

Clinical Communications

Timing and predictors of repeat epinephrine administration among children hospitalized for anaphylaxis

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Clinical Implications

- Debate exists over the optimal observation period for children with anaphylaxis cared for in the emergency department. We found that observation periods of 4 hours may be optimal for children with anaphylaxis to monitor for symptoms requiring repeat epinephrine administration.

TO THE EDITOR:

During the past decade, US emergency department (ED) visits for anaphylaxis increased by nearly 200% among children.¹ Clinicians are responsible for identifying children at risk of recurrent, persistent, or worsening symptoms necessitating prolonged ED observation, hospitalization, or treatment with further doses of epinephrine.

There is limited evidence to guide decision making regarding the optimal length of ED observation after initial epinephrine administration. Although the natural history of symptoms could guide observation duration, timing of repeat epinephrine administration may be a more relevant marker for the presence of reactions requiring prolonged observation or hospitalization because mild recurrent reactions may not necessitate treatment with epinephrine.

We sought to identify the timing and cumulative risk of repeat epinephrine administration in the prehospital, ED, and inpatient settings among children hospitalized for anaphylaxis. We also aimed to evaluate predictors of repeat administration on the basis of information available to the clinician at the time of initial ED evaluation. These findings may inform optimal ED observation periods and need for hospitalization in children with anaphylaxis.

We conducted a single-center retrospective cohort study of children and young adults aged 6 months to 21 years presenting to the ED for anaphylaxis and were hospitalized from January 2009 to June 2016. Cases were identified using automated ED discharge diagnostic codes for allergic reactions or adverse drug reactions^{2,3} and manually reviewed by the primary author and a research coordinator to confirm the presence of anaphylaxis using the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).⁴ Children who received intramuscular epinephrine in the prehospital or ED setting were also included. We excluded children who did not receive intramuscular epinephrine in the prehospital setting or within 2 hours of ED arrival (to avoid omitting cases with ambiguity about the

diagnosis of anaphylaxis), encounters in which timing of first administered dose of epinephrine was not documented, anaphylactic reactions secondary to treatments received in the ED, patients with a tracheostomy or receiving home respiratory support, as well as children with hereditary angioedema, mast cell activation disorders, and somatoform disorder.

To assess the timing of repeat epinephrine administration, we performed a survival analysis where time to event was defined as the time in hours between first and second administered doses of epinephrine and time 0 was ascribed to the first administered dose of epinephrine. We determined the cumulative risk of repeat epinephrine exposure at 2, 4, and 6 hours from the initial dose among eligible patients.

We performed a survival analysis using Cox proportional hazards regression to determine predictors of time to repeat epinephrine administration. Univariate and multivariate analyses were performed to assess performance of candidate predictors including information from the prehospital setting and at the time of initial ED evaluation. For these analyses, we excluded patients transferred from outside facilities because of concerns around limited documentation of physical examination findings. Candidate predictors included age, sex, unknown trigger, history of anaphylaxis or asthma, hypotension, wide pulse pressure, gastrointestinal involvement, respiratory distress, wheezing, stridor, and time from symptom onset to first administered dose of intramuscular epinephrine.⁵

Among 731 children hospitalized for allergic reactions, 437 were excluded and 294 were analyzed (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Patient characteristics are presented in Table I. Median time from first to second doses of epinephrine was 1.2 hours (interquartile range, 0.68-2.42). Time to event data for repeat epinephrine administration in the prehospital, ED, and inpatient settings are shown in Figure E2 in this article's Online Repository at www.jaci-inpractice.org. The cumulative risks (95% CI) of receiving a second dose of epinephrine at 2, 4, and 6 hours after the initial dose among patients who had not already received a second dose nor were discharged by the given time interval were 0.19 (0.14-0.25 [n = 22]), 0.24 (0.18-0.30 [n = 11]), and 0.25 (0.20-0.32 [n = 7]).

Characteristics from the univariate and multivariate models associated with repeat epinephrine administration are presented in Table II. In the univariate model, history of anaphylaxis (hazard ratio, 1.93; 95% CI 1.01-3.68) and hypotension (hazard ratio, 4.72; 95% CI, 1.83-12.13) were associated with repeat epinephrine administration. However, in the multivariate analysis, only hypotension reached statistical significance (hazard ratio, 5.3; 95% CI, 1.27- 22.1).

In this study of hospitalized children with anaphylaxis, 26% of patients received repeat epinephrine in the prehospital, ED, or inpatient setting, which is significantly higher than previously published data (6%-17%),⁶⁻⁸ likely related to our exclusion of children discharged from the ED. Repeat epinephrine administration occurred most commonly within 2 hours from the initial dose and was rare (n = 7 [2.4%]) beyond 4 hours. Presence of hypotension was predictive of repeat epinephrine administration after adjusting for clinically relevant covariates.

TABLE I. Characteristics of hospitalized children with anaphylaxis, stratified by doses of epinephrine received

Characteristic	Single-dose epinephrine (n = 217)	Multiple-dose epinephrine (n = 77)
Demographic		
Age (y), median (interquartile range)	5.8 (2.7-12.1)	5.7 (3.2-13.1)
<2	35 (16.1)	8 (10.4)
2-5	76 (35.0)	32 (41.6)
6-9	33 (15.2)	12 (15.6)
10-13	24 (11.1)	7 (9.1)
≥14	49 (22.6)	18 (23.4)
Sex: male	123 (56.7)	44 (57.1)
Race		
White	88 (43.1)	33 (47.1)
Black	51 (25.0)	14 (20.0)
Other	65 (31.9)	23 (32.9)
Ethnicity		
Hispanic	44 (23.2)	11 (17.2)
Language		
English	189 (90.0)	67 (90.5)
Medical history		
Anaphylaxis	57 (26.3)	28 (36.4)
Asthma	92 (42.4)	38 (49.4)
Reaction trigger		
Food	136 (62.7)	54 (70.1)
Medication	13 (6.0)	5 (6.5)
Venom	2 (0.9)	0
Other	3 (1.4)	0
Unknown	63 (29.0)	18 (23.4)
Clinical manifestations of anaphylaxis		
Respiratory	191 (88.0)	72 (93.5)
Cardiac	27 (12.4)	15 (19.5)
Gastrointestinal	124 (57.1)	46 (59.7)
Dermatologic or mucosal	198 (91.2)	74 (96.1)

Values are n (%) unless indicated otherwise.

The exclusion of discharged patients allowed us to evaluate children with severe anaphylactic reactions, which is the population most likely to require observation and/or repeat epinephrine. Our findings suggest that most children with anaphylaxis may be candidates for ED discharge after 4 hours of observation. Patients with hypotension likely require prolonged observation beyond 4 hours, because children in our cohort who were hypotensive were more likely to receive repeat epinephrine and because cardiovascular involvement and wide pulse pressure may be risk factors for biphasic anaphylaxis.^{3,9}

Limitations of this study are mainly related to the retrospective and single-center design. Physical examination findings and symptomatology in the prehospital setting, as well as rationale for epinephrine administration, are not reliably documented in the electronic medical record. Furthermore, our inclusion of only hospitalized children, and exclusion of transferred patients, may limit the generalizability of some of our findings.

Among children hospitalized with anaphylaxis, repeat epinephrine administration occurred most commonly within 2 hours from the initial dose and was rare beyond 4 hours. The

TABLE II. Predictors of repeat epinephrine administration (n = 204)*

Demographic and clinical characteristic	Hazard ratio (95% CI)	
	Univariate model	Multivariate model
Age (y)†	1.04 (0.99-1.09)	1.03 (0.96-1.10)
Sex: male	1.16 (0.60-2.24)	1.10 (0.42-2.85)
Unknown trigger	0.82 (0.40-1.69)	1.19 (0.42-3.42)
Medical history		
Asthma	1.33 (0.70-2.55)	1.37 (0.52-3.62)
Anaphylaxis	1.93 (1.01-3.68)	1.48 (0.62-3.57)
Respiratory		
Respiratory distress‡	1.03 (0.54-1.97)	0.79 (0.30-2.09)
Wheezing	0.75 (0.39-1.45)	0.88 (0.34-2.30)
Stridor	1.77 (0.54-5.77)	1.08 (0.11-10.21)
Cardiac		
Hypotension§	4.72 (1.83-12.13)	5.30 (1.27-22.10)
Wide pulse pressure	1.31 (0.55-3.14)	1.20 (0.38-3.79)
Gastrointestinal	0.95 (0.50-1.81)	0.72 (0.28-1.86)
Time from symptom onset to first intramuscular epinephrine (h)	0.86 (0.66-1.13)	0.86 (0.64-1.16)

Bold values indicate statistically significant hazard ratios.

*Excluding children transferred from outside facilities (n = 90).

†Continuous variable.

‡Dyspnea, retractions.

§Low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 y, <(70 mm Hg + [2 × age]) from 1 to 10 y, and <90 mm Hg from 11 to 17 y. Among children with hypotension (n = 9), 4 children (44.4%) had a history of anaphylaxis and asthma; food was the most common allergen (n = 7 [77.8%]).

||Defined as diastolic blood pressure lower than or equal to half the systolic blood pressure.

presence of hypotension was a predictor for repeat epinephrine administration. These findings may inform the derivation and validation of decision models to help standardize and reduce observation periods among children with anaphylaxis.

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ONLINE REPOSITORY

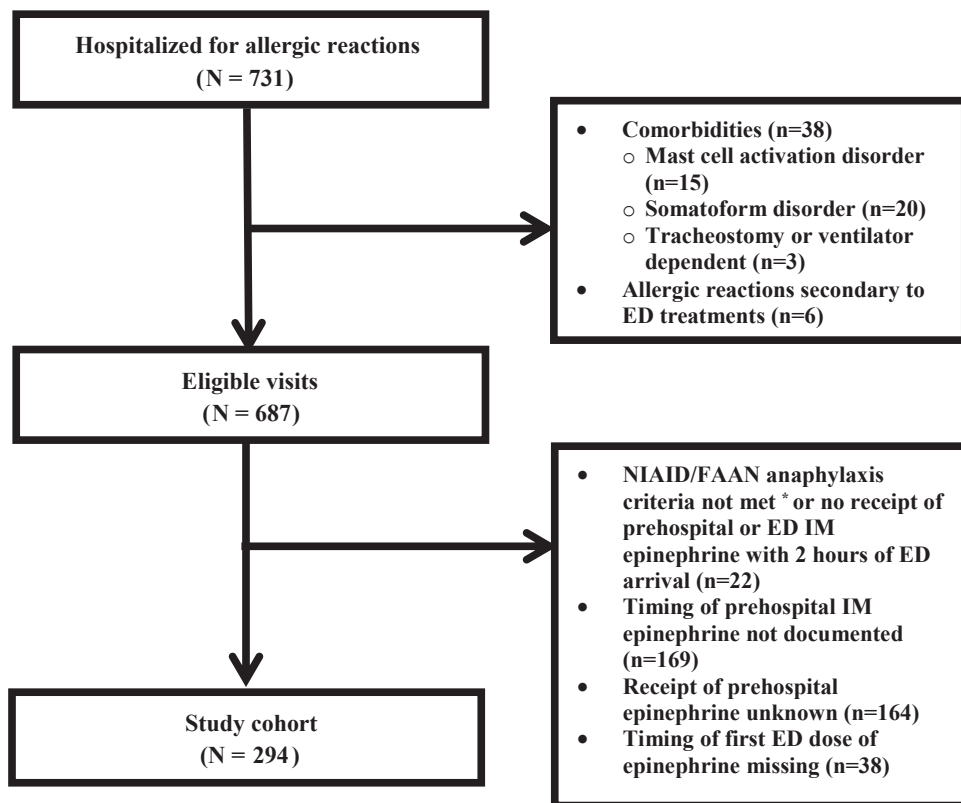


FIGURE E1. Patient flow diagram. *FAAN*, Food Allergy and Anaphylaxis Network; *IM*, intramuscular; *NIAID*, National Institute of Allergy and Infectious Diseases. *Manual chart review performed applying the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis.^{E1}

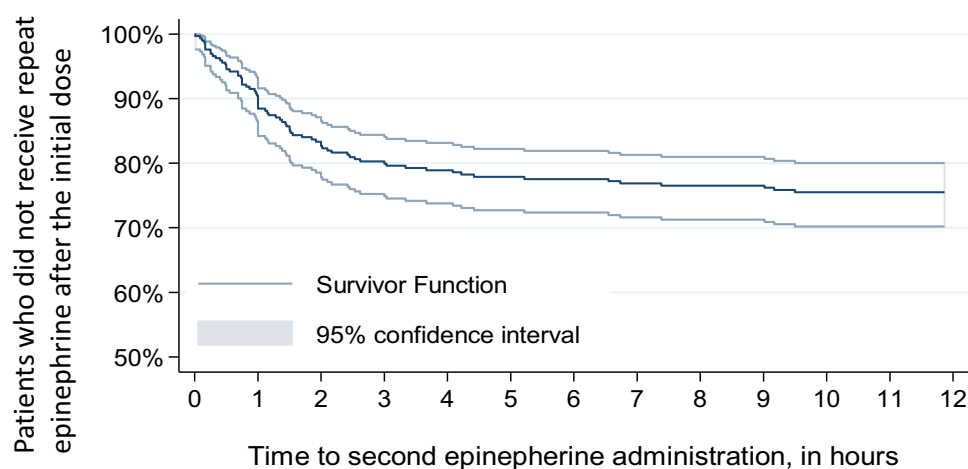


FIGURE E2. Kaplan-Meier estimates of repeat epinephrine-free survival.

TABLE E1. Clinical criteria for diagnosing anaphylaxis^{E1}

Anaphylaxis is highly likely when any 1 of the following 3 criteria is 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, and swollen lips-tongue-uvula)

AND AT LEAST 1 OF THE FOLLOWING

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

BP, Blood pressure.

*Low systolic BP for children is defined as <70 mm Hg from 1 mo to 1 y, <(70 mm Hg + [2 × age]) from 1 to 10 y, and <90 mm Hg from 11 to 17 y.^{E1}

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