Original Article

Further Evaluation of Factors That May Predict Biphasic Reactions in Emergency Department Anaphylaxis Patients

Sangil Lee, MD, MS[a], Alexa Peterson, BA[b], Christine M. Lohse, MS[c], Erik P. Hess, MD, MSc[c], and Ronna L. Campbell, MD, PhD[c] *Iowa City, Iowa; Fort Lauderdale, Fla; and Rochester, Minn*

What is already known about this topic? Biphasic reaction is a recurrence of anaphylaxis symptoms without reexposure to an inciting trigger.

What does this article add to our knowledge? The rate of biphasic reaction meeting National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria was 4%. Prior anaphylaxis, unknown inciting trigger, and delayed epinephrine use were risk factors; patients with none of the identified risk factors had a 1.6% risk of a biphasic reaction, whereas patients with all 3 risk factors had a 20% risk of a biphasic reaction.

How does this study impact current management guidelines? The presence or absence of these risk factors can assist clinicians in optimizing the duration of observation for patients with anaphylaxis.

BACKGROUND: Anaphylaxis is a systemic allergic reaction that is commonly treated in the emergency department (ED). The risk of a biphasic reaction is the rationale for observation.
OBJECTIVE: To derive a prediction rule to stratify ED anaphylaxis patients at risk of a biphasic reaction.
METHODS: We conducted an observational study of a cohort of patients presenting to an academic ED with signs and symptoms of anaphylaxis. We collected clinical data on biphasic reactions meeting National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network diagnostic criteria. Logistic regression analyses were conducted to identify predictors of biphasic reactions, and odds ratios (ORs) with 95% CIs are reported. The predictive ability of the model features is summarized using the area under a receiver operating characteristics curve, or AUC. Internally validated AUCs were obtained using bootstrap resampling.
RESULTS: We identified 872 anaphylaxis-related visits. Thirty-six (4.1%) visits resulted in biphasic reactions. Multivariable analysis showed that prior anaphylaxis (OR, 2.74; 95% CI, 1.33-5.63), unknown inciting trigger (OR, 2.40; 95% CI, 1.14-4.99), and first epinephrine administration more than 60 minutes after symptom onset (OR, 2.29; 95% CI, 1.09-4.79) were statistically significantly associated with biphasic reactions. The AUC of this model was 0.70 (95% CI, 0.61-0.79), with an internally validated AUC of 0.67 (95% CI, 0.59-0.76). The *P* value from the goodness-of-fit test was .91.
CONCLUSIONS: Our study demonstrated a 4.1% rate of biphasic reactions and found that prior anaphylaxis, unknown inciting trigger, and delayed epinephrine use were risk factors for biphasic reactions. **(J Allergy Clin Immunol Pract 2017;5:1295-301)**

Key words: *Anaphylaxis; Biphasic reaction; Prediction model*

Anaphylaxis is a potentially life-threatening allergic reaction.[1] Contemporary studies have shown that biphasic anaphylaxis can occur in less than 1% to 15% of anaphylactic reactions.[2,3] Currently, there is no universal agreement on the definition of a biphasic anaphylactic reaction. Some studies define biphasic reactions as those with recurrent signs and symptoms meeting National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria for anaphylaxis.[4] Other studies have used a broader definition of any recurrent sign or symptom after resolution of the initial reaction, or used a more pragmatic definition of recurrent symptoms severe enough to require a therapeutic intervention.[5-7] Studies in the 1980s and 1990s established that biphasic anaphylaxis could be fatal.[8,9] Thus, current consensus guidelines recommend 4 to 24 hours of emergency department (ED) observation after initial symptom resolution because of the risk of a biphasic reaction.[1,4,10]

Our previous study demonstrated that 4% of our ED anaphylaxis patients developed a biphasic reaction, a finding

[a]Department of Emergency Medicine, the University of Iowa Carver College of Medicine, Iowa City, Iowa
[b]Nova Southeastern University, Fort Lauderdale, Fla
[c]Department of Emergency Medicine, Mayo Clinic, Rochester, Minn
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Corresponding author: Sangil Lee, MD, MS, Department of Emergency Medicine, the University of Iowa Carver College of Medicine, 1008 Roy Carver Pavillion, 200 Hawkins Dr, Iowa City, IA 52242. E-mail: sangil-lee@uiowa.edu.
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Abbreviation used
AUC- Area under the curve
ED- Emergency department
NIAID/FAAN- National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
OR- Odds ratio

supported by a meta-analysis of existing studies.[6,11] In addition, we found that a history of prior anaphylaxis, unknown inciting trigger, symptoms of diarrhea, and wheezing were associated with an increased risk of a biphasic reaction in a univariable setting.[11] Alqurashi et al[3] also described variables associated with a biphasic reaction including delay in presentation to the ED longer than 90 minutes after the onset of the initial reaction, wide pulse pressure at triage, treatment of the initial reaction with more than 1 dose of epinephrine, and administration of inhaled β-agonists in the ED. In addition, they found that among patients who received at least 1 dose of epinephrine, delayed epinephrine administration over 90 minutes from symptom onset was associated with a biphasic reaction.[3] Accurate identification of patients at low or high risk of developing a biphasic reaction may safely decrease ED length of stay and unnecessary health care utilization.

Our objective was to build upon our previous work as well as the work of others who have identified variables associated with biphasic reactions to derive a clinical decision rule that (1) identifies patients at increased risk of a biphasic anaphylactic reaction who would benefit from observation and (2) facilitates identification of low-risk patients who could be safely dismissed without prolonged observation.[3,6,11,12] To do this, we have expanded our previous patient cohort and conducted a multivariable analysis to test the associations of previously identified candidate predictor variables with biphasic reactions meeting NIAID/FAAN criteria as well as recurrent reactions requiring any additional therapeutic interventions or health care utilization.

METHODS

Study design and setting

We conducted an observational study from 2008 to 2015 of patients presenting to an academic ED with approximately 73,000 annual visits. The Saint Mary's Hospital ED at Mayo Clinic is a 72-bed facility with a 9-bed observation unit where observation unit protocols for care of patients with anaphylaxis are commonly used in practice. This study was approval by the institutional review board.

Participants

ED patients of all ages meeting NIAID/FAAN diagnostic criteria for anaphylaxis were included in the study. Potential anaphylaxis cases were identified both retrospectively and prospectively. Patients were identified retrospectively on the basis of ED diagnosis. Patients whose electronic medical records included an ED diagnosis with the text "anaph," "allerg," or "sting" from 2008 to 2015 were reviewed if the patient had provided research authorization. If NIAID/FAAN criteria were met, the patient was included. For the anaphylaxis cases identified prospectively, a study coordinator received a text page when a patient arrived at triage with a chief complaint including the text "allergic," "reaction," "anaphy-," "angio-," "sting," "hives," or "rash" from 2010 to 2015. A coordinator approached the ED provider to determine eligibility. If the patient was suspected of having an allergic reaction or anaphylaxis, they were considered eligible for enrollment and consent was obtained.

Predictor variables

Candidate predictors of interest included age at visit, sex, history of asthma, history of anaphylaxis, inciting trigger, signs or symptoms of syncope, diarrhea, hypotension, wide pulse pressure, wheezing, delayed ED presentation, timing, location and number of epinephrine doses, steroid administration, and the use of a bronchodilator. We defined "unknown trigger" when the provider in the ED was not able to identify the trigger.

Definition of anaphylaxis, biphasic anaphylaxis, and outcomes

The NIAID/FAAN diagnostic criteria were used to identify cases of anaphylaxis in our study.[4] The primary outcome of interest was the occurrence of a biphasic anaphylactic reaction defined as recurrent symptoms and signs of anaphylaxis meeting NIAID/FAAN criteria after resolution of the initial reaction without reexposure to an inciting trigger occurring within 72 hours of the initial reaction. A secondary composite outcome of any adverse event was defined as (1) biphasic anaphylaxis (as defined above); (2) recurrence of any signs or symptoms (not meeting NIAID/FAAN criteria) requiring treatment; (3) ED return visit within 72 hours for recurrent signs or symptoms related to the initial reaction; or (4) direct hospitalization within 72 hours of ED discharge for recurrent signs or symptoms related to the initial reaction.

Data source and measurement

All medical records for previously identified patients were retrieved and reviewed to confirm cases of anaphylaxis. Patients who met diagnostic criteria for anaphylaxis were included in the study. The principal investigators (S.L. or R.L.C.) and trained research assistants reviewed medical records for up to 72 hours after the index ED visit for anaphylaxis and extracted demographic information, history, signs and symptoms, medication administration, and treatment received. Any phone note, outpatient follow-up visit, ED visit, or hospitalization up to 72 hours after initial ED visit was reviewed to identify a potential biphasic reaction. The first 20% of records were reviewed in duplicate by the abstracting research assistant and a principal investigator to assess interrater agreement, develop guidelines for ongoing abstraction, and resolve discrepancies. Abstractors and principle investigators met periodically to discuss any ambiguous records.

Bias

We controlled for selection bias by defining the primary and secondary outcomes *a priori* and using well-established clinical criteria for anaphylaxis. Informational bias was minimized by measuring interobserver agreement on the first 20% of records. Last, 2 outcome models were tested to reduce potential confounding in the analysis.

Quantitative variables

A delayed ED presentation was defined as ED presentation greater than 90 minutes after symptom onset. Age was categorized into 4 groups according to quartiles of distribution. Wide pulse pressure was defined as a diastolic blood pressure less than or equal to one-half of the systolic blood pressure as recorded by emergency medical services or in the ED, whichever was recorded first. The timing of first epinephrine administration was categorized as none, less than 60 minutes after symptom onset, and more than 60 minutes after symptom onset.