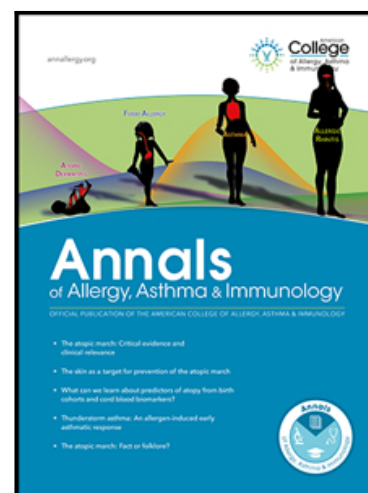


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Title: Risk Factors for Multiple Epinephrine Doses in Food-Triggered Anaphylaxis in Children

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Abstract: Background: Food-related anaphylactic reactions may require treatment with more than one dose of epinephrine. Current guidelines advise patients at risk of anaphylaxis to carry two epinephrine autoinjectors.

Objective: The objective of this study was to determine risk factors of multiple dose epinephrine treatment in pediatric food-related anaphylaxis.

Methods: Parents of children with physician-confirmed diagnosis of food allergy were administered a standardized questionnaire at the time of their clinic visit. These patients were then followed-up prospectively by phone.

Results: Six hundred forty-two subjects had allergic reactions. Twentysix percent of patients reported at least one reaction treated with epinephrine for a total of 221 reactions. Among reactions treated with epinephrine, twenty-four reactions (11%) received two or more doses of epinephrine. The most common triggers were milk (30%) and peanut (18%). Milk-triggered allergic reactions (odds ratio (OR) 3.2, 95% confidence interval (CI) 1.2-8.4) and treatment with oxygen (OR 5.0, 95% CI 2.0- 12.4) were significant risk factors for requiring multiple doses of epinephrine to treat an allergic reaction.

Conclusion: This study demonstrates that treatment of anaphylaxis may require more than one epinephrine injection. Reactions triggered by milk or requiring treatment with oxygen are at higher risk for needing more than one dose of epinephrine. Families of food-allergic children should be counseled on the importance of carrying two epinephrine auto-injectors.

Key words: Food allergy, anaphylaxis, epinephrine, children, cow's milk allergy, asthma

Abbreviations:

CI – Confidence Interval

OR – Odds Ratio

IQR – Interquartile Range

EMS – Emergency Medical Services

ED – Emergency Department

Trial Registration: not applicable

Conflicts of Interest: none

Introduction

Anaphylaxis is a severe, potentially fatal allergic reaction, and better clinical outcomes are reported when anaphylaxis is recognized and treated early.¹⁻³ The majority of cases with anaphylaxis presenting to the pediatric emergency room has been shown to be due to food allergy.⁴⁻⁷ While the reported prevalence of food allergies varies between studies, allergy to food is increasingly common among children in recent years.^{8,9} Intramuscular epinephrine is the recommended treatment in the setting of anaphylaxis, and the current recommendation is for patients to carry two doses of self-injectable epinephrine.¹⁰

Previous studies have evaluated food-induced allergic reactions that require multiple epinephrine injections in the emergency department (ED). Among cases of food-induced anaphylaxis presenting to the ED, two or more epinephrine doses were administered in up to 16-17% of adult patients with anaphylaxis.^{11,12} In a study evaluating specifically the pediatric population presenting to the ED with food-induced anaphylaxis, 12% received multiple epinephrine injections.¹³

One study assessed for predictors of multiple epinephrine injections to treat anaphylaxis of any trigger presenting to the ED in both adult and pediatric patients.¹⁴ The following predictors were associated with increased risk of needing more than one epinephrine dose: history of anaphylaxis, presence of flushing or diaphoresis, and the presence of dyspnea. Another study among the pediatric population found older age and transfer from an outside hospital to be risk factors for multiple epinephrine doses.¹³

It remains unclear what factors contribute towards multiple doses of epinephrine for food-induced reactions among pediatric patients. This study aims to determine the frequency

and risk factors of reactions that require multiple dose epinephrine treatment for food-related anaphylaxis in children.

Methods

Children ages 0 through 17 years were administered a standardized, questionnaire at the time of their regular office visit at the Jaffe Food Allergy Institute at Mount Sinai Hospital, New York from November 2009 to June 2011. This was an extension of a previous earlier study among the same population conducted by Jarvinen, *et al.*¹⁵ Questionnaires were distributed at random during these visits to any patient with a physician-confirmed diagnosis of food allergy. Written informed consent was obtained from the parent or guardian. Questions included demographics, a history of atopy (asthma, allergic, rhinitis, or atopic dermatitis), and the number of reactions treated with epinephrine in their lifetime. Asthma was assessed by parental reporting of a history of asthma or prior albuterol use in their child to include children who have a diagnosis of reactive airway disease. The questionnaire was arranged so that the details of up to four allergic reactions that had been treated with epinephrine could be collected. For each reaction, information was requested regarding the following: age, what caused the reaction, where the reaction occurred, treatments given, number of epinephrine doses, person who administered epinephrine, and location of epinephrine injection. Of note, all patients seen at this clinic with a physician-diagnosis of IgE-mediated food allergies are prescribed and recommended to carry epinephrine autoinjectors regardless of asthma status.¹⁰

Follow-up data was collected prospectively from patients that had previously filled out the questionnaire. We contacted all participants after 6 months by telephone to document new food exposures and reactions. They were asked to report whether the patient was exposed to a

known food allergen and whether a reaction occurred. If the subject had an allergic reaction, the parents were also asked to contact the investigator promptly. Details of each reaction were collected including what triggered the reaction and how the reaction was treated.

Data was analyzed using STATA 11.2 (College Station, TX). The groups of interest for analysis were subjects who were treated with one epinephrine dose versus those that were treated with more than one epinephrine dose. As the questionnaires were completed by parents, there was limited information regarding whether the reaction met the criteria for anaphylaxis. Whether a reaction was treated with any epinephrine was used as a measure of an anaphylactic reaction for the purpose of analysis. Chi-squared and Fisher's exact tests were used to compare proportions, and t-test was used to compare means. Univariate and multivariate logistic regression was used to determine odds ratios. A P-value of less than 0.05 was considered statistically significant. This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai in New York, NY.

Results

Characteristics of Subjects and Allergic Reactions

We distributed a total of 779 surveys, 684 were completed, including a total of 642 surveys reporting allergic reactions (Table 1). The median age of subjects at the time of questionnaire completion was 2.5 years (interquartile range (IQR) 1.5 - 4 years). Fifty-nine percent of subjects were male, 77% Caucasian, 98% resided in the Tri-State area (New York, New Jersey, Connecticut), and 96% had private health insurance. The reported known allergies were as follows: peanut (73%), tree nut (70%), egg (51%), milk (43%), seeds (35%), shellfish (21%), soy (15%), fish (14%), and wheat (12%). Twenty-six percent of those with an allergic

reaction (n=166) reported an allergic reaction treated with one or more doses of epinephrine. Among these 166 subjects, there were 221 reactions reported to have received one or more epinephrine dose.

Allergic Reactions Treated with Epinephrine

Among allergic reactions treated with epinephrine, cow's milk (30.0%), peanut (18%), tree nuts (10%), egg (9%), and wheat (6%) were identified as the cause for the majority of reactions that were treated with epinephrine. Allergic reactions most frequently occurred at home (49.1%), followed by restaurant (10.7%), and then school or daycare (8.3%). Additional reactions occurred while visiting family (5.8%), while traveling (5.6%), at a friend's house (4.7%), or during sports (1.9%). When assessing reactions by food-trigger, the most frequent location of reactions was consistently at home for milk (71.7%), egg (64.3%), peanut (58.8%), and tree nut (41.2%).

More often, the first or only dose of epinephrine was given by the patient, parent, or caregiver (57%), while 43% were given by a healthcare professional (school nurse, emergency medical services (EMS), emergency medicine doctor, or pediatrician). Epinephrine was administered as soon as symptoms appeared in 13% of reactions; while the majority of reactions (52%) were treated with epinephrine by 10 minutes. Twenty percent of reactions were treated with epinephrine more than 30 minutes after symptom onset. Having an allergic reaction that was treated with epinephrine was shown to be significantly associated with the following: allergy medication use, history of asthma or albuterol use, allergic rhinitis, and allergy to shellfish, seeds, milk, wheat, tree nuts, and eggs (Table 2).

Twenty-four allergic reactions (11%) treated with epinephrine received more than one dose. Of these 24 reactions, 19 were treated with two epinephrine injections, four were treated with three epinephrine injections, and one was treated with four epinephrine injections. The majority of the first doses of epinephrine were given at the scene of the reaction (52%), while most of the second and third doses of epinephrine were given in the ED (55% and 100% respectively).

Single versus Multiple Doses of Epinephrine

Characteristics between allergic reactions that were treated with one dose versus multiple doses of epinephrine were compared (Table 3). There was no significant difference between the single versus multiple epinephrine groups in terms of average age as well as history of atopy (atopic dermatitis, asthma, allergic rhinitis). There were significantly more reactions to milk that received multiple doses of epinephrine ($P=0.03$), while no significant difference was noted for other foods including peanut, egg, and tree nuts. There was also no association between being treated with multiple doses of epinephrine and the time from symptom onset to epinephrine injection or location where the reaction occurred. The first dose of epinephrine was more likely to be given by EMS ($P=0.019$) in reactions treated with multiple epinephrine doses versus single dose. Reactions that received multiple epinephrine doses were also more likely to be treated with oxygen ($P<0.0001$).

Initial univariate analysis showed that having a milk-triggered allergic reaction (OR 3.2, 95% CI 1.2-8.4) and treatment with oxygen by EMS or in the ED (OR 5.0, 95% CI 2.0-12.4) were strongly associated with multiple treatments of epinephrine (Table 4). Analysis was done to further evaluate the relationship between milk-triggered reactions and multiple epinephrine

doses. Several possible confounders were identified that may affect the association between a reaction to milk and multiple epinephrine dose treatments based on a review by Kemp.¹⁶ These potential confounders included: the age of the patient, allergic reaction to peanut, tree nuts or egg, history of asthma, allergic rhinitis, eczema, albuterol use, or antihistamine use. While age, reaction to peanut, tree nuts or egg, and history of asthma, eczema and albuterol were all associated with milk-triggered reactions, none of these variables were associated with multiple epinephrine dose treatments. Therefore these variables did not meet the criteria of a confounding factor to be fitted into a multivariate regression model, and this further supports the conclusion that milk-related allergic reactions are associated with a three-fold increase in odds of being treated with multiple epinephrine doses.

Prospective Data

Additional data was collected prospectively among the 180 subjects who completed the original survey with a response rate of 26.3% (180/684). The median age of the participants responding to the prospective follow up was 7.5 years (IQR 2-15 years), and 63% were male. Among these subjects, 67 patients (37%) had at least one reaction, including 5 with multiple reactions, for a total of 75 reactions. Fourteen out of the 75 reactions (8.7%) were treated with epinephrine. Those with a history of allergy to milk, eggs, seeds, fish, or shellfish or history of albuterol use had increased odds of having any allergic reaction during the 6-month follow-up period (Table 5).

Subjects with respiratory symptoms (OR 15.0, 95% CI 3.6-62.2) were more likely to receive epinephrine. The reactions that required epinephrine were triggered by ingestion of milk (21%), peanut (14%), tree nuts (14%), egg (7%), or seeds (7%). One of the 14 patients that were

treated with epinephrine required more than one dose of epinephrine to treat an allergic reaction. This subject was treated with a total of two doses of epinephrine, and the allergic reaction was triggered by ingestion of milk.

Discussion

Our study among children with food allergies found that 11% of reactions treated with epinephrine received more than one injection of epinephrine. Subjects with milk-triggered allergic reactions and treatment with oxygen by EMS or in the ED were more likely to require more than one dose of epinephrine. Patients reporting respiratory symptoms had increased odds of receiving any epinephrine treatment. In addition, asthmatics or subjects who reported albuterol use were more likely to have reactions treated with any epinephrine and more than one allergic reaction during the prospective period.

The incidence of reactions that were treated with more than one epinephrine dose was 11% among reactions treated with any epinephrine. This is consistent with a recent study by Campbell, *et al.* with an estimated incidence of 8% of anaphylaxis cases requiring treatment with more than one epinephrine dose.¹⁴ Campbell, *et al.* included non-food triggers of anaphylaxis, and evaluated both pediatric and adult patients presenting to the emergency room. Higher incidences of multiple epinephrine treatments are reported in earlier studies. Among studies focusing on food-triggered anaphylaxis presenting to the emergency room, 12% of reactions required two doses of epinephrine among a pediatric population;¹³ while 16% to 17% of adults needed more than one epinephrine dose.^{11,12} A prior study done on children with food-related reactions in our clinic showed that up to 19% required two or more doses of epinephrine.¹⁵ Our study involves the youngest population in comparison to these other studies with a median age of

2.5 years. With this and other studies collectively reporting a range of 8 to 19% of allergic reactions being treated with multiple epinephrine doses, needing at least a second dose of epinephrine is a real and significant risk even amongst young children. Patient education should emphasize the possibility of requiring a second epinephrine dose, and the importance of carrying two epinephrine auto-injectors.

When comparing those reactions that received one epinephrine dose versus two or more doses, allergic reactions triggered by cow's milk were shown to be associated with a three-fold increased odds of treatment with multiple doses of epinephrine. Although peanut was the most common known allergen, a history of milk allergy doubled the odds of having a reaction treated with any epinephrine. Additionally, subjects with a history of milk allergy had increased odds of having any allergic reaction during the prospective 6-month follow-up period. Interestingly, the one reaction that occurred during the follow-up period and received treatment with two doses of epinephrine was triggered by milk. These findings regarding milk supports the conclusion from a prior study that showed cow's milk-triggered reactions comprised 16% of single injection reactions and 33% of multiple injection reactions.¹⁵ Furthermore, this was a younger population and because of age, these children may have been less likely to have been eating peanuts or tree nuts in comparison to milk.

There were no fatalities among our study's population. A registry of food allergy-related fatalities in the US reported that cow's milk was identified as responsible for 8% of fatalities caused by food allergies.^{1,2} Milk was also the identified cause for 21% of anaphylaxis fatalities among children less than 16 years of age based on a national database in England and Wales (1992-2012).¹⁷ In both the US and UK registries, milk was overall the third most common cause of anaphylactic fatality, preceded by peanuts and tree nuts. Our study supports the view that

cow's milk is a potent allergen and can trigger severe anaphylaxis. This is also reflected in our clinical experience as there is an increasing proportion of milk allergic children whose allergy persists into adulthood.¹⁸ Milk is a ubiquitous allergen that is present in schools, home, as well as in processed and store bought foods. The difficulty in strictly avoiding milk is demonstrated in our finding that most milk-triggered allergic reactions occurred at home. Milk allergy is increasing in relevance, and heightened awareness regarding potential milk allergy severity is necessary.

A history of asthma and albuterol use was strongly associated with the occurrence of a reaction that required any epinephrine treatment. The prospective follow-up data also showed that those with a history of albuterol use were more likely to experience an allergic reaction during the follow-up period. Prior studies have shown that having a history of asthma is linked with severe anaphylactic reactions¹⁹ that are more likely to result in fatality.^{1,2,17} Additionally, Elizur et al. reported that among milk-allergic children prior to undergoing oral immunotherapy, subjects who had asthma of any severity were more likely to have experienced an anaphylactic reaction compared to those without asthma.²⁰ While the results of our study showed no significant association between asthma and using multiple doses of epinephrine, asthma status and control were not assessed at the time of the reaction. However, those that complained of respiratory symptoms were more likely to receive any epinephrine, and subjects needing treatment with oxygen had a five-fold increased odds of treatment with multiple doses of epinephrine. Similar to other studies, presentation with dyspnea¹⁴ as well as wheezing, stridor, or cyanosis was associated with receiving more than one dose of epinephrine.²¹ While having a history of asthma did not increase one's risk for multiple epinephrine treatments, healthcare

providers should be aware of the increased likelihood of needing additional epinephrine doses once respiratory symptoms develop in a patient.

The baseline study was limited by the primarily retrospective design and would benefit from a larger study population. Results were dependent on recollection of prior reactions by the patient or parents and were susceptible to recall bias. Some reactions may have occurred several years ago and were traumatic for the families, which may make it more difficult to recollect details. This study was enriched by the addition of the prospective follow-up data, but there was an insufficient number of reactions treated with multiple epinephrine injections for statistical analysis. It highlights the difficulty of prospectively collecting data when the outcome of interest occurs infrequently. Despite this challenge, future studies should be done prospectively on a larger scale to further examine risk factors for multiple epinephrine doses. Furthermore, the population was skewed as the subjects were predominantly younger, Caucasian, and with private insurance. An additional limitation was the possibility that not every reaction treated with epinephrine met the criteria for anaphylaxis. Due to the specialized nature of the clinic where this study was conducted, there may be heightened awareness of food allergies and families could be more inclined to give epinephrine. However, the majority of second and third doses of epinephrine were administered by a healthcare professional, and these reactions were likely to have been severe.

In summary, this study provides evidence that the occurrence of food-related allergic reactions needing treatment with more than one dose of epinephrine is a significant risk, especially for children with milk allergy and those needing treatment with oxygen. Additionally, food-allergic children with asthma have an increased risk of allergic reactions treated with any

epinephrine. Families of children with food allergies, particularly milk allergies, should be counseled on the importance of carrying two epinephrine auto-injectors.

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Table 1: General Demographics and Characteristics of Study Population that Completed Surveys

Category	N=684
Age (median)	2.5 years (IQR 1.5-4 years)
Male	59%
Caucasian	77%
Lives in Tri-State Area (NY, NJ, CT)	98%
Known Food Allergies	
Peanut	73%
Tree nut	70%
Egg	51%
Milk	43%
Seeds	35%
Shellfish	21%
Soy	15%
Fish	14%
Wheat	12%
Reported Allergic Reactions	94%

Table 2: Risk Factors for Having an Allergic Reaction Treated with Any Epinephrine

Category	Risk Factors	Odds Ratio (Univariate)	95% Confidence Interval	P value
Medical History	Albuterol Use	3.31	2.21-4.96	<0.0001
	Allergy Medication Use	1.68	1.18-2.40	0.004
	Asthma History	3.00	2.07-4.34	<0.0001
	Allergic Rhinitis History	1.45	1.01-2.09	0.045
	Eczema	1.12	0.77-1.59	0.578
Food Allergy History	Shellfish	2.65	1.74- 4.03	<0.0001
	Seeds	2.57	1.75- 3.77	<0.0001
	Milk	2.26	1.55-3.29	<0.0001
	Tree Nut	1.96	1.26-3.07	0.003
	Wheat	2.15	1.28-3.61	0.004
	Egg	1.71	1.18-2.49	0.005
	Peanut	1.48	0.95- 2.28	0.081
	Fish	1.56	0.94- 2.61	0.086
	Soy	1.26	0.76-2.08	0.366

Table 3: Demographics and Characteristics of Reactions Treated with Epinephrine

	Reactions Treated with 1 Epinephrine Dose n (%)	Reactions Treated with 2 or More Epinephrine Doses n (%)	P-value
	197 (89%)	24 (11%)	
Mean age (years)	3.2	3.1	0.90
Male	86 (68%)	9 (53%)	0.28
Ethnicity			
Caucasian	96 (77%)	14 (82%)	0.76
African American	6 (5%)	0 (0%)	1.0
Hispanic	4 (3%)	1 (6%)	0.48
Asian	7 (6%)	0 (0%)	1.0
Indian	1 (0.8%)	0 (0%)	1.0
Other	13 (10%)	1 (6%)	1.0
Private health insurance	121 (95%)	16 (94%)	0.59
Atopic dermatitis	77 (61%)	9 (53%)	0.60
Asthma	78 (63%)	11 (69%)	0.79
Allergic rhinitis	58 (47%)	8 (53%)	0.78
Albuterol	98 (77%)	14 (82%)	0.76
Known Trigger			
Peanut	35 (22%)	3 (16%)	0.77
Egg	16 (10%)	3 (16%)	0.42
Milk	55 (36%)	12 (63%)	0.03
Tree nut	21 (14%)	0 (0%)	0.13
Soy	3 (2%)	0 (0%)	1.0
Wheat	12 (8%)	1 (6%)	1.0
Seeds	8 (5%)	0 (0%)	1.0
Fish	5 (3%)	0 (0%)	1.0
Shellfish	1 (0.7%)	0 (0%)	1.0
Treatments			
Oxygen	24 (13%)	10 (42%)	0.001
Steroid	63 (33%)	12 (50%)	0.11
IV Fluids	30 (16%)	7 (29%)	0.15
Albuterol	27 (14%)	6 (26%)	0.22
Antihistamine	134 (69%)	18 (75%)	0.64

Table 4: Single dose of Epinephrine versus Multiple Doses of Epinephrine for a Single Allergic Reaction

Category	Risk Factors	Odds Ratio	95% Confidence	P value
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		(Univariate)	Interval	
Treatments	Oxygen Treatment	4.97	1.99-12.44	0.001
	Steroid	2.06	0.878-4.85	0.097
	IV Fluids	2.20	0.839- 5.75	0.109
	Albuterol	2.10	0.762- 5.81	0.151
	Antihistamine	1.32	0.499-3.50	0.575
Food Trigger	Milk	3.17	1.16-8.38	0.024
	Egg	2.30	0.680-7.78	0.180
	Peanut	0.664	0.183-2.41	0.534
	Wheat	0.696	0.851-5.69	0.735

Table 5: Risk Factors for Any Allergic Reaction During 6-Month Follow-up Period

Category	Risk Factor	No Reaction n (%)	Reaction n (%)	Odds Ratio (Univariate)	95% Confidence Interval	P value
Medical History	Albuterol Use	57 (52%)	50 (67%)	1.86	1.01-3.42	0.045
	Eczema	59 (54%)	49 (65%)	1.63	0.889-2.98	0.114
	Allergic Rhinitis	38 (36%)	32 (43%)	1.38	0.754-2.54	0.294
	Asthma	47 (43%)	33 (45%)	1.06	0.586-1.92	0.843
Food Allergy History	Shellfish	14 (13%)	24 (32%)	3.26	1.55-6.84	0.001
	Fish	9 (8%)	15 (20%)	2.83	1.17-6.87	0.018
	Egg	48 (43%)	51 (68%)	2.79	1.51-5.15	0.001
	Milk	44 (40%)	47 (63%)	2.56	1.40-4.67	0.002
	Seeds	34 (31%)	39 (52%)	2.45	1.34-4.50	0.003
	Soy	11 (10%)	14 (19%)	2.09	0.89-4.89	0.086
	Wheat	12 (11%)	13 (17%)	1.73	0.74-4.03	0.20
	Peanut	71 (64%)	54 (72%)	1.45	0.77-2.74	0.25
	Tree nut	72 (65%)	50 (67%)	1.08	0.58-2.01	0.80