Use of multiple doses of epinephrine in food-induced anaphylaxis in children

Kirsi M. Järvinen, MD, PhD, Scott H. Sicherer, MD, Hugh A. Sampson, MD, and Anna Nowak-Wegrzyn, MD
New York, NY

Background: Food allergy is the most common cause of anaphylaxis outside the hospital setting.
Objective: We sought to determine the rate, circumstances, and risk factors for repeated doses of epinephrine in the treatment of food-induced anaphylaxis in children.
Methods: Anonymous questionnaires were distributed to families of children with food allergies during allergy outpatient visits to a food allergy referral center. Demographic information, allergy and reaction history, and details regarding the last 2 anaphylactic reactions requiring epinephrine were collected.
Results: A total of 413 questionnaires were analyzed. Seventy-eight children (median, 4.5 years of age; range, 0.5-17.5 years) reported 95 reactions for which epinephrine was administered. Two doses were administered in 12 (13%) and 3 doses in an additional 6 (6%) reactions treated with epinephrine. Peanut, tree nuts, and cow's milk were responsible for >75% of reactions requiring epinephrine. Patients receiving multiple doses of epinephrine more often had asthma ($P = .027$) than children receiving a single dose. The amount of food ingested or a delay in the initial administration of epinephrine were not risk factors for receiving multiple doses. The second dose of epinephrine was administered by a health care professional in 94% of reactions.
Conclusion: In this referral population of children and adolescents with multiple food allergies, 19% of food-induced anaphylactic reactions were treated with more than 1 dose of epinephrine. Prospective studies are necessary to identify risk factors for severe anaphylaxis and to establish rational guidelines for prescribing multiple epinephrine autoinjectors for children with food allergy. (J Allergy Clin Immunol 2008;122:133-8.)

Key words: *Food allergy, autoinjector, self-injectable, epinephrine, children, anaphylaxis, food-induced anaphylaxis, peanut allergy, tree nut allergy, cow's milk allergy, milk allergy*

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.[1] In the United Kingdom, the estimated annual incidence is 10.2 in 100,000, which represents almost a doubling over a period of 4 years, and food-induced anaphylaxis increased more than other etiologies,[2] as also shown especially in children less than 5 years of age in a report from Australia.[3] Anaphylaxis may sometimes follow a biphasic course (initial symptomatic period followed by an asymptomatic period of 30 minutes to 72 hours) or protracted course (symptoms not responding to treatment and lasting up to 72 hours).[4,5] Epinephrine is the drug of choice for the treatment of anaphylaxis.[1,6,7] Prompt use of epinephrine in the field reduces the need for hospital admission for anaphylaxis in children, whereas delayed administration of epinephrine has been identified as a risk factor for fatal food-induced anaphylaxis.[5,6,8-11]

Allergic reactions to foods affect as many as 6% of children,[12] and food allergy is the most common cause of anaphylaxis in children (81% of reactions).[13] Reports from predominantly mixed or adult populations indicate that 16% to 35% of anaphylactic reactions from a variety of causes require more than 1 dose of epinephrine.[14-19] There are few previous data about epinephrine use in food-induced anaphylaxis, especially in children. By using a questionnaire, the Anaphylaxis Campaign in the United Kingdom found that a second dose of epinephrine was given in 1 (10%) out of 10 children and 3 (25%) out of 12 adults with anaphylaxis requiring epinephrine in the community, although details about epinephrine administration were not available (when given, where, by whom, and so forth).[15] Another report with a focus on food-related anaphylactic reactions was based on a retrospective chart review of 19 patients who presented to the emergency department. Twelve (63%) patients with anaphylaxis, including 3 children, were administered at least 1 dose of epinephrine (most of which were administered subcutaneously), and 3 patients (16%), all adults, were administered a second dose.[14] Even less is known about how often 3 doses of epinephrine are required in any population. In a retrospective chart review of 105 anaphylactic reactions requiring epinephrine in adults and

From the Division of Pediatric Allergy and Immunology and the Jaffe Institute for Food Allergy, Mount Sinai School of Medicine.

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Reprint requests: Kirsi M. Järvinen, MD, PhD, Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: kirsi.jarvinen@mssm.edu.

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Abbreviation used
EAI: Epinephrine autoinjector

children for insect venom immunotherapy or live stings (Hymenoptera such as bees, wasps, and hornets), 35.5% were given more than 1 dose, and 16% were administered 3 or more doses of epinephrine.[16] It has been suggested that the patients at risk for severe anaphylaxis[19] or food-induced anaphylaxis[14] should always carry 2 doses of epinephrine.

There often are differences in the clinical presentations of allergic reactions between adults and children; pediatric data are scarce on the incidence of food-induced anaphylaxis requiring multiple doses of epinephrine. The purpose of the study was to determine the prevalence and risk factors for administration of repeated doses of epinephrine in food-induced anaphylaxis in children.

METHODS

An anonymous questionnaire (1 page/10 items general questions and additional 1 page/21 items each to report as many as 2 anaphylactic reactions) was administered to parents or caregivers of the consecutive patients presenting for an initial or follow-up evaluation for food allergy to the hospital-based pediatric allergy clinic and to our private practice-based pediatric food allergy referral clinic at Mount Sinai Hospital, New York, between September 2006 and February 2007. Patients as old as 18 years were included. English-speaking or Spanish-speaking children of all ethnic backgrounds were included, and families were provided questionnaires in their native languages. Details were sought regarding demographic information, history of food allergies, present history of asthma, number of past anaphylactic reactions, and the last 2 anaphylactic reactions requiring epinephrine: foods suspected, onset of symptoms and timing of treatment with single or multiple doses of epinephrine. As many as 2 most recent reactions requiring epinephrine without time limit were included, and the time of recall was recorded. Because of the anonymous nature of this questionnaire, all information was based on self-report without review of medical records.

Symptoms were considered consistent with anaphylaxis if they occurred rapidly within minutes to several hours after exposure and affected at least 2 major organ systems, according to recently established guidelines.[1] The severity of reaction was graded on the basis of the scoring described by Sampson.[20]

Data were analyzed by using SigmaStat (Version 2.03; SPSS, Chicago, Ill). The Mann-Whitney rank-sum test was used for comparisons of medians and *t* test for comparisons of means. The χ^2 test and Fisher exact test were applied to determine differences in proportions. A P value less than .05 was considered statistically significant. The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, New York, NY.

RESULTS

A total of 542 questionnaires were distributed, 512 (94%) were returned, and after review, 99 were excluded (78, no food allergy; 4, >18 years of age; 17, mostly incomplete), leaving 413 questionnaires for analysis (81%). Table I describes the clinical characteristics of the patients. The median age of the patients was 4.5 years, and the majority had multiple food allergies. Fifty-one percent of the subjects reported a history suggestive of a systemic reaction to food, but only 20% had ever used epinephrine. Sixty-two (28%) of those 211 patients who reported a history suggestive of a systemic reaction did not carry an epinephrine autoinjector (EAI) to the appointment, and of these, 36 (58%) reported a history of multiple systemic reactions.

TABLE I. Clinical characteristics, reaction history, and prescription details of study participants

Total N	413
Age (y), median (range)	4.5 (0.5-17.5)
Sex, male	262 (63%)
Insurance, private	404 (98%)
English-speaking, non-Hispanic	408 (99%)
Time from reaction to recall (mo), median (range)	24 (0.25-147)
Current asthma	152 (37%)
Food allergy to:	
Peanut	290 (70%)
Tree nuts*	202 (49%)
Hen's egg	182 (44%)
Cow's milk	168 (41%)
Soybean	107 (26%)
Seeds†	94 (23%)
Wheat	76 (18%)
Shellfish	72 (17%)
Fish	69 (17%)
Epinephrine ever prescribed	347 (84%)
EAI present at the appointment	195 (47%)
History suggestive of a systemic reaction to food‡	211 (51%)
Ever used epinephrine	84 (20%)

*Almond, Brazil nut, cashew, hazelnut, macadamia, pecan, pine nut, pistachio, and walnut.
†Mustard, sesame seed, poppy seed, and sunflower seed.
‡Answered positively to the question, "Has your child ever had allergic reactions after eating food that included 1 or more of the following: throat closing, cough, respiratory distress, wheeze, low blood pressure, or passing out?"

The parents of the subjects were asked to record the details of as many as 2 allergic reactions that had been treated with epinephrine, describing the most recent episodes if there were more than 2. The median time to recall was 24 months (Table I). Seventeen subjects reported details of 2 reactions, and 61 reported 1 reaction, giving a total of 95 reactions in 78 children for analysis. Of the 95 reactions treated with epinephrine, 77 reactions (81%) were treated with a single dose of epinephrine, and 18 reactions (19%) were treated with multiple doses of epinephrine. In 2 reactions, it was not clear whether more doses were given, and therefore, these reactions were classified as requiring a single dose only. The demographics of the subjects and circumstances of the reactions treated with either a single dose or with multiple doses of epinephrine are presented in Table II. Peanut, tree nuts, and cow's milk were responsible for 2/3 of the reactions. The proportions of children with allergy to peanut (8.2%), tree nuts (7.3%), and cow's milk (10.7%) who reported reactions treated with epinephrine to the food in question were not significantly different. However, children with cow's milk–induced anaphylaxis were significantly younger (median, 2.2 years; range, 0.5-5.3 years) than children with peanut-induced or tree nut–induced anaphylaxis (median, 3.7 years; range, 1-13 years; $P = .021$). Reactions occurred at home in 52% of those given a single dose and in 39% of those given multiple doses of epinephrine. The subjects treated with multiple doses of epinephrine more often reported asthma at the time of completion of the survey ($P = .005$) than those treated with a single dose, but otherwise there was no difference in the sex, age, onset of reaction, food, amount of food, or location of the reaction between the groups. Lack of skin symptoms was not associated with delayed administration of epinephrine, and in fact, those subjects who presented without hives were treated with epinephrine earlier (median, 10 minutes; range, 1-45

TABLE II. Demographic and reaction details in 95 food-induced anaphylactic reactions that were administered either a single dose or multiple doses of epinephrine

	Single dose	Multiple doses	*P* value
No. of reactions	77 (81%)	18 (19%)	
Age (y), median (range)	3 (0.5-13.8)	4.1 (0.5-9.8)	.54
Sex, male	54 (70%)	15 (83%)	.38
Asthma	43 (56%)	17 (94%)	.005
Onset (min), median (range) min	5 (1-120)	3.5 (2-60)	.37
Food			
Peanut	18 (23%)	6 (33%)	.38
Tree nut	9 (12%)	3 (17%)	.69
Peanut or tree nut*	4 (5%)	0	.10†
Cow's milk	12 (16%)	6 (33%)	.10‡
Hen's egg	0 (0%)	1 (6%)	.19
Wheat	9 (12%)	0	.20
Soybean	2 (3%)	0	1.0
Fish/shellfish	2 (3%)	1 (6%)	1.0
Seed	2 (3%)	0	1.0
Other	4 (5%)	0	1.0
Unknown/no answer	15 (19%)	2 (11%)	.51
Location			
Home	40 (52%)	7 (39%)	.46
Other	30 (39%)	9 (50%)	.55
No answer	7 (9%)	2 (11%)	.68
Amount ingested			
Full/half serving	24 (31%)	3 (17%)	.35
A bite/teaspoon	22 (29%)	4 (22%)	.97
A tiny taste	7 (9%)	3 (17%)	.39
Not ingested§	3 (4%)	2 (11%)	.24
Unknown/no answer	21 (27%)	6 (33%)	.81

*Unknown whether peanut or tree nut was responsible.
†Peanut, tree nut (almond, Brazil nut, cashew, hazelnut, macadamia, pecan, pine nut, pistachio, walnut), and peanut or tree nut; $P = .72$.
‡Peanut, tree nut, peanut or tree nut, and milk; $P = .059$.
§Reported exposure via inhalation or skin contact.

TABLE III. Details of the first dose of epinephrine and other treatments given in 95 food-induced anaphylactic reactions that were administered either a single dose or multiple doses of epinephrine

	Single dose (n = 77)	Multiple doses (n = 18)	*P* value
Who administered first dose			
Parent/self	45 (58%)	9 (50%)	.69
School nurse	3 (4%)	1 (6%)	.58
Emergency department	21 (27%)	3 (17%)	.55
Emergency medical service	5 (6%)	2 (11%)	.61
Doctor's office	3 (4%)	3 (17%)	.22
Why first dose not administered by caretaker/self*			
N	29	8	.43
First reaction	17 (59%)	3 (38%)	.56
Not available	4 (14%)	0	.0
Not sure when to use/afraid to use	4 (14%)	1 (13%)	.049
No answer	4 (14%)	4 (50%)	
Other treatments			
Antihistamine, oral	54 (70%)	14 (78%)	.72
Steroid, oral/intravenous	31 (40%)	6 (33%)	.79
Albuterol, inhaled	14 (18%)	2 (11%)	.73
Oxygen via mask	5 (6%)	2 (11%)	.61
Intravenous fluids	6 (8%)	5 (28%)	.031
Observation, median (range)†	4 (0‡-120) h	6 (2-24) h	.09

*School nurse is considered a caretaker when child is at school.
†Time under physician observation from resolution of the symptoms to discharge.
‡The patient was not brought to medical attention after the use of EAI despite general recommendations.

minutes) than those who presented with hives (median, 20 minutes; range, 1-180 minutes; $P = .03$).

The initial severity of reaction[20] was comparable between the subjects who received a single (mean anaphylaxis score, 4; range, 2-5) or multiple (mean anaphylaxis score, 4; range, 1-5) injections. In 3 reactions in which a single dose of epinephrine was administered, epinephrine was given prophylactically without appearance of any symptoms. However, there was a tendency for the subjects treated with multiple doses of epinephrine to present more often with feelings of throat closure ($P = .055$) than those who were administered only a single dose of epinephrine, but otherwise there was no difference in the frequency of symptoms between the groups. Details of treatments given in both groups are presented in Table III. In those subjects who were treated with multiple doses of epinephrine, intravenous fluids were used more often ($P = .031$); there was a tendency for the first dose of epinephrine to be administered earlier ($P = .07$) and the observation period under physician supervision before discharge for home tended to be longer ($P = .09$) than in those treated with a single dose. In about half the cases overall, the first (or only) dose of epinephrine was not administered by the caretaker or the subject, but by a health care professional (Table III), and in 59% and 38% of such episodes, this was because it was a first reaction in patients given a single and multiple doses or epinephrine, respectively (Table III). Half the patients with multiple doses of epinephrine gave no answer why a health care professional had given the first dose of epinephrine despite options given (not available, not sure when to use, afraid to use, other), whereas only 14% of those with single dose gave no answer ($P = .048$). Protracted symptoms over the following 24 to 48 hours were reported in 7 subjects requiring a single dose (4 with urticaria, 2 with diarrhea, and 1 with skin erythema) and in 1 subject requiring multiple doses of epinephrine (nonspecified), totaling 9% of the whole cohort. None of these late symptoms was treated with epinephrine.

Details of 18 reactions requiring multiple doses of epinephrine are presented in Table IV. Among those, 6 reactions, representing 1/3 of the reactions that were treated with 2 doses of epinephrine and 6% of the total of 95 reactions, were administered 3 doses of epinephrine. The first dose was administered by a health professional in 9 of 18 reactions (50%). The second dose was administered by a health professional in 17 of 18 reactions (94%) and the third dose in 100% of the reactions. A subgroup analysis showed that in reactions in which 3 doses of epinephrine were administered, compared with those receiving 2 doses, peanut was a more common trigger ($P = .013$), and difficulty swallowing ($P = .022$), throat closure ($P = .014$), and hypotension ($P = .022$) were reported more frequently. Groups were otherwise comparable with regard to the eliciting foods and amount of food ingested, reaction location, timing of symptom onset, time to the first dose of epinephrine, and additional treatments given (data not shown).

TABLE IV. Details of 18 reactions treated with 2 and 3 doses of epinephrine

Food	Route	Age (y)	Asthma	Symptom	Location	Onset of symptoms (min)	First dose* (min)	Giver	Why first dose not given by parent or self?	Second dose* (min)	Giver	Why second dose not given by parent or self?	Third dose* (min)	Giver	Late symptoms
Reactions requiring 2 doses of epinephrine (n = 12)															
Cow's milk	Ing	0.5	Yes	U, TC	NA	2	2	Parent		NA	ED	Not answered	NA	NA	No
Cow's milk	Ing	0.5	Yes	U, TC	NA	2	2	Parent		NA	ED	Not answered	NA	NA	No
Cow's milk	Ing	1.5	Yes	U, H	Daycare	?	?	ED	NA	NA	ED	Parent did not give first dose	NA	NA	No
Cow's milk	?	*3*†	Yes	U, TC, W, MI, SOB	Home	2	3	Parent		5	EMS	Not sure when to use	NA	NA	No
Cow's milk	Ing	5	Yes	MI	Home	2	5	Parent		30	Office	Taken to doctor's office	NA	NA	No
Tree nut	Ing	*1.25*†	Yes	U, W, MI, C, SOB	Home	60	90	Parent		5	EMS	EMS arrived	NA	NA	No
Tree nut	Ing	2.75	Yes	U, TC, V, W, C	Friend/ family	30	30	ED	NA	NA	ED	Parent did not give first dose	NA	NA	No
Tree nut	Ing	6.5	No	MI	Friend/ family	2	5	Parent		60	ED	Not answered	NA	NA	No
Peanut	Ing	4.5	Yes	U, C, SOB	Home	<5	<15	EMS	First reaction	15	ED	First reaction	NA	NA	No
Peanut	Skin/ inh‡	10	Yes	U, TC, SOB, AP	Home	?	?	ED	Not sure when to use	20	ED	Parent did not give first dose	NA	NA	No
Egg	Ing	NA	Yes	U, MI, SOB, HT	Restaurant	5	5	Parent		?	Parent	NA	NA	NA	Yes
?	?	3	Yes	U, H, TC, MI, AP, DS	Friend/ family	?	?	Parent		15	ED	Not answered	NA	NA	No
Reactions requiring 3 doses of epinephrine (n = 6)															
Peanut	Ing	2.5	Yes	U, H, TC, W, HT, PO, DS	Friend/ family	5	?	Office	First reaction	10	Office	First reaction	?	ED	No
Peanut	Ing	6	Yes	DS, TC, MI, SOB	Friend/ family	?	?	Office	NA	?	Office	Parent did not give first dose	?	ED	No
Peanut	Ing	6.5	Yes	AP, TC, SOB, DS	Friend/ family	?	?	Office	NA	?	Office	Parent did not give first dose	?	ED	No
Peanut	Ing	9	Yes	U, TC, V, MI, SOB, HT, AP	School	20	30	School nurse	At school	45	ED	At school	120	ED	No
Cow's milk	Ing	4.5	Yes	U, TC, S, V, SOB, C, HT, PO, AP	Home	2	10	EMS	First reaction	5	EMS	First reaction	?	ED	No
Peanut/ milk	Kiss‡	3.5	Yes	U, H, TC, C, SOB, HT, AP, DS	Other	5	20	Parent		15	EMS	Not answered	25	ED	No

AP, Abdominal pain; *C,* cough; *DS,* difficulty swallowing; *ED,* emergency department; *EMS,* emergency medical service; *H,* hoarseness; *HT,* hypotension; *ing,* ingested; *inh,* inhalation; *MI,* mouth itching; *NA,* not applicable; *office,* doctor's office; *PO,* passing out; *S,* sneezing; *SOB,* shortness of breath; *TC,* throat closing; *U,* urticaria; *V,* vomiting; *W,* wheeze; *?,* unknown.

*Time is calculated from exposure to administration of the first dose or from the previous dose with epinephrine to the second and the third dose.

†Ages in italics present the same patient.

‡Two subjects reported reactions on inhalation, skin contact, or kissing; lack of ingestion could not be further verified.

DISCUSSION

Previous data regarding epinephrine use in childhood food-induced anaphylaxis are scarce. Reports from predominantly adult or mixed age populations indicate that 16% to 35% of anaphylactic reactions require more than 1 dose of epinephrine.[14-19] We report that a second dose of epinephrine was administered in 19% and a third dose in 6% of food-induced anaphylactic reactions occurring in children with multiple food allergy.

In our cohort, peanut, tree nuts, and cow's milk were responsible for >75% of reactions requiring single or multiple doses of epinephrine. Cow's milk was responsible for 16% and 33% of reactions requiring single and multiple injections, respectively. Children with cow's milk-induced anaphylaxis were younger than those with peanut-induced or tree nut–induced anaphylaxis. In a US food allergen–induced fatality registry (n = 63), peanut or tree nuts were responsible for 87% and cow's milk for 8% of fatalities (fish and shellfish were responsible for the remainder).[8,9] Although cow's milk allergy often resolves[21] and may often account for mild symptoms, our data and the data from the fatality registry underscore the important point that cow's milk can be a potent allergen. In our survey, 2/3 of the reactions to cow's milk treated with epinephrine occurred at home (based on 16 reactions for which location was available), indicating the difficulty in avoiding this ubiquitous allergen.

According to a review by Kemp,[22] known risk factors for food-induced anaphylaxis in childhood include older age, asthma, previous reactions involving the respiratory tract, peanut or tree nut allergy, reactions to trace exposures, and a strong positive allergy skin test response. Indeed, we found that current asthma was more common in children who were given multiple doses of epinephrine, although history of asthma was not assessed at the time of the reaction. Asthma has previously been identified as a significant comorbidity for severe and fatal anaphylaxis,[5,8,9,23,24] and it has been associated with requirement for multiple doses of epinephrine.[15] Data suggest that if the bronchospasm is exacerbated during an allergic reaction, reversing the episode will be more difficult,[5] suggesting that the recommendation to carry 2 doses of epinephrine should at minimum be extended to individuals with asthma and significant food allergies.

In our survey, in those subjects who were treated with multiple doses of epinephrine, there was a tendency that the first dose of epinephrine was administered earlier, and intravenous fluids were used more often. The earlier administration of epinephrine during reactions eventually treated with multiple doses of epinephrine likely reflects increased initial severity and more rapid progression of the symptoms. It may also support the view that need for multiple doses of epinephrine is not always a result of a delay in administration of the first dose of epinephrine, although our finding must be confirmed in a larger number of subjects.

In the current study, administration of the second and the third dose of epinephrine occurred usually within 30 minutes from the administration of the previous dose, although this was subject to significant recall bias. This observation supports the view that, in the majority of the reactions, the requirement for multiple doses of epinephrine is not a result of the biphasic nature of the reactions but the lack of response to the initial dose. Additional reasons for requiring a second dose of epinephrine include inadequate dose of epinephrine per kilogram of body weight, an expired device, or improper use of the device, none of which could be captured in our anonymous survey. Use of the subcutaneous route of administration for epinephrine has been suggested as a possible explanation for lack of response,[25] although the ½-inch (14.29-mm) needle of the EAI should allow intramuscular access, the preferred route, in most children.[7]

In the review of the subjects' previous reactions, it was surprising that although 51% of the subjects reported a history suggestive of a systemic reaction to food, only 20% had ever used epinephrine. Similar findings were reported previously by the Canadian Surveillance Program,[13] in which only 32% of anaphylactic episodes were treated with epinephrine. It may be assumed that symptoms resolved either spontaneously or by using other medications. The rate of resolution of symptoms of anaphylaxis left untreated with epinephrine is not known, and relying on medications other than epinephrine for treatment of anaphylaxis is not recommended[1]; therefore, this patient response is not in accordance with typical medical advice and suggests a deficit in patient education. On the other hand, the high incidence of subjective symptoms such as feeling of throat closure, especially in those reactions for which multiple doses of epinephrine were administered, may raise the question whether epinephrine was administered too liberally in some circumstances. Whether caused by anxiety or not, the majority (94%) of the second doses were in fact administered by a health care professional, which suggests that these doses were truly required. Although it is also possible that health professionals assessing subjective symptoms such as a feeling of throat closing might be more likely to err on the side of caution and administer another dose of epinephrine, additional factors support the more severe nature of reactions treated with more than 1 dose. These include the observation that these reactions were mostly described to include additional severe and objective symptoms, and that a third dose of epinephrine was given for 1/3 of the reactions receiving a second dose. In all cases, the third dose was administered by a health professional, again pointing toward significant severity of symptoms.

Regarding who administered the first dose epinephrine, in about half the cases the first dose of epinephrine was not administered by the caretaker or the subject, but by a health care professional. In 59% and 38% of such cases in which the subject was given a single and multiple doses of epinephrine, respectively, administration by a health care professional was understandable because it was the subject's first reaction. However, a significantly larger proportion (½) of the patients with multiple doses of epinephrine gave no answer for why a health care professional had given the first dose of epinephrine despite ready options given, whereas only minority of those with single dose gave no answer. This might be a result of anxiety involved with reactions with increased initial severity and more rapid progression of the symptoms as may have been the case with those requiring multiple doses of epinephrine, or it might simply have been a result of long recall time.

The limitations of our study include a retrospective design that lends itself to a recall bias and/or loss of recall, both of which might affect the accuracy of the number of doses of epinephrine given and especially the circumstances including the amount of food eliciting the reaction and time to symptoms and to treatment with epinephrine; a follow-up prospective investigation is planned. Another limitation concerns the selected population of children with multiple food allergies, predominantly residing in urban and suburban areas of New York, New Jersey, and Connecticut. Less severely affected children may have reduced needs for epinephrine, and access to care may influence the dependence on carrying

additional doses. For example, 90% of reactions in our subjects received their second or third dose of epinephrine under medical observation, which may not have been the case for persons in more rural settings where carrying additional doses may be even more important. More than 90% of participants had private insurance, so our data are representative of a more affluent population for whom access to care and availability of prescribed EAIs were not interfering with management of food-induced anaphylactic reactions. It could be surmised that use is more problematic in less affluent populations.

Some experts[14,19] have advised carrying 2 doses of epinephrine despite limited data about the need. Our survey performed in a highly selected patient population indicates that a significant number of respondents received a second dose of epinephrine. Although prospective studies are needed, our results contribute to the evidence base required to identify risk factors for severe anaphylaxis, and to establish rational guidelines for prescribing 1 or more doses of self-injectable epinephrine for the growing number of children at risk for anaphylaxis.

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Clinical implications: Our results contribute to the evidence base required to identify risk factors for severe anaphylaxis and to establish guidelines for prescribing multiple doses of self-injectable epinephrine for children at risk for anaphylaxis.

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