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**Increase in epinephrine administration for food-induced anaphylaxis in pediatric
emergency departments from 2007 to 2015**

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Abstract

Background: Epinephrine is underused in the treatment of anaphylaxis, despite being the first-line treatment, which reflects the challenges in diagnosing anaphylaxis and understanding the appropriate therapy.

Objective: To describe trends in epinephrine administration for patients visiting the pediatric emergency department with food-induced anaphylaxis from 2007 to 2015.

Methods: This retrospective cohort study included children 0 years to 17 years of age with food-induced anaphylaxis from 46 children's hospitals in the United States between 2007 and 2015. Multivariable regression was used to identify factors associated with epinephrine administration.

Results: A total of 15318 cases of food-induced anaphylaxis cases were seen in the pediatric emergency departments from 2007 to 2015. Among these emergency department visits, 7600 visits (49.6%) had at least 1 dose of epinephrine administered in the ED. Administration of epinephrine for anaphylaxis in the pediatric emergency department increased by 4% each year (odds ratio: 1.04, 95% CI: 1.03-1.05, $P < 0.001$). Sensitivity analysis by census region demonstrated that hospitals in the Northeast and the West were associated with an increase in epinephrine administration per year (Northeast odds-ratio 1.18, 95% CI: 1.13 – 1.22, $P < 0.001$, West odds ratio 1.14, 95% CI: 1.10 – 1.18, $P < 0.001$).

Conclusions: Epinephrine administration for food-induced anaphylaxis in the pediatric ED has increased over time, reflecting the need for continued advocacy for the optimal management of food-induced anaphylaxis. Further research is warranted to identify optimal strategies for proper recognition and early administration of epinephrine for anaphylaxis.

Highlights Box:

- What is already known about this topic? Food allergic reactions are the leading cause of anaphylaxis seen in the emergency department. Epinephrine is underused in the treatment of anaphylaxis, especially in the pediatric population.
- What does this article add to our knowledge? Epinephrine administration for cases of food-induced anaphylaxis in the pediatric emergency department is increasing over time, even after adjusting for demographic factors and severity.
- How does this study impact current management guidelines? Clinician awareness of the proper use of epinephrine for anaphylaxis may be increasing, reflecting the importance of continued advocacy for the optimal management of FIA. The increase in food allergic reactions over time highlights the need to further explore strategies for proper recognition and administration of epinephrine for anaphylaxis.

Keywords

Food-induced anaphylaxis, epinephrine, food allergy, emergency department

Abbreviations

Emergency department (ED), Pediatric Health Information System (PHIS), Food-induced anaphylaxis (FIA), extracorporeal membrane oxygenation (ECMO), Food Allergy Research & Education (FARE), Consortium of Food Allergy Research (CoFAR)

Introduction

Food allergy is a potentially life-threatening condition that is becoming more common in the pediatric population. The Centers for Disease Control and Prevention reported that the prevalence of food allergy in U.S. children increased from 3.4% in 1997–1999 to 5.1% in 2009–2011.¹ A population-based survey between October 2015 and September 2016 found the prevalence of food allergy in U.S. children to be 7.6%.² Rates of emergency department (ED) visits for anaphylaxis is increasing especially in the pediatric population, with food allergic reactions comprising one of the leading causes of anaphylaxis seen in the ED.^{3,4} One study from a pediatric ED in Canada found that peanuts, followed by tree nuts, and milk, account for the most reactions.⁴

Intramuscular injection of epinephrine is recommended at 0.01 mg/kg, to a maximum of 0.3 mg in children and 0.5 mg in adolescents, as first-line treatment during an anaphylaxis event.^{5,6} At the recommended dosage and route of administration, the alpha-adrenergic vasoconstrictive effects of epinephrine reverse peripheral vasodilation, which alleviates hypotension and reduces erythema, urticaria, and angioedema, and its beta-adrenergic properties cause bronchodilation, increase myocardial output and contractility, and suppress further mediator release from mast cells and basophils.⁵ Epinephrine is the only treatment known to be effective in the management of anaphylaxis and its therapeutic benefit exceeds the risk when given at the appropriate dose and route.⁵ Additional therapies such as antihistamines, bronchodilators, corticosteroids, fluids are considered adjunctive therapy.

Epinephrine is underused in the treatment of anaphylaxis, which reflects the challenges in diagnosing anaphylaxis and understanding its correct treatment. A prospective study in the United States found that only 30% of severe allergic reactions were treated with epinephrine in a cohort of preschool children with known food allergy.⁷ A study from Korea that compared anaphylaxis treatment in the pediatric population to adults found that only 24% of pediatric patients were treated with epinephrine compared to 36.9% in adults between 2004 and 2013.⁸ This pattern is concerning as delayed epinephrine administration has been associated with higher mortality.⁹ Delayed epinephrine is also associated with higher risk of hospitalization.¹⁰ Physician barriers to the underuse of epinephrine for anaphylaxis include complexity of diagnosis, lack of knowledge as well as misconceptions regarding epinephrine administration.¹¹

Comprehensive studies examining epinephrine administration are important for improving public awareness and directing public health initiatives to reduce morbidity and mortality from food-induced anaphylaxis (FIA). The objective of this retrospective study was to examine descriptions and patterns of epinephrine administration for cases of FIA encountered in pediatric emergency departments across the United States.

Methods

Study Design and Setting

This retrospective cohort study utilized the Pediatric Health Information System (PHIS) database, which contains clinical data for inpatient, ambulatory surgery, emergency department, and observation unit patient encounters from tertiary care pediatric hospitals across the United States. The PHIS database was developed by the Children's Hospital Association and collects

data on demographics, diagnoses, procedures, interventions, and outcomes in multiple healthcare settings including the ED. Available data elements are abstracted and coded by the collaborating medical records departments using PHIS data quality guidelines. The institutional review board at the University of Chicago approved this study. Data was extracted from PHIS in November 2019.

Study Participants

The study included patients aged under 18 years who were cared for in the ED of a PHIS hospital with a primary discharge diagnosis code indicating food-induced anaphylaxis from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, codes 995.6 - 995.69) from January 1, 2007 to December 31, 2015 (Online Repository I). A total of 17808 ED visits were identified. ED visits without recorded pharmacy data were excluded (n = 2490) as the primary purpose of the study was to trend epinephrine administration in the ED. Of note, PHIS only records pharmacy data according to billed pharmacy CTC codes.

Covariates

Covariates measured were age, gender, race (categorized into Black, White, and other), insurance (categorized into (1) government insurance or self-pay, (2) private insurance or TRICARE, and (3) unknown), geographic location (by census region), type of allergen (according to ICD-9 codes indicating peanut, tree nut/seeds, egg, fish, crustacean, milk, fruit/vegetable, food additive, or unspecified), medications administered (according to billed pharmacy data in PHIS), disposition (categorized into discharge, observation, admission,

transfer, expired), interventions associated with severity of illness (intensive care unit admission, multiple doses of epinephrine, intubation, extracorporeal membrane oxygenation (ECMO)).

Measures

The primary outcome measure was epinephrine administration for each ED visit with a primary diagnosis of food-induced anaphylaxis. Each ED visit was marked as severe if the visit resulted in one of the following: intensive care unit admission, administration of more than one dose of epinephrine, intubation, ECMO, or death.

Analysis

Descriptive statistics were used to analyze demographic characteristics. Multivariable logistic regression was used to examine factors associated with epinephrine administration. This study specifically analyzed epinephrine administration by year by calculating an odds ratio after converting year to a continuous variable. The odds ratio was then adjusted for clinical and demographic factors including age, gender, race, type of insurance, and disease severity. A sensitivity analysis was performed by census region.

Results

Visits Characteristics

A total of 15318 ED visits from 13917 patients were included for analysis. Mean age of visits was 6.3; and 3249 (21.2%) were under the age of 2. Children who presented to the ED for food induced allergic reactions were more likely to be white and male. Among these ED visits, 7600 visits (49.6%) had at least 1 dose of epinephrine administered in the ED, while 7718 (50.4%) did not. Patients that received epinephrine were more likely to be black (52% vs. 48%, $p < 0.01$),

have government insurance or self-pay (53% vs. 47%, $p < 0.01$, or have more severe disease (85% vs. 15%, $p < 0.01$) as compared to patients that did not receive epinephrine. There was no statistically significant difference in epinephrine administration by gender (female: 49.7% vs. 50.3%, $p = 0.95$). Overall, 3% of anaphylactic reactions that had at least one marker of severity (intensive care unit admission, intubation, ECMO, or death) did not have documented epinephrine administration (Table I). Markers of severity were similar among children 0 to <12 months of age; 12 to < 24 months of age; and older children. Overall, the percentage of reactions flagged as severe was stable across all years (figure 1).

Epinephrine administration by year

From 2007-2015, the odds of receiving epinephrine for anaphylaxis in the pediatric emergency department increased by 4% each year (OR: 1.04, 95% CI: 1.03-1.05, $P < 0.001$), with a corresponding rate increase from 46 per 100,000 ED visits in 2007 to 78 per 100,000 ED visit in 2015. This association persisted after adjusting for gender, race, age, insurance, and severity of illness (OR: 1.06, 95%CI: 1.04-1.07, $P < 0.001$) (Tables II, III, IV).

The most common identified triggers were peanut (29.9%) and tree nuts and seeds (19.3%) which together accounted for half of all visits; although, 27.9% of all visits did not have an associated trigger. Those diagnosed with shellfish allergy were more likely to receive epinephrine in the ED (56% vs. 44%, $p < 0.01$). Of the visits that were marked as severe, the most likely associated food trigger was peanuts ($n=447$, 29%).

Epinephrine administration by reaction severity.

Each ED visit was marked as severe if the visit resulted in one of the following: intensive care unit admission, administration of more than one dose of epinephrine, intubation, ECMO, or death. There were 1522 cases of severe anaphylaxis cases during the study period out of a total of 15318 ED visits for anaphylaxis or 10% of cases. Overall, there were 7 cases of death (ages 6, 10, 11, 11, 11, 15, 15 years), 600 cases of ICU admissions (3.9%), 150 cases of intubation (1.0%), 1049 cases of multiple epinephrine administration (6.8%), and 2 cases of ECMO. Overall, the rate of severe reactions per year was stable over time as demonstrated in figure 1. The breakdown of severe cases by age group (0 to <12 months, 12 to <24 months, 2-3 years, 4-11 years, 12-17 years) is presented in table V and reflects no observable difference in severe cases by age group.

Epinephrine administration by region

A sensitivity analysis was performed by census region (Figure 2). In the Northeast, the odds of receiving epinephrine increased by 18% each year (OR: 1.18, 95% CI: 1.13 - 1.22, $P < 0.001$). In the West, the odds of receiving epinephrine increased by 14% each year (OR: 1.14, 95% CI: 1.10 - 1.18, $P < 0.001$). There was no statistically significant increase in epinephrine administration per year in the Midwest and South (OR: 1.02, 95% CI: 0.99-1.04, $P = 0.28$; OR: 0.98, 95% CI: 0.95 – 1.01, $P = 0.21$, respectively). These numbers are adjusted for gender, race, insurance, age, and severity of illness (figure 2).

Discussion

We analyzed trends in epinephrine administration for food-induced anaphylaxis in the pediatric ED from 2007 to 2015. Our study found that the administration of epinephrine for anaphylaxis

has significantly increased over time. This association persisted after adjusting for demographic factors and severity indicating that the increased use of epinephrine was not a result of an overall increase in the severity of reactions presenting to the ED. Our sensitivity analysis found that the Northeast and West regions primarily accounted for the increased rate of epinephrine administration over time independent of the increase in overall ED visits for allergic reactions, while the Midwest and South did not have a significantly increased rate. As part of our regional analysis we attempted to determine if potentially having a Consortium of Food Allergy Research (CoFAR) site influenced rate of epinephrine use, but the trends did not clearly follow regional demographics of CoFAR sites. Finally, the annual percentage of severe reactions remained stable from 2007-2015 across all sites. We thus conclude that improvement in epinephrine use for FIA likely reflects advocacy and awareness at a national level.

One reason for this observed trend may be improved awareness and education among patients and providers leading to the increase in the number of ED visits for anaphylaxis as well as increased acceptance of epinephrine as first line therapy by providers. In our study, the rates of food-induced anaphylaxis increased from 46 per 100,000 ED visits in 2007 to 78 per 100,000 ED visit in 2015. The uptrend in the number of in ED visits for food-induced anaphylaxis over time is consistent with previous studies. A similar study that examined ED visits from 2007 to 2012 found that the number of cases of food-induced anaphylaxis increased from 41 to 72 per 100,000 ED visits.¹² Another study similarly found that pediatric ED visits for food-induced anaphylaxis in privately insured and Medicare Advantage enrollees increased by 214%, from 6.40 per 100,000 enrolled children in 2005 to 20.05 in 2014.¹³ The increase in epinephrine use is likely also secondary to improvement adherence to practice guidelines by providers. A study by Clark

et al, showed improvement in epinephrine use in the ED for FIA in 2013 to 2015 compared to 1999 to 2001 in general EDs, reflecting concordance with guidelines of FIA management.¹⁴

In our study, 52% of the Black population received epinephrine versus 47% of the White population. A recent study by Gupta et al. demonstrated significant differences in convincing food allergy prevalence pertaining to race with non-Hispanic African American children at a significantly elevated risk relative to non-Hispanic white children (odds ratio [OR] = 1.4 [95% CI: 1.1–1.7]).² The increase in epinephrine administration may be the result of higher prevalence of food allergy within the Black population. Alternatively, these data may be representative of white children receiving epinephrine prior to arriving to the ED. In our study, patients that received epinephrine were more likely to have government insurance or self-pay (52%). A previous study by Owusu-Ansah et al. has demonstrated that epinephrine is under-prescribed to Medicaid patients in the pediatric EDs. The higher rates of epinephrine administration in the ED in the government insurance may be explained by lower epinephrine autoinjector prescription rates.¹⁵ However, this area needs further investigation.

These data also raise the question as to the “correct” rate of epinephrine use in pediatric EDs. If food allergy advocacy has been effective as hypothesized, many children will have been successfully treated with epinephrine prior to their arrival in the ED and only require monitoring for delayed reactions. Therefore, we would not expect that 100% of children arriving in the ED need to receive epinephrine. Further research is needed to better understand when one demographic of children is being overtreated with epinephrine rather than another group being undertreated.

Interestingly these data did not demonstrate a significant difference in epinephrine use or severity of reactions between age groups. Little is known about the overall severity of reactions and epinephrine use in very young children. Among those who presented to the ED, infants and toddlers were equally likely to receive multiple doses of epinephrine, require ICU admission or intubation as older children. These data are limited, however, to reactions that are treated in the ED. Infants and toddlers may be less likely to present to the ED after an allergic reaction because initial reactions are less severe or parents new to food allergy have not yet received an action plan instructing ED utilization for an allergic reaction.

A strength of this study is the large number of cases examined across several regions of the United States. However, the retrospective nature of the study confers several limitations. Misclassification is a potential bias and coding accuracy cannot be confirmed. Furthermore, a significant limitation is that we were unable to determine which patients received epinephrine prior to arrival in the ED, either in the home or by first-responders, which would influence treatment in the ED.

In conclusion, epinephrine administration for food-induced anaphylaxis in the pediatric ED is significantly increasing across all ages over time, especially in the Northeast, while severity has remained stable. Given that the association between time and epinephrine administration persisted after adjusting for demographic factors and severity of illness, these results may indicate that clinician awareness of the use of epinephrine for anaphylaxis is increasing.

Further research could identify optimal strategies for proper recognition and administration of epinephrine for anaphylaxis. For example, with the formation of data through Food Allergy Research & Education (FARE), it would be conceivable for each FARE institution to pull more descriptive data from emergency room records.

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Figure Legends

Figure 1: Trends in epinephrine administration

The black line (triangle plotting symbol) demonstrates the percentage of visits for which epinephrine was administered out of total ED visits for cases of food-induced anaphylaxis by year. There is overall an upward trend. The blue line (circle plotting symbol) represents the percentages of severe reactions per year and the red line (square plotting symbol) reflects the percentage of visits for which epinephrine was administered for cases of severe reactions. The percentages of severe reactions per year and the rates of epinephrine administration for the severe group remained stable over time.

Figure 2: Odds of epinephrine administration per year by region

Odds of receiving epinephrine in each census region per year, adjusted for gender, race, insurance, age, and severity of illness

Table I: ED visit demographic characteristics stratified by epinephrine administration

	Epinephrine not administered	Epinephrine administered	Total
n	7718	7600	15318
Number between 0-12 months (%)	540	550	1090
Number between 13-24 months (%)	1102	1057	2159
Age (mean (sd))	6.24 (5.10)	6.35 (5.17)	6.30 (5.14)
Gender (%)			
Male	4608 (50.4)	4535 (49.6)	9143 (59.7)
Race (%)			
Black	2129 (48.0)	2311 (52.0)	4440 (29.0)

White	3445 (52.9)	3063 (47.0)	6508 (42.5)
Other	2144 (49.1)	2226 (50.1)	4370 (28.5)
Insurance (%)			
Government, self pay	2577 (47.2)	2883 (52.8)	5460 (35.6)
Private, TRICARE	4442 (52.0)	4114 (48.1)	8556 (55.9)
Unknown	699 (53.7)	603 (46.3)	1302 (8.5)

Table II: ED visit by year and region stratified by epinephrine administration

	Epinephrine not administered	Epinephrine administered	Total
n	7718 (50.4)	7600 (49.6)	15318
ED visit year (%)			
2007	460 (58.9)	321 (41.1)	781 (5.1)
2008	493 (51.6)	462 (48.4)	955 (6.2)
2009	628 (57.0)	473 (43.0)	1101 (7.2)
2010	732 (52.3)	667 (47.7)	1399 (9.1)
2011	822 (48.2)	884 (51.8)	1706 (11.1)
2012	1047 (50.9)	1010 (49.1)	2057 (13.4)
2013	1104 (49.4)	1130 (50.6)	2234 (14.6)

2014	1255 (47.2)	1402 (52.7)	2657 (17.3)
2015	1177 (48.5)	1251 (51.5)	2428 (15.9)

Census Region (%)

Northeast	1398 (48.2)	1505 (51.8)	2903 (19.0)
South	2304 (51.8)	2144 (48.2)	4448 (29.0)
West	1718 (50.9)	1656 (49.1)	3374 (22.0)
Midwest	2298 (50.0)	2295 (50.0)	4593 (30.0)

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395 **Table III: ED visit by severity and food type stratified by epinephrine administration**

Marker of severity, overall (%)	234 (15.4)	1288 (84.6)	1522 (9.9)
Marker of severity, by year (%)			
2007	11 (12.5)	77 (87.5)	88 (5.8)
2008	11 (11)	89 (89)	100 (6.6)
2009	13 (13.1)	86 (86.9)	99 (6.5)
2010	39 (22.9)	131 (77.1)	170 (11.2)
2011	24 (14.1)	146 (85.9)	170 (11.2)
2012	34 (15.8)	181 (84.2)	215 (14.1)
2013	35 (16.3)	179 (83.6)	214 (14.1)
2014	41 (15.1)	230 (84.9)	271 (17.8)
2015	26 (13.3)	169 (86.7)	195 (12.8)
Food type			
Additives	28 (51.9)	26 (48.1)	54 (0.4)
Eggs	369 (52.4)	335 (47.6)	704 (4.6)
Fish	476 (47.5)	526 (52.5)	1002 (6.5)
Fruits and vegetables	221 (52.9)	197 (47.1)	418 (2.7)
Milk	474 (54.7)	392 (45.3)	866 (5.7)
Peanuts	2392 (52.3)	2183 (47.7)	4575 (29.9)
Shellfish	206 (44.1)	261 (55.9)	467 (3.0)
Tree nuts and seeds	1396 (47.2)	1562 (52.8)	2958 (19.3)
Unspecified	2156 (50.4)	2118 (49.6)	4274 (27.9)

Table IV: Odds ratio for epinephrine administration by year

The odds of receiving epinephrine in the emergency department increases by 6% ($p < 0.001$) each year from 2007-2015. This is adjusted for age, gender, race, insurance, and severity of reaction.

Variables	OR	CI	P-value
Year	1.04	1.03 - 1.05	<0.001
Year, adjusted for age, gender, race, insurance	1.04	1.03 - 1.06	<0.001
Year, adjusted for age, gender, race, insurance, and severity	1.06	1.04 - 1.07	<0.001

Table V: Analysis of severe reactions by age group

Age	Total severe reactions/Total ED visits (%)	Epinephrine administration/Total ED visits (%)	ICU admission (%)	Intubation (%)	Multiple doses of epinephrine (%)	ECMO (%)	Death (%)
0 to <12 months	107/1090 (10)	550/1090 (50.5)	30 (2.8)	11 (1.0)	76 (7.0)	0	0
12 to <24 months	197/2159 (9.1)	1057/2159 (49)	57 (2.6)	12 (0.5)	145 (6.7)	0	0
2-3 years	291/3025 (9.6)	1476/3025 (48.8)	102 (3.4)	17 (0.56)	198 (6.5)	0	0
4-11 years	529/5784 (9.1)	2872/5784 (49.7)	206 (3.6)	51 (0.9)	383 (6.6)	2 (0.03)	5 (0.09)
12-17 years	398/3260 (12.2)	1645/3260 (50.5)	205 (6.3)	59 (1.8)	247 (7.6)	0	2 (0.06)
Total	1522/15318 (10)	7600/15318 (49.6)	600 (3.9)	150 (1.0)	1049 (6.8)	2 (0.013)	7 (0.046)



