

## Letter to the Editor

**Obesity is not a risk factor for repeat epinephrine use in the treatment of anaphylaxis**

To the Editor:

Epinephrine is widely accepted as the first-line treatment for all forms of anaphylaxis.<sup>1,2</sup> Approximately 10% to 20% of the patients treated with epinephrine for anaphylaxis receive a second dose,<sup>3-6</sup> but the risk factors associated with repeat epinephrine use remain poorly defined. Previous studies have suggested that epinephrine administration with autoinjectors may be influenced by a patient's body habitus.<sup>7</sup> Therefore, we sought to determine whether obesity increases the risk for requiring 2+ epinephrine doses among patients who present to the emergency department (ED) with anaphylaxis due to food allergy or stinging insect hypersensitivity.

We performed a chart review at 4 New England teaching hospitals: Brigham and Women's Hospital (January 1, 2001, to December 31, 2006), Children's Hospital Boston (January 1, 2001, to December 31, 2006), Hasbro Children's Hospital (January 1, 2004, to December 31, 2009), and Massachusetts General Hospital (January 1, 2001, to December 31, 2006). We identified all patients presenting to the ED for food allergy or stinging insect hypersensitivity by using relevant *International Classification of Diseases, Clinical Modification Codes, Ninth Revision*,<sup>8</sup> including 558.3 (allergic gastroenteritis), 693.1 (dermatitis due to food), 708.0 to 708.9 (urticaria), 989.5 (toxic effect due to venom), 995.0 (other anaphylactic shock), 995.1 (angioneurotic edema), 995.3 (allergy, unspecified), 995.60 (anaphylactic shock due to unspecified food), 995.61 to 995.69 (anaphylactic shock due to a specified food), and 995.7 (other adverse food reactions, not elsewhere classified). Cases were confirmed by allergist review. We focused on the total number of epinephrine treatments given during an anaphylaxis episode (including before and during the ED visit) and the patient's anthropomorphic data. Weight and height measurements documented at the ED visit were preferentially used. If measurements had been taken more than 3 months from the ED visit, height/weight at the time of the ED visit was estimated by using Centers for Disease Control and Prevention growth charts in children (<18 years) and estimates of average weight gain in US adults. Calculated body mass indexes were classified according to Centers for Disease Control and Prevention growth indicators as underweight, healthy, overweight, or obese. Medians with interquartile ranges were presented for continuous variables that were not normally distributed. Comparisons between groups were evaluated by using Kruskal-Wallis rank sum tests for continuous variables and the  $\chi^2$  test or the Fisher exact test for categorical variables, as appropriate. Multivariable models were performed using logistic regression. A 2-sided *P* value of less than .05 was considered statistically significant.

The study population comprised 321 ED patients (261 children and 60 adults) who received epinephrine for anaphylaxis and had data for both height and weight; 267 (83%) received 1 dose of epinephrine, while 54 (17%) received 2+ doses. There was no difference in the need for additional doses of epinephrine between children and adults (*P* = .94) and no difference among the 4 institutions (*P* = .60). Demographic data, reaction history, and ED treatments are summarized in Table I. Patients had a median age of 8.5 (intraquartile range 3.0-16.4) years, and 47% were males.

When comparing patients who received 1 and 2+ doses of epinephrine, there was no difference in the inciting allergen, organ system involvement, or timing/dosing of epinephrine. While those receiving 2+ doses of epinephrine were more likely to receive  $\beta$ -agonists, there was no significant difference in other adjunctive medications, including corticosteroids (85% vs 79%; *P* = .38).

Overall, 27 (8%) patients were underweight, 168 (52%) healthy weight, 57 (18%) overweight, and 69 (22%) obese. The distribution of body mass index categories was similar in those receiving 1 versus 2+ doses (*P* = .83). There was no difference when separately examining these distributions among children (*P* = .92) and adults (*P* = .81). There was also no significant association when comparing categories of underweight/healthy versus overweight/obese (data not shown). Finally, when adjusting for age and sex, there remained no significant association between obesity (vs nonobesity) and receiving 2+ doses (odds ratio 1.22; 95% CI 0.77-1.93; *P* = .40).

Anaphylaxis is a potentially life-threatening medical emergency that is frequently incited by exposure to foods or stinging insects.<sup>1</sup> The primary treatment for anaphylaxis is the prompt administration of epinephrine. Current practice guidelines recommend that all patients at risk for anaphylaxis receive a prescription for an epinephrine autoinjector and education on its proper use.<sup>1,2</sup> Furthermore, on the basis of recently published data that 10% to 20% of the patients require repeat dosing,<sup>3-6</sup> experts now recommend that patients at risk for anaphylaxis always carry 2 doses.<sup>2</sup> Our current analysis—based on a partially overlapping population of ED patients who were included in our previous studies<sup>5,6</sup>—is consistent with the reported percentages of anaphylaxis patients who require repeat doses of epinephrine.

Repeat dosing could be a result of biphasic reactions or inadequate treatment response. In prior work,<sup>5</sup> we reported that most patients received the second dose within 1 hour of the first dose, suggesting that inadequate treatment response was the more likely explanation. Lack of response to epinephrine could be a result of failure to administer it in a timely manner or a rapid progression of the anaphylactic event. Other studies have supported that older age and asthma may be associated with additional treatments, which may be a reflection of increased reaction severity.<sup>4,6</sup> In the current study, all patients had reactions that met criteria for anaphylaxis and organ system involvement was similar among patients who received 1 versus 2+ doses of epinephrine.

Another possible explanation is that additional doses are required because of inadequate dosing and/or suboptimal route of administration. In the United States, epinephrine autoinjectors are exclusively available in 2 fixed doses (0.15 mg and 0.30 mg) and it is recommended that all adults and children weighing more than 25 kg be prescribed 0.30 mg regardless of their weight or body habitus.<sup>2</sup> With regard to the mode of administration, it has been recommended that epinephrine be given intramuscularly for optimal absorption.<sup>9</sup> However, studies using imaging modalities have found that the length of the epinephrine autoinjector needle is sometimes not long enough to reach muscular tissue in the thighs of obese individuals.<sup>7</sup>

Taken together, we hypothesized that the patient's weight or body habitus could play a role in requiring additional epinephrine treatments. This is the first study to investigate obesity as a possible risk factor. Limitations of our study were the lack of current height

**TABLE I.** Demographic characteristics, medical history, and treatment summary of patients presenting to the ED with anaphylaxis due to food or insect sting who received at least 1 epinephrine treatment\*

|                                                            | n (%)             |                  |                   | P value |
|------------------------------------------------------------|-------------------|------------------|-------------------|---------|
|                                                            | Overall (N = 321) | 1 Dose (n = 267) | 2+ Doses (n = 54) |         |
| Demographic and anthropomorphic characteristics            |                   |                  |                   |         |
| Age (y), median (IQR)                                      | 8.8 (3.0-16.2)    | 8.2 (2.9-16.3)   | 11.8 (4.5-15.6)   | .27     |
| Males                                                      | 151 (47)          | 128 (48)         | 23 (4)            | .47     |
| BMI category                                               |                   |                  |                   | .82     |
| Underweight                                                | 27 (8)            | 24 (9)           | 3 (6)             |         |
| Healthy weight                                             | 168 (52)          | 139 (52)         | 29 (54)           |         |
| Overweight                                                 | 57 (18)           | 48 (18)          | 9 (17)            |         |
| Obese                                                      | 69 (22)           | 56 (21)          | 13 (24)           |         |
| Medical/reaction history*                                  |                   |                  |                   |         |
| Known allergy to reaction trigger                          | 171 (54)          | 137 (52)         | 34 (63)           | .14     |
| Specific trigger causing reaction                          |                   |                  |                   |         |
| Peanuts                                                    | 84 (26)           | 65 (25)          | 17 (33)           | .26     |
| Tree nuts                                                  | 72 (24)           | 65 (25)          | 11 (21)           | .55     |
| Fruits and vegetables                                      | 20 (6)            | 14 (5)           | 6 (12)            | .10     |
| Shellfish                                                  | 24 (8)            | 23 (9)           | 1 (2)             | .09     |
| Fish                                                       | 12 (4)            | 11 (4)           | 1 (2)             | .43     |
| Milk products                                              | 40 (13)           | 36 (14)          | 4 (8)             | .22     |
| Eggs                                                       | 18 (6)            | 13 (5)           | 5 (10)            | .20     |
| Wheat                                                      | 2 (1)             | 2 (1)            | 0 (0)             | .53     |
| Other food                                                 | 48 (15)           | 38 (15)          | 10 (19)           | .41     |
| Insect sting                                               | 10 (3)            | 8 (3)            | 2 (4)             | .79     |
| Anaphylaxis symptoms                                       |                   |                  |                   |         |
| Cutaneous                                                  | 299 (93)          | 248 (93)         | 51 (94)           | .68     |
| Gastrointestinal                                           | 153 (48)          | 133 (50)         | 20 (37)           | .09     |
| Respiratory                                                | 262 (82)          | 213 (80)         | 49 (91)           | .06     |
| Cardiovascular                                             | 21 (7)            | 18 (7)           | 3 (6)             | .75     |
| ED treatment summary                                       |                   |                  |                   |         |
| Time to administration of first dose of epinephrine (min)† | 21 (9-50)         | 20 (10-50)       | 27 (7-55)         | .76     |
| First epinephrine dose given (mg)‡                         | 0.30 (0.15-0.30)  | 0.30 (0.15-0.30) | 0.30 (0.25-0.30)  | .050    |
| Adjunctive medications given                               |                   |                  |                   |         |
| Antihistamine                                              | 210 (64)          | 173 (65)         | 37 (69)           | .60     |
| Steroid                                                    | 183 (84)          | 157 (85)         | 26 (79)           | .38     |
| β-agonist                                                  | 88 (27)           | 65 (24)          | 23 (43)           | .006    |

BMI, Body mass index; IQR, intraquartile range.

\*Medical history based on patient report at the time of ED presentation.

†Time between patient's arrival in the ED and first dose of epinephrine administered (if applicable).

‡Dosing data not available for those doses administered prior to the patient's arrival in the ED.

and weight data in some patients, which necessitated the use of estimations. Nevertheless, in our population of more than 300 ED patients with anaphylaxis due to food allergy or stinging insect hypersensitivity who were treated with epinephrine, obesity was not associated with receipt of 2+ doses. These data suggest that repeat dosing is not the result of obesity leading to insufficient dosing or suboptimal medication delivery. Further research, including duplication in other populations, is needed to identify factors to help in the risk stratification of anaphylaxis patients.

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