Original Article

Predictors of Repeat Epinephrine Administration for Emergency Department Patients with Anaphylaxis

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What is already known about this topic? Epinephrine is the treatment of choice for anaphylaxis. Some patients require more than 1 dose. Studies of risk factors for repeat epinephrine use have had mixed results.

What does this article add to our knowledge? Among emergency department patients of all ages and trigger types, a history of anaphylaxis and presenting signs of flushing, diaphoresis, or dyspnea were associated with the need for more than 1 dose of epinephrine.

How does this study impact current management guidelines? Our findings support the current guidelines that patients with anaphylaxis should be prescribed more than 1 epinephrine autoinjector.

BACKGROUND: Risk factors that predict which patients with anaphylaxis might require repeat doses of epinephrine are poorly understood.

OBJECTIVE: The objective of this study was to identify risk factors associated with the need for multiple doses of epinephrine during an anaphylactic reaction.

METHODS: Patients were included if they met diagnostic criteria for anaphylaxis on presentation to the emergency department (ED) at our academic medical center between April 2008 and February 2014. Data were collected on allergic history, presenting signs and symptoms, anaphylaxis management, and disposition. Univariable and multivariable analyses were performed to estimate associations between possible risk factors and the need for multiple doses.

RESULTS: Of 582 ED patients with anaphylaxis, 45 (8%) required multiple doses of epinephrine. By multivariable analysis, factors associated with the need for repeat doses were a history of anaphylaxis (odds ratio [OR], 2.5 [95% CI, 1.3-4.7]; $P = .005$), the presence of flushing or diaphoresis (OR, 2.4 [95% CI, 1.3-4.5]; $P = .007$), and the presence of dyspnea (OR, 2.2 [95% CI, 1.0-5.0]; $P = .046$). Patients who received more than 1 dose were more likely to be admitted to the general medical floor (OR, 2.8 [95% CI, 1.1-7.2]; $P = .03$) or intensive care unit (OR, 7.6 [95% CI, 3.7-15.6]; $P < .001$).

CONCLUSION: Patients with a history of anaphylaxis, flushing or diaphoresis, or dyspnea may require multiple doses of epinephrine to treat anaphylactic reactions. Patients who require more than 1 dose are more likely to be admitted to the hospital, thus increasing health care resource utilization. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Allergy criteria; Anaphylaxis; Emergency department; Epinephrine; Hypersensitivity; Risk factors*

Anaphylaxis is an allergic reaction that frequently involves multiple organ systems and varies in severity. It is most commonly treated in the emergency department (ED).[1] The treatment of choice for anaphylaxis is intramuscular administration of epinephrine.[2] However, a single dose of epinephrine is not always sufficient for treatment of anaphylaxis.[3-11]

A previous study of patients presenting to the ED with anaphylaxis to any trigger showed that 13% required more than 1 dose of epinephrine during the management of the reaction.[8] Studies of ED patients with anaphylaxis to food have found that 5% to 16% required more than 1 dose of epinephrine.[6,9,11]

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Abbreviations used
BP- Blood pressure
DMS- Display Manager System
ED- Emergency department
EDOU- Emergency department observation unit
FAAN- Food Allergy and Anaphylaxis Network
ICU- Intensive care unit
NIAID- National Institute of Allergy and Infectious Diseases
OR- Odds ratio

Despite the well-established fact that many patients will require more than a single dose of epinephrine, little is known about the possible associated factors that predict the need for multiple doses.[3-11] Prior studies evaluating such risk factors are limited by the small number of patients and reviews that included only 1 or a few triggers.[3-11] Thus, the elucidation of risk factors has been challenging.

The objective of this study was to identify factors associated with the need for multiple doses of epinephrine in patients presenting to the ED with anaphylaxis.

METHODS

Study design and setting

This observational cohort study examined consecutive patients who presented to the ED of Mayo Clinic Hospital, Saint Marys Campus, Rochester, Minn, a tertiary care academic medical institution with approximately 73,000 ED patient visits annually. The Mayo Clinic Institutional Review Board approved the study protocol.

Selection of study patients

Patients of all ages were eligible for inclusion in the study if they or their caregiver had previously or currently provided informed consent for the use of their medical records for research purposes. Both prospective and retrospective data were recorded and analyzed. For patients who had multiple ED visits, only data from the first visit were abstracted.

Retrospective enrollment. The retrospective review of the electronic medical records of patients whose ED diagnoses included the text "anaph-," "allerg-," or "sting" from April 2008 through February 2014 was conducted. We searched all ED patient records (Picis ED PulseCheck) for the specified diagnoses by using an electronic patient tracking system that was designed at our institution to facilitate ED clinical research. An additional small cohort of potentially eligible patients with other diagnoses was identified by the study coordinator during the review process.

Data on allergic history, presenting signs and symptoms, anaphylaxis management, and disposition were extracted from the electronic medical record using a standardized extraction procedure, and data were entered into an SAS-Display Manager System (DMS) database. The SAS-DMS database was programmed to determine whether the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) criteria for anaphylaxis were met on the basis of the acuity of symptom onset, presence of a likely or known trigger, and individual patient signs and symptoms.

Case definition. Anaphylaxis was defined on the basis of the criteria agreed on by the NIAID/FAAN Second Symposium on the Definition and Management of Anaphylaxis (adapted from Sampson et al;[12] used with permission). Only those patients who met these criteria were included.

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 an involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, 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, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, 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; defined as less than 70 mm Hg from 1 month to 1 year, less than 70 mm Hg plus 2×age from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Prospective enrollment. A cohort of prospective patients was identified at the time of their ED visit from April 2010 to March 2013 on the basis of their chief concern. Patients were identified if they had a concern that included "allergic," "reaction," "anaphy-," "angio-," "sting," "hives," or "rash." At our institution, the patient's chief concern is entered by the triage nurse before any significant clinical evaluation has occurred. In contrast, the patient diagnosis is not entered into the medical record until after the patient has been evaluated by the provider. Although the diagnosis can be entered into the medical record while the patient is still undergoing evaluation or observation, it frequently occurs after the patient has been dismissed from the ED. Thus, we searched for chief concerns and kept the range of eligible concerns intentionally broad to increase the sensitivity for identifying patients with anaphylaxis.

Study coordinators received a text page that was automatically generated by the ED electronic patient-tracking system whenever an ED patient registered with any of the specified chief concerns. Study coordinators then approached the ED provider caring for the patient to determine if the patient was eligible for the study. Any patient whom the ED provider suspected of having anaphylaxis or an allergic reaction was considered eligible for enrollment, and consent was obtained. Data on allergic history, presenting signs and symptoms, and prehospital management were obtained from the patient or caregiver. The primary provider caring for the patient completed a questionnaire on physical findings. Additional data on anaphylaxis management and disposition were extracted from the electronic health record using a standardized extraction procedure. All data were entered into an SAS-DMS database programmed to determine