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Factors associated with epinephrine administration for anaphylaxis in children before arrival to the emergency department

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ABSTRACT

Background: Epinephrine is the first-line treatment for anaphylaxis but may be underused by patients and medical personnel.

Objective: To evaluate factors associated with anaphylaxis management before arrival at the emergency department (ED) or urgent care center (UCC).

Methods: We performed a retrospective review of electronic medical records for all patients aged 0 to 25 years presenting with anaphylaxis to the ED or UCC at a pediatric academic referral center during 2009 to 2013.

Results: A total of 408 patients (mean age, 7.25 years; 62% male) were included for analysis. Only 148 patients (36.3%) received epinephrine before arrival at the ED or UCC. Reactions occurring at home ($n = 36/114$) were less likely to be treated with epinephrine compared with reactions occurring at school ($n = 30/49$) (odds ratio [OR], 0.29; 95% confidence interval [CI], 0.15–0.59). The odds of receiving epinephrine before arrival at the ED or UCC were significantly lower with a 2-organ system (OR, 0.50; 95% CI, 0.30–0.85) or 3-organ system (OR, 0.41; 95% CI, 0.21–0.81) presentation compared with 1-organ system involvement. Foods (342 [83.8%]) were the most commonly reported provoking trigger. Patients who did not receive epinephrine before arrival at the ED or UCC were significantly less likely to be discharged to home (OR, 0.56; 95% CI, 0.37–0.86; $P = .01$).

Conclusion: This study identifies factors associated with prehospital management of anaphylaxis for children, which highlight that epinephrine administration may be occurring with considerable delay. Increased awareness and education of caregivers, patients, and medical professionals are necessary to provide optimal management.

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Introduction

Anaphylaxis is a rapidly progressive, systemic allergic reaction that is potentially fatal.^{1,2} The prevalence of anaphylaxis has been increasing during the past 2 decades, with recent estimates of the incidence rate in children with known food allergy as high as 7 per 100 person-years.^{3–7} Food allergens are the most common trigger of anaphylaxis in children, with additional causes including medications, venom, and latex.^{6–10} For all causes, prompt administration of epinephrine is the only recommended first-line treatment.^{1,11–15} Prompt and early treatment with epinephrine prevents fatalities, stabilizes blood pressure, and reduces hospitalization.^{2,16}

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Despite the availability of multiple published guidelines regarding anaphylaxis management, there continue to be deficiencies in anaphylaxis treatment, particularly for children.^{5,10} Multiple studies have observed knowledge deficits and delays in recognition of anaphylaxis among emergency medical personnel, teachers, and even health care professionals.^{17–20} Treatment with epinephrine is often delayed or avoided and may be substituted with other treatment options, such as antihistamines.^{4,21} Survey research has shown poor understanding of indications for the use of epinephrine among families with food allergic children, school nurses, and emergency responders, likely contributing to the underuse of epinephrine before the arrival at the emergency department (ED).^{17,20,22–25}

Aside from patient surveys, data are limited on the prehospital administration rates of epinephrine before arrival at the ED among children experiencing anaphylaxis. The primary objective of our study was to use the electronic medical record (EMR) to evaluate factors associated with epinephrine administration in children

Table 1
Factors Associated With Epinephrine Administration Before Arrival at the ED or UCC

Factor	No. (%) of patients			Odds ratio (95% CI)
	Total (N = 408)	No epinephrine before ED or UCC (n = 216)	Epinephrine before ED or UCC (n = 148)	
Sex				
Male	257 (63)	134 (62)	91 (62)	0.97 (0.64–1.50)
Female	151 (37)	82 (38)	57 (38)	1.0 [Reference]
Age, y				
0–5	193 (47)	100 (46)	64 (43)	0.88 (0.58–1.35)
6–12	117 (29)	72 (33)	39 (26)	0.72 (0.45–1.14)
13–17	91 (22)	40 (19)	43 (29)	1.80 (1.10–2.95)
≥18	7 (2)	4 (2)	2 (1)	0.73 (0.13–4.01)
History of anaphylaxis				
Yes	264 (65)	121 (56)	125 (85)	4.27 (2.54–7.17)
No	144 (35)	95 (44)	23 (16)	1.0 [Reference]
Location of reaction				
No documentation	175 (43)	93 (43)	47 (32)	0.62 (0.40–0.95)
Home	120 (29)	78 (36)	36 (24)	0.57 (0.36–0.901)
School	49 (12)	19 (9)	30 (20)	2.64 (1.42–4.89)
Work	3 (1)	0	3 (2)	10.4 (0.53–203.1)
Restaurant	12 (3)	7 (3)	5 (3)	1.04 (0.33–3.35)
Party	7 (2)	2 (1)	4 (3)	2.97 (0.54–16.44)
Other	33 (8)	9 (4)	22 (15)	4.02 (1.79–8.99)
Relative's home	9 (2)	8 (4)	1 (0.6)	0.18 (0.02–1.43)
Presenting symptoms				
Skin or mucosal only	52 (13)	24 (11)	26 (18)	1.04 (0.94–3.11)
Respiratory only	20 (5)	8 (4)	11 (7)	2.09 (0.82–5.32)
GI only	1 (0)	0	1 (0.6)	4.40 (0.18–108.8)
≥2 Organs	335 (82)	184 (85)	110 (74)	0.50 (0.30–0.85)
Skin and respiratory	189 (46)	94 (44)	71 (48)	1.20 (0.79–7.82)
Skin and GI	50 (12)	30 (14)	14 (10)	0.65 (0.33–1.27)
Respiratory and GI	9 (2)	9 (4)	0	0.07 (0.01–1.27)
Skin, respiratory, and GI	87 (21)	51 (24)	25 (17)	0.65 (0.39–1.12)

Abbreviations: CI, confidence interval; ED, emergency department; GI, gastrointestinal; UCC, urgent care center.

experiencing anaphylaxis before arrival at the ED or urgent care center (UCC) of a tertiary care pediatric academic medical center.

Methods

This study was a retrospective cohort evaluation of patients presenting to the ED or UCC at Nationwide Children's Hospital located in Columbus, Ohio. Patient records were included for selection by search of the institution's EMR system (Epic Systems, Verona, Wisconsin), for all patients seen for an acute care visit in the ED or UCC between 2009 and 2013 who met the age criteria of 0 to 25 years, with the visit discharge *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes 693.1 (dermatitis due to food taken internally), 995.0 (other anaphylactic shock, not elsewhere classified), 995.1 (angioneurotic edema, not elsewhere classified), 995.3 (allergy unspecified, not elsewhere classified), and 995.60 to 995.69 (anaphylactic shock due to unspecified food, peanuts, crustaceans, fruits and vegetables, tree nuts and seeds, fish, food additives, milk products, eggs, other specified food). All encounter dates and locations for patients who met the initial criteria were extracted automatically through a query of the electronic data warehouse. Additional data specific to the patient and the encounter were extracted manually through record review.

A total of 532 cases were identified from the initial search. Cases were included for analysis (n = 408) based on additional medical care professional documentation during the encounter that supported a diagnosis of anaphylaxis, including presenting signs and symptoms as well as physical examination findings, if documentation of symptoms and/or physical examination findings were consistent with anaphylaxis in patients with prior history of anaphylaxis and exposure to known allergen or in accordance with the diagnostic criteria from the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network

(NIAID/FAAN) 2006 guidelines.¹ To test concordance among data extractors, a pilot cohort of 25 cases were reviewed by 2 authors (M.R. and D.S.), which demonstrated an interrater reliability (κ) of 88% (n = 22/25) in agreement of inclusion criteria. The remaining EMR review was conducted by one author (M.R.). Cases were excluded from analysis (n = 124) based on information within the EMR that was incomplete or inconsistent with a diagnosis of anaphylaxis¹ or for patients who were outside our age range.

After the cases were identified for inclusion, these encounters were then further examined and data abstracted pertaining to age, sex, prior history of anaphylaxis (as stated in the ED or UCC encounter or from review of previous allergy list or encounters within the EMR, including anaphylaxis to specific foods), previous epinephrine administration, medications administered before ED or UCC arrival, persons administering medications, presumed triggers of the event, symptoms present (recorded at the level of affected organ system, eg, skin, respiratory, cardiac, gastrointestinal), discharge disposition, discharge follow-up instructions, and epinephrine prescription administration. Individual encounters were transcribed to a Microsoft Excel spreadsheet (Microsoft Corp, Redmond, Washington). A study number was assigned to each patient so that the data were completely deidentified on storage in the spreadsheet. Variables were chosen based on clinical relevance at the discretion of the authors.

Data were uploaded to STATA SE, version 13 (StataCorp, College Station, Texas) and were explored for general descriptive frequencies, as well as analyzed with both logistic regression and χ^2 or Fisher exact test for assessment of bivariate and proportional trends. Multivariable logistic regression was used to assess factors associated with epinephrine administration. Predictive probabilities for regression models were calculated using the STATA margins command. This study was approved by the institutional review board at Nationwide Children's Hospital.

Results

A total of 408 patients who met the eligibility requirements were included in this study. Documentation of epinephrine administration was not available for 44 patients (10.8%). Among all 408 patients, 193 (47.3%) were 5 years or younger. For purposes of data analysis, patients were divided into 4 age categories: 0 through 5 years (toddler/preschool), 6 through 12 years (elementary school), 13 through 17 years (high school/adolescent), and 18 years and older (postgraduation). The 13- to 17-year-old group was more likely to receive epinephrine (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.10–2.95), whereas no associations were observed with other age groups.

Table 1 details factors associated with epinephrine (and other medication) administration before arrival at the ED or UCC. Before arrival in the ED, 331 of the 408 patients (81.1%) received at least one medication for their reaction, including 148 (36.3%) who received epinephrine and 194 (47.8%) who received a histamine₁-antihistamine. The location of reaction was documented in 233 records (57.1%). The odds of receiving epinephrine for a reaction before arrival were significantly lower for reactions that occurred at home ($n = 36/114$) compared with reactions that occurred at school ($n = 30/49$) (OR, 0.29; 95% CI, 0.15–0.59) (**Fig 1**). When epinephrine was administered at home, it was given by a parent or guardian in 19 patients (52.8%) and by emergency responders in 9 patients (25%). For those patients receiving epinephrine at school, 10 (33.3%) received the epinephrine from school personnel, 8 (26.7%) from a parent or guardian, and 8 (26.7%) from emergency responders.

A total of 264 patients (64.7%) had a known history of a prior anaphylactic reaction, among which 195 (47.9%) had been previously prescribed self-injectable epinephrine before this event. Among all patients who had been prescribed self-injectable epinephrine, 190 (97.4%) had a prior history of anaphylaxis. Only 136 of 195 patients (69.7%) who had been prescribed a source of self-injectable epinephrine confirmed this was present at the time of the event, and 117 of 136 (86.0%) received this before arrival at the ED or UCC. The odds of receiving epinephrine before arrival at the ED or UCC were significantly higher in patients with multiple food allergies compared with those with a single food allergy (OR, 3.9; 95% CI, 1.7–8.9).

Record-documented triggers of events are detailed in **Table 2**. The odds of the encounter being related to a food trigger decreased significantly (OR, 0.997; 95% CI, 0.994–0.999) with increasing age, and this effect was parabolic because of a significant interaction effect of age $\times$ age (**Fig 2**). The odds of receiving epinephrine before

Table 2

Patient-Reported Triggers of Anaphylaxis

Trigger	No. (%) of patients (N = 408)
Food	342 (83.8)
Peanut or tree nut	236 (57.8)
Milk	66 (16.2)
Egg	61 (15.0)
Seafood	51 (12.5)
Unidentified	47 (11.5)
Medication	18 (4.4)
Latex	1 (0.2)

arrival at the ED or UCC were not significantly associated with a food vs nonfood trigger.

A total of 378 (92.6%) of all patients had reported cutaneous symptoms (flushing, urticaria, angioedema), with 305 (74.8%) having documentation of respiratory symptoms and 147 (36.0%) having gastrointestinal symptoms. Most patients had documentation of symptoms affecting 2-organ systems (248/408 [60.8%]) compared with 87 of 408 (20.3%) having 3-organ system involvement and 73 of 408 (17.9%) with symptoms affecting 1-organ systems. Patients with documentation of only cutaneous symptoms ($n = 52$) were included in analysis because they all had a prior history of anaphylaxis and/or food allergy and their presentation included a combination of both urticaria and angioedema. The odds of receiving epinephrine before arrival at the ED or UCC were significantly lower with 2-organ system (OR, 0.50; 95% CI, 0.30–0.85) or 3-organ system (OR, 0.41; 95% CI, 0.21–0.81) presentations compared with 1-organ system involvement.

On arrival to the ED or UCC, 50% of all patients received epinephrine, and those who did receive epinephrine before arrival were significantly less likely to be treated with epinephrine on arrival (OR, 0.07; 95% CI, 0.04–0.13) (**Table 3**). Disposition data were analyzed for the 364 patients with clear documentation of epinephrine administration or lack of administration before arrival at the ED or UCC (**Table 4**). There were no fatalities reported in our cohort. Patients who received epinephrine before arrival at the ED or UCC (216/364 [59.3%]) were more likely to be discharged to home compared with those who did not receive epinephrine (148/364 [40.7%]) (OR, 0.56; 95% CI, 0.37–0.86) (**Table 4**). Food triggers were significantly associated with a lower odds of hospital admission (OR, 0.59; 95% CI, 0.35–0.99) when adjusted for number of presenting symptoms, history of anaphylaxis, and location of where epinephrine was administered.

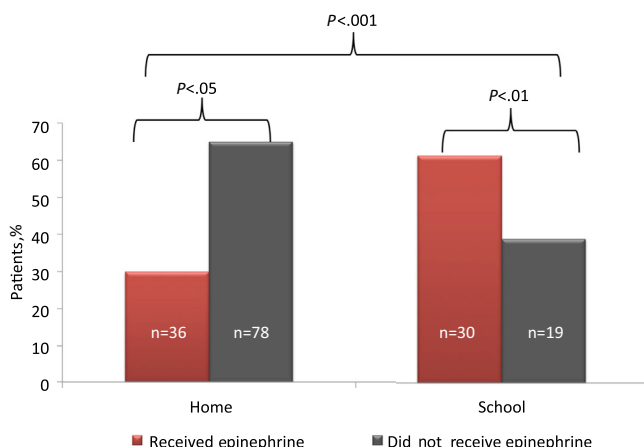


Figure 1. Pre-hospital epinephrine administration according to location of anaphylaxis.

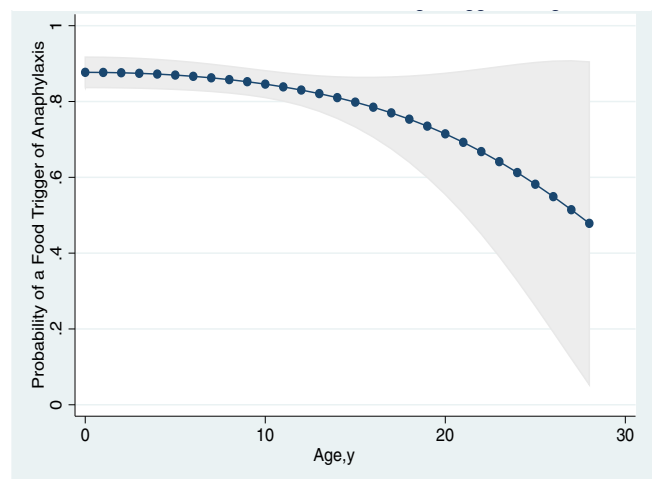


Figure 2. Predicted probability of a food allergy trigger by age.

Table 3

Epinephrine Administration on Arrival to the ED or UCC

Epinephrine given in ED or UCC	No. (%) of patients				Odds ratio (95% CI)
	Total (N = 408)	Unknown epinephrine before ED or UCC (n = 44)	No epinephrine before ED or UCC (n = 216)	Epinephrine before ED or UCC (n = 148)	
No	205 (50)	12 (27)	66 (31)	127 (86)	0.07 (0.04–0.13)
Yes	204 (50)	32 (73)	150 (69)	21 (14)	1.0 [Reference]

Abbreviations: CI, confidence interval; ED, emergency department; UCC, urgent care center.

There were 74 patients who presented initially to a UCC who were then transferred to the ED for additional management or observation. Eighty-one patients (91%) who were transferred from the UCC to the ED for further management did not receive epinephrine before arrival at the UCC. Only 11 total patients (2.7%) were admitted to the pediatric intensive care unit. These patients were older (mean [SD] age, 12.9 [4.4] years) and mostly male (n = 8). Type of symptoms or food trigger was not associated with any differences in disposition.

Discussion

In our study, less than half of all children presenting to a tertiary care referral center for anaphylaxis received epinephrine before arrival at the ED or UCC. Foods, particularly peanuts or tree nuts, were the reported allergic trigger for most cases. Although 65% of these children had experienced a prior anaphylactic reaction, less than half of that cohort had been prescribed self-injectable epinephrine previously, and only approximately two-thirds of those with prior epinephrine prescriptions had their unit(s) available at the time of symptom onset.

These findings are consistent with prior data that have identified similar deficits in the availability of epinephrine among individuals with food allergy who had an additional reaction after prescription of this device. Multiple past studies have corroborated the finding that epinephrine is reported as not always available or, worse, available and not used, a finding in particular associated with food allergy fatality in teenagers and young adults.^{2,22,24,26,27} The circumstances of why this finding persists are beyond the scope of this study but may relate to social disparities, access to specialty care, or multiple physician-related factors that have influence on how subsequent reactions are managed.^{12,28,29} A retrospective review by Carillo et al³⁰ published in 2016 produced similar findings to our study, with 54% of pediatric patients with anaphylaxis receiving epinephrine before ED arrival. However, our study is one of the few to find demonstrable outcomes and disposition related to such practices.

In our population, factors associated with a higher likelihood of receiving epinephrine before arrival at the ED or UCC included anyone with a prior history of anaphylaxis, children between 13 and 17 years of age, reactions occurring at school, and having only 1-organ system involved. Ninety-three percent of patients in our study had documentation of cutaneous findings, which is also consistent, albeit somewhat higher, than prior reports.^{1,6,11,12}

Reactions occurring at home or not involving any cutaneous symptoms were less likely to be treated with epinephrine before arrival at the ED or UCC. Importantly, patients with symptoms affecting more than one organ system were less likely to receive epinephrine. The reasons for this were beyond the scope of this study, and admittedly this is a very ominous and illogical finding, considering a marked campaign in recent years specifically identifying multiorgan system reactions and reactions beyond “just hives” as prime indications for epinephrine administration. The implications of this finding are unclear; this may reflect regional preferences or advice for treatment, regional emergency medical services practices, or a failure at the patient level to simply implement anaphylaxis management plans. This finding would benefit from future qualitative study of these individuals to better understand why epinephrine was not used.

Consensus criteria between allergy and emergency medicine for the diagnosis and management of anaphylaxis have existed since 2006 and were updated recently in a practice parameter in 2014 that again involved both disciplines.^{1,12} However, there are sparse data regarding adherence to such criteria and minimal studies showing their validation.³¹ A recent prospective validation study in an adult population found a 95% sensitivity in identification of anaphylaxis according to NIAID/FAAN criteria with 71% specificity.³² In addition, the NIAID/FAAN criteria in particular were developed according to expert consensus at the time to simplify outpatient anaphylaxis management at the patient level, aimed to assist in better case identification and more rapid administration of epinephrine. No data exist to support that the criteria have been helpful in identifying more cases of anaphylaxis than before establishing the criteria or if the criteria have promoted more widespread use of epinephrine.^{18,28,31} Therefore, despite these efforts, underuse of epinephrine by physicians and medical personnel remains prominent, with prior studies finding epinephrine use within the ED setting ranging from 39% to 68%, which is consistent with our study, which found that 50% of patients received epinephrine on presentation to the ED or UCC.^{33–37} Interestingly, our study also suggests that pre-hospital use of epinephrine for anaphylaxis may significantly affect the need to receive epinephrine within the ED or UCC setting, data not always available or included in other similar studies.

In addition to studies that evaluated the care received before and during ED evaluation for anaphylaxis, data regarding provision of epinephrine autoinjectors and referral to an allergist on

Table 4

Disposition From ED or UCC Based on Administration of Epinephrine Before Arrival

Disposition	No. (%) of patients		Odds ratio (95% CI)
	Did not receive epinephrine (n = 216)	Did receive epinephrine (n = 148)	
Discharge home	83 (38.4)	78 (52.7)	0.56 (0.37–0.86)
Admission to floor	62 (28.7)	56 (37.8)	0.66 (0.42–1.03)
PICU admission	5 (2.3)	6 (4.1)	0.56 (0.17–1.87)
Transfer from UC to ED	66 (30.6)	8 (5.4)	7.70 (3.57–16.62)

Abbreviations: CI, confidence interval; ED, emergency department; PICU, pediatric intensive care unit; UCC, urgent care center.

discharge from the ED setting show opportunities for improvement as well.^{36,38} Although the severity of prior reactions does not necessarily correlate with severity of future reactions, presentation to an ED for presumed anaphylaxis should stratify patients into a high-risk category and ideally promote close follow-up with an allergist, review of the signs and symptoms of anaphylaxis, and proper treatment with epinephrine autoinjectors, including hands-on practice with a training device.

Strengths of our study include the use of objectively documented data at the medical care professional level, obtained through review of the EMR within a large tertiary health care system, as opposed to self-report caregiver and patient measures used in previous similar studies. In addition, our study included a large number of patients studied during a 4-year period and evaluated multiple associated factors with reactions. Limitations include some cases with incomplete documentation even within an EMR, possible underreporting of epinephrine use before arrival at the ED or UCC, limited numbers of teenagers and young adults included in the study, lack of objective validation that epinephrine was given in the home setting when reported, and data that emanate from a single center and thus may be subject to clustering effects or reflective of regional practices associated with this medical center and health care system. It is also possible that potential cases during this period were missed and not included because of coding errors, leading to billing diagnoses that were incongruent with the ICD-9 diagnoses selected for our EMR query. There was no access to documentation from emergency medical services before arrival at the ED or UCC, and any pretreatment was determined from documentation within the EMR. Individual patients and families were also not interviewed for details surrounding the anaphylactic episodes, although recall bias would likely be introduced given the amount of time from reactions. Lastly, any patients with anaphylaxis occurring in our community during this period who did not present to our institution's ED or UCC were not included in our analysis because of a lack of resources to identify these patients.

In conclusion, this study identifies that more than half of all children presenting to a tertiary care pediatric referral center for treatment of anaphylaxis did not receive epinephrine before arrival at the hospital and that epinephrine administration before arrival was associated with a higher likelihood of being discharged to home. Prompt administration of epinephrine is first-line therapy for anaphylaxis, regardless of the cause, and is a feature of current anaphylaxis management guidelines. However, our data indicate that this is not optimally executed. Future work to enhance the knowledge base should include a medical care professional-level study of guideline adherence to better understand the trends reflected in the patient-level data. Ongoing efforts to provide education to patients and medical care professionals regarding appropriate and timely recognition of anaphylaxis and prompt epinephrine are needed, as are more discrete outcomes-based studies to determine barriers to use of existing anaphylaxis criteria and epinephrine administration, as well as costs associated with missed or delayed epinephrine use.

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