Factors associated with repeated use of epinephrine for the treatment of anaphylaxis

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Background: Studies looking at the use of repeated doses of epinephrine in patients experiencing anaphylaxis are limited.

Objective: To determine which patients are most likely to receive repeated doses of epinephrine during anaphylaxis management.

Methods: A population-based study with medical record review was conducted. All patients seen during the study period who met the criteria for the diagnosis of anaphylaxis were included.

Results: The cohort included 208 patients (55.8% female). Anaphylaxis treatment included epinephrine in 104 patients (50.0%). Repeated doses were used in 27 patients (13.0%), 13 (48.1%) of them female. The median age of those who received repeated doses was 18.9 (interquartile range, 10–34) years vs 31.1 (interquartile range, 15–41) years for those who did not receive repeated doses ($P = .06$). The inciting agents were food (29.6%), insects (11.1%), medications (22.2%), others (7.4%), and unknown (29.6%). Patients who received repeated doses were more likely to have wheezing ($P = .03$), cyanosis ($P = .001$), hypotension and shock ($P = .03$), stridor and laryngeal edema ($P = .007$), nausea and emesis ($P = .04$), arrhythmias ($P < .01$), and cough ($P = .04$) and less likely to have urticaria ($P = .049$). They were more likely to be admitted to the hospital than patients who did not receive repeated doses (48.2% vs 15.6%; $P < .001$). There was no significant difference in the history of asthma between patients who received repeated doses and those who did not ($P = .17$).

Conclusions: Of the patients, 13.0% received repeated epinephrine doses. Patients were younger and were likely to present with wheezing, cyanosis, arrhythmias, hypotension and shock, stridor, laryngeal edema, cough, nausea, and emesis and less likely to have urticaria. A history of asthma did not predict use of repeated doses of epinephrine. Our results help identify high-risk patients who may benefit from carrying more than 1 dose of epinephrine.

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INTRODUCTION

Anaphylaxis is a serious systemic allergic reaction that occurs in susceptible individuals on exposure to specific antigens. The incidence of anaphylaxis appears to be increasing.[1,2] Epinephrine is the treatment of choice for anaphylaxis and has been shown to be effective when used in a timely fashion.[3] The precise dose of epinephrine needed to reverse symptoms due to anaphylaxis is difficult to ascertain.

Studies looking at the use of repeated doses of epinephrine in patients experiencing anaphylaxis have been limited. Further, these studies focused on patients presenting to either emergency departments (EDs) or outpatient allergy clinics. To our knowledge, this is the first population-based study to specifically evaluate patients who received more than 1 dose of epinephrine. The primary study objective was to determine which patients were most likely to receive repeated doses of epinephrine during the management of an anaphylactic reaction.

METHODS

The resources of the Rochester Epidemiology Project, organized in 1966, were used to conduct a population-based study. The Rochester Epidemiology Project is a medical records linkage system that links and indexes almost all health care providers in Olmsted County, Minnesota.[4,5] Virtually all residents of Olmsted County who presented to health care professionals with anaphylaxis from January 1, 1990, to December 31, 2000, were identified. This retrospective cohort study included patients presenting to 2 EDs in Rochester, Minnesota (1 with approximately 70,000 ED visits per year and the other with approximately 19,000 ED visits per year), and all other health care providers in the city. The study was approved by the institutional review boards at both centers.

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Anaphylaxis is likely when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue, or uvula)

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, or incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin or mucosal tissue (eg, generalized hives, itch or flush, swollen lips, tongue, or uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, or incontinence)
   d. Persistent gastrointestinal tract symptoms (eg, crampy abdominal pain or vomiting)
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure[a]
   b. Adults: systolic blood pressure <90 mm Hg or >30% decrease from that person's baseline

[a] Low systolic blood pressure for children is defined as lower than 70 mm Hg from 1 month to 1 year, lower than (70 mm Hg + [2 × age]) from 1 to 10 years, and lower than 90 mm Hg from 11 to 17 years. Taken from Sampson et al.[6]

Figure 1. National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Criteria. Taken from: Manivannan V, Decker WW, Stead LG, Li JT, Campbell RL. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis [published online before print February 25, 2009]. *Int J Emerg Med*. 2009;2(1):3–5.

The appropriate *Hospital Adaptation of the International Classification of Diseases, Second Edition* codes or the *International Classification of Diseases, Ninth Revision* codes were used to identify patients. Patients with a new diagnosis code related to anaphylaxis and who gave research authorization were included in our database. A review of 248 patients with codes for the following diagnoses was conducted: anaphylactic shock; anaphylactic shock due to food; anaphylactic shock not elsewhere classified; and shock, anaphylactic, following sting. Random samples of 600 patients (from 2,442 potential cases with the following diagnoses) were also reviewed: 300 patients diagnosed as having a venom, bee sting, or toxic effect of venom and 300 patients diagnosed as having allergy, foodstuff; adverse effect, food; dermatitis due to food taken internally; or toxic effect of specific food. All patients who met the criteria (discussed later) for the diagnosis of anaphylaxis were included in the study.

Case Definition

This study was started before the second symposium on the definition and management of anaphylaxis.[6] The criteria used in the study by Yocum et al[7] to establish a diagnosis of anaphylaxis were used to identify cases of anaphylaxis. The criteria used in the study by Sampson et al[6] were very similar to those developed by the second symposium on the definition and management of anaphylaxis (Fig 1). Two hundred eleven cases of anaphylaxis were initially identified using the criteria of Yocum et al. These cases were subsequently reanalyzed using the criteria proposed by the second symposium. There were only 3 cases that did not meet the criteria proposed by the second symposium, and these were removed, leaving a total of 208 cases of anaphylaxis.

Statistical Analysis

Distributions were calculated for each of the variables. The median and interquartile range (IQR) were reported to sum-

marize the age of patients, and nonparametric tests were used to compare median age in different groups. Percentages were used to summarize categorical data, and percentages were compared using the χ^2 test.

Based on the exploratory nature of this study, we did not correct P values to account for testing multiple hypotheses; therefore, the probability of finding significance is not controlled at the overall nominal .05 level under the null hypotheses. Thus, considerably more than 5% of the significant findings may be spurious. Statistical analyses were performed using JMP 7.01 software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Overall, the cohort included 208 patients, of whom 116 (55.8%) were female. Of these patients, 91.8% were white; their median age was 30.3 years (IQR, 14–41 years). Treatment of anaphylaxis included epinephrine in 104 patients (50.0%). Two or more doses of epinephrine were used in 27 patients (13.0%). The second dose of epinephrine was administered by a health care professional in all cases (Table 1).

The median age of those who received 2 or more doses of epinephrine was 18.9 (IQR, 10–34) years vs 31.1 (IQR, 15–41) years ($P = .06$) for those who received 0 or 1 dose of epinephrine. Of a total of 65 children, 12 (18.5%) received 2 or more doses. Among the 27 patients who received 2 or more doses of epinephrine, 13 (48.1%) were female. The inciting agents were determined after taking into consideration the history and results of any allergy testing and were not statistically different between the 2 groups. Of the 27 patients who received repeated epinephrine doses, 13 (48.1%) were admitted to the hospital, compared with 27 (15.6%) of 181 patients who received 0 or 1 dose of epinephrine (χ^2 test, P lt] .001). There were no case fatalities. Of the 27 patients who required repeated doses of epinephrine, 10 (37.0%) had a history of asthma, whereas 44 (24.3%) of 181 patients receiving 0 or 1 dose of epinephrine had a history of asthma (χ^2 test, $P = .17$). The mean first dose of intravenous epinephrine given was 0.31 mL (1:10,000); the intramuscular epinephrine given was 0.27 mg. The mean second dose of intravenous epinephrine given was 0.28 mL (1:10,000); the intramuscular epinephrine given was 0.26 mg. There were 5 patients who received a first dose of more than 0.5 mL (1:10,000) intravenously and 1 patient who received more than 0.5 mg intramuscularly.

Table 1. Sites of Epinephrine Administration During the Anaphylactic Events

No. of doses of epinephrine received	No. of patients	Place of epinephrine administration (No. of patients)
0	104	NA
1	77	Home (3), EMS (3), and ED (71)
2	25	Home and ED (2), EMS and ED (1), and ED (22)
3	2	One dose at home and 2 in the ED (1) and 2 doses by the EMS and 1 in the ED (1)

Abbreviations: ED, emergency department; EMS, emergency medical services; NA, not applicable.

Of the 27 patients who received more than 1 dose of epinephrine, 21 did not have a prior prescription for self-injectable epinephrine. Of these 21 patients, 15 (71.4%) were prescribed self-injectable epinephrine on dismissal from the ED or hospital. Of the 181 patients who did not receive more than 1 dose of epinephrine, 163 did not have a prior prescription for self-injectable epinephrine. Of these 163 patients, 64 (39.3%) were prescribed self-injectable epinephrine on dismissal from the ED or hospital ($P = .005$ for the comparison between prescription of self-injectable epinephrine at dismissal in those who required ≥ 2 doses vs < 2 doses). An allergist referral was made in 14 (51.9%) of the 27 patients who received more than 1 dose of epinephrine and in 73 (40.3%) of the 181 patients who received fewer than 2 doses of epinephrine (χ^2 test, $P = .28$). Table 2 gives the demographics, the inciting allergen, clinical characteristics, allergist referral, and self-injectable epinephrine prescriptions for 208 anaphylactic reactions in patients receiving 0, 1, and 2 or more doses of epinephrine.

Patients who received 2 or more doses of epinephrine were more likely to present with wheezing (χ^2 test, $P = .03$), cyanosis (χ^2 test, $P = .001$), hypotension and shock (χ^2 test, $P = .03$), arrhythmias (χ^2 test, $P < .01$), stridor and laryngeal edema (χ^2 test, $P = .007$), and nausea and emesis (χ^2 test, $P = .04$) and less likely to have urticaria (χ^2 test, $P = .049$). Cough was also more likely to be common in patients who received epinephrine but was statistically significant only when patients receiving 2 or more doses of epinephrine were compared with those who did not receive epinephrine ($P = .04$).

Presenting signs and symptoms after stratification based on number of doses of epinephrine are given in Table 3.

DISCUSSION

Epinephrine has been shown to be an effective treatment for anaphylaxis, and poor outcomes are associated with receiving epinephrine late.[3,8–12]

Studies regarding use of repeated doses of epinephrine are limited. Most of the studies evaluated patients presenting to outpatient allergy clinics.[13–15] One study examined patients presenting to the ED.[16] Furthermore, previous studies were limited to specific allergens or immunotherapy injections.[13,14,16]

Use of the resources of the Rochester Epidemiology Project permitted the collection of data on patients who received epinephrine at home, from emergency medical service providers, and in the ED. Thus, to our knowledge, we are able to present the largest community-based cohort of pa-

Table 2. Demographics, Inciting Allergen, Clinical Characteristics, Allergist Referral, and Self-injectable Epinephrine Prescriptions for 208 Anaphylactic Reactions in Patients Receiving Repeated Doses of Epinephrine Compared With Those Not Receiving Repeated Doses of Epinephrine[a]

Variables	Patients receiving 0 doses of epinephrine (n = 104)	Patients receiving 1 dose of epinephrine (n = 77)	Patients receiving ≥2 doses of epinephrine (n = 27)
Race and ethnicity			
White	89 (85.6)	67 (87.0)	19 (70.4)
Black	5 (4.8)	0 (0)	1 (3.7)
Hispanic	1 (1.0)	0 (0)	0 (0)
Asian–Pacific Islander	2 (1.9)	4 (5.2)	1 (3.7)
Other	0 (0)	1 (1.3)	0 (0)
Unknown	7 (6.7)	5 (6.5)	6 (22.2)
Age, y			
Median	30.5	31.2	18.9
Interquartile range	15–43	14–40	10–34
Female sex	67 (64.4)[b]	36 (46.8)	13 (48.1)
Inciting agent			
Food	32 (30.8)	28 (36.4)	8 (29.6)
Insect	20 (19.2)	16 (20.8)	3 (11.1)
Medications	12 (11.5)	11 (14.3)	6 (22.2)
Other	11 (10.6)	6 (7.8)	2 (7.4)
Unknown	29 (27.9)	16 (20.8)	8 (29.6)
Hospital admission	10 (9.6)[b]	17 (22.1)[c]	13 (48.1)[d]
History of asthma	23 (22.1)	21 (27.3)	10 (37.0)
Prescription of self-injectable epinephrine[e]	26 (25.0)[f]	38 (49.4)	15 (55.6)[g]
Allergist referral	40 (38.5)	33 (42.9)	14 (51.9)

[a] Data are given as number (percentage) of patients in each group unless otherwise indicated. Percentages may not total 100 because of rounding.
[b] $.01 \leq P \leq .05$ for comparison of 0 and 1 dose of epinephrine.
[c] $.01 \leq P \leq .05$ for comparison of 1 and 2 dose of epinephrine.
[d] $P \leq .001$ for comparison of 0 and 2 doses of epinephrine.
[e] Adjusted value according to prior prescription of self-injectable epinephrine.
[f] $P \leq .001$ for comparison of 0 and 1 dose of epinephrine.
[g] $P \leq .01$ for comparison of 0 and 2 doses of epinephrine.

tients who received repeated doses of epinephrine. To our knowledge, this is the first population-based study to evaluate risk factors for the use of repeated doses of epinephrine in patients with anaphylaxis. Furthermore, we have studied the use of repeated doses of epinephrine in patients presenting with anaphylaxis irrespective of the inciting allergen.

In this study, we found that 13.0% of the patients presenting with anaphylaxis received more than 1 dose of epinephrine. This is consistent with previous studies, demonstrating that it is not uncommon for patients to receive repeated doses of epinephrine.[13]

We found that patients receiving more than 1 dose of epinephrine tended to be younger. This may be because physicians were reluctant to give epinephrine to older patients who are more likely to have cardiovascular comorbidities. However, to our knowledge, there are no data to suggest that a history of known coronary artery disease is a contraindication to epinephrine.[17] Alternatively, it is possible that younger patients had more severe or persistent symptoms.

A history of asthma did not significantly predict the use of repeated doses of epinephrine in our population of patients with diverse allergens. However, patients with a history of asthma tended to receive more than 1 dose of epinephrine. A previous study of food-induced anaphylaxis in children found that asthma was significantly associated with receiving repeated doses of epinephrine.[13] Our results suggest that a history of asthma may not be present in many patients who will require repeated doses of epinephrine.

Signs involving the respiratory system, such as wheezing, cyanosis, laryngeal edema, and stridor, had the most significant relationship to the use of repeated doses of epinephrine. These findings are comparable with a study involving children presenting with food-induced anaphylaxis in which throat closure was more common in patients receiving numerous doses of epinephrine.[13]

Patients who received repeated doses of epinephrine tended to be more likely to receive a prescription for self-injectable epinephrine. However, the overall prescription rates of self-injectable epinephrine are still low, consistent with previous studies. Collaboration between allergy and ED personnel would likely increase prescription rates.[18–20]

The retrospective design of this study is the primary limitation. In addition, our study population was primarily white

Table 3. Presenting Signs and Symptoms of Patients Who Received Repeated Doses of Epinephrine Compared With Those Who Did Not Receive Repeated Doses of Epinephrine

Signs and symptoms	No. (%) of patients receiving 0 doses of epinephrine (n = 104)	No. (%) of patients receiving 1 dose of epinephrine (n = 77)	No. (%) of patients receiving ≥2 doses of epinephrine (n = 27)
Mucocutaneous symptoms			
Urticaria	71 (68.3)	57 (74.0)[a]	14 (51.9)
Angioedema	65 (62.5)	53 (68.8)	20 (74.1)
Pruritus	57 (54.8)	32 (41.6)	14 (51.9)
Flushing and diaphoresis	41 (39.4)	35 (45.5)	14 (51.9)
Conjunctivitis and chemosis	18 (17.3)[b]	2 (2.6)[a]	5 (18.5)
Cardiovascular system			
Tachycardia	33 (31.7)	31 (40.3)	11 (40.7)
Chest pain	14 (13.5)	12 (15.6)	5 (18.5)
Presyncope and orthostatic hypotension	14 (13.5)	12 (15.6)	4 (14.8)
Hypotension and shock	11 (10.6)	9 (11.7)	7 (25.9)[c]
Syncope	7 (6.7)	5 (6.5)	2 (7.4)
Arrhythmia	4 (3.8)	4 (5.2)[a]	6 (22.2)[d]
Bradycardia	2 (1.9)	3 (3.9)	3 (11.1)
Respiratory system			
Dyspnea	44 (42.3)[e]	44 (57.1)	15 (55.6)
Tightness/fullness of throat	40 (38.5)	33 (42.9)	11 (40.7)
Wheezing/bronchospasm	25 (24.0)	19 (24.7)	12 (44.4)[c]
Cough	11 (10.6)	13 (16.9)	7 (25.9)[c]
Hoarseness and aphonia	8 (7.7)	12 (15.6)	3 (11.1)
Stridor and laryngeal edema	3 (2.9)[e]	9 (11.7)	6 (22.2)[d]
Cyanosis	2 (1.9)	4 (5.2)[a]	5 (18.5)[d]
Gastrointestinal system			
Nausea and emesis	23 (22.1)	18 (23.4)	11 (40.7)[c]
Dysphagia	11 (10.6)	9 (11.7)	5 (18.5)
Abdominal pain	13 (12.5)	3 (3.9)	1 (3.7)
Diarrhea	8 (7.7)	4 (5.2)	2 (7.4)

[a] $.01 \leq P \leq .05$ for comparison of 1 and 2 doses of epinephrine.
[b] $P \leq .01$ for comparison of 0 and 1 dose of epinephrine.
[c] $P \leq .05$ for comparison of 0 and 2 doses of epinephrine.
[d] $P \leq .01$ for comparison of 0 and 2 doses of epinephrine.
[e] $P \leq .05$ for comparison of 0 and 1 dose of epinephrine.

and, therefore, our results may not be generalizable to minority or ethnic populations.

In conclusion, 13.0% of patients received 2 or more doses of epinephrine. The second dose of epinephrine was administered by a health care professional in all cases, and the final dose was always given by an ED physician, indicating that repeated dosing was needed to resolve the symptoms. Patients receiving repeated doses of epinephrine tended to be younger and were more likely to present with wheezing, cyanosis, hypotension and shock, arrhythmias, stridor and laryngeal edema, cough, nausea, and emesis and less likely to have urticaria.

A history of asthma did not significantly predict the use of repeated doses of epinephrine. The results of this population-based study make a significant contribution to the evidence needed to identify high-risk patients who may benefit from carrying more than 1 dose of epinephrine. Prospective studies are needed for further confirmation.

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