

Evaluation of near-fatal reactions to allergen immunotherapy injections

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Background: The overall incidence of near-fatal reactions (NFRs) after immunotherapy injections is unknown. Investigation of NFRs might identify preventive strategies that could avert fatal immunotherapy reactions.

Objective: We sought to determine the incidence and characteristics of NFRs to allergen immunotherapy.

Methods: In a brief survey of fatal reactions (FRs) and NFRs administered to practicing allergists, 273 of 646 respondents reported NFRs after immunotherapy injections; a NFR was defined as respiratory compromise, hypotension, or both requiring emergency epinephrine. Respondents were mailed a 105-item questionnaire regarding the details of NFRs and circumstances of these events.

Results: During the period from 1990 through 2001, the incidence of unconfirmed NFRs was estimated at 23 per year (5.4 events per million injections). There were 68 confirmed NFRs on the basis of responses to the long survey, with a mean case incidence of 4.7 per year or 1 NFR per million injections. Asthma was present in 46% of near-fatal reactors and in 88% of fatal reactors identified in this study. Hypotension was reported in 80% and respiratory failure occurred in 10% of NFRs and exclusively in asthmatic subjects. Epinephrine was delayed or not administered in 6% of NFRs versus 30% of reported FRs (OR, 7.3; 95% CI, 1.4-39.8; $P = .01$).

Conclusions: Confirmed NFRs were 2.5 times more frequent than FRs. Favorable outcomes of NFRs when compared with FRs could be related to lower asthma prevalence and appropriate management of life-threatening anaphylaxis. (J Allergy Clin Immunol 2006;117:169-75.)

Key words: Immunotherapy, anaphylaxis, near-fatal reactions, asthma, epinephrine

Immunotherapy with subcutaneous injections of aeroallergen extracts has proved beneficial in reducing symptoms of allergic rhinitis and asthma.¹ However, injection-related systemic reactions reportedly occur in

Abbreviations used

AAAAI: American Academy of Allergy, Asthma and Immunology

FR: Fatal reaction

NFR: Near-fatal reaction

OR: Odds ratio

5% to 7% of patients receiving build-up and maintenance injections of allergen immunotherapy in North America.²⁻⁴

In these surveys there were few if any descriptions of serious near-fatal systemic reactions.^{3,4} In North America several studies have been conducted over the past 20 years with the purpose of characterizing and estimating the incidence of fatal reactions (FRs) to immunotherapy.^{5,6} In the first of these surveys, Lockey et al⁵ reported 24 FRs that occurred between 1973 and 1984 and estimated that 1 FR occurred in every 2.8 million injections. Subsequently, Reid et al⁶ described 15 immunotherapy-related fatalities that transpired between 1985 and 1989 and estimated 1 fatality in every 2.0 million injections. Recently, we reported the results of an immunotherapy fatality survey that documented 41 FRs between 1990 and 2001, and from these data, we estimated 1 FR in every 2.5 million injections.⁷

Despite characterization of susceptibility factors for immunotherapy fatalities, dissemination of earlier survey findings, and publication of immunotherapy practice parameters, the apparent incidence rate of immunotherapy-related deaths has not changed in the past 40 years.⁸ Although characteristics of immunotherapy-related fatalities have been well defined, there are no data that define factors that contribute to serious near-fatal reactions (NFRs). Characterization of NFRs and effective interventions that prevent fatal outcomes could be useful in formulating guidelines aimed at reducing future fatal events. We conducted a retrospective cross-sectional national survey of immunotherapy-induced NFRs; the objectives were to estimate the incidence of NFRs, define characteristics and treatment of NFRs, and compare characteristics of NFRs with those of FRs.

METHODS

The first phase of the study was initiated with a brief 6-question survey distributed to all physician members of the American Academy of Allergy, Asthma and Immunology (AAAAI) by fax,

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e-mail, and the organizational newsletter between 2000 and 2001. The short survey (available in the Online Repository of this article at www.jacionline.org) queried about both FRs and NFRs associated with immunotherapy injections, and results of fatal events have already been published.⁷ Individuals who did not respond initially were resent the form at least twice; one completed survey response was requested from each allergy practice. In the survey a NFR was defined as severe respiratory compromise, hypotension, or both requiring emergency treatment with epinephrine. On the basis of billing codes, respondents were asked to provide the total number of immunotherapy injections administered in their respective clinics during the previous 1 and 3 years.

Physicians who reported FRs to immunotherapy or skin testing in the short survey were subsequently sent an 87-item questionnaire (available in the Online Repository of this article at www.jacionline.org), which they were asked to complete. Results of the latter survey of FRs have been published.⁷ In this final phase of the study, conducted during 2003 and 2004, detailed 105-item questionnaires were sent to 273 physicians who had reported NFRs on the initial short survey. Key elements captured in the latter questionnaire included (1) demographics; (2) clinical indications for starting immunotherapy; (3) classification of asthma severity, asthma exacerbations, emergency department and hospital visits for acute asthma, and oral steroid requirements; (4) clinical setting where events occurred (allergist vs primary care office); (5) dosing errors, allergen extract concentration, and schedule for immunotherapy administration; (6) timing of immunotherapy injections relative to patient's pollen season; (7) prior local, systemic, or both injection-related reactions; (8) observance by patients of postinjection waiting periods; (9) time of onset of reactions; (10) clinical manifestations of NFRs; (11) treatment of NFRs, including details of epinephrine administration; and (12) physicians' assessments of key factors leading to NFRs.

As described in our previous article on FRs, estimates of incidence rates of NFRs per million injections were based on assumptions that injection data of 646 respondents were representative of 2404 AAAAI member physicians. Analysis of the data was performed with SAS (version 8.1; SAS Institute, Cary, NC) and Epistat (Epistat Services, Richardson, Tex). Because the number of injections was not normally distributed, geometric mean data are presented and used in the calculation of incidence rates. *Confirmed NFRs* refers to the 68 cases reported in both the short and long surveys, whereas *unconfirmed NFRs* are those that were only reported on the initial short survey.

RESULTS

The sample represented 646 (27%) of 2404 clinical practices affiliated with the AAAAI who responded to the short survey. All were located in the United States and Canada. Physicians in 273 practices identified a NFR. Of these, 70 respondents completed the 105-item questionnaire after repeated requests were made through e-mail, fax, and personal communication through the AAAAI. No NFRs to skin testing were reported. There was one report of a vasovagal response after an immunotherapy injection and a second patient who experienced a mild systemic urticarial reaction. The results of 68 reported events meeting the NFR definition are presented below.

Incidence of NFRs

Data from the initial short survey used to estimate the mean annual number of injections administered in allergy

practices reporting no systemic reactions, NFRs, and FRs have already been published.⁷ As reported in the latter article, the geometric mean number of injections administered over 3 years was highest in the practices reporting FRs (mean number, 27,447 injections), followed by those experiencing NFRs (mean number, 23,860 injections). The clinic groups that reported no life-threatening reactions administered a significantly lower geometric mean number of immunotherapy injections (15,835) compared with the groups reporting FRs and NFRs ($P = .016$, ANOVA). Pairwise comparison indicated that the mean number of injections was significantly greater in the near-fatal reactor group versus the nonreactor group ($P < .05$). Similar comparisons were significant among all 3 groups when the mean number of injections administered during 1 year was analyzed.

On the basis of directly reported NFRs (68 cases) and the geometric mean number of injections administered for all respondents, the incidence of confirmed NFRs was 1.0 event per million injections. This rate was approximately 2.5 times greater than the incidence of confirmed FRs (1 per 2.54 million injections). The incidence of unconfirmed NFRs was 5.4 events per million injections. The average incidence of confirmed NFRs was 4.7 events per year, which was 2.8 times more frequent than the incidence of confirmed FRs (1.7 cases per year) during the same reporting period. The average incidence rate of (all) unconfirmed NFRs was estimated at 23 cases per year, which is 5.4 times higher than that of confirmed NFRs.

Patient characteristics

The mean age of the nonfatal reactors was 35.9 years (median, 37.5 years; range, 5-70 years), including 35 (51%) male subjects and 33 (49%) female subjects. Six (9%) NFRs were reported in children 12 years of age or younger (range, 5-12 years). Five of the children were given diagnoses of asthma, one of whom (an 11-year-old subject) had respiratory failure requiring intubation.

Reported comorbid conditions were rare and included 1 patient with diabetes and 5 patients with hypertension. At the time of the NFR, 2 patients were receiving concomitant angiotensin II receptor blockers, and 1 patient was receiving a β -blocker (atenolol, 25 mg daily). The latter patient experienced hives and bronchospasm that responded to inhaled albuterol and 0.3 mg of subcutaneous epinephrine; glucagon was not required. Ten (15%) patients with NFRs had reported taking H₁ blockers on the day of the NFR; there was no trend suggesting less severe reactions among those patients. There were no reports of concomitant angiotensin-converting enzyme inhibitors.

Clinical indication for immunotherapy. Indications for immunotherapy included allergic rhinitis in 33 (49%) of 68 near-fatal reactors, allergic rhinitis and asthma in 29 (43%), asthma alone in 2 (3%), and hymenoptera anaphylaxis in 4 (6%).

Asthma Severity. There were 31 asthmatic subjects, and respondents were asked to categorize asthma severity according to the National Heart, Lung, and Blood Institute classification.⁹ Seventeen (55%) were categorized as

having mild intermittent or mild persistent asthma, 11 (35%) as having moderate persistent asthma, and 3 (10%) as having severe persistent asthma. Although only 20 respondents reported FEV₁ values, 8 (40%) individuals had baseline (before initiation of immunotherapy injections) FEV₁ of less than 70% of predicted values; 4 (50%) experienced respiratory failure requiring intubation during their NFRs versus 2 (17%) of 12 with FEV₁ values of greater than 70%. There were 7 (23%) asthmatic subjects treated with oral corticosteroids within the 6 months before the NFR. Nearly all asthmatic subjects (85%) were receiving inhaled corticosteroids; 5 (16%) were also receiving a concomitant long-acting β -agonist, and 4 (13%) were using leukotriene antagonists exclusively for asthma management. Two (7%) asthmatic subjects were taking oral corticosteroids at the time of the NFR, and physicians reported that 23 (74%) of 31 asthmatic subjects were compliant with recommended inhaled corticosteroids before the NFR. Furthermore, 9% had had emergency department visits for asthma in the past, and 4% had been hospitalized.

Prior reactions to allergen injections. During the 6 months preceding NFRs, local and systemic reactions were reported in 13 (19%) and 6 (9%) respondents, respectively. Prior systemic reactions in 6 patients were manifested as acute bronchospasm in 2 patients, upper airway obstruction in 1 patient, hypotension in 1 patient, and pruritus and hives in 2 patients. Epinephrine was not administered, suggesting that these systemic reactions were not perceived as serious. The next immunotherapy doses were reduced in 1 patient; the remaining 5 patients remained at the same dose that elicited the systemic reaction.

Details of immunotherapy administration

In 67 (99%) of 68 NFRs, allergen extracts were prescribed by board-certified allergists. The near-fatal injections were administered subcutaneously in all but 3 (4%) individuals who received intramuscular injections, which physician respondents attributed to administration errors. Sixty-three (93%) near-fatal events occurred in clinics of board-certified allergists who were present during the reaction; the remaining 5 (7%) NFRs occurred in primary care settings. There were no reports of NFRs in unsupervised clinics or after self-administration. Thirty-eight (58%) received near-fatal injections from maintenance extracts, and the remainder were from build-up vials. Twelve (18%) NFRs followed an initial injection from a new nonmaintenance vial, and only 2 of 68 respondents noted a recent change in allergen extract manufacturer. Nearly all (98%) of the near-fatal injections were administered from vials that were 6 months old or less. NFRs reportedly occurred during the patients' allergy season in 38 (56%) subjects, and dosing errors were reported in 15 (25%) of the near-fatal events.

Clinical manifestations of NFRs

Time of onset. Initial manifestations of NFRs began 30 minutes or less after immunotherapy injection in 65 (96%) of 68 patients, and late-onset reactions occurred in 3

individuals more than 30 minutes after immunotherapy administration. Two of the 3 latter individuals returned to the clinic 45 minutes after receiving the injection, and both experienced pruritus, hives, and bronchospasm. Epinephrine was delayed (>30 minutes) but administered in both individuals. The third patient experienced pruritus and severe hypotension 60 minutes after the injection was administered by a primary care physician; epinephrine was administered immediately on arrival.

Clinical features. Fig 1 shows the clinical manifestations of NFRs, as well as previously reported FRs from this survey.⁷ Nearly all near-fatal reactors experienced hypotension (88%), but fewer had respiratory features of upper airway obstruction (41%) or bronchospasm (51%). There were 20 (30%) patients who experienced no cutaneous manifestations during NFRs (ie, urticaria, angioedema, and/or pruritus). Three (4%) individuals had late-onset reactions (occurring >30 minutes after immunotherapy administration), and 30 (44%) of 68 near-fatal reactors experienced loss of consciousness. Respiratory failure occurred in 7 (10%) of 68 near-fatal reactors, all of whom had moderate or severe asthma; 4 (57%) of 7 requiring intubation had pretreatment FEV₁ values of less than 70% of predicted value. Four of 5 near-fatal reactors who had cardiopulmonary arrest were asthmatic subjects.

Circumstances contributing to near-fatal outcomes

Respondents were queried about factors that significantly contributed to NFRs. Important contributing factors included administration of injections during the height of the allergy season (46% of respondents), allergen vaccine dosing errors (25%), less than optimal asthma control at the time of the NFR (10%), history of previous systemic reactions to allergen injections (9%), concomitant medication (eg, β -blockers; 3%), and premature clinic departure before the end of the required waiting period (3%).

Management of NFRs

One patient who experienced a NFR in a primary care clinic did not receive epinephrine and was managed with intravenous fluids and antihistamines. Eighty-two percent (56/68) of NFRs were treated within 3 minutes of onset of NFRs, and 94% received epinephrine within 20 minutes. The initial epinephrine dose was 0.3 to 0.5 mg in 58 (85%) patients, whereas 7 patients received less than 0.2 mg and 2 patients received more than 0.5 mg. Epinephrine was administered subcutaneously in 45 (66%) patients by the intramuscular route in 18 (27%) patients and by both routes in 4 (6%) patients. There was no significant difference in mean total epinephrine dose between patients receiving subcutaneous (0.6-1.0 mg) versus those receiving intramuscular (0.3-0.6 mg) dosing. Four received both subcutaneous and subsequently intramuscular epinephrine for persistent hypotension and respiratory symptoms. Three patients received intravenous epinephrine (1:10,000). Of 67 patients given epinephrine, 53 (78%) also received systemic corticosteroids, 51 (75%) received H₁

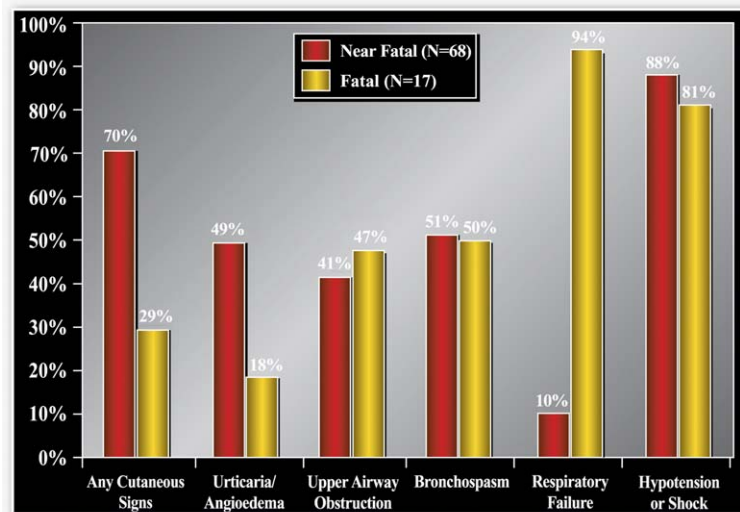


FIG 1. Comparison of clinical features during FRs and NFRs. *Any cutaneous signs* refers to hives, angioedema, and/or pruritus. *Hypotension* refers to either transient or sustained decrease in blood pressure, and *shock* refers to cardiovascular collapse.

antihistamines, 47 (69%) were given oxygen, and 28 (41%) were given intravenous fluids, and vasopressors were begun in 3 (4%) near-fatal reactors. Antihistamines and systemic corticosteroids were administered along with epinephrine in 43 (63%) NFRs.

Comparisons of near-fatal and fatal reactors

Characteristics and management of 68 patients with NFRs were compared with previously reported characteristics of 17 patients with fatal events in this survey.⁷ Common items used in both fatal and near-fatal surveys facilitated these comparisons. It was noteworthy that 15 (88%) of 17 fatal reactors had been given diagnoses of asthma compared with 46% in the larger NFR group. As shown in Fig 1, a similar proportion of patients with FRs (81%) and NFRs (88%) experienced hypotension or shock. Severe airway obstruction leading to respiratory failure was far less common with NFRs. Near-fatal reactors experienced cutaneous symptoms (ie, urticaria and angioedema) more often than fatal reactors.

As shown in Fig 2, there was a higher frequency of responses for all questionnaire items reflecting poorly controlled asthma in fatal reactors. Fatal reactors were much more likely to have had a prior emergency department visit (54% vs 9%; odds ratio [OR], 12.1; 95% CI, 2.6-61.1; $P < .001$) and to have been hospitalized for asthma (61.5% vs 4%; OR, 34.7; 95% CI, 5.7-251; $P < .001$).

It is noteworthy that 93% of NFRs occurred in clinics staffed by allergists in contrast to 59% of fatal events (OR, 8.5; 95% CI, 1.98-41.3; $P = .002$). There were no NFRs in a medically unsupervised setting compared with 2 (12%) of 17 FRs that were reported with home administration of immunotherapy.

Epinephrine was delayed for longer than 20 minutes or not administered in 30% of FRs compared with 6% of NFRs (OR, 7.3; 95% CI, 1.4-40; $P = .01$). Intubation was

required for respiratory failure more frequently among FRs (88%) compared with among NFRs (9%) (OR, 130.7; 95% CI, 13.9-53.5; $P < .001$).

DISCUSSION

This is the first large evaluation of NFRs caused by subcutaneous immunotherapy injections. We acknowledge that the retrospective nature of this survey might lead to recall and reporting bias. Our approach differed from those of previous studies of serious immunotherapy reactions in that we administered a brief 6-item survey to a large group of practicing allergists-immunologists to gather reports of fatal and near-fatal events.^{5,6} The intent of the brief survey was to obtain a high response rate among clinicians and to capture additional information pertaining to NFRs and mean numbers of allergen injections administered in clinics of respondents. Despite multiple efforts, we achieved response rates of 27% and 25% for the short and long surveys, respectively. This degree of participation is typical for professional surveys, and the low responder rate does not diminish the importance of our findings. We also received only 5 (7%) reports of NFRs that occurred in primary care clinics; it is likely that many more might have occurred in this setting. Thus these factors are likely to result in significant underestimates of the true incidence of NFRs.

NFRs occurred in all age groups (ages 5-70 years), including 6 children 5 to 12 years of age; 1 child with respiratory failure required intubation. In the published fatality survey conducted in the initial phase of this study, FRs were also reported in 2 children with asthma, ages 5 and 12 years.⁷ Our observations bear similarity to a prior study by Ostergaard et al,¹⁰ who documented 6 serious anaphylactic reactions (3 were life-threatening) that were

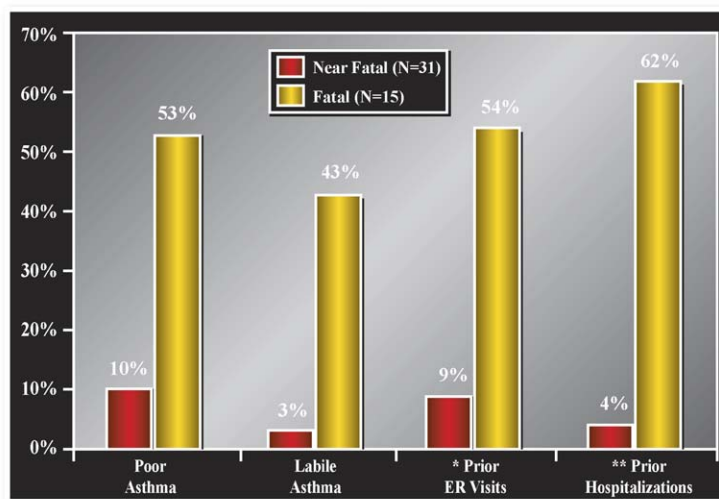


FIG 2. Comparison of asthma severity in fatal and near-fatal reactors. *OR, 12.1 (95% CI, 2.6-61.0; $P < .001$); **OR, 34.7 (95% CI, 5.7-251.1; $P < .001$). ER, Emergency department.

attributed to injections with maintenance doses of mold extract in 106 asthmatic children. More recent prospective studies of asthmatic children reported no serious systemic reactions to pollen, dust mite extracts, or both.^{11,12} Clearly our survey indicates that NFRs and FRs occur among children and primarily in asthmatic subjects. However, there are insufficient data to estimate the risk relative to that seen in adult patients.

We estimated that one confirmed NFR occurred with every 1 million injections and at a rate that was 2.5 times greater than that found for confirmed FRs.⁷ This translated into nearly 5 NFRs per year in North America. However, because unconfirmed NFRs based on responses to the brief survey alone yielded more than 5 times more cases, it is likely that analyzing “confirmed” NFRs (ie, long NFR survey responders) greatly underestimated the true incidence rates of NFRs. As noted in our previous report of FRs, the number of injections administered in clinics reporting NFRs was significantly greater than that in clinics reporting no serious or life-threatening immunotherapy reactions.⁷ This interesting observation could be attributable to reduced probability of NFRs because of fewer overall injections or to the fact that physicians who administer fewer injections are more selective in excluding high-risk patients.

As in fatal surveys, we examined putative contributing factors. Only one of the near-fatal reactors was receiving a β -blocking agent. Interestingly, this therapy did not appear to inhibit treatment responses to epinephrine, nor was glucagon required. The infrequent use of β -blockers in this study likely reflects adherence to published immunotherapy guidelines recommending avoidance of these drugs.^{8,13} Hepner et al¹⁴ conducted a prospective study of β -blocker use in more than 3100 patients receiving immunotherapy, including 68 patients receiving β -blockers. They concluded that the risk of injection-related systemic reactions was not increased but cautioned that β -blockade might increase severity of reactions as they occur.

However, current guidelines advise avoidance of immunotherapy in patients requiring β -blockers.⁸ Because no patients in this study were receiving angiotensin-converting enzyme inhibitors, the effects of these agents in NFRs could not be assessed.

It was not surprising that the majority (54%) of NFRs were reported in nonasthmatic subjects, which contrasted sharply with reports of fatal reactors, most of whom had asthma that was often suboptimally controlled.^{5-7,15} In our study the most severe reactions manifested by acute respiratory failure occurred in 7 patients with asthma, 4 (57%) of whom had reported baseline FEV₁ values below 70% of predicted value. Bousquet and Michel¹⁶ have recommended that immunotherapy with aqueous extracts be withheld from such patients in light of data indicating that asthmatic subjects with FEV₁ value of less than 70% of predicted value are at greater risk for systemic reactions. This report of NFRs further demonstrates the heightened risk of life-threatening reactions in patients with asthma with moderate and severe airway obstruction.

Physician respondents identified immunotherapy administration during peak allergy seasons (46% of respondents) and dosing errors (25% of respondents) as the 2 most important factors contributing to NFRs. In a large physician survey, dosing errors were reported by most respondents and were most often attributed to misidentification of patients and injection of incorrect doses.¹⁷ Our data suggest that dosing mistakes can have serious consequences. As with FR reports, NFRs were more common after injections from maintenance rather than build-up vials.^{2,7,10} It is possible that reactions to maintenance injections might have been related to priming by natural allergen exposure, which could have enhanced sensitivity to doses of previously well-tolerated allergens. Furthermore, intramuscular administration of immunotherapy in a few responders was attributed to error in administration of immunotherapy injection. Although this is definitely in

TABLE I. Summary of key findings from the Near Fatal Reaction Survey and proposed recommendations aimed at preventing life-threatening reactions after immunotherapy injections

Study findings	Proposed recommendations
Patients with reduced FEV ₁ (<70% of predicted value) experienced respiratory failure requiring intubation.	Consider withholding immunotherapy in patients with moderate or severe airway obstruction. Assess all patients for worsening asthma and monitor lung function (PEFR) before immunotherapy injections. Withhold immunotherapy injections if asthma worsens.
Prior systemic reactions were present in 9% of near-fatal reactors.	Reduce subsequent immunotherapy doses. Dispense self-injectable emergency epinephrine to all patients who are continued on immunotherapy. Consider discontinuation of immunotherapy in high-risk patients (eg, those with severe asthma).
Forty-six percent of NFRs occurred during the height of an allergy season.	Consider reduction of immunotherapy doses during relevant pollen seasons.
Dosing errors were implicated in 25% of NFRs.	Prevent dosing errors. ¹⁷ Continuing education of clinic staff. Give injections from patient-specific vials and not "off the board." Use standardized forms and protocols. Routinely check patient identity (name, birth date) before each injection. Same staff person that prepares immunotherapy injection should administer. Allow only 1 patient at a time in the injection room.
Patients depart prematurely from clinic after injections.	All patients should be required to wait 30 minutes in a medically supervised setting after immunotherapy injections.

PEFR, Peak expiratory flow rate.

contrast to usual practice, the need for continual physician and office staff education and awareness of proper administration of immunotherapy is required.

It is noteworthy that 93% of patients experienced NFRs in the offices of allergists, and there were no reports of self-administration in medically unsupervised settings.⁷ This might have facilitated timely treatment of NFRs in that 94% of patients received epinephrine within 20 minutes of onset of reactions. Two late-onset NFRs were reported at 45 and 60 minutes after injections. In previous fatality surveys, most but not all FRs commenced within 30 minutes, whereas non-life-threatening systemic reactions have commonly been reported to begin at 30 to 60 minutes after injections.^{4,18,19} Therefore there is disagreement about the optimal postinjection waiting period. The Joint Task Force allergen immunotherapy practice parameters have recommended a 20- to 30-minute waiting period, whereas the British Society for Allergy and Clinical Immunology has advised 60 minutes.^{8,15}

Prior systemic reactions were noted in 9% of near-fatal reactors, but immunotherapy doses had been reduced in only 1 of 6 patients. According to recent immunotherapy practice parameters (there are no evidence-based guidelines for dose adjustment after systemic reactions), it is usual practice to reduce the dose or consider discontinuation of immunotherapy. This result strongly suggests that after serious systemic reactions, allergists must either

reduce doses to those previously tolerated or discontinue immunotherapy altogether.⁸ Those patients experiencing severe systemic reactions are considered at higher risk for future serious reactions, and physicians must consider discontinuing immunotherapy injections or, at a minimum, significantly reducing future immunotherapy doses.

Clinical manifestations of NFRs were instructive. Hypotension was common (88%), but few patients had respiratory failure (10%). This is likely explained by the low prevalence of poorly controlled asthma. Interestingly, cutaneous manifestations were absent in 30% of patients with NFRs. Taken together with absent cutaneous signs reported in 81% of FRs in this study, the absence of urticaria, angioedema, or both cannot be used as a major criterion for diagnosing life-threatening anaphylaxis.⁷

Delay or failure to administer epinephrine for immunotherapy-induced anaphylaxis has been associated with poor outcomes.^{7,15} In this study timely administration of epinephrine likely contributed to nonfatal outcomes. Intramuscular epinephrine, which achieves higher plasma levels than subcutaneous epinephrine, was administered in 31% of NFRs. However, we were unable to detect any differences in clinical outcomes attributable to route of administration.²⁰⁻²² It is noteworthy that 37% of NFRs were not treated with either systemic corticosteroids or antihistamines, and this did not apparently make a difference in outcomes. However, optimal therapy for anaphylaxis

should include treatment with epinephrine, diphenhydramine, and corticosteroids.

The major findings of this survey and the proposed recommendations aimed at preventing life-threatening reactions after immunotherapy injections are listed in Table I. These recommendations address measures aimed at preventing severe reactions associated with moderate to severe airway obstruction, prior systemic reactions, reactions during the height of an allergy season, and dosing errors.

In conclusion, NFRs are not uncommon, and the incidence of fatal immunotherapy reactions has not changed in the past 40 years. More effort is needed to identify and develop methods to control risks associated with NFRs.⁷ NFRs occur more frequently than FRs. Near-fatal events were managed successfully with prompt administration of epinephrine in physician-supervised clinic settings, affirming recent recommendations of the Joint Task Force Allergen immunotherapy practice parameters that immunotherapy be given in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis are assured.⁸ Patients with asthma and reduced lung function (<70%) appeared to be at greatest risk for severe respiratory compromise during a NFR. This highlights the importance of weighing risks and benefits before initiating immunotherapy in patients with severe asthma and the need to carefully monitor asthma symptoms and lung function before immunotherapy injections.⁸ Finally, patients who have experienced a NFR should be considered at increased risk for future FRs or NFRs, and the physician should consider the risks versus benefits of continuing immunotherapy in this setting.

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REFERENCES

- Abramson M, Puy R, Weiner J. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003;4: CD001186.
- Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM, Scordamaglia A, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. *J Investig Allergol Clin Immunol* 1997;7:151-4.
- Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. *J Allergy Clin Immunol* 1986;77:865-70.
- Ragusa VF, Massolo A. Non-fatal systemic reactions to subcutaneous immunotherapy: a 20-year experience comparison of two 10-year periods. *Allerg Immunol (Paris)* 2004;36:52-5.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993;92:6-15.
- Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
- Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2003;90: 1-40.
- National Heart, Lung and Blood Institute. Guidelines for the diagnosis and management of asthma. *Lippincott Health Promot Lett* 1997;2:1, 8-9.
- Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. *Allergy* 1986; 41:588-93.
- Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. *J Investig Allergol Clin Immunol* 1997;7:90-7.
- Pifferi M, Baldini G, Marrazzini G, Baldini M, Ragazzo V, Pietrobelli A, et al. Benefits of immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract in asthmatic children: a three-year prospective study. *Allergy* 2002;57:785-90.
- Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol* 1996;98:1001-11.
- Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Ewald D, Brown EB. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990;86:407-11.
- Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. *BMJ* 1993;307:919-23.
- Bousquet J, Michel FB. Safety considerations in assessing the role of immunotherapy in allergic disorders. *Drug Saf* 1994;10:5-17.
- Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. *J Allergy Clin Immunol* 2004;113:1117-21.
- Greenberg MA, Kaufman CR, Gonzalez GE, Trusewicz ZP, Rosenblatt CD, Summers RJ. Late systemic-allergic reactions to inhalant allergen immunotherapy. *J Allergy Clin Immunol* 1988;82:287-90.
- Altintas D, Akmanlar N, Guneser S, Burgut R, Yilmaz M, Bugdayci R, et al. Comparison between the use of adsorbed and aqueous immunotherapy material in *Dermatophagoides pteronyssinus* sensitive asthmatic children. *Allergol Immunopathol (Madr)* 1999;27:309-17.
- Hughes G, Fitzharris P. Managing acute anaphylaxis. New guidelines emphasise importance of intramuscular adrenaline. *BMJ* 1999;319:1-2.
- Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998; 101:33-7.
- Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001; 108:871-3.