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



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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. © 2017 American Academy of Allergy, Asthma & Immunology (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

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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 al³ 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 approved 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.

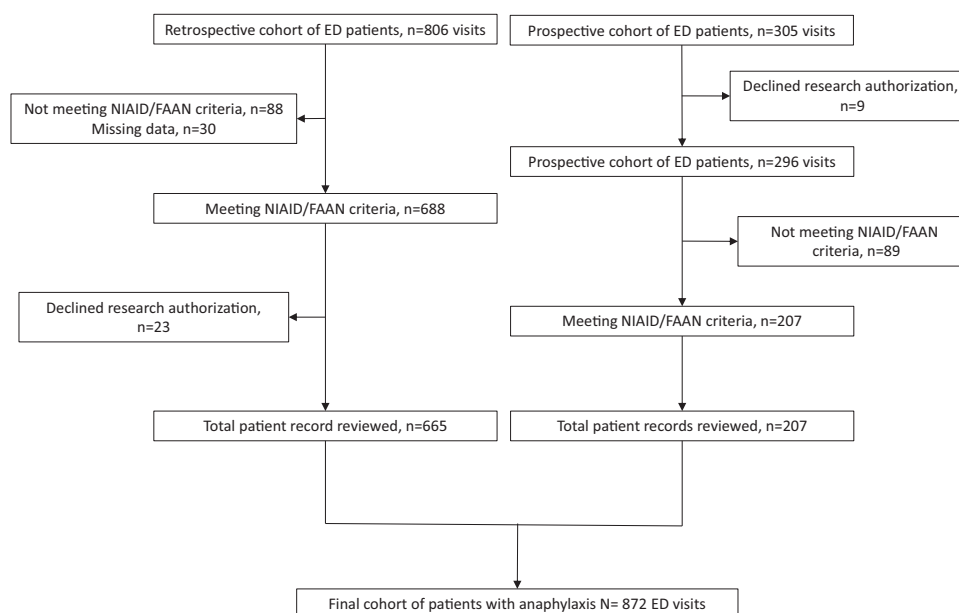


FIGURE 1. Patient selection process.

STATISTICAL ANALYSIS

Continuous features were summarized with means and SDs, or medians with interquartile range as appropriate for the distribution of the data; categorical features were summarized with frequency counts and percentages. To facilitate comparison of our findings with existing literature, we used candidate variables from previous studies.^{3,6,11,13} Associations of the candidate predictors with the outcomes of interest were evaluated using univariable and multivariable logistic regression models and summarized with odds ratios (ORs) and 95% CIs. Multivariable models were developed using forward stepwise selection, with the *P* value for a feature to enter or leave the model set to .05 with the requirement that at least 10 outcomes were needed to support each feature included in a multivariable model. The predictive ability of the feature(s) in a model was summarized using the area under a receiver operating characteristics curve, or AUC. The AUC can range from 0.5 to 1.0, with higher values indicating improved predictive ability. Internally validated AUCs were obtained using bootstrap resampling with 500 bootstrap samples. Model calibration was summarized using the Hosmer and Lemeshow goodness-of-fit test. A statistically significant *P* value from this test would reject the null hypothesis that the features in the model fit the data well. We calculated predicted probabilities for the entire sample on the basis of results of the multivariable logistic regression models. Statistical analyses were performed using version 9.4 of the SAS software package (SAS Institute, Cary, NC). All tests were 2-sided and *P* values of less than .05 were considered statistically significant.

RESULTS

Participants

A total of 807 patients with a total of 872 visits to the ED for anaphylaxis were identified between April 2008 and April 2015 (Figure 1).

Descriptive data

The candidate predictors for the 872 patient visits under study are summarized in Table I. The median age was 34 years (interquartile range, 17-53), 504 (58%) were female, 265 (30%) had a history of anaphylaxis, and 249 (29%) had a history of asthma. Food was the most common inciting trigger (*n* = 305 [35%]), followed by medication (*n* = 173 [20%]) and venom (*n* = 108 [12%]). One hundred ninety-four patients (22%) had an unknown inciting trigger. At least 1 dose of epinephrine was administered in 514 (59%) visits. Of these, epinephrine was administered before ED arrival in 199 (23%) visits. A total of 79 (9%) visits required multiple doses of epinephrine. Most patients received steroids (*n* = 781 [90%]).

Outcome data

Thirty-six (4.1%) visits in 35 patients resulted in biphasic anaphylaxis, with recurrent symptoms and signs meeting NIAID/FAAN criteria. The median time of biphasic reaction from the initial reaction was 3 hours (interquartile range, 1-13 hours; range, 0.5-44 hours). A total of 65 (7.5%) visits from 64 distinct patients met criteria for the composite outcome of any adverse event. All 65 of these visits resulted in a recurrence requiring some type of treatment. Included in these 65 visits were 24 (2.8% of total visits) visits associated with an ED return visit within 72 hours and 1 (0.1% of total visits) visit that resulted in direct hospitalization within 72 hours after ED discharge.

Of the 36 visits with biphasic reactions meeting NIAID/FAAN criteria, 17 (47%) required treatment for a recurrent symptom with epinephrine. Of the 65 visits with any adverse outcome, 23 (35%) required treatment for a recurrent symptom with epinephrine. There was a statistical significance between the frequency of epinephrine use in the reactions classified as anaphylaxis and in the reactions not classified as anaphylaxis (47% vs 21%; *P* = .03). Also, there was a positive correlation between the time of epinephrine for the initial reaction and the

TABLE I. Summary of candidate predictors (N = 872)

Predictor	n (%)
Age at visit (y)	
0-17	225 (26)
18-34	224 (26)
35-54	225 (26)
≥55	198 (23)
Sex	
Male	368 (42)
Female	504 (58)
History of anaphylaxis	265 (30)
History of asthma	249 (29)
Suspected inciting trigger	
Food	305 (35)
Medication	173 (20)
Venom	108 (12)
Latex	3 (<1)
Contrast	46 (5)
Other	43 (5)
Unknown	194 (22)
Syncope	49 (6)
Diarrhea	57 (7)
Hypotension	77 (9)
Wide pulse pressure (<i>N</i> * = 773)	143 (19)
Wheezing	252 (29)
Hives/urticaria	201 (23)
Flushing/diaphoresis	335 (38)
Pruritus (<i>N</i> * = 871)	432 (50)
Angioedema (<i>N</i> * = 870)	527 (61)
Emesis	154 (18)
Abdominal pain	146 (17)
Dyspnea (<i>N</i> * = 871)	609 (70)
Stridor (<i>N</i> * = 871)	27 (3)
Hypoxemia (<i>N</i> * = 870)	45 (5)
Delayed ED presentation (<i>N</i> * = 820)	287 (35)
No. of total epinephrine doses	
0	358 (41)
1	435 (50)
≥2	79 (9)
No. of epinephrine doses before ED arrival	
0	673 (77)
1	160 (18)
≥2	39 (4)
No. of epinephrine use after ED arrival	
0	533 (61)
1	313 (36)
≥2	26 (3)
Timing of first epinephrine administration (<i>N</i> * = 799)	
None administered	358 (45)
≤60 min of symptom onset	249 (31)
>60 min of symptom onset	192 (24)
No. of bronchodilator doses	
0	626 (72)
1	158 (18)
≥2	88 (10)
Administration of steroids	781 (90)

*Sample sizes for features with missing data are indicated in italics in parentheses.

time to biphasic reaction for those with this outcome, although it did not achieve statistical significance (Spearman rank correlation = 0.43; $P = .11$). We did not find any statistically significant difference in biphasic anaphylaxis (4.4% vs 3.4%; $P = .54$) or the combined outcome (7.7% vs 6.8%; $P = .66$) between the retrospective and prospective cohorts.

Main results

Univariable associations with biphasic anaphylaxis meeting NIAID/FAAN criteria are summarized in Table II. The use of steroid was not associated with biphasic anaphylaxis in the analysis ($P = .061$). In multivariable analysis, history of 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 60 minutes after symptom onset (OR, 2.29; 95% CI 1.09-4.79) were statistically significantly associated with biphasic anaphylaxis (Table III). The AUC of this model was 0.70 (95% CI, 0.61-0.79), and the internally validated AUC was 0.67 (95% CI, 0.59-0.76). The P value from the goodness-of-fit test was 0.91. The predicted probabilities of a biphasic reaction meeting NIAID/FAAN criteria for the combinations of these 3 features are summarized in Table IV. 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. Of those with 1.6% probability, 158 (47%) were admitted to the ED observation unit or hospital for admission, and of those with more than 20% probability, 8 (62%) were admitted to the ED observation unit or hospital for admission.

Univariable associations with any adverse outcome are summarized in Table III. In a multivariable analysis, unknown inciting trigger and first use of epinephrine after 60 minutes of symptom onset were statistically significantly associated with any adverse outcome (Table IV). The AUC of this model was 0.67 (95% CI, 0.60-0.74), and the internally validated AUC of this model was 0.67 (0.60-0.74). The P value from the goodness-of-fit test was 0.98. The predicted probabilities of any adverse outcome are summarized in Table V.

DISCUSSION

Main findings

We found that the rate of biphasic reactions meeting NIAID/FAAN criteria was 4.1%. A history of anaphylaxis, unknown inciting trigger, and first epinephrine use after 60 minutes of symptom onset were associated with an increased risk for a biphasic reaction and on the basis of these risk factors we presented the prediction probabilities. Patients with none of the identified risk factors had a 1.6% risk of a biphasic reaction meeting NIAID/FAAN criteria, whereas patients with all 3 risk factors had a 20% risk of a biphasic reaction.

Interpretation of study findings

Our study found that the rate of biphasic reactions with recurrent signs and symptoms meeting NIAID/FAAN criteria was 4.1%. However, the rate of recurrent symptoms requiring some type of therapeutic intervention was 7.5%. Lee and Greenes⁷ defined biphasic reaction as any reaction that requires any treatment after resolution of symptoms and reported that the rate of biphasic reaction was 6% in their pediatric cohort. A recent study from Grunau et al² reported that the rate of

TABLE II. Univariable associations with biphasic recurrence meeting NIAID/FAAN criteria or any adverse outcome (N = 872)

Feature	Biphasic reaction meeting NIAID/FAAN criteria, n (%)				Any adverse outcome, n (%)			
	No (N = 836)	Yes (N = 36)	OR (95% CI)	P value	No (N = 807)	Yes (N = 65)	OR (95% CI)	P value
Age at visit (y)								
0-17	215 (26)	10 (28)	1.0 (reference)		212 (26)	13 (20)	1.0 (reference)	
18-34	216 (26)	8 (22)	0.80 (0.31-2.06)	.64	212 (26)	12 (18)	0.92 (0.41-2.07)	.85
35-54	213 (25)	12 (33)	1.21 (0.51-2.86)	.66	202 (25)	23 (35)	1.86 (0.92-3.77)	.086
≥55	192 (23)	6 (17)	0.67 (0.24-1.88)	.45	181 (22)	17 (26)	1.53 (0.72-3.24)	.26
Sex								
Male	355 (42)	13 (36)	1.0 (reference)		344 (43)	24 (37)	1.0 (reference)	
Female	481 (58)	23 (64)	1.31 (0.65-2.61)	.45	463 (57)	41 (63)	1.27 (0.75-2.14)	.37
History of anaphylaxis	248 (30)	17 (47)	2.12 (1.09-4.15)	.028	241 (30)	24 (37)	1.38 (0.81-2.33)	.24
History of asthma	237 (28)	12 (33)	1.26 (0.62-2.57)	.52	231 (29)	18 (28)	0.96 (0.54-1.68)	.87
Suspected inciting trigger								
Food	292 (35)	13 (36)	2.00 (0.44-9.05)	.37	286 (35)	19 (29)	1.46 (0.48-4.41)	.50
Medication	166 (20)	7 (19)	1.90 (0.39-9.33)	.43	161 (20)	12 (18)	1.64 (0.51-5.24)	.40
Venom	107 (13)	1 (3)	0.42 (0.04-4.71)	.48	105 (13)	3 (5)	0.63 (0.14-2.88)	.55
Latex, contrast, other	90 (11)	2 (6)	1.0 (reference)		88 (11)	4 (6)	1.0 (reference)	
Unknown	181 (22)	13 (36)	3.23 (0.71-14.63)	.13	167 (21)	27 (42)	3.56 (1.21-10.49)	.022
Suspected inciting trigger								
Known	655 (78)	23 (64)	1.0 (reference)		640 (79)	38 (58)	1.0 (reference)	
Unknown	181 (22)	13 (36)	2.05 (1.02-4.12)	.045	167 (21)	27 (42)	2.72 (1.62-4.59)	<.001
Syncope	48 (6)	1 (3)	0.47 (0.06-3.50)	.46	48 (6)	1 (2)	0.25 (0.03-1.82)	.17
Diarrhea	55 (7)	2 (6)	0.84 (0.20-3.57)	.81	54 (7)	3 (5)	0.68 (0.21-2.22)	.52
Hypotension	75 (9)	2 (6)	0.60 (0.14-2.53)	.48	74 (9)	3 (5)	0.48 (0.15-1.57)	.22
Wide pulse pressure EMS/ED	135 (18)	8 (25)	1.50 (0.66-3.40)	.34	131 (18)	12 (20)	1.14 (0.59-2.20)	.71
Wheezing	240 (29)	12 (33)	1.24 (0.61-2.52)	.55	228 (28)	24 (37)	1.49 (0.88-2.52)	.14
Hives/urticaria	194 (23)	7 (19)	0.80 (0.35-1.85)	.60	184 (23)	17 (26)	1.20 (0.67-2.14)	.54
Flushing/diaphoresis	324 (39)	11 (31)	0.70 (0.34-1.43)	.32	313 (39)	22 (34)	0.81 (0.47-1.38)	.43
Pruritus	411 (49)	21 (58)	1.44 (0.73-2.84)	.29	394 (49)	38 (58)	1.47 (0.88-2.46)	.14
Angioedema	507 (61)	20 (56)	0.81 (0.41-1.58)	.53	489 (61)	38 (58)	0.91 (0.54-1.52)	.72
Dyspnea	580 (69)	29 (81)	1.82 (0.79-4.21)	.16	556 (69)	53 (82)	1.99 (1.04-3.78)	.037
Stridor	25 (3)	2 (6)	1.91 (0.43-8.38)	.39	24 (3)	3 (5)	1.58 (0.46-5.38)	.47
Hypoxemia	44 (5)	1 (3)	0.51 (0.07-3.83)	.52	41 (5)	4 (6)	1.22 (0.42-3.53)	.71
Emesis	147 (18)	7 (19)	1.13 (0.49-2.63)	.77	144 (18)	10 (15)	0.84 (0.42-1.68)	.62
Abdominal pain	138 (17)	8 (22)	1.45 (0.65-3.24)	.37	134 (17)	12 (18)	1.14 (0.59-2.19)	.70
Delayed ED presentation	271 (34)	16 (48)	1.79 (0.89-3.60)	.10	256 (34)	31 (50)	1.96 (1.17-3.30)	.011
No. of total epinephrine doses								
0	347 (42)	11 (31)	1.0 (reference)		339 (42)	19 (29)	1.0 (reference)	
1	416 (50)	19 (53)	1.44 (0.68-3.07)	.34	396 (49)	39 (60)	1.76 (1.00-3.10)	.051
≥2	73 (9)	6 (17)	2.59 (0.93-7.24)	.069	72 (9)	7 (11)	1.74 (0.70-4.28)	.23
No. of total epinephrine doses								
0 or 1	763 (91)	30 (83)	1.0 (reference)		735 (91)	58 (89)	1.0 (reference)	
>2	73 (9)	6 (17)	2.09 (0.84-5.19)	.11	72 (9)	7 (11)	1.23 (0.54-2.80)	.62
Timing of first epinephrine administration								
None administered	347 (45)	11 (34)	1.0 (reference)		339 (46)	19 (32)	1.0 (reference)	
≤60 min of symptom onset	241 (31)	8 (25)	1.05 (0.42-2.64)	.92	233 (32)	16 (27)	1.23 (0.62-2.43)	.56
>60 min of symptom onset	179 (23)	13 (41)	2.29 (1.01-5.22)	.048	167 (23)	25 (42)	2.67 (1.43-4.99)	.002
Timing of first epinephrine administration								
None or ≤60 min of symptom onset	588 (77)	19 (59)	1.0 (reference)		572 (77)	35 (58)	1.0 (reference)	
>60 min of symptom onset	179 (23)	13 (41)	2.25 (1.09-4.64)	.029	167 (23)	25 (42)	2.45 (1.42-4.20)	.001
No. of bronchodilator doses								
0	602 (72)	24 (67)	1.0 (reference)		583 (72)	43 (66)	1.0 (reference)	
>1	234 (28)	12 (33)	1.29 (0.63-2.61)	.49	224 (28)	22 (34)	1.33 (0.78-2.28)	.30
Administration of steroids	746 (89)	35 (97)	4.22 (0.57-31.19)	.16	718 (89)	63 (97)	3.91 (0.94-16.23)	.061

EMS, Emergency medical services.

TABLE III. Multivariable model to predict biphasic reaction meeting NIAID/FAAN criteria and any adverse outcome (N = 799)

Feature	NIAID/FAAN		Any adverse outcome	
	OR (95% CI)	P value	OR (95% CI)	P value
History of anaphylaxis	2.74 (1.33-5.63)	.006		
Suspected inciting trigger				
Known	1.0 (reference)		1.0 (reference)	
Unknown	2.40 (1.14-4.99)	.021	3.02 (1.75-5.21)	<.001
Timing of first epinephrine administration				
None or ≤60 min of symptom onset	1.0 (reference)		1.0 (reference)	
>60 min of symptom onset	2.29 (1.09-4.79)	.028	2.28 (1.32-3.95)	.003

TABLE IV. Predicted probabilities from multivariable model to predict biphasic recurrence meeting NIAID/FAAN criteria

History of anaphylaxis	Inciting trigger	Timing of first epinephrine administration	Predicted probability (%)
No	Known	None or ≤60 min	1.6
No	Known	>60 min	3.7
No	Unknown	None or ≤60 min	3.8
Yes	Known	None or ≤60 min	4.4
No	Unknown	>60 min	8.3
Yes	Known	>60 min	9.4
Yes	Unknown	None or ≤60 min	9.8
Yes	Unknown	>60 min	20

TABLE V. Predicted probabilities from multivariable model to predict any adverse outcome

Unknown inciting trigger	>60 min to first epinephrine administration	Predicted probability (%)
No	No	4.2
No	Yes	9.1
Yes	No	12
Yes	Yes	23

clinically important biphasic reactions (defined as recurrent or new symptoms meeting the NIAID/FAAN criteria for anaphylaxis) was 0.4% in their retrospective cohort of adult ED patients. Alqurashi et al³ reported that the rate of a biphasic reaction (defined as recurrent signs or symptoms severe enough to require a therapeutic intervention) was 14.7% in their retrospective pediatric ED cohort. Thus, the utilization of variable definitions used in previous studies has influenced the reported rates of biphasic reactions and associated risk factors.^{7,8,13-16} Therefore, we addressed this by assessing associations with biphasic reactions meeting NIAID/FAAN diagnostic criteria as well as any recurrent reaction requiring therapeutic intervention or additional health care utilization.

We found that of the 36 visits with biphasic reactions meeting NIAID/FAAN criteria, 17 (47%) resulted in treatment with epinephrine. The rate of epinephrine use in our study was similar to that in Alqurashi et al³ who reported 49% of biphasic reactions treated with epinephrine. Grunau et al² also reported that the 2 patients who developed a clinically significant biphasic reaction in their study both required epinephrine. The fact that nearly half the patients developing a biphasic reaction in our

study required epinephrine indicates that these reactions were clinically significant. However, the fact that more than 50% did not receive epinephrine suggests that many may have been self-limited and less severe.

We found that a history of anaphylaxis, unknown inciting trigger, and first epinephrine after 60 minutes of symptom onset were associated with the development of a biphasic reaction. The absence of all these factors was associated with a 1.6% risk of developing a biphasic reaction, and the presence of all the risk factors was associated with a 20% risk. Risk factors for a biphasic reaction in pediatric patients reported by Alqurashi et al³ included age 6 to 9 years, ED presentation more than 90 minutes after symptom onset, wide pulse pressure, multiple epinephrine doses, and the use of an inhaled beta-agonist. In a previous meta-analysis, we reported risk factors and concluded that because of the variability of risk factors for a biphasic reaction in the literature, a prediction model to assist clinicians in stratifying the risk among these patients would be helpful. Further external validation is needed to refine this prediction model before clinical implementation.

Importantly, our study demonstrated that delayed epinephrine use was associated with a biphasic reaction. This is similar to findings by Alqurashi et al³ who 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. Fleming et al¹⁷ reported that children seen in the ED due to food allergy were less likely to be hospitalized when epinephrine was given before ED presentation compared with those who received it after arrival. Pumphrey¹⁸ reported that 62% of fatal reactions in the United Kingdom were treated with epinephrine but only 14% received it before arrest. There are insufficient data to recommend the optimal time of administration, but given the typical time course of anaphylaxis, we recommend the administration within a few minutes of onset, rather than 30 to 60 minutes.^{1,4,10}

A substantial number of patients with anaphylaxis have an unknown trigger.¹⁹ An unknown inciting trigger as a risk factor for a biphasic reaction is somewhat problematic, because the definition of biphasic reaction requires that there is no reexposure to the trigger. In previous studies, data from Nagano et al²⁰ and Smit et al¹³ showed that an unknown inciting trigger was associated with biphasic reaction. A previous study found that approximately 55% of patients with an unknown trigger in the ED still had an unknown trigger after allergy follow-up.²¹ Thus, it is possible that patients with an unknown trigger could have reencountered the trigger inadvertently. However, it is also

possible that a significant subset of these patients could have idiopathic anaphylaxis or a mast cell activation disorder.

The median time of biphasic reaction from the initial reaction in our study was 3 hours. The optimal duration of observation after anaphylaxis is unknown. The joint task force guideline on anaphylaxis management suggests 4 to 8 hours of observation,¹ whereas the European guideline recommends up to 24 hours of observation.^{4,10} Given that biphasic reactions are uncommon, it seems reasonable to customize the observation of patients on the basis of the severity of their reaction, access to self-injectable epinephrine and emergency care, as well as their risk factors for a biphasic reaction.^{2,3,11} Thus, if these findings are externally validated, a clinician can use the identified risk factors (history of anaphylaxis, unknown trigger, and receipt of first epinephrine dose after 60 minutes of symptoms onset) to assist in optimizing the duration of observation.

Study limitations

Our study has several potential limitations. First, the low event rate could not support a lot of features in the multivariable model. Second, because of the low rate of outcomes of interest, the coefficients from the regression analyses were estimated with large CIs. Third, the retrospective data had some missing values that could impact data reliability. Fourth, we cannot be certain that patients with an unknown inciting trigger were not reexposed to the trigger. Fifth, the treatment effect of steroid is yet to be determined, because we did not have sufficient data on the timing, dose, and route in our cohort. Sixth, it is possible that we may not have exhausted all the risk factors for biphasic reaction.

Implications for clinical care

Our study findings can improve evidence-based clinical management of anaphylaxis in the ED by identifying patients who may not require prolonged monitoring, thus leading to a decreased length of stay for those considered at low risk for recurrent symptoms. Our findings will require external validation before clinical utilization.

CONCLUSIONS

We found that the rate of biphasic reactions meeting NIAID/FAAN criteria was 4.1%, and the rate of any adverse outcome was 7.5%. A total of 3 risk factors for a biphasic reaction were identified: a history of anaphylaxis, unknown inciting trigger, and first epinephrine administration 60 minutes after symptom onset. Risk stratification for a biphasic reaction of patients presenting to the ED with anaphylaxis may optimize patient care and lead to effective observation and counseling prepared for postdischarge care. A prospective study to externally validate our study findings is necessary.

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