, E-mail, and the AAAAI newsletter. To avoid redundant responses, one member from each clinical practice was asked to respond. The short survey (posted in the Online Repository at www.mosby.com/jaci) queried about fatal reactions associated with skin tests and immunotherapy injections, both in the respondent's clinic and other practices located in their communities. The survey asked about near-fatal reactions, which were defined as severe respiratory compromise, decrease in blood pressure requiring emergency treatment with epinephrine, or both. On the basis of billing or procedure codes, respondents were asked to provide total numbers of patients receiving injections, as well as the numbers of injections administered during the previous 1 and 3 years. Individuals who did not respond initially to the short survey were re-sent the form at least twice. Approximately 25% of practice entities responded to

Abbreviations used
AAAAI: American Academy of Allergy, Asthma and Immunology
ACE: Angiotensin-converting enzyme
GM: Geometric mean

the short survey. A brief 3-item survey was sent to 112 respondents who, on the short survey, had reported fatal immunotherapy reactions occurring in another clinic in their geographic area. This follow-up survey ensured that indirectly reported cases had not already been reported. Long questionnaires (phase 2) were mailed to those respondents reporting fatal reactions (questionnaire posted in the *JACI* Online Repository). The questionnaire included 87 items adapted from previous surveys[6,7] and aimed to capture the following information: demographics; asthma, allergic rhinitis, or both; prior hospital visits for asthma; FEV_1 values before immunotherapy and values obtained just before fatal events; concomitant medications; type of physician present during fatal injections; allergen dosing errors; allergen vials and contents; occurrence of events during build-up or maintenance dosing; postinjection waiting period; prior local or systemic allergic reactions; onset of reaction relative to injection; clinical manifestations of fatal reactions; management of severe anaphylaxis; explanation as to what might have been done differently; and circumstances that might have contributed to fatal outcomes.

Because the distribution of numbers of injections was skewed and log transformation made it normally distributed, geometric mean (GM) data are presented in addition to arithmetic mean data. The numbers of injections administered by groups of respondents reporting fatal, nonfatal, and no reactions were compared by means of ANOVA. Estimates of incidence rates of fatal reactions per numbers of injections were based on the assumption that injection data were representative of the entire sample of 646 respondents and generalizable to all AAAAI physicians.

RESULTS

Short survey

Physicians representing 646 practice entities responded to the short survey, 99% of whom resided in the United States and Canada. The sample represented about 25% of 2404 clinical entities in North America staffed with AAAAI members (personal communication, AAAAI). Twenty fatal immunotherapy reactions were directly reported that had occurred between 1990 and 2001; a single fatal reaction that had occurred in 1987 was excluded from incidence calculations. An additional 21 indirectly reported fatal reactions were confirmed. A single fatal reaction with skin testing was confirmed. In the short survey physicians representing 273 practice entities reported near-fatal reactions to immunotherapy in their clinical practices. These reactions will be evaluated in a separate study.

Incidence of fatal reactions

Data from the short survey were used to estimate the mean number of annual injections in all respondents, as well as respondent subsets reporting no systemic reactions, near-fatal reactions, and fatal reactions, to determine incidence rates of systemic and fatal reactions. Of 646 respondents, injection data were provided for the previous 1 and 3 years by 506 and 504 respondents, respectively. The GM number of injections over 1 year was greater in the group of practices with fatal reactions (9321 [n = 17]) than in the near fatal and nonreactor groups (7864 [n = 237] and 5541 [n = 252], respectively), and differences between groups were significant ($P = .016$, ANOVA). Pairwise comparison indicated that the mean number of injections was significantly greater ($P < .05$) in the near-fatal group versus the nonreactor group. Similar significant differences were also noted among all 3 groups ($P = .007$, ANOVA), as well as between near-fatal (GM = 23,860) and nonreactors (GM = 15,835) by pairwise comparison when 3-year mean number of injections was analyzed.

On the basis of directly reported fatal reactions (20 cases) and the GM number of injections administered in 646 responding clinics, the incidence of fatal reactions was 1 per 2,540,000 injections. On the basis of the arithmetic mean number of annual injections, the incidence rate of directly reported fatal cases per total number of injections given in 646 clinics was 1 in 6,850,000 injections. On the basis of 41 fatal immunotherapy reactions estimated to have occurred in 12 years of this survey (1990-2001), a mean 3.4 deaths occurred per year. The majority of cases (9/16 [56%]) occurred in the first quarter of the year, with 4 during January, 2 during February, and 3 during March. On the basis of the assumption that 41 fatalities (direct and indirect cases) might have occurred in 2404 clinical practice entities, fatal immunotherapy reactions were estimated to have occurred in 1.7% of member clinical practices.

Results of long survey

Detailed characteristics were provided by 17 of 21 physicians responding to the long questionnaire and were comprised of 6 female and 11 male fatal reactors, with ages ranging from 5 to 81 years (mean age, 39.3 ± 20.5 years). As mentioned, this synopsis includes a fatal reaction that occurred in 1987.

Asthma status

Before beginning immunotherapy, 15 (88%) of 17 fatal reactors had been given a diagnosis of asthma, and 2 were given an exclusive diagnosis of allergic rhinitis. Six of 14 asthmatic patients were identified with labile asthma, and 8 of 13 reportedly had experienced a prior hospital admission (n = 4), emergency room visit (n = 7), and/or respiratory arrest (n = 1) for asthma. At baseline evaluation, 1 asthmatic patient was classified as having mild episodic disease, 5 as having mild persistent disease, 7 as having moderate persistent disease, and 2 as having severe persistent disease. When respondents were asked to reclassify asthma severity status while receiving immunotherapy (and pharmacotherapy), 2 patients were identified as having mild episodic disease, and only 1 of 15 was identified as having severe persistent asthma. At initial evaluation, baseline FEV_1 values were less than 70% of predicted value in 5 of 10 patients in whom spirometry was performed. The mean FEV_1 significantly

increased from 2.02 L (62% of predicted value) at initial evaluation to 2.31 L (69.4% of predicted value) in 7 patients who underwent spirometry before and after initiation of immunotherapy ($P = .02$). Thus available data suggested that asthma status either improved or did not deteriorate before reported fatal events.

Twelve (80%) of 15 asthmatic patients were prescribed inhaled glucocorticoids. Two of 3 patients not receiving an inhaled glucocorticoid had actually refused treatment despite their physicians' recommendations. Interestingly, only 1 patient was prescribed a high-potency agent (ie, fluticasone propionate). Three patients received salmeterol combined with an inhaled glucocorticoid. Two patients were prescribed inhaled cromolyn sodium as the exclusive controller agent. One patient (no. 13) was being treated with oral prednisone (20 mg administered twice daily) for 9 days leading up to the date of the fatal event.

Concomitant drugs and aeroallergen sensitization

Two patients were given a diagnosis of diabetes, and 2 were given a diagnosis of hypertension; none had preexisting cardiac disorders. An elderly man (patient 8) with asthma was receiving an angiotensin-converting enzyme (ACE) inhibitor (captopril) when the fatal reaction occurred and was marked by upper airway obstruction, hypotension, and angioedema; he had experienced a systemic reaction to a previous injection 7 years earlier. It was noteworthy that the allergen vial concentration was quite low (1:1,000,000 wt/vol pollen mixture). No patients were receiving β-blockers. Five patients had been prescribed H_1 blockers. A high degree of baseline allergen sensitivity (many positive skin prick test responses) was reported in 5 (29%) patients, and moderate sensitivity (some positive skin prick test responses) was reported in 11 (59%) patients. One patient reacted exclusively to intradermal tests.

Clinic settings and modes of allergen administration

Data on clinic settings and modes of allergen administration are shown in Table I. In all 17 fatal cases, board-certified allergists prescribed the allergen extracts. Sixteen injections were administered subcutaneously, and there were no reports of intramuscular administration. Ten (59%) fatal events occurred in clinics of board-certified allergists who were present during the reaction. Five events occurred in outside clinics of primary care physicians, and 2 fatal reactions occurred during home administration. An overdose was suspected but not confirmed in a patient who self-administered a fatal injection at home, despite having been instructed to receive injections in the presence of a physician. In another case that occurred at home, epinephrine was administered but was not effective in preventing respiratory arrest in a patient who, 1 week earlier, had a late-onset asthmatic reaction to an immunotherapy injection. Another fatal event transpired in a medically unsupervised employee health clinic; epinephrine was not immediately available.

Ten (59%) of 17 patients received injections from maintenance extracts, whereas concentrations were being increased in 7 patients. Two fatal reactions followed an initial injection from a new nonmaintenance vial. One of 16 respondents noted a recent change in allergen extract manufacturer. In 10 of 16 patients, a standardized allergen was used in formulating the allergen extracts. Fatal injections occurred during the patients' allergy season in 5 (29.4%) of 17 cases. One respondent reported accidental administration of an 18-fold greater than prescribed cat allergen dose (2500 BAU) in a primary care clinic. Except for the latter case, doses given to other fatal reactors were appropriate.[9]

Prior reactions to allergen injections

Local reactions were reported after previous injections by 5 (38%) of 13 respondents. Local reactions were immediate in onset in 3 patients and late in onset in 2 patients. Subsequent fatal doses occurred after dose increases of greater than the previous dose causing a local reaction in 2 patients and after the same dose in 3 patients. Four (28.6%) of 14 respondents (patients 1, 2, 8, and 16) reported prior injection-related systemic reactions; all 4 had asthma. In 3 patients prior systemic reactions were manifested by acute bronchospasm 1 hour after an injection 12 months earlier, acute dyspnea 4 years earlier, and an asthmatic exacerbation noted 2 hours after the most recent injection 10 days earlier, requiring treatment in an emergency department. In the latter case fatal anaphylaxis ensued with the next injection, despite a 50% allergen dose reduction. The fourth case was described as a moderate systemic reaction that occurred 7 years before the fatal reaction.

Clinical manifestations of fatal reactions

Time of onset. Initial manifestations of fatal reactions began less than 30 minutes after injections in 10 (77%) of 13 respondents (Table I). In all but one patient (ie, terbutaline was given to patient 2) in whom fatal reactions began in supervised medical clinics, epinephrine was initiated either immediately or within 5 minutes of onset of fatal immunotherapy reactions (Table II). In 3 patients reactions began more than 30 minutes after allergen injections. In one patient the reaction began outside the clinic 35 minutes after the injection; emergency treatment was not administered until 45 minutes after the injection. A second late reaction occurred in a general clinic after the patient had left the clinic early. It was estimated that treatment might not have been initiated for at least 50 minutes after the injection. A third late reaction occurred in the office of a primary care physician and began 30 to 40 minutes after the injection. Treatment was initiated at 20 minutes after onset of the reaction.

Clinical features. As listed in Table I, fatal reactions were marked by signs of either upper airway obstruction (2/16), lower airway obstruction (8/16), or both (6/16). Shock or hypotension was reported in 13 (81%) of 16

TABLE I. Characteristics of individual fatal reactions to immunotherapy injections in 17 patients from long surveys

Patient no.	Onset (min)	Initial symptoms	Symptoms	Allergens, dose	Patient susceptibility*	Cause of death and autopsy findings
1	>30	P	LAO, S, C	DM 125 AU/mL (M)	Prior systemic reaction to immunotherapy, treated in ED	Anaphylactic shock
2	10-20	LAO	LAO, S, H, C	DM, T, G, W 1:1000 vol/vol	Prior systemic reaction, unstable asthma	Asthma and CV collapse
3	>30	LAO	LAO, S, H, C	DM, C, R, G, T, EP 1:100 wt/vol (M)	Prior ED visit (asthma), noncompliance with medications, left clinic early	Asthma and arrhythmia; autopsy→laryngeal, tracheal, and bronchial edema
4	UK	Not feeling well	LAO	DM, R, T, G, W, M 1:100 wt/vol (M)	ASA allergic reaction	Anaphylactic shock
5	UK	D	Dead on arrival	T, G, W 1:500 wt/vol	Prior ED visit for asthma, possible noncompliance	No response
6	0-3	UAO	LAO, UAO, S, H, C	DM 150 AU; Cat 150 BAU; T, G, R 1000 PNU	Switch from nonstandardized to standardized extract	Upper airway edema, anaphylactic shock, arrhythmia, asthma, hypotension
7	3-10	Facial erythema	LAO	DM 100 AU/mL T 1:2000	Asthma control not optimal	Asthma, seizure, CV collapse
8	10-20	UAO	LAO, UAO, A, S, H, C	T, R, W (M) 1:1,000,000 wt/vol	Prior systemic reaction to injection; ACE inhibitor	Upper airway edema, anaphylactic shock
9	0-3	LOA	LAO, C, S	DM, C, D, T, G, W, M 1:150 vol/vol (M)	Asthma control not optimal, self administered, peak of pollen season	Anaphylactic shock, asthma; autopsy→lower airway edema
10	UK	UAO	UAO, A	DM, M, C, D, P 1:100 wt/vol (M)	None	Upper airway edema; autopsy→lingual, glottic edema
11	0-3	GI	UAO, LAO, S, C, GI	DM, C, T, G, R, W 1:200 wt/vol (M)	None	Upper airway edema
12	UK	UAO	UAO, P, LOA, H, G, C, S	DM, G, C 1:200 wt/vol	Height of pollen season, prior ED visit for asthma	Asthma, anaphylactic shock, upper airway edema, CV collapse
13	3-10	D	D, LAO, UAO, C, H	W, G, T 1:400 wt/vol; Cat 500 BAU/mL, DM 1000 AU/mL (M)	Recent asthma exacerbation	Asthma, laryngeal edema
14	0-3	UAO	UAO, LAO, H, C	DM 1000 AU/mL (M)	Suboptimal control of asthma	Upper airway edema
15	10-20	LAO	LAO, S, GI, D, Cy	DM, M, T, G, W 1:200-1:400 wt/vol	None, left facility within minutes of injection and returned 20 minutes into reaction	Asthma, anaphylactic shock
16	3-10	LAO	LAO, H, C	DM 1000 AU/mL; M, RW, T, G, W 1000 PNU/mL	Height of pollen season, prior systemic reaction to immunotherapy 1 week earlier treated in ED; hospitalization for asthma	Anaphylactic shock, asthma, cardiac arrhythmia
17	>30	Something in throat	A, P, H, UAO	DM, D, C, RW, T, GW 1000 PNU/mL	None	Anaphylactic shock, pulmonary edema

*Factors physicians identified as major contributors to fatal outcomes.

ED, Emergency department; *CV,* cardiovascular; *UK,* unknown; *ASA,* aspirin.

Symptoms: *P,* Pruritus; *LAO,* lower airway obstruction; *S,* shock; *C,* loss of consciousness; *H,* hypotension; *UAO,* upper airway obstruction; *A,* angioedema; *GI,* gastrointestinal symptoms; *D,* dyspnea; *Cy,* cyanosis.

Allergens: *DM,* Dust mite; *(M),* maintenance; *T,* tree mix; *G,* grass mix; *W,* weed mix; *C,* cat; *R,* ragweed; *EP,* English plantain; *M,* mold mix; *D,* dog; *P,* pollens.

TABLE II. Treatment of fatal reactions to immunotherapy injections

Patient no.	Administration site	Time from reaction to initiation of Epi	Epi initial dose	Epi total dose	Epi route administration	CPR	Intubation attempted	Time to intubation after respiratory failure
1	Allergist	>30 min	2 mg	2 mg	IV	Yes	Yes	40 min
2	Allergist	Immediate terbutaline*	None	None	NA	Yes	Yes	UK
3	PCP	10-20 min	UK	UK	UK	Yes	Yes	UK
4	PCP	UK	UK	UK	IM, SL	Yes	Yes	UK
5	Home†	None	None	None	NA	UK	UK	UK
6	Allergist	Immediate	0.3-0.5 mg	UK	IM	Yes	Yes	25 min
7	Allergist	Immediate	0.3-0.5 mg	0.6 mg	UK	Yes	Yes	Unsuccessful
8	Allergist	0-3 min	0.3-0.5 mg	UK	SQ, IV	Yes	Yes	10 min
9	Work clinic	None	None	None	NA	UK	UK	UK
10	Allergist	Immediate	0.3 mg	0.6 mg	SQ	Yes	Yes	5 min
11	PCP	0-3 min	0.3-0.5 mg	1.2 mg	SQ	Yes	Yes	1 min
12	Allergist	Immediate	0.3-0.5 mg	UK	SQ	Yes	Yes	Unsuccessful
13	Allergist	Immediate	0.3-0.5 mg	0.9 mg	SQ	No	Yes	30 min
14	Allergist	Immediate	0.3-0.5 mg	0.6 mg	SQ, IV	Yes	Yes	Unsuccessful
15	Allergist	Immediate	0.3-0.5 mg	UK	SQ, IV, IT	Yes	Yes	3-5 min
16	Home†	Immediate	UK	UK	UK	Yes	Yes	UK
17	PCP	20-30 min	0.3-0.5 mg	0.6 mg	SQ	No	Yes	UK

EPI, Epinephrine; *CPR,* cardiopulmonary resuscitation; *IV,* intravenous; *NA,* not applicable; *PCP,* primary care physician; *UK,* unknown; *IM,* intramuscular; *SL,* sublingual; *SQ,* subcutaneous; *IT,* intratracheal.
*Terbutaline, 0.3 to 0.5 mg, administered subcutaneously in lieu of epinephrine.
†Injection administered in patient's home.

patients. First manifestations of fatal reactions were respiratory in 12 of 17 and cutaneous in 2 of 17 patients.

Physician respondents were queried as to which susceptibility factors they thought contributed to fatal outcomes. As listed in Table I, 4 respondents cited previous systemic reactions to immunotherapy. Nine of 17 patients had histories of asthma that was not optimally controlled, reflected by exacerbations requiring treatment in hospital or emergency departments (5 patients) and by noncompliance with medications (2 patients). Administration of injections during peak pollen seasons was cited as a contributing factor in 3 patients, and a recent switch to a standardized extract was suspected in one case.

Treatment of fatal reactions (Table II). Epinephrine was not administered to 3 of 17 patients. In one case, a patient (patient 2) was administered 0.3 to 0.5 mg of subcutaneous terbutaline. No epinephrine was administered in 2 patients who received their fatal injections in medically unsupervised settings (patients 5 and 9). During treatment of anaphylaxis, H_1 blockers were administered to 8 of 13 fatal reactors, H_2 blockers were given acutely to 3 of 13 fatal reactors, and parenteral corticosteroids were administered in 6 of 13 acute fatal reactions. Vasopressor agents were given to 4 of 11 patients, and oxygen was initiated in 14 of 15 cases.

Cardiopulmonary resuscitation was initiated in 13 of 15 patients (Table II). Intubation was attempted in 15 patients but was unsuccessful in 3 patients. Seven respondents indicated that airways were established at intervals ranging from between 1 and 40 minutes after recognition of acute respiratory insufficiency.

Causes of death and autopsy findings. Respondents cited the major cause of death as upper airway edema in 5 patients, asthma in 6 patients, and shock in 6 patients. Upper airways edema, lower airways edema, or both were the most common findings on autopsy reports provided for 3 patients.

Skin test fatality. One skin test fatality was confirmed in a young woman with allergic rhinitis, moderate persistent asthma, and food allergy who had a fatal anaphylactic reaction after application of scratch tests to 90 food antigens (including fish, egg, shellfish, nut, and peanut) by using a Dermapik (Greer Laboratories, Lenoir, NC) skin prick test device. Two weeks before the reaction, the FEV_1 was 1.7 L (36% of predicted value), and the patient was prescribed salmeterol and flunisolide. Treatment with 0.2 mg of subcutaneous epinephrine was initiated 10 to 20 minutes after the onset of severe bronchospasm. Five minute later, the patient experienced respiratory arrest, and resuscitation efforts were unsuccessful.

DISCUSSION

The aims of this survey were to estimate the incidence of fatal immunotherapy reactions and identify possible contributing factors associated with these events. Our approach differed from those of previous studies in that a short survey was first administered to identify both fatal and near-fatal immunotherapy reactions, fatal skin test reactions, and incidence rates on the basis of annual reported numbers of injections. We identified 41 immunotherapy fatalities spanning a 12-year period (1990-2001) through direct and indirect physician reports or an average of 3.4 fatal immunotherapy reactions per year. The latter result resembled the most recent immunotherapy fatality survey of events between 1985 and 1989,

which estimated 4 fatalities annually.[7] The low response rate is likely due to the voluntary and sensitive nature of the survey. Because only 25% of eligible participants responded to the survey, our data might underestimate the sum total experience of allergists in the United States and Canada. However, our inability to obtain a more complete response does not diminish these important findings, which could guide future management strategies.

Our immunotherapy fatality rate estimate of 1 per 2.5 million injections approximated the incidence rates reported by Lockey et al[6] and Reid et al[7] of 1 per 2.8 million injections and 1 per 2 million injections, respectively. It should be noted that incidence rates reported by Lockey et al[6] were based on injection data obtained from a health information provider and might therefore not be directly comparable with our results.

The mean number of injections administered by allergy clinics reporting near-fatal reactions was 51% greater than in clinics reporting no life-threatening immunotherapy reactions. This suggests a reduced likelihood of severe reactions in clinics administering fewer injections. Although unproved, clinics administering fewer injections could also use patient selection criteria that exclude those at higher risk for serious reactions.

It should be emphasized that data in the long surveys were collected retrospectively and therefore are subject to recall bias. In addition, there were no active comparator groups (eg, patients surviving near-fatal reactions) to allow more precise definition of susceptibility and effective interventions that can avert fatal reactions after immunotherapy injections. Nevertheless, the evidence is compelling in this and other surveys that the vast majority of fatal reactors are asthmatic.[6,8,10-12] Fifteen of the 17 patients in this survey had preexisting asthma, most of whom were labile, reflected by prior hospital admissions and emergency department visits, or had moderate or severe airway obstruction. Despite the use of appropriate pharmacotherapy, asthma was considered to be suboptimally controlled at the time of the injection in 60% (9/15) of patients. These observations are consistent with prior observations indicating that patients with unstable asthma and those with reduced lung function are at increased risk for nonfatal systemic reactions.[13]

In this survey it is noteworthy that none of the patients were receiving β-blockers. This might reflect better adherence to well-publicized guidelines advising against coadministration of β-blockers.[14] One fatal reactor who was receiving an ACE inhibitor was reported to have exhibited marked angioedema during the fatal reaction, suggesting that the ACE inhibitor might have facilitated the reaction. Although ACE inhibitors are known to elicit life-threatening angioedema, a large controlled study of nonfatal systemic immunotherapy reactions is needed to define the relative risk of concomitant use of ACE inhibitors in patients receiving them.[15-18]

In contrast to previous surveys, in which most fatal reactions occurred during the build-up phase of immunotherapy, the majority of fatalities occurred with maintenance doses of allergen.[6,7] Although unproved, it is possible that improved clinical practices (eg, reduction in dosing errors during build-up) might have led to a decrease in fatal reactions during the build-up phase.[6,7,14]

Inappropriate clinical settings where injections were given (ie, at home or in an unsupervised clinic) likely contributed to the inability to optimally manage and treat fatal anaphylactic reactions in 3 patients. These patients might have survived in a completely staffed and equipped clinic. In at least 6 cases, intubation attempts were either delayed or unsuccessful.

In approximately one third of cases, epinephrine was not administered in a timely fashion (≤5 minutes, Table II). Delay in administration of epinephrine for severe food-induced anaphylaxis has been associated with poor outcomes.[19] The subcutaneous route predominated in this group, and only 2 patients received intramuscular epinephrine. In this series of patients, use of subcutaneous epinephrine was the standard of practice and predated recent recommendations favoring intramuscular administration as the preferred initial route because high plasma levels can be achieved more rapidly.[20-22] Recently, the United Kingdom Resuscitation Council has recommended that 0.5 mg of intramuscular epinephrine be given as the initial dose for treating life-threatening anaphylaxis in patients 12 years and older and repeated if necessary.[23] Intravenous or intramuscular routes, considered superior to subcutaneous epinephrine, were not used to treat 5 fatal reactors. Thus future adoption of the intramuscular route for initial delivery of a high epinephrine dose combined with timely administration of intravenous epinephrine in patients not responding to intramuscular therapy might significantly reduce injection-related fatalities.

As noted, 3 fatal reactions may have started more than 30 minutes after injections with delay in initiation of epinephrine. Three of 24 fatal cases reported by Lockey et al[6] over 25 years and 2 of 26 fatalities reported in the United Kingdom[24] began 30 minutes or more after injections. Late-onset nonfatal systemic reactions to immunotherapy are not uncommon, representing as many as 38% of all systemic reactions.[25] The most recent immunotherapy practice parameters recommend a waiting period of 20 to 30 minutes but acknowledge that a subset of patients experience late-onset systemic reactions. This guideline recommends that patients at increased risk or with prior late-onset systemic reactions be issued self-injectable epinephrine and that the observation period may need to be extended beyond 30 minutes.[9] It should be noted that only 1 of 3 of late reactors in our survey experienced a previous systemic reaction, and thus late reactions could not have been predicted on that basis.

One fatal reaction was confirmed to have followed skin prick testing with 90 commercial food antigens. On the basis of this survey and others, fatal reactions to skin testing are extremely infrequent. To our knowledge, this is the first report of a fatality associated exclusively with percutaneous testing. All but 1 of 6 fatal reactions reported before 1984 were in asthmatic patients, and all received intradermal testing.[6] Thus even skin puncture testing to

TABLE III. Summary of key findings on data collected in the long survey and authors' suggested recommendations for reducing the future number of fatal reactions to injection immunotherapy and skin testing

Study findings	Proposed recommendations
One fatal reaction to skin prick testing with multiple food allergens	Avoid skin testing in patients with uncontrolled asthma. Minimize the number of test antigens in severe asthmatics.
Asthma symptoms not optimally controlled in 60% of fatal reactors and pretreatment FEV_1 <70% in 50% of asthmatic patients	Consider risk versus benefit before initiating immunotherapy. Withhold immunotherapy if asthma is not well controlled. Assess asthma and PEFR before injections. Dispense self-injectable epinephrine in high-risk patients. Extend the waiting period beyond 30 minutes in high-risk patients.
Fatal reactions at home or in unsupervised clinics	Administer immunotherapy in fully equipped clinic by trained personnel and never at home.
Inadequate epinephrine dosing	Administer epinephrine 1:1000 IM 0.3-0.5 mg; repeat 2× if needed. If no response to IM dosing, give 1:10,000 epinephrine IV infusion.
Difficulty in establishing an airway	Clinical staff must be prepared to establish and maintain airway when necessary.

multiple allergens is not without risk and should be withheld in asthmatic patients whose symptoms are not optimally controlled (Table III).

In conclusion, although fatal reactions to immunotherapy injections are extremely rare events, they continue to occur at approximately the same incidence as reported during the late 1980s.[7] The major findings of this survey and the authors' recommendations to improve patient safety are listed in Table III. Dosing errors and β-blockers were not major contributing factors, as in previous surveys.[6] However, fatal events with administration of immunotherapy at home or in unsupervised medical settings are still being reported. Delay or failure to administer adequate doses of epinephrine is a common feature of fatal reactions. This highlights the need to prohibit injection therapy in any clinic that is not fully equipped and staffed to treat severe anaphylaxis (Table III).

Asthmatic patients whose disease is less than optimally controlled appear to be at highest risk, which highlights the importance of evaluating all asthmatic patients with either peak flow assessments or spirometry before administration of injections. Because in the United Kingdom most fatal reactions occurred in asthmatic patients, the British Society for Allergy and Clinical Immunology issued recommendations that injection immunotherapy should be withheld from patients with chronic asthma or mild seasonal asthma.[8] This view is neither shared nor endorsed by professional societies in most other countries, who acknowledge that immunotherapy is clearly efficacious in seasonal asthma and has a potential role in modifying the natural history of the disease.[26,27] Because the small risk is justified by the overall benefit of immunotherapy for asthma,[1] it is essential to institute aggressive strategies for preventing fatal reactions in this population. As shown in Table III, prevention could be addressed in labile or severely obstructed asthmatic patients by withholding immunotherapy in those with poorly controlled disease, by training patients in the use of self-injectable emergency epinephrine, and by prolonging the observation period. It is likely that immunotherapy fatalities can be reduced in the future by strictly adhering to practice guidelines on patient selection, postinjection observation, preinjection screening of asthmatic patients, and management of anaphylaxis (Table III).[9]

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