
Food-induced anaphylaxis and repeated epinephrine treatments

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Background: Research on the use of more than 1 dose of epinephrine in the treatment of food-induced anaphylaxis is limited.

Objective: To perform a medical record review to examine the frequency of repeated epinephrine treatments in patients presenting with food-induced anaphylaxis to the emergency department (ED).

Methods: We reviewed 39 medical records of patients who presented with food-induced allergic reactions to the Massachusetts General Hospital ED during a 1-year period. The analysis focused on the timing of the onset of symptoms and on the number of epinephrine treatments given before and during the ED visit.

Results: Of the 39 patients, 34 had an acute food-induced allergic reaction. Nineteen had anaphylaxis. Twelve patients with anaphylaxis (63%; 95% confidence interval, 38%–84%) received at least 1 dose of epinephrine, and 3 (16%; 95% confidence interval, 3%–40%) were given 2 doses. Although statistical analysis was not possible, repeated epinephrine treatment occurred in patients with anaphylaxis to peanut or tree nut and hypotension. There was no apparent association between time from ingestion of the causative agent to epinephrine treatment(s).

Conclusions: Of patients presenting to the ED with food-induced anaphylaxis, approximately 16% were treated with 2 doses of epinephrine. This study supports the recommendation that patients at risk for food-induced anaphylaxis carry 2 doses of epinephrine. Further study is needed to confirm these results and to expand them to patients who do not present to the ED because that group may have a lower frequency of epinephrine use.

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INTRODUCTION

Food-induced anaphylaxis is a life-threatening acute allergic reaction that leads to at least 29,000 emergency department (ED) visits in the United States each year.¹ In addition, approximately 125 to 150 deaths per year are attributed to food-induced anaphylaxis.¹ Prompt recognition and treatment of these reactions are critical to preventing substantial morbidity and mortality.

In 2005 the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology issued a practice parameter that stated that epinephrine is the treatment of choice for the management of anaphylaxis.² The parameter specifically recommends that aqueous epinephrine, 1:1,000 dilution, be administered at a dose of 0.2 to 0.5 mL (0.01 mg/kg in children, with a maximum 0.3-mg dose) intramuscularly, preferably into the lateral aspect of the thigh.² This dose may be repeated every 5 minutes if symptoms continue.² Based on these recommendations, all patients at risk for anaphylaxis should be prescribed a self-injectable form of epinephrine.³

Recently it has been suggested that patients at risk for anaphylaxis should always carry 2 doses of self-injectable epinephrine.⁴ This was based on a review of 2 studies and on the author's review of his patients receiving allergen immunotherapy; only 1 study focused on food-induced anaphylaxis.^{5,6} The food-induced anaphylaxis study by Uguz et al⁵ was a survey of patients with anaphylaxis in the United Kingdom. Of 6,000 members of the Anaphylaxis Campaign, 113 (<2% response rate) responded to the survey and experienced a total of 126 allergic reactions. In this small group of responders the authors found that a second dose of epinephrine was administered in 1 of 88 allergic reactions in children (1.1%) and 3 of 38 allergic reactions in adults (7.9%). When an analysis was performed to determine the approximate percentage of all epinephrine-treated patients who received a second dose of epinephrine, the results were 10% (1 of 10) of children and 25% (3 of 12) of adults.

The other studies that addressed the number of doses of epinephrine needed for the treatment of anaphylaxis were a retrospective review of the medical records from 2 allergists' offices and a clinical trial with live Hymenoptera stings⁶ and the recent 5-year review of patients receiving allergen immunotherapy.⁴ The 1999 publication by Korenblat et al⁶ examined 105 anaphylactic reactions to allergen immunotherapy or live Hymenoptera challenges and found that 38 of 105 patients (36%) received 2 or more epinephrine injections. The authors also noted a linear relationship between the severity of the anaphylactic reaction and the need for multiple injections of epinephrine. The review by Kelso⁴ of patients receiving allergen immunotherapy in a single practice found that of

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64 severe systemic reactions to immunotherapy requiring epinephrine treatment, 10 (16%) were administered more than 1 dose of epinephrine.

The study by Uguz et al⁵ has several major limitations, including the self-reported data, the very small number of patients, and the high likelihood of selection bias. The generalizability of the data presented by Korenblat et al⁶ and Kelso⁴ to patients outside the allergy clinic and the relevance to food allergy is not known. We sought to address these limitations by determining the frequency of administration of 2 or more epinephrine doses in the treatment of food-induced anaphylaxis among patients presenting to the ED for food-induced anaphylaxis. This study was limited to food-induced anaphylaxis in the ED to provide data addressing the need for more than 1 dose of epinephrine for the acute phase of the reaction. This effectively removed other indications for carrying a second epinephrine autoinjector, such as device failure or the biphasic response.

METHODS

This study was performed as an extension of an earlier study by Clark et al⁷ in 2004 that evaluated the management of food-induced allergic reactions in the ED. We obtained identifying information from this previously identified case series (found using *International Classification of Diseases, Ninth Revision*, codes 693.1, 995.0, 995.3, and 995.60–995.69) and, under the same institutional review board approval, reviewed the medical records of patients who presented to the Massachusetts General Hospital ED for food allergy. The requirement for informed consent was waived because this was a medical record review study. A single investigator (E.O.) trained in allergy and immunology individually reviewed all available medical records for the following: identification of food-induced anaphylaxis and its likely cause; sex and age; time from ingestion to onset of symptoms, arrival at the ED, and administration of epinephrine; concomitant therapies (ie, H₁ and H₂ antagonists, corticosteroids, and nebulized β -agonists); medical history of asthma or previous anaphylaxis; tryptase measurement; ownership of an epinephrine autoinjector before anaphylaxis or on discharge from the ED; and whether a follow-up appointment with a specialist in allergy and immunology was made.

RESULTS

Of 40 patients presenting to the Massachusetts General Hospital ED for food-induced reactions between June 1, 1999, and June 30, 2000, 39 medical records were available for review. Thirty-four patients were deemed to have had an acute allergic reaction due to food ingestion. Of these patients, 19 (56%) were considered to have met the criteria for anaphylaxis as defined by the 2005 symposium on the definition and management of anaphylaxis.³ Fourteen of the 34 patients (41%) with a food-induced allergic reaction received epinephrine treatment in the field or in the ED. Twelve of the 19 patients with anaphylaxis (63%; 95% confidence interval [CI], 38%–84%) received treatment with at least 1 dose of

epinephrine in the field or in the ED. Of the 14 patients who received any epinephrine, 3 (21%; 95% CI, 25%–59%) were given a second dose. All 3 of these repeated epinephrine treatments were administered in patients with anaphylaxis. Thus, of all the patients presenting to the ED with food-induced anaphylaxis, approximately 16% (95% CI, 3%–40%) were treated with 2 doses of epinephrine.

The causes of food-induced acute allergic reactions included egg (n = 2), Fig Newton (n = 1), fish (n = 3), grape (n = 1), milk (n = 1), mushroom (n = 1), peanut (n = 6), sesame (n = 2), shellfish (n = 6), tree nut (n = 9), and unclear cause (n = 2). Three patients had vascular involvement, and these accounted for 2 of the cases in which a second dose of epinephrine was administered. These cases were due to peanut (n = 1) and tree nut (n = 2).

Twelve patients (35%) were asthmatic, but patients with asthma accounted for 10 of the 19 cases (53%) of anaphylaxis and 8 of 12 cases (67%) of anaphylaxis in which epinephrine was used. Fourteen patients (41%) with an acute allergic reaction and 8 of 19 (42%) with anaphylaxis had a history of anaphylaxis. Of the 12 patients with anaphylaxis treated with epinephrine, 3 (25%) had been previously prescribed an epinephrine autoinjector. However, only 1 of these patients with a prescription for an epinephrine autoinjector received a dose of epinephrine in the field, and she used a friend's EpiPen (Dey Laboratories, Napa, California) because she was not carrying her own. Eleven of the 19 patients with anaphylaxis (58%) and 8 of the 12 anaphylactic cases (67%) treated with epinephrine were given a prescription for an epinephrine autoinjector on discharge from the ED. Seven patients (21%) presenting to the ED with an acute allergic reaction due to food were given an appointment to see a specialist in allergy and immunology. Only 3 patients had tryptase levels measured, and, of these, only 1 was obtained within 6 hours of the reaction (slightly elevated at 12 ng/mL; reference value, <10 ng/mL). The details of the 12 cases of food-induced anaphylaxis treated with epinephrine are described in Table 1.

DISCUSSION

To our knowledge, this is the first study to document multiple epinephrine treatments administered in the management of anaphylaxis in the ED setting. We found that of 19 patients with food-induced anaphylaxis presenting to the ED of the Massachusetts General Hospital, 3 (16%) received 2 doses of epinephrine. Although statistical analysis was not possible, repeated epinephrine treatment occurred in patients with anaphylaxis to peanut or tree nut and hypotension. There was no apparent association between time from ingestion of the causative agent to epinephrine treatment(s).

By focusing on the ED evaluation and management of food-induced acute allergic reactions we obtained objective data at the time of presentation rather than relying on questionnaires and their inherent recall bias. Furthermore, we determined the frequency of multiple epinephrine treatments as ordered by physicians in an attempt to capture those doses that were indicated for continued or refractory anaphylaxis.

Table 1. Details of the 12 Cases of Food-Induced Anaphylaxis Treated With Epinephrine

	Patient age, y	Time of ingestion	Onset of symptoms, min	Symptoms	Epinephrine, time, mg, route		Time from ingestion to dose of epinephrine, min
					First dose	Second dose	
Egg	<1	3 PM	<5	Respiratory, cutaneous	4:30 PM, 0.1, SQ	Not applicable	90
Milk	18	8 PM	10	Respiratory (intubation)	8:55 PM, 0.4, SQ	Not applicable	55
Peanut	18	1:30 AM	20	Cutaneous, vascular (near-syncope)	2 AM, 0.3, SQ	3:10 AM, 0.3, SQ ^a	30
	1	12:45 PM	20	Cutaneous, vascular (BP, 62/40 mm Hg), syncope	1:40 PM, 0.1, SQ	Not applicable	55
	16	11:30 AM	30	Respiratory, cutaneous	2:11 PM, 0.3, SQ	Not applicable	161
	19	Not known	NA	Respiratory, cutaneous	In field, EpiPen 0.3	Not applicable	40
	18	11:30 PM		Respiratory, cutaneous	12:05 AM, 0.3, SQ	Not applicable	35
Shellfish	44	10:30 PM	<15	Respiratory, cutaneous	In field, 0.3, SQ	11:35 PM, 0.3, SQ ^a	50
Tree nut	46	11:30 PM	30	Respiratory (intubation), vascular (BP, 80/palp)	In field, EpiPen 0.3	2:55 AM, 0.3, SQ ^a	155
	22	12 PM	NA	Respiratory, cutaneous	2 PM, 0.3, SQ	Not applicable	120
	23	3 PM	NA	Respiratory, cutaneous	4:15 PM, 0.25, SQ	Not applicable	75
	25	9:20 PM	5	Respiratory, cutaneous	9:30 PM, 0.3	Not applicable	10

Abbreviations: BP, blood pressure; NA, not available; SQ, subcutaneous.

^a No patient received more than 2 doses of epinephrine.

This also removed the possibility of device failure and limited the likelihood of treatment of a biphasic reaction as an indication for an additional dose of epinephrine. The finding that 16% of patients with food-induced anaphylaxis presenting to the ED received more than 1 dose of epinephrine suggests that patients at risk for food-induced anaphylaxis should carry at least 2 doses of self-injectable epinephrine.

Uguz and colleagues⁵ provided the first attempt to quantify the real-world use of repeated epinephrine treatments in the management of food-induced anaphylaxis. Despite the low response rate and the reliance on questionnaire data, that study found that 25% of adults with severe food-induced systemic reactions received a second dose of epinephrine. The present study did not rely on questionnaire data but rather gathered details of epinephrine treatment from the ED medical record. In addition, a recent survey found that a second dose of epinephrine was used in 23% of children with a history suggestive of food-induced anaphylaxis.⁸ Despite the small sample sizes the results are consistent across 3 studies^{5,6,8} showing that approximately 20% of patients with food-induced anaphylaxis receive a second dose of epinephrine.

By focusing on ED data we captured patients with acute allergic reactions to food without introducing the referral bias inherent in studies of patients seen by an allergy specialist. We also obtained information on epinephrine use “in the field” by reviewing the notes of first responders and triage nurses. The study was designed to review epinephrine treatment only for the acute phase of the food-induced reaction and not the biphasic reaction. One patient receiving the second dose of epinephrine 155 minutes after the initial dose had continuous symptoms documented from the time of

emergency medical services arrival and, thus, was not likely having a biphasic reaction. As Ellis and Day⁹ recently reported, biphasic reactions may occur in 19% of all cases of anaphylaxis presenting to the ED or admitted to the hospital, but these reactions have an average time to onset of 10 hours after the initial anaphylactic reaction.

An additional strength of the present study is that a probable cause of the food-induced acute allergic reaction was obtained in 94% of the cases, suggesting that the anaphylaxis was indeed due to the suspected allergen. Although confirmation of the true cause of the reactions was not possible given the design of this review, a physician trained in allergy and immunology (E.O.) believed that the listed foods were likely to be the true cause of the reactions.

This study has several important limitations. Foremost is the small sample size. We concentrated on data from a 1-year period at a single institution that resulted in 34 cases of acute allergic reactions to food and 19 cases of food-induced anaphylaxis. In addition, all doses of epinephrine, except those administered via the EpiPen, were given subcutaneously. As reported by Simons et al¹⁰ in 2001, the intramuscular route of administration (especially to the thigh) is the preferred route, with higher peak plasma levels than those obtained through the subcutaneous route. Because 2 of the 3 patients receiving a second dose of epinephrine had been administered the first dose by the subcutaneous route, it is unknown whether administration of epinephrine by means of intramuscular injection would have prevented these repeated epinephrine treatments. Because this study relied on data completed by ED physicians and staff and collected retrospectively from the medical record, it is not possible to determine whether the

repeated epinephrine doses were truly required. Except for 1 case in which persistent hypotension was documented after the first epinephrine dose and resolution was shown after the second, all other decisions to administer epinephrine were made by the ED physician, first responders in the field, or the patients themselves without documentation of indications for those doses. We have, therefore, chosen to describe epinephrine doses as having been received rather than being required.

Although this study aimed to evaluate all patients who present to the ED with a "food allergy" and then rely on a trained physician to further define those with anaphylaxis, it is impossible to account for any patient who used an epinephrine autoinjector in the field and did not seek follow-up care in the ED. This has the potential to decrease the true rate of use of multiple doses of epinephrine for the treatment of food-induced anaphylaxis.

In conclusion, these results suggest that the use of multiple doses of epinephrine in the management of food-induced anaphylaxis is not a rare occurrence. The finding that approximately 16% of patients with food-induced anaphylaxis received more than 1 dose of epinephrine suggests that patients at risk for food-induced anaphylaxis should consider carrying epinephrine autoinjectors capable of dispensing multiple doses. Given the small sample size, larger studies are warranted to confirm these results. Ideally, a prospective study would be designed enrolling all patients prescribed epinephrine autoinjectors to confirm the frequency of use of multiple doses of epinephrine in the outpatient and ED treatment of this life-threatening allergic reaction.

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