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# PREHOSPITAL ADMINISTRATION OF EPINEPHRINE IN PEDIATRIC ANAPHYLAXIS – A STATEWIDE PERSPECTIVE

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## ABSTRACT

**Objective:** Timely administration of epinephrine is critical in the treatment of anaphylaxis. This study sought to determine the frequency of administration of epinephrine by EMS providers caring for pediatric patients in the prehospital setting. **Methods:** We examined data from the NC EMS database (PreMIS) from 2010–3 to determine frequency of epinephrine administration in pediatric patients with anaphylaxis. We studied patients <18 years of age with an EMS provider impression of “allergic reaction.” Anaphylaxis was present if there was hypotension (defined as SBP < 90 or DBP < 45 for patients age 11 and older, and SBP < 70 + (2 × age) for patients ages 0–10), or impaired respirations (defined as description of labored or absent respirations, or RR < 12 or > 30). We determined the overall frequency of epinephrine administration. A multivariate logistic regression was then constructed to examine the impact of the following variables on appropriate epinephrine administration: age < 10, non-white race, rural county of case origin, duration of transportation from scene, and presence of a paramedic. **Results:** A total of 504 patients met inclusion criteria, of which 471 demonstrated anaphylaxis as previously defined. A total of 153 patients with anaphylaxis received epinephrine (32.4%, 95% CI 28.3–36.9%). Age < 10 was associated with increased odds of not receiving epinephrine appropriately (OR 2.90, 95% CI 1.85–4.54,  $p < 0.001$ ). Other variables did not have

statistically significant impact on epinephrine administration. **Conclusion:** There are missed opportunities for prehospital administration of epinephrine in pediatric patients with anaphylaxis. Very young children (age < 10) had increased odds for not receiving epinephrine. **Keywords:** EMS; prehospital; anaphylaxis; epinephrine

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## INTRODUCTION

Anaphylaxis is a life threatening, systemic allergic reaction that must be treated quickly. Food allergy is the leading cause of anaphylaxis (1). Food allergy is especially prevalent in children. Rates are highest in those under 5 years of age, with nearly 4% of the U.S. pediatric patient population reporting a food allergy (2). It is clear that food allergy prevalence is increasing globally, in both developed and low-middle income countries (2, 3). In addition, the incidence of pediatric anaphylaxis presenting to the emergency care system is also increasing (4). We hope to emphasize the importance of appropriate treatment of anaphylaxis in this age group.

The American Academy of Allergy Asthma and Immunology Practice Parameter recommendations state that all patients who have experienced anaphylaxis should be prescribed an epinephrine auto injector, instructed in its use (including parents or other members of care team such as school nurses where appropriate), and provided with a clear and concise action plan for treatment of immediate hypersensitivity and anaphylaxis (1).

Epinephrine is the best treatment for anaphylaxis and it is very important for prehospital providers to administer epinephrine to patients suffering from anaphylaxis to help prevent death from complications such as airway compromise or hypotension (5–7). Recently published data suggests a concerning delay in or absence of administration of epinephrine in prehospital patients presenting with anaphylaxis (8–12). Delayed administration of epinephrine is associated with worse patient outcomes as mentioned above (12, 13). We conducted a statewide study of patients aged less than 18 years of age treated for allergic reaction in the prehospital setting. Our goal was to determine rates of prehospital epinephrine administration for pediatric patients with anaphylaxis, and to describe factors that may be affecting treatment rates.

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Supplemental data for this article can be accessed on the [publisher's website](#).

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## METHODS

### Study Setting and Population

We performed a retrospective study of deidentified emergency medical services (EMS) encounters collected from the North Carolina EMS database, the Prehospital Medical Information System (PreMIS), from 2010–2013. All public and private EMS services in the state are required to submit standardized patient data to the repository for each patient encounter. Most data fields consist of numeric or categorical variables, limiting confusion engendered by free text data entry. A primary provider impression of “allergic reaction” was required for inclusion in the data set, and we selected those patients with an age < 18 years at the time of the encounter for this analysis. Given that the data provided were deidentified, an administrative review from staff of the Institutional Review Board at Wake Forest University determined that this was exempt from formal review, and did not require informed consent for analysis of deidentified data.

### Data Definitions

We defined epinephrine administration as any epinephrine concentration by any route during the EMS encounter. Using the World Allergy Organization clinical criteria for diagnosis of anaphylaxis (14, 15) and American Heart Association (AHA) vital sign parameters for pediatric patients (16), we defined anaphylaxis warranting epinephrine administration as at least one of the following conditions, hypotension or respiratory distress, being present:

- Hypotension
  - Systolic blood pressure (SBP) < 90 mmHg or diastolic blood pressure (DBP) < 45 mmHg for patients age 11 and older
  - $SBP < (70 + (2 \times \text{age}))$  mmHg for patients ages 1–10
- Respiratory distress
  - Respirations coded as “labored,” “fatigued,” or “absent” OR
  - Respiratory rate (RR) < 12 or > 30 breaths per minute

A provider impression of “allergic reaction” was required to be included in the dataset. This is consistent with the World Allergy Association definition of anaphylaxis which includes exposure to a provoking agent.<sup>14</sup> As a result, patients with simple asthma exacerbation or isolated hypotension were not included in the dataset if there was no provider impression of “allergic reaction”.

Race/ethnicity as determined by EMS provider was dichotomized as white/non-white. After graphic examination of the age distribution data (Figure 1),

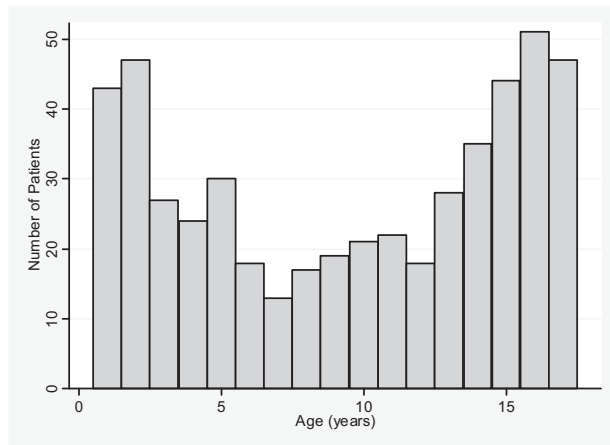


FIGURE 1. Age distribution of the cohort.

and after consideration of the age cut point for vital signs consistent with the AHA definitions, we treated age as a dichotomous variable with the break point of 10 years or less, vs. 11–17 years. When multiple sets of vital signs were recorded during an EMS encounter, the first vital sign of each type (heart rate, pulse oximetry, SBP, DBP, RR) was abstracted. The highest level of prehospital provider present in the EMS team was extracted; for this analysis, this was coded as EMT-paramedic or other. The county of origin for the EMS encounter was coded as urban vs. rural per the United States Department of Agriculture/ Office of Management and Budget. As prehospital provider willingness to administer epinephrine may also be influenced by the amount of time the patient was under their care, we included transportation time as recorded in the PreMIS database as a continuous variable.

### Data Analysis

Descriptive statistics were calculated with means and exact 95% confidence intervals (CI<sub>95</sub>) for continuous data, and binomial CI<sub>95</sub> for categorical data. We used cases with complete data to construct a multiple variable logistic regression model to analyze the impact of patient- and EMS-level covariates on the odds of not receiving epinephrine in the setting of hypotension and/or respiratory distress. The variable “transit time” was examined graphically and noted to have a positive skew with rare outlier long transit times; therefore, log-transformation was considered for this variable for purposes of model building. After the model was constructed, the results were inspected for specification errors, multicollinearity, outliers, and overly influential covariate patterns. We found no evidence of such, and thus we present the full model inclusive of predetermined clinically relevant variables. We did not perform stepwise reduction in model covariates. We created biologically plausible interaction terms via

TABLE 1. Characteristics of the study cohort

|                       | Total (N = 504)<br>Number (percentage, CI) | Received epinephrine<br>(n = 157) Number (percentage, CI) | Did not receive epinephrine<br>(n = 347) Number (percentage, CI) |
|-----------------------|--------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------|
| Age ≤10 years         | 238 (47%, 43–52%)                          | 53 (34%, 26–42%)                                          | 185 (53%, 48–59%)                                                |
| Male                  | 257 (51%, 47–56%)                          | 84 (54%, 45–61%)                                          | 173 (50%, 45–56%)                                                |
| White                 | 275 (56%, 52–61%)                          | 86 (56%, 48–64%)                                          | 189 (57%, 51–62%)                                                |
| Epinephrine indicated | 471 (93%, 91–95%)                          | 153 (97%, 94–99%)                                         | 318 (92%, 88–94%)                                                |
| Hypotensive           | 100 (24%, 20–29%)                          | 27 (20%, 13–27%)                                          | 73 (27%, 22–32%)                                                 |
| Respiratory Distress  | 247 (53%, 48–57%)                          | 108 (73%, 65–80%)                                         | 139 (43%, 38–49%)                                                |
| Abnormal RR           | 198 (41%, 36–45%)                          | 49 (32%, 25–40%)                                          | 149 (44%, 39–50%)                                                |
| Rural County          | 158 (32%, 28–37%)                          | 47 (30%, 23–38%)                                          | 111 (33%, 28–38%)                                                |
| EMT-P present         | 442 (92%, 89–94%)                          | 138 (93%, 88–97%)                                         | 304 (91%, 87–94%)                                                |

CI = Confidence Interval; RR = respiratory rate; EMT-P = Paramedic.

the product method and tested them for inclusion on an individual basis, with retention if the Wald p-value was less than 0.05. We used the Hosmer-Lemeshow goodness of fit test to evaluate the final model. We did not perform formal a priori sample size analysis, as we were constrained by the number of subjects within the data set. However, given the standard rule of 10 outcomes for every degree of freedom considered for inclusion in a logistic regression model, we were confident that the model would not be overfit with this data set. Statistics were calculated using Stata IC 11.2 (College Station, TX).

## RESULTS

Between 2010 and 2013, there were 504 patients from the PreMIS database meeting inclusion criteria as previously described. Information was not reliably available on epinephrine given before arrival of EMS. Table 1 provides baseline characteristics of the cohort. The overall average age of the cohort was 9.5 (CI<sub>95</sub> 9.0–10.0) years. The average age of the group receiving epinephrine was 11.1 (CI<sub>95</sub> 10.3–12.0) years, and 8.7 (CI<sub>95</sub> 8.1–9.3) years for the group not receiving epinephrine. The overall amount of missing data was low (online supplement table). It should be noted that no child in the data set was missing all elements of blood pressure, respiratory rate, and qualitative respiratory assessment. Epinephrine was administered in 157/504 patients (31.1%, CI<sub>95</sub> 27.1–35.4%). Respiratory distress and/or hypotension was noted in 471 patients (93.4%, CI<sub>95</sub> 90.9–95.5%). Of these 471 patients, 153 received epinephrine (32.4%, CI<sub>95</sub> 28.3–36.9%). Epinephrine was administered to four patients without documented hypotension or respiratory distress. Transit time did not vary between the groups with epinephrine given (17.4 (CI<sub>95</sub> 15.6–19.2) minutes) and epinephrine not given (17.3 (CI<sub>95</sub> 15.9–18.8) minutes). Although transit time was not normally distributed, the median transit time for the cohort (16 minutes, interquartile range 9–23 minutes) was not appreciably different than the mean cohort time (17.4 minutes, CI<sub>95</sub> 16.2–18.5 minutes). Only 4

outliers had transit times greater than 50 minutes (the 99<sup>th</sup> percentile of the data): 54, 66, 81, and 118 minutes.

Table 2 provides the full multiple variable logistic regression model. There were 404 patients with both epinephrine indicated and complete data available for model building. The only factor significantly affecting epinephrine use was age less than or equal to 10 years, with an odds ratio of not receiving epinephrine when indicated of 2.90 (CI<sub>95</sub> 1.85–4.54, Wald p-value < 0.001). No interaction terms significantly affected the model. The log-transformation of transit time did not affect the model, and therefore we retained the more intuitive non-transformed transit time. The Hosmer-Lemeshow goodness of fit test indicated no reason to reject the model as poorly fit (p = 0.70).

## DISCUSSION

This study demonstrates a substantial frequency of not administering epinephrine when warranted to pediatric patients with anaphylaxis. Our results are consistent with the frequency of epinephrine administration found in other studies of children with anaphylaxis (8, 17–20).

This is the first study looking at epinephrine for pediatric anaphylaxis in North Carolina. The fact that the study included 100 counties and the Qualla Boundary Cherokee Reservation, representing a great deal of economic, demographic, and geographic diversity, increases its generalizability to other settings. Given the results of this study and other similar studies

TABLE 2. Logistic regression model against the outcome of not receiving epinephrine when indicated

| Variable               | OR   | CI <sub>95</sub> | Wald p-value |
|------------------------|------|------------------|--------------|
| Age ≤ 10 years         | 2.89 | 1.85–4.53        | <0.001       |
| Male                   | 0.75 | 0.49–1.17        | 0.210        |
| White                  | 1.10 | 0.72–1.71        | 0.650        |
| Rural                  | 1.21 | 0.75–1.93        | 0.440        |
| EMT-P present          | 0.83 | 0.36–1.92        | 0.660        |
| Transit time (minutes) | 0.99 | 0.97–1.009       | 0.360        |

EMT-P = Paramedic; OR = Odds Ratio; CI<sub>95</sub> = 95% Confidence interval.

EMS Medical Directors and agencies need to address the need for administration of epinephrine to pediatric patients having anaphylaxis. Increased emphasis should also be given to educating prehospital providers about the recognition and treatment of anaphylaxis. In addition, parents of children at risk for anaphylaxis should ensure that their children have an action plan that indicates when to administer epinephrine.

As demonstrated by the data above, there are many examples of missed opportunities for epinephrine administration in pediatric patients. In our study, we defined an opportunity for epinephrine administration by vital sign abnormalities or respiratory distress – arguably the most severe presentations of anaphylaxis. We are concerned that the frequency of epinephrine administration is so low despite clearly meeting criteria for administration. Presence of subjective “respiratory distress” seems to be the major driver, other than age, of who got epinephrine. Hypotension, which is a clear indication for giving epinephrine, triggered administration less often than respiratory distress.

Regarding the statistically significant difference in epinephrine administration rates in the pediatric population with an age of 10 years or less, we believe several factors need to be considered. It is conceivable that providers are reluctant to administer a medication that is more often associated with treatment for cardiac arrest rather than allergic reactions. It is also possible that many caregivers may not recognize hypotension in children given that blood pressure varies with age. Caregivers may choose to rely on adjunctive therapies such as antihistamines, steroids, and/or short acting beta agonists instead. The younger pediatric patients may be unable to accurately describe subjective symptoms that could convince providers that epinephrine is necessary. Education to caregivers, including providers, first responders, and parents is important to improve the treatment of allergic reaction and anaphylaxis. Appropriate treatment of allergic reaction and anaphylaxis in this age group is of great interest with food allergies being more prevalent in children.

## LIMITATIONS

Detailed exams and history are not recorded during an EMS encounter. We did not have information about bystander epinephrine administration, history of allergies, or other physical exam findings such as hives or angioedema for each patient; thus, these criteria were not considered. Respiratory distress and/or hypotension were conditions that were noted in the electronic health record by the EMS providers during their evaluation so even if epinephrine had been given by a layperson before arrival there could have been indications for a second dose. In addition, as this is a

prehospital data set, we do not have hospital based outcomes for this cohort.

## CONCLUSION

Pediatric patients presenting to EMS with recognized allergic reactions and evidence of severe anaphylaxis frequently experience a missed opportunity for epinephrine administration. This risk is greater in children less than 10 years of age. Further education must occur for EMS services regarding guideline-based appropriate treatment for pediatric anaphylaxis.

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