

Predictors of Biphasic Reactions in the Emergency Department for Patients With Anaphylaxis

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What is already known about this topic? Biphasic reactions are uncommon and unpredictable, and risk factors for biphasic reactions are poorly understood.

What does this article add to our knowledge? Patients with a history of prior anaphylaxis, an unknown precipitant, or who present with symptoms of diarrhea or wheezing may be at increased risk for a biphasic reaction.

How does this study impact current management guidelines? This study will add additional data for possible risk factors management for biphasic reactions.

BACKGROUND: A biphasic reaction is the recurrence of anaphylaxis symptoms within 72 hours of the initial anaphylactic event, without re-exposure to the trigger. Biphasic reactions are uncommon and unpredictable, and risk factors for biphasic reactions are poorly understood.

OBJECTIVE: To identify predictors of biphasic anaphylactic reactions in patients with anaphylaxis in the emergency department (ED).

METHODS: Patients of all ages who presented to the ED and met diagnostic criteria for anaphylaxis from April 2008 to January 2013 at an academic medical center with 73,000 annual patient visits were consecutively included. We collected data on patient characteristics, suspected triggers, signs and symptoms, ED management, and disposition. Univariate analyses were performed to estimate the association between potential predictor variables and biphasic reactions. We report associations as odds ratios (OR) and corresponding 95% CIs.

RESULTS: Among 541 patients with anaphylaxis, median age was 34.6 years (interquartile range, 18-52 years), and 320 (59%) were female patients. Twenty-one patients (4%) had biphasic reactions. Two pediatric patients, ages of 5 years old and 16 years old, developed a biphasic reaction. The median time between the resolution of initial symptoms and onset of the biphasic reaction was 7 hours (range, 1-72 hours). Biphasic reactions were associated with a history of prior anaphylaxis (OR 2.6 [95% CI, 1.1-6.4]; $P = .029$), unknown precipitant (OR 2.6 [95% CI, 1.1-6.2]; $P = .03$),

symptoms of diarrhea (OR 4.5 [95% CI, 1.4-14.0]; $P = .024$), and wheezing (OR 2.6 [95% CI, 1.4-8.9]; $P = .029$).

CONCLUSIONS: Patients with a history of prior anaphylaxis, an unknown precipitant, or who present with symptoms of diarrhea or wheezing may be at increased risk for a biphasic reaction. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:281-7)

Key words: Anaphylaxis; Biphasic reactions; Risk factors; Emergency department

Anaphylaxis is a systemic allergic reaction that is most commonly treated in the emergency department (ED).^{1,2} Signs and symptoms can vary from relatively mild to life-threatening.³⁻⁵ A biphasic reaction is a recurrent reaction that meets criteria for anaphylaxis and occurs after resolution of symptoms without re-exposure to the trigger.^{6,7} Rates of biphasic reactions vary widely, and relatively few studies have reported risk factors for biphasic reactions.⁶⁻¹⁰ In addition, both protective and risk factors are not consistently found among study populations. Thus, biphasic reactions are poorly understood. The objectives of this study were to determine the incidence and characteristics of biphasic reactions and to identify protective or risk factors for biphasic reactions among patients who present to the ED with anaphylaxis.

METHODS

Study design and setting

This was an observational cohort study of consecutive patients who presented with anaphylaxis to the Saint Mary's Hospital ED of the Mayo Clinic, a tertiary care academic ED with 73,000 annual patient visits.

Selection of participants

Electronic medical records of patients of all ages in the ED were queried. Records of all patients who had any ED diagnosis that contained "allerg," "anaphy," or "sting" were reviewed, and those who met the National Institute of Allergy and Infectious Disease—Food Allergy and Anaphylaxis Network diagnostic criteria³ for anaphylaxis were included. Diagnostic criteria for anaphylaxis are summarized here.

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Abbreviations used

COPD- Chronic obstructive lung disease

ED- Emergency department

ICU- Intensive care unit

IQR- Interquartile range

OR- Odds ratio

PEF- Peak expiratory flow

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives; pruritus or flushing; swollen lips, tongue, uvula), and at least one 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 a known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or more than 30% decrease in systolic BP
 - b. Adults: systolic BP of less than 90 mm Hg or more than 30% decrease from that person's baseline

A previous study¹¹ reported that the criteria were 96.7% sensitive and 82.4% specific for anaphylaxis. The study was conducted from April 2008 to January 2013. The Mayo Clinic Institutional Review Board approved the study protocol.

Data collection and outcome measures

Data were collected by using a standardized data abstraction form. We collected data on daily medication use, medical history, suspected triggers of the anaphylaxis episode (based on the documented trigger at the time of the ED evaluation), clinical signs and symptoms, ED management, and disposition. We defined a biphasic reaction as any recurrent anaphylactic reaction that occurred after initial treatment and resolution of symptoms without re-exposure to the trigger.⁶ Patient electronic medical records were reviewed for follow-up a minimum of 30 days after the initial presentation.

Statistical analysis

Continuous data are presented as medians with interquartile range (IQR) as appropriate for the skewed distribution of the data, and categorical data are presented as percent frequency of occurrence. Univariate logistic regression models were fit to estimate the association between predictor variables and biphasic reactions. Odd ratios (OR) with corresponding 95% CIs were calculated to estimate the strength and direction of each

association. *P* values represent 2-sided hypothesis testing unless otherwise noted, and *P* values $\leq .05$ were considered statistically significant. Statistical analyses were performed by using JMP software, version 9.0 (SAS Institute Inc, Cary, NC).

RESULTS**Demographics**

From April 2008 to January 2013, there were 541 adults who met the National Institute of Allergy and Infectious Diseases—Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis. Baseline characteristics, suspected triggers of anaphylaxis, underlying lung disease, and disposition and management of the patients in the study cohort are summarized in Table I. The median age of the cohort was 35 years (IQR, 18-52 years). Three hundred twenty patients were female patients (59%), and 474 were white (88%). One hundred twenty-five patients (23%) had a history of prior anaphylaxis, 146 patients (27%) had a history of asthma and 11 (7.5%) had a history of chronic obstructive pulmonary disease.

Disposition and management

Two hundred fifty-one patients (46%) were discharged directly from the ED. A total of 72 (13%) were admitted to the hospital; 23 (4%) were admitted to a general ward, and 49 (9%) to the intensive care unit. A total of 218 (40%) were admitted to the ED observation unit and followed a protocol for observation and management that has been described previously.³ Eleven patients (2%) underwent endotracheal intubation for management of their anaphylactic reaction. (Table I).

Triggers

Four hundred and fourteen patients (77%) stated a distinct trigger that they believed to be responsible for the reaction. There were 193 patients (36%) who reported food as a trigger. Medication was the second largest group (*n* = 114 [21%]), and venom was the third (*n* = 60 [11%]). There were 127 patients (23%) who did not have an identifiable trigger at the time of the ED evaluation (Table I).

Clinical features

The overall clinical features are shown in Table II. Mucocutaneous features were the most frequently reported (*n* = 538 [99%]). Respiratory features were present in 445 patients (83%), followed by gastrointestinal features in 201 (38%). Cardiovascular features were reported in 197 patients (36%).

Biphasic reactions

Twenty-one patients (4%) had a biphasic anaphylactic reaction after documented resolution of the initial presenting clinical features (Table II). The median age for patients with biphasic reactions was 41 years (IQR, 31-51 years), including 2 pediatric patients. There were 13 female patients (62%). The median time between the resolution of initial symptoms and onset of the biphasic reaction was 7 hours (range, 1-72 hours), the mean time was 17 hours.

Univariate associations between demographic and clinical characteristics and biphasic reactions are shown in Table II. Biphasic reactions were associated with a history of prior anaphylaxis (OR 2.6, [95% CI, 1.1-6.4]; *P* = .03), unknown precipitant (OR 2.6 [95% CI, 1.1-6.2]; *P* = .03), wheezing (OR 2.6 [95% CI, 1.1-6.4]; *P* = .04), and symptoms of diarrhea (OR 4.5 [95% CI, 1.4-14]; *P* = .02). The presence of diarrhea as a

symptom was not significantly associated with any of the trigger categories (data not shown). The association between pruritus and a biphasic reaction had an OR of 2.5 (95% CI, 0.99-6.3); $P = .04$. In our study, tryptase was measured in a total of 59 patients with anaphylaxis (11%), and, among those, 6 had biphasic reactions. Biphasic reactions were not significantly associated with treatment with any type of steroids (OR 8.2 [95% CI, 0.5-137]; $P = .15$) or epinephrine (OR 1.3 [95% CI, 0.5-3.1]; $P = .55$) as part of the initial management. After exclusion of pediatric patients, biphasic reactions remained associated with a history of prior anaphylaxis (OR 2.9 [95% CI, 1.1-7.3]; $P = .02$), wheezing (OR 3.5 [95% CI, 1.4-9]; $P < .01$), and diarrhea (OR 4.2 [95% CI, 1.3-13.8]; $P < .01$); however, there was no longer an association with unknown triggers (OR 2.3 [95% CI, 0.9-5.8]; $P = .08$). In addition, a significant association was found for diffuse urticaria (OR 2.9 [95% CI, 1.1-7.6]; $P = .02$). In univariate analysis, there were no significant associations between biphasic reactions and anti-hypertensive use among adults (data not shown). Further analysis was conducted for younger adults (defined as age 18-50 years) and older adults (defined as age older than 50 years).

After subgroup analysis, the association between biphasic reactions and a history of anaphylaxis was no longer statistically significant in younger adults (OR 2.2 [95% CI, 0.7-6.5]; $P = .2$) nor older adults (OR 5.8 [95% CI, 0.9-36.3]; $P = .07$). Younger adults who had biphasic reactions were more likely to have an unknown trigger (OR 3.5 [95% CI, 1.2-10]; $P = .02$); however, the initial symptom of wheezing (OR 1.9 [95% CI, 0.6-5.9]; $P = .3$), diarrhea (OR 2.6 [95% CI, 0.5-12.6]; $P = .23$), or abdominal pain (OR 1.2 [95% CI, 0.2-5.5]; $P = .7$) were not associated with biphasic reactions. Older adults who experienced biphasic reactions were more likely to have an initial symptom of wheezing (OR 20.5 [95% CI, 2.2-192]; $P < .01$), diarrhea (OR 11 [95% CI, 1.6-76]; $P = .04$), and abdominal pain (OR 12.8 [95% CI, 1.8-89]; $P = .03$) but not an unknown trigger (OR 0.7 [95% CI, 0.1-6.0]; $P = .99$) compared with those who did not develop biphasic reactions.

Details of each of the 21 biphasic reactions and management of the patients are shown in Table III. Mucocutaneous and respiratory manifestations were the most common (90%), followed by gastrointestinal (24%) and cardiovascular symptoms (14%). The majority ($n = 18$ [86%]) of biphasic reactions were mild to moderate in severity, and clinical features were similar to the initial reaction (Table III). There were only 3 patients who had involvement of organ systems that were not involved in the original reaction (2 patients with cardiovascular involvement manifested as hypotension and 1 patient with gastrointestinal symptom involvement manifested as vomiting). Three of the biphasic reactions were more severe than the initial reaction. More than half of the patients had their biphasic reactions at home or work.

Biphasic reaction management

Of the 21 patients with biphasic reactions, 10 (48%) received epinephrine before ED evaluation or in the ED (Table III). Two patients (10%) were admitted to a general ward, and 3 patients (14%) were transferred to the intensive care unit, including 1 patient who required endotracheal intubation.

DISCUSSION

In this study of 541 patients with anaphylaxis, we observed a 4% incidence of biphasic reactions. The median time between

TABLE I. Demographics of patients with anaphylaxis who presented to the ED ($n = 541$)

Variable	
Demographics	
Female, no. (%)	320 (59)
Age, median (IQR) (y)	35 (18-52)
Race, no. (%)	
White	474 (88)
Hispanic	0 (0)
Black	15 (3)
Asian/Pacific islander	12 (2)
Other	32 (6)
Unknown	2 (0.2)
Trigger, no. (%)	
Food	193 (36)
Medication	114 (21)
Venom	60 (11)
Latex	2 (0.3)
Contrast	23 (4)
Other	20 (4)
Unknown	127 (23)
History, no. (%)	
Previous anaphylaxis	125 (23)
Asthma and/or COPD	152 (28)
Disposition and management, no. (%)	
Discharge from ED	251 (46)
ED observation unit	218 (40)
Hospital ward	23 (4)
ICU admission	49 (9)

COPD, Chronic obstructive pulmonary disease; ICU, intensive care unit.

the resolution of initial symptoms and onset of the biphasic reaction was 7 hours and ranged from 1 to 72 hours. Biphasic reactions were associated with a history of prior anaphylaxis, unknown trigger, symptoms of diarrhea, and wheezing. The previously reported studies on biphasic reactions are summarized in Table IV. The 4% rate of biphasic reactions among patients in our cohort is consistent with rates of biphasic reactions in other retrospective and prospective studies.^{6,10-14} However, a few studies reported significantly higher rates.^{7,9} The higher incidence of biphasic reactions observed in studies conducted in an inpatient setting may be attributed to differences in study populations and study settings because inpatients would be expected to have had more severe reactions.

Most of the patients in our study had biphasic reactions that were similar to the initial reaction. However, there were 3 patients (14%) who had involvement of organ systems that were not involved in the initial reaction, and 3 patients (14%) who had a biphasic reaction with symptoms more severe than the initial reaction, including 1 patient who required endotracheal intubation for airway protection due to progressive airway edema. These findings are consistent with previous studies that also found that the majority of biphasic reactions involve the same organ systems as the original reaction and are unlikely to be life-threatening.^{6,8,13,14}

A history of anaphylaxis was associated with biphasic reactions in our cohort. Sampson et al¹⁵ described fatal cases of anaphylaxis related to food ingestion and found that patients who

TABLE II. Clinical features of anaphylaxis and biphasic reactions at presentation (n = 541)

	Total no. (%) (N = 541)	Biphasic no. (%) (N = 21)	OR (95% CI)	P value
Demographics				
Age, median, (IQR) (y)	35 (18-52)	41 (31-51)	NA	
Women	230 (59)	13 (62)	1.1 (0.5-2.8)	.8
History				
Prior anaphylaxis	125 (23)	9 (43)	2.6 (1.1-6.4)*	.03*
Angioedema	28 (5)	2 (10)	2.0 (0.4-9.0)	.3
Seasonal allergies	104 (19)	7 (33)	2.2 (0.9-5.5)	.09
Asthma or COPD	157 (29)	6 (29)	0.79 (0.3-2.2)	.7
Trigger				
Food	193 (36)	4 (19)	0.41 (0.14-1.2)	.2
Medicine	114 (21)	5 (24)	1.2 (0.4-3.3)	.8
Venom	60 (11)	1 (5)	0.39 (0.05-3.0)	.5
Other	45 (8)	2 (9.5)	1.2 (0.3-5.5)	.7
Unknown	127 (24)	9 (43)	2.6 (1.1-6.2)	.03*
Symptoms				
Mucocutaneous	538 (99)	21 (100)	0.6 (0.03-11.8)	1.0
Diffuse urticaria	224 (41)	13 (62)	2.4 (0.9-5.8)	.05
Angioedema	298 (55)	9 (43)	2.0 (0.4-9.0)	.03
Throat tightness	262 (48)	14 (67)	2.2 (0.9-5.5)	.09
Pruritus	245 (45)	14 (67)	2.5 (0.99-6.3)	.04*
Flushing	193 (36)	9 (43)	1.4 (0.6-3.3)	.5
Respiratory	445 (83)	20 (95)	1.2 (0.6-2.4)	.6
Voice change	99 (18)	7 (33)	2.3 (0.9-5.9)	.07
Dyspnea	356 (66)	18 (85.7)	3.2 (0.9-11.0)	.06
Wheeze	125 (23)	9 (43)	2.6 (1.1-6.4)*	.04*
Stridor	17 (3)	0	NA	
Hypoxemia	28 (5)	2 (10)	2. (0.4-9.0)	.3
Gastrointestinal	201 (38)	9 (43)	2.2 (0.6-7.3)	.2
Vomiting	96 (18)	5 (24)	1.5 (0.5-4.1)	.5
Diarrhea	30 (6)	4 (19)	4.5 (1.4-14.2)*	.02*
Abdominal pain	64 (12)	4 (19)	1.8 (0.6-5.5)	.3
Cardiovascular	197 (36)	3 (14)	1.2 (0.6-2.4)	.7
Dizzy and/or lightheaded	121 (22)	5 (23.8)	1.1 (0.4-3.)	.9
Collapse and/or syncope	31 (6)	1 (5)	0.82 (0.1-6.3)	1.0
Hypotension	44 (8)	2 (10)	1.2 (0.3-5.3)	.7
Treatment				
Any type of steroid	458 (85)	21 (100)	8.2 (0.5-137.0)	.2
Epinephrine	275 (51)	12 (57)	1.3 (0.5-3.1)	.6

NA, Not available; COPD, chronic obstructive pulmonary disease.

*Statistical significance.

experienced a biphasic reaction had a history of previous reactions to certain foods. However, an analysis of previous anaphylactic reactions was not included. Several studies found that biphasic reactions were not significantly associated with a history of allergy or anaphylaxis.^{13,14,16-19} Thus, conflicting results exist with regard to a history of anaphylaxis, and a larger study will be necessary to address this issue.

Previous studies showed that respiratory symptoms defined as wheezing, dyspnea, respiratory arrest,⁸ or laryngeal edema⁹ were associated with biphasic reactions. These results are consistent with our finding of an association between wheezing and biphasic reactions. In contrast, Smit et al¹⁴ found that patients with respiratory symptoms on initial presentation were less likely to develop a biphasic reaction. Previous studies did not find an association between diarrhea and biphasic reactions. It is notable that the association between diarrhea and biphasic reactions

remained after exclusion of pediatric patients and was strongest among patients older than 50 years of age.

Results of several studies²⁰⁻²² suggested that the serum tryptase level is important in anaphylaxis of venom patients. Unfortunately, tryptase was measured in a small proportion of patients in our cohort, and there was insufficient power to measure its association with a biphasic reaction. We did not find a protective effect with steroid or epinephrine treatment. It has previously been suggested that delayed administration of epinephrine may increase the risk of a biphasic reaction.^{6,18} We did not evaluate the timing of epinephrine administration relative to symptom onset and, therefore, cannot comment on the effect of delayed epinephrine administration. Although some studies^{9,13} demonstrated a statistically insignificant trend toward a decreased rate of biphasic reactions in patients treated with any type of steroid, other studies also have failed to find this

TABLE III. Characteristics and management of patients with biphasic reactions

Patient no.	Age (y)	Sex	Trigger	Time of onset after resolution, h	Disposition after initial reaction	Location of biphasic reaction onset	Initial signs and/or symptoms	Biphasic signs and/or symptoms	Treatment biphasic reaction	Disposition after biphasic reaction
1	5.1	F	Unknown	29	Home	Home	MC/R/GI	MC/R	H1, S	Home
2	16.4	M	Contrast	6	Home	Home	MC/R	MC/R*	Epi, H1, H2, S, V, B	ICU
3	19.9	F	Unknown	7	EDOU	Home	MC/R	R/GI	H1, B	Home
4	29.3	M	Food (fish)	12	EDOU	EDOU	MC/R/GI/CV	MC/ R	Epi, H1, B	Home
5	30.0	F	Food	36	EDOU	Home	MC/R/GI	MC/R/GI	H2, S, B	EDOU>home
6	31.8	M	Unknown	3	EDOU	EDOU	MC/R	MC/R	Epi, H1	Home
7	33.6	F	Unknown	24	EDOU	Home	MC/R	MC/R	H1, H2, S	Home
8	35.5	M	Unknown	24	EDOU	Home	MC/R	MC/R	H1, H2, S, B	EDOU>home
9	37.3	F	Unknown	72	EDOU	Home	MC/R	MC/R	H1, H2, S	Home
10	40.0	M	Medication (lidocaine)	4	EDOU	EDOU	MC/R/GI	MC/GI	H1	GM
11	41.1	F	Venom	6	EDOU	Home	MC/R/GI/CV	MC/R	Epi, H1, H2, S	EDOU>home
12	45.0	F	Food	17	EDOU	Home	MC/R	MC/R/CV	Epi, S, H1, B	Home
13	46.4	M	Unknown	1	Home	Home	MC/R/CV	MC/R	Epi, B	EDOU>home
14	46.5	F	Medication (ibuprofen)	6	EDOU	EDOU	MC/R	MC/R	H1, H2, S	Home
15	47.5	F	Food (soy)	3	EDOU	EDOU	MC/R	MC/R/CV*	Epi, H1, H2, S, V, I	ICU
16	49.6	F	Unknown	10	EDOU	Outside	MC/R	MC/R	H1	Home
17	51.6	M	Unknown	6	EDOU	EDOU	MC/R/GI	MC/R	Epi, H1, H2, S	Home
18	60.3	F	Medication (clindamycin)	3	EDOU	Home	MC/R/GI/CV	MC/R/GI*	H1, H2, S, B	EDOU>GM>ICU
19	62.8	M	Contrast	23	Home	Work	MC/GI/CV	MC/CV	H1, H2, S	EDOU>home
20	64.8	F	Medication (sulfamethoxazole and trimethoprim)	48	EDOU	Home	MC/R/GI/CV	MC/R	Epi, S, H1, H2, B	EDOU>home
21	69.5	F	Medication (aspirin)	2	EDOU	EDOU	MC/R/GI/CV	R/GI	Epi, H1, H2, S	EDOU>home

EDOU, emergency department observation unit; MC, mucocutaneous signs/symptoms; R, respiratory signs/symptoms; GI, gastrointestinal symptoms; CV, cardiovascular signs/symptoms; H1, H1 antihistamines; S, steroids; Epi, epinephrine; H2, H2 antihistamines; V, vasopressor; B, bronchodilator; I, intubation; ICU, intensive care unit; GM, general medical floor.

TABLE IV. List of previous studies

Study, y	Study design	Population	No. of patients, biphasic; anaphylaxis total incidence (%)	Onset time of biphasic, h range (mean, median)	Features associated with biphasic reaction	Association, <i>P</i> value (OR or RR)	Clinical feature similar to initial
Stark et al, ⁹ 1986	Prospective	ED visits and hospitalizations	5; 25 (20)	1-8 (NA, NA)	Late onset of initial reaction and oral ingestion	.03 (RR, 2.8)	No specific clinical features
Douglas et al, ⁸ 1994	Retrospective	Clinic, hospitalization	4; 59 (6.7)	1-24 (12.5, 12.5)	Hypotension, respiratory tract obstruction	NA	Biphasic more severe than initial
Brady et al, ¹⁰ 1997	Retrospective	ED visits and hospitalizations	2; 67 (3)	NA (NA, NA)	Hypotension, laryngeal edema	NA	No specific clinical features
Brazil and MacNamar, ⁷ 1998	Retrospective	Hospitalization	6; 34 (17)	4.5-29.5, 16.3, 15.4	More than 1 dose of epinephrine	.03	No specific clinical features
Lee and Greenes, ⁶ 2000	Retrospective	Hospitalized, pediatric	4; 108 (3.7)	5.8-28.4, NA, NA	Delayed epinephrine	.03	Clinical feature similar to initial, a few severe
Smit et al, ¹⁴ 2005	Retrospective	ED	15; 282 (5.3)	1-23, 8, NA	Absence of respiratory symptom (absence of dyspnea, less use of SABA, respiratory rate)	.0023, .023, .02	Longer hours to develop biphasic reaction
Ellis et al, ¹³ 2007	Prospective	ED, hospitalization	5; 109 (4.6)	1.5-38, 10.1, 8.5	Longer duration of initial symptom, received less epinephrine	.03, .048	Clinical feature similar to initial
Mehr et al, ¹⁹ 2009	Retrospective	ED	12; 109 (11)	1.2-13.8 (NA, 8.8)	More than 1 dose of epi, fluid bolus	.01, .01	No specific clinical features
Scranton et al, ²⁵ 2009	Prospective	Clinic	3; 47 (6.4)	5-12 (8.2, 7.5)	Female, elderly, >1 dose of epi	.03, .01, <.001	No specific clinical features
Confino-Cohen and Goldberg, ¹⁶ 2010	Prospective	Clinic	11; 131 (8.4)	1.3-3 (2, 1.7)	Decreased PEF, tendency for asthma	.03	Clinical feature similar to initial
Lertnawapan and Maek-a-nantawat, ¹⁸ 2011	Retrospective	ED	13; 208 (6.3)	1-70, (NA, 1)	Delayed epinephrine	≤.01	No specific clinical features
Lee et al, ¹² 2013	Retrospective	Clinic	9; 614 (1.5)	2-24 (NA, NA)	Multiple system involvement	NA	No specific clinical features

RR, Relative risk; NA, not available; epi, epinephrine; SABA, short-acting β -agonist; PEF, peak expiratory flow.

association.^{6,7,9,14,19} A further study that investigates the effectiveness of glucocorticoids and epinephrine will likely be required to answer these questions.

The mean time to onset of the biphasic reaction was 17 hours in our cohort. This is longer than studies by Ellis and Day¹⁷ and Smit et al,¹⁴ which found mean times of 10 and 8 hours, respectively. The range of symptoms onset of 1 to 72 hours of symptoms was similar to results reported by Douglas et al.⁸ Current guidelines recommend an observation period of 4 to 6 hours based on reaction severity, risk factors for severe or fatal reactions, patient reliability, and access to emergency care.^{3,23,24} Other investigators have suggested an observation period of up to 24 hours.⁷ Eleven patients in our cohort (52%) experienced the onset of the biphasic reaction beyond 6 hours, and 4 had an onset after 24 hours. Thus, more than half of the patients had their biphasic reactions at home or at work. An observation period of 24 hours would have captured 80% of all biphasic reactions in our cohort. Given the elusiveness of consistently defined risk factors for biphasic reactions, it seems most reasonable to base recommendations for observation on the factors suggested in the current guidelines and to strongly consider observation longer than 6 hours for patients unable to rapidly access emergency care or with factors that place them at an increased risk of a fatal reaction.

Limitations

Our study has several limitations. Data quality relies on the accuracy of the medical record because of the nature of the retrospective cohort design. However, standardized data abstraction forms were used to reduce random and systematic errors and to enhance the precision and accuracy of the variables collected. Also, this study was conducted at a single center with a predominantly white cohort, which can limit external validity. Many of our patients had an unknown trigger, and we were not able to exclude the possibility that they were re-exposed to the trigger a second time rather than experiencing a biphasic reaction. Although patients are advised to take antihistamines after discharge, these also are available as over-the-counter medications and are not always prescribed; therefore, capturing reliable data is not feasible, and we were unable to study the effect of outpatient oral antihistamine use on the incidence of biphasic reactions. Of the 21 patients with biphasic reactions, 3 had only mucocutaneous symptoms and dyspnea. Given the subjective nature of dyspnea, it is possible that, although these 3 patients met Food Allergy and Anaphylaxis Network criteria, the reactions were not truly anaphylaxis but potentially represented allergic symptoms associated with anxiety or a sensation of dyspnea secondary to oropharyngeal edema. Also, the relatively small number of biphasic reactions in our cohort precluded further adjustment for potential confounding factors.

CONCLUSIONS

Based on our study, patients with a history of prior anaphylaxis and those who present with an unknown trigger, symptoms of wheezing, or diarrhea may be at increased risk for a biphasic reaction. There was no significant association between the specific precipitant and the risk of a biphasic reaction. Many biphasic reactions developed beyond 6 hours after initial symptom resolution. Use of any type of steroid or epinephrine was not associated with the odds of developing a biphasic reaction. To our knowledge, this is the largest study of patients in the ED

with biphasic anaphylactic reactions. However, further studies are needed to continue to identify predictors of these reactions to better guide management decisions.

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