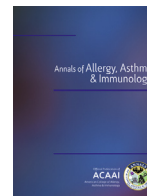




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Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis

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ABSTRACT

Background: Epidemiologic data regarding biphasic reactions in children with anaphylaxis are sparse.

Objective: To investigate the incidence and clinical predictors of biphasic reactions in children presenting to the emergency department (ED) with anaphylaxis.

Methods: A health records review of ED visits at 2 large Canadian academic pediatric EDs was conducted. All visits that satisfied anaphylaxis diagnostic criteria of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network were included. Predictors of biphasic reaction were analyzed using univariate and multiple logistic regression analyses.

Results: Of 1,749 ED records reviewed, 484 visits met the study inclusion criteria. Seventy-one patients (14.7%) developed biphasic reactions. The median age was 6 years (interquartile range 2.7–10.1) and 51 (71.8%) were boys. Forty-nine of the 71 (69%) delayed reactions involved respiratory and/or cardiovascular manifestations and 35 (49%) were treated with epinephrine. Five independent predictors for biphasic reactions were found: age 6 to 9 years (odds ratio [OR] 3.60, 95% confidence interval [CI] 1.5–8.58), delay in presentation to the ED longer than 90 minutes after the onset of the initial reaction (OR 2.58, 95% CI 1.47–4.53), wide pulse pressure at triage (OR 2.92, 95% CI 1.69–5.04), treatment of the initial reaction with more than 1 dose of epinephrine (OR 2.7, 95% CI 1.12–6.55), and administration of inhaled β -agonists in the ED (OR 2.39, 95% CI 1.24–4.62).

Conclusion: Biphasic reactions seem to be associated with the severity of the initial anaphylactic reactions. We identified clinical predictors that could ultimately be used to identify patients who would benefit from prolonged ED monitoring and enable better utilization of ED resources.

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Introduction

Anaphylaxis is a severe hypersensitivity reaction that is rapid in onset and can result in death.¹ The true pediatric population-based prevalence of anaphylaxis from all triggers is unknown.^{1,2} Several studies have shown that anaphylaxis is under-recognized by patients and caregivers and underdiagnosed by health professionals.³ Despite this, the rate of occurrence appears to be globally increasing, particularly in children.^{4–7} Anaphylactic reactions account for approximately 2 to 4 per 1,000 pediatric emergency department (ED) visits in North America.^{8–10}

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The pattern of an anaphylactic reaction can be uniphasic, biphasic (also called *delayed* or *late phase*), or refractory in nature.¹¹ Owing to concerns about potentially fatal biphasic reactions,¹² most guidelines recommend a prolonged period of observation and monitoring after treatment of the initial reaction. The dilemma that most emergency physicians encounter is identifying the optimum duration of this observation.¹³ Guidelines vary considerably in their recommendations: some suggest anywhere from 6 to 24 hours and others provide no specific time.^{1,2,14,15} This lack of consensus about the duration of observation originates from a lack of strong and validated clinical predictors for this phenomenon.

In light of increasing ED crowding in recent years, the lack of predictors of biphasic reactions, coupled with the growing evidence suggesting an increased rate of anaphylaxis among children in the past decade, may have a detrimental impact on the quality of care provided to this vulnerable population. The available literature

on the epidemiology and predictors of a biphasic reaction in children is very sparse. This dearth of data is reflected in the recent report from the National Institute of Allergy and Infectious Diseases¹⁶ and in the updated World Allergy Organization anaphylaxis guidelines, published in 2013.¹⁷ These guidelines identified significant knowledge gaps in the incidence and treatment of biphasic reactions and recommended further research. Therefore, the primary objective of this study was to investigate the incidence and predictive factors of biphasic reactions in children with anaphylaxis.

Methods

Study Design and Setting

A health record review was conducted of patients who presented to the ED with anaphylaxis during the calendar year 2010. The study was conducted at 2 pediatric tertiary care centers in Ontario, Canada: the Children's Hospital of Eastern Ontario in Ottawa and the Hospital for Sick Children in Toronto. The Children's Hospital of Eastern Ontario is the only pediatric center in Ottawa with approximately 70,000 annual ED visits. The Hospital for Sick Children is the primary care pediatric hospital for the downtown core of Toronto and has approximately 60,000 ED visits annually. The research ethics boards at the 2 sites approved this study.

Selection of Participants

Patients were identified using the hospitals' health record databases. The ED charts of patients whose primary or secondary diagnoses matched any of the *International Classification of Diseases, Tenth Revision* codes were reviewed. These search codes included, but were not limited to, "anaphylactic shock due to shell fish (crustaceans)" (T78.01), "anaphylactic shock due to other fish" (T78.02), "anaphylactic shock due to fruits and vegetables" (T78.03), "anaphylactic shock due to tree nuts and seeds" (T78.04), "anaphylactic shock due to milk and dairy products" (T78.06), "anaphylactic shock due to eggs" (T78.07), "anaphylactic shock due to other food products" (T78.08), "anaphylactic shock due to unspecified food products" (T78.09), "other adverse food reactions, not classified elsewhere" (T78.1), "anaphylactic shock, unspecified" (T78.2), and "allergy, unspecified" (T78.4). Patients younger than 18 years and whose ED visits met the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis were included in the study.¹⁸

Patient encounters were excluded if any of the following criteria were met: allergic event did not match the strict 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network anaphylaxis diagnostic criteria; anaphylaxis that occurred in the context of a suicide attempt or intoxication; anaphylaxis episode confounded by other medical diagnoses, such as food poisoning or mastocytosis; anaphylaxis that occurred during an outpatient clinic visit or inpatient hospitalization; or anaphylaxis episodes in which the trigger, symptoms, or treatments of the reaction were not documented.

Data Abstraction and Processing

A standard paper data extraction form was developed, piloted, and agreed to by the authors. Nursing triage notes and nursing monitoring sheets were used in addition to data from each patient's ED record as primary sources for data regarding the time of events, such as drug administration or a change in a patient's clinical status. The ambulance call report was used to supplement or confirm historical data about all anaphylactic episodes attended by the emergency medical services personnel. When available, this report was used as the main

source of data regarding prehospital reaction management at the scene and during transport to the hospital. For patients with anaphylaxis to a new allergen who were referred to an allergy specialist by the emergency physician, the consultation note from the allergist, when available, was used to document the relevant trigger.

Data were abstracted from 4 main categories of variables: history, physical examination, prehospital and ED treatments and interventions, and ED monitoring period and subsequent visits. The authors chose the variables to be assessed a priori based on data from reports in the literature.^{11,12,19–34} These variables included, but were not limited to, age; sex; history of anaphylaxis and atopic diseases (such as eczema and asthma); historical details of the anaphylactic event (such as name of the allergen, if identified, and location of the allergic event); recorded vital signs at triage and clinical manifestations of the episode; and epinephrine, systemic steroid, and antihistamine treatments for the anaphylactic reaction before and after ED presentation. In addition, the following variables were abstracted if the patient developed a biphasic reaction during monitoring in the ED after the initial anaphylactic episode or subsequently returned to ED within 72 hours from the initial ED visit: time of onset, clinical manifestations, and details of therapeutic interventions for the biphasic reaction.

Ten percent of the total ED visits were randomly selected for data extraction inter-rater agreement. One emergency physician at each site extracted data from every 10th visit as listed by the health record department. This list is sorted chronologically by date of visit and had only the medical record number and date of the ED visit matching the *International Classification of Diseases, Tenth Revision* codes specified earlier. Interobserver agreement for variables with high impact of errors related to patient eligibility, development of the primary outcome, and treatment of the reaction with epinephrine before and after arrival to the ED were measured using the κ -coefficient with 95% confidence intervals.

Definition and Assessment of Outcome

Emergency department visits that matched the diagnosis of anaphylaxis were divided further into 2 groups: uniphasic and biphasic. For an anaphylactic reaction to be classified as biphasic, it had to match the following criteria: (1) the initial anaphylactic reaction should be followed with a period of resolution for longer than 1 hour, during which there are no new symptoms or treatment administered; (2) this period should be followed by a second phase of new or recurrent anaphylaxis symptoms or signs not caused by antigen re-exposure; and (3) these symptoms or signs should be severe enough to require therapeutic intervention. If there were no new or recurrent symptoms or signs matching the criteria listed earlier, the reaction was considered uniphasic.

Because a biphasic reaction has been reported to occur up to 72 hours after the initial anaphylactic reaction, health records were reviewed for subsequent ED visits within this period.¹¹ If the patient was admitted, then the inpatient chart was reviewed. If the patient was discharged from the ED or the inpatient service (before 72 hours), then the authors searched for evidence of return visits to the ED up to 72 hours after the index visit. If a return visit occurred, then records were reviewed to determine whether the subsequent visit was related to the initial visit for the anaphylaxis episode.

Data Analysis

Data entry and analysis were performed using SPSS 20 (SPSS, Inc, Chicago, Illinois). A random 20% of the completed abstraction forms were checked for accuracy of data entry into the database. In addition, accuracy of data collection and entry was verified further by regular frequency reports and visual checks. Any queries were clarified by reviewing the original record.

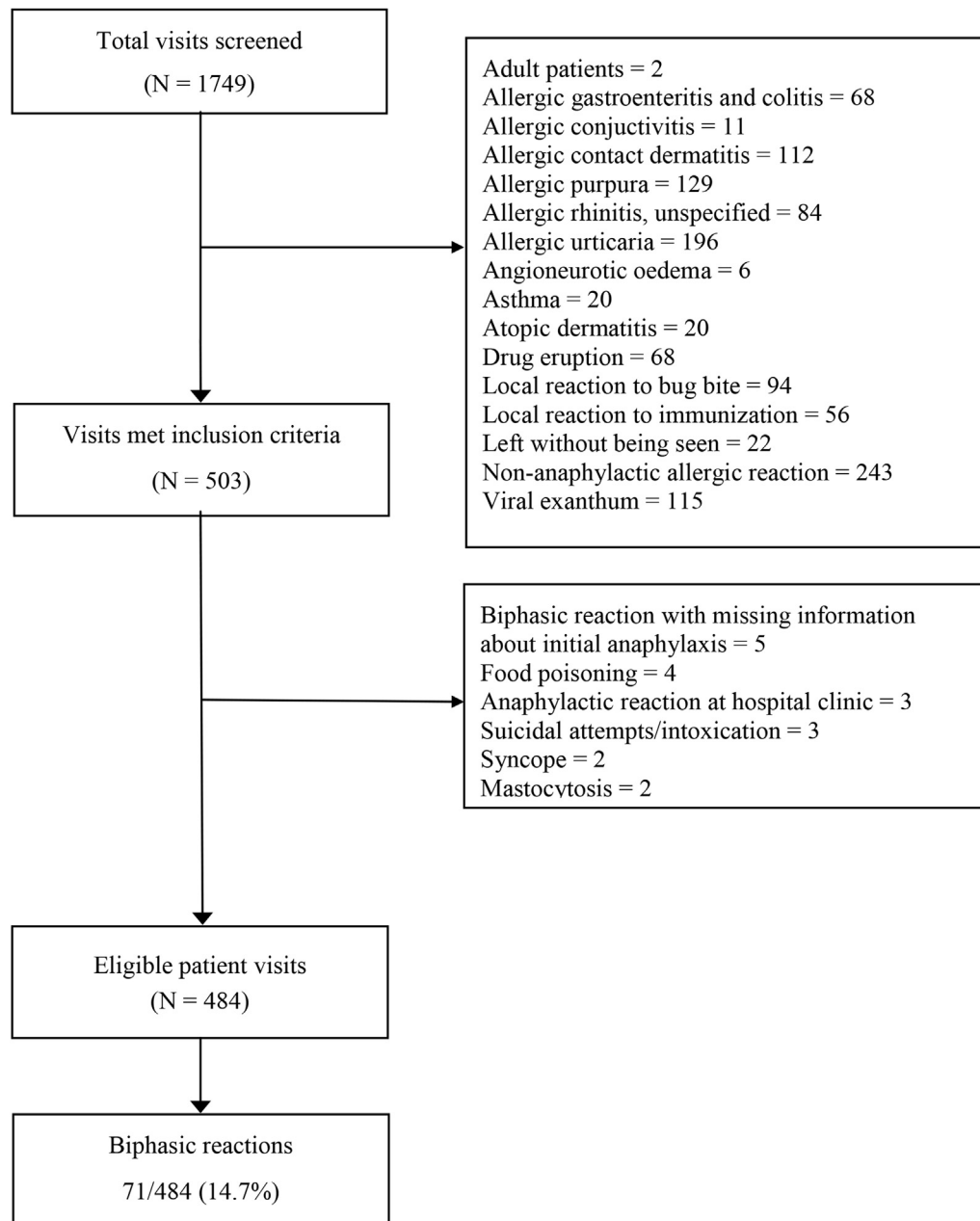


Figure 1. Flow of study patient visits to the emergency departments.

Univariate analysis was performed to determine the association of all predictor variables to the primary dichotomous outcome (biphasic vs uniphasic reaction). The χ^2 or Fisher exact test was used for nominal variables. Unpaired 2-tailed *t* test was used for univariate analysis of continuous clinical predictor variables. The Mann-Whitney *U* test was used to analyze correlations in nonparametric data. Then, variables were selected based on clinical and statistical grounds. Only predictor variables with a *P* value less than .2 were considered for multivariate analysis. The stepwise backward selection method was used for multivariate logistic regression analysis to identify statistically significant independent predictors to determine the independent association of factors related to the occurrence of biphasic reactions and to control for potential confounding. Statistical significance of independent variables was assessed using the likelihood ratio test (*P* < .05 statistically significant).

Results

Study Flow and Interobserver Agreement

During the study period, 1,749 ED visits owing to allergic symptoms were screened for potential eligibility. Of these visits, 1,246 (71.2%) were excluded because they did not fulfill the diagnostic criteria for anaphylaxis. Figure 1 illustrates study flow and details of the excluded visits. Five hundred three visits (28.9%) met the inclusion criteria, of which 19 (4%) met the exclusion criteria. As a result, 484 of 1,749 (27.6%) visits were screened and included in the study.

Interobserver agreements were calculated for appropriate inclusion of patients and for variables related to the primary outcome. There was 100% agreement on the included ED visits, the development of biphasic reactions, and the proportion of patient visits treated with epinephrine before and after ED presentation.

Table 1
Characteristics of patients who developed biphasic reactions (n = 71)

Characteristics	
Demographics	
Age (y), median (IQR)	6 (2.7–10.1)
Age range (y), n (%)	
<2	11 (15.5)
2–5	24 (33.8)
6–9	18 (25.4)
10–13	10 (14.1)
≥14	8 (11.3)
Boys, n (%)	51 (71.8)
Arrival status	
Arrival by ambulance, n (%)	20 (28.2)
Heart rate (beats/min), mean (SD)	117.4 (27.3)
Respiratory rate (breaths/min), mean (SD)	26.8 (7.7)
Systolic blood pressure (mmHg), mean (SD)	108.1 (13.5)
Diastolic blood pressure (mmHg), mean (SD)	61.7 (13.9)
SaO ₂ by oximetry, median (IQR)	99 (97–100)
Onset of biphasic reactions, n (%)^a	
Before ED discharge	53 (74.6)
After ED discharge	18 (25.4)
Time (h) from onset of initial reaction to onset of biphasic reaction, median (IQR)	
Before ED discharge	4.7 (3.3–6)
After ED discharge	18.5 (9.2–25.2)
Clinical manifestations of biphasic reactions, n (%)	
Cutaneous	59 (85.5)
Respiratory	28 (40)
Cardiac	21 (29.9)
Gastrointestinal	8 (11.3)
Treatment given in ED for biphasic reactions, n (%)	
Oxygen	7 (9.8)
Epinephrine	35 (49.3)
Inhaled β-agonists	13 (18.3)
H ₁ antihistamine	47 (66.2)
H ₂ antihistamine	16 (22.5)
Systemic steroids	27 (38)
Intravenous fluid	12 (16.9)
Magnesium sulfate infusion	1 (1.4)

Abbreviations: ED, emergency department; IQR, interquartile range; SaO₂, oxygen saturation.

^aIn relation to ED presentation for the initial anaphylactic reaction.

Characteristics of Biphasic Reactions

Biphasic reactions were noted in 71 of 484 anaphylactic reactions (14.7%). The characteristics of these reactions are presented in Table 1. The median age of this group was 6 years (interquartile range 2.7–10.1), and approximately 72% were boys. In 53 of 71 (74.6%) delayed reactions, the onset of reactions was before ED discharge at a median time of 4.7 hours (interquartile range 3.3–6) after the onset of the initial reaction. The rest occurred after discharge from the ED with a median time of 18.5 hours (interquartile range 9.2–25.2) after the onset of the initial reaction (Table 1). The main difference between early and late reactors was in the proportion treated with epinephrine for the initial reactions. Patients who developed biphasic reactions after ED discharge were less likely to be treated with epinephrine for their initial reactions compared with those who developed biphasic reactions before ED discharge (55.6% vs 84.9%, $P = .02$). Although 49 of the 71 (69%)

Table 3
Independent predictors of biphasic reaction as determined by stepwise logistic regression analysis for anaphylaxis episodes^a

Variable	β	P value	Odds ratio	95% CI
Age 6–9 y	1.28	.01	3.60	1.5–8.58
Delay in presentation to ED >90 min from onset of initial reaction	0.95	.001	2.58	1.47–4.53
Wide pulse pressure at triage ^b	1.07	<.001	2.92	1.69–5.04
Treatment of initial reaction with >1 dose of epinephrine	0.99	.03	2.70	1.12–6.55
Administration of inhaled β-agonists in ED	0.87	.01	2.39	1.24–4.62
Intercept	–3.36	<.001	0.04	

Abbreviations: CI, confidence interval; ED, emergency department.

^aModel developed for 481 patients without missing values (Hosmer-Lemeshow goodness-of-fit test 0.697, area under receiver operating characteristic curve 0.742, 95% CI 0.682–0.803).

^bDefined as diastolic blood pressure that is lower than or equal to half the systolic blood pressure.

delayed reactions involved respiratory and/or cardiovascular manifestations, only 35 (49%) were treated with epinephrine (Table 1). There were no fatalities in this anaphylaxis cohort.

Table 2 presents time interval comparisons between the biphasic and uniphasic groups. Compared with the uniphasic group, the median time from the reaction's onset to ED presentation was longer in the biphasic group (96 vs 75 minutes, $P = .03$). However, the median time from triage to physician assessment was shorter (13 vs 24 minutes, $P < .001$). Based on the Canadian Pediatric Triage and Acuity Scale, which ranks patient visits from 1 (resuscitation) to 5 (nonurgent), the time from triage to physician assessment reflects the acuity of the condition (the higher the acuity, the shorter the time).³⁵ Based on this scale, the median scales were 2 (emergent) and 3 (urgent) for biphasic and uniphasic reactors, respectively.

Variables Associated with Biphasic Reactions

eTable 1 presents a univariate association of demographic and historical variables with biphasic reactions. There was no difference in median age and sex between the biphasic and uniphasic groups; however, the proportion of patients 6 to 9 years old was larger in the biphasic group (25.5% vs 13.1%). The association of a biphasic reaction with variables from physical examinations is presented in eTable 2. Among all vital signs, wide pulse pressure at initial triage presentation was the only variable associated with the biphasic reaction ($P = .01$). Wide pulse pressure was defined according to the Pediatric Advanced Life Support guidelines as a diastolic blood pressure lower than or equal to half the systolic blood pressure.³⁶ No other clinical feature at the time of the initial anaphylactic reaction reliably distinguished uniphasic from biphasic reactors.

eTable 3 presents the association of therapeutic interventions given before and after arrival to the ED as treatments for the initial anaphylactic reaction (before developing delayed reaction). Overall, patients in the biphasic group received more treatment interventions compared with patients in the uniphasic group, which likely indicates the severity of the initial reaction. At the time of the initial anaphylaxis, patients in the biphasic group were more likely to have received epinephrine treatment (77.5% vs 61.5%, $P = .01$), to be treated with more than 1 dose of epinephrine (14.1% vs 6.5%, $P = .03$), and to receive intravenous fluid therapy in the ED (30% vs 7.3%, $P < .001$) compared with the uniphasic group. There were no significant differences between the 2 groups with respect to the time epinephrine was first administered. However, in a subgroup analysis of the 309 patients who received epinephrine treatment for their initial reaction, a time delay to epinephrine treatment longer than 90 minutes from the onset of the initial reaction was significantly associated with a biphasic reaction ($P = .01$).

Table 2
Comparison of intervals between biphasic and uniphasic episodes

Variable	Biphasic (n = 71)	Uniphasic (n = 413)	P value
Time (min) from onset of reaction to ED presentation, median (IQR)	96 (53–173)	72 (51–121)	.03
Time (min) from triage to physician assessment, median (IQR)	13 (9–28)	24 (14–48)	<.001
Length of ED stay (h), median (IQR)	5.9 (4.7–7.5)	4.5 (2.9–6)	<.001

Abbreviations: ED, emergency department; IQR, interquartile range.

There were no significant differences between the 2 groups in the proportion who received systemic steroids regardless of the total dose, formulation, or time to systemic steroids administered at the time of the initial anaphylactic reaction (eTable 3). Similarly, neither first- nor second-generation antihistamines showed a significant association with the biphasic reaction.

Predictors of Biphasic Reactions

The final regression model identified 5 independent predictors of biphasic reactions (Table 3). This model has a sensitivity of 95.8% (95% confidence interval 88.1–99.1%) and specificity of 19.5% (95% confidence interval 15.8–23.7%) in predicting biphasic reaction after an anaphylactic episode. The variable “intravenous fluid administration in the ED” was a confounder; therefore, it was removed from the included variables in the regression model.

Discussion

Main Findings

The present study examined children presenting to the ED with anaphylaxis and found the incidence of biphasic reaction in this population to be 14.7%. Approximately 75% of these reactions occurred within 6 hours of onset of the initial reaction. Almost half the delayed reactions were treated with epinephrine. In addition, the severity of the initial anaphylactic reactions, as reflected in the identified predictors, was associated with an increased risk of biphasic reaction. Overall, children who subsequently developed biphasic reactions had evidence of anaphylactic shock at ED presentation, required multiple doses of epinephrine, and required multiple other therapeutic interventions in the ED, including an inhaled bronchodilator, to treat their initial anaphylactic reaction.

Previous Studies

There is a wide range of the reported incidence of biphasic reactions from the previous literature, ranging from 3% to 23%.^{11,12,19–34} These studies vary considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), and definition and severity of anaphylaxis and biphasic reaction. These epidemiologic factors should be carefully considered when making data comparisons. The overall incidence of biphasic reaction of approximately 15% in the present study is not significantly different from previously reported pediatric studies (6% in the study by Lee and Greenes²⁵ and 11% in the study by Mehr et al²⁷). However, these studies looked at patients from more than 2 decades ago, a time after which there has been a documented increase in the rate of pediatric anaphylaxis.^{4–7} The reported incidences from previous ED studies of adult or mixed pediatric and adult populations are similar to the present estimated incidence.^{19,20,22,32,37}

Little is known of the nature and pathophysiology of the biphasic reaction.³⁸ The association of a biphasic reaction with the severity of the initial reaction has just recently emerged as a potential risk factor.³⁹ In 1992, Sampson et al¹² reported on a series of 13 children with anaphylaxis, of which 3 cases proved fatal. Then, in 1994, Douglas et al¹¹ reported on a series of 4 adult patients with biphasic reactions, 2 of whom presented initially with hypotension. Subsequently, studies by Smit et al³² and several others reported similar findings.^{23,34} Although these studies provide some insight about this association, the reported cases are too small to reliably predict this association. Also, the definition of severity used in these studies is inconsistent and not based on objective scoring. Nevertheless, to date, the most robust report documenting this association by incorporating immunologic mediators and clinical severity scoring was recently published by Brown et al.³⁷ In their prospective cohort study of adults with anaphylaxis, a biphasic reaction

was associated with the severity of the initial reaction (particularly hypotension). They hypothesized that a biphasic reaction is the result of a protracted inflammatory response.³⁷ The predictors identified in the present report strongly support this association. The authors found that children with biphasic reactions had a higher triage acuity score, had manifestation of anaphylactic shock with wide pulse pressure, needed multiple epinephrine treatments for their initial reaction, and had significant respiratory distress that required treatment with inhaled β -agonists compared with those with uniphasic reactions.

Although several studies looking at adult patients have reported asthma as a risk factor for fatal anaphylaxis and delayed reaction,^{21,30,37,40} the authors found, as did previous pediatric studies, no association between asthma and biphasic reactions.^{24,25,27,41} It also should be noted that treatment with inhaled β -agonists is not a proxy for asthma, because wheezing and lower airway symptoms causing respiratory distress also have been found to manifest in children and adults with anaphylaxis without underlying asthma.^{37,42}

The other major factor associated with a biphasic reaction is delayed epinephrine treatment for the initial reaction or delayed ED presentation. The present study showed that delayed presentation to the ED is a risk factor for biphasic reaction, which is consistent with previous studies.^{12,25,26,29,32} In addition, recent studies investigating the role of platelet-activating factor (PAF) in human anaphylaxis have indicated that serum PAF levels are significantly increased and correlate directly with the severity of anaphylaxis.^{37,43} This mediator peaks at 60 to 90 minutes from the onset of the reaction.⁴⁴ Using human vascular smooth muscle cells, Vadas and Perelman⁴⁵ examined the effect of the timing of epinephrine addition on the action of PAF and found that epinephrine was most effective when administered before stimulation with PAF but was progressively less effective with time after PAF stimulation. Furthermore, Ellis and Day²² found that early treatment of the initial anaphylactic reactions with epinephrine was associated with a lower risk of developing biphasic reactions. Fleming et al⁴⁶ found that children with food-induced anaphylaxis who received epinephrine before arrival to the ED were less likely to be hospitalized (17% vs 43%, $P < .001$) or to require antihistamines, corticosteroids, or inhaled β -agonists compared with those who received epinephrine in the ED. Therefore, the present subgroup analysis and cumulative evidence from previous laboratory and clinical reports indicate that epinephrine treatment is a time-sensitive intervention and should be administered promptly after the onset of an allergic reaction.

Strengths and Limitations

To the authors' knowledge, this is the largest cohort of patients with biphasic reaction in the literature. The authors used a standard definition for anaphylaxis and biphasic reaction and identified predictors that are clinically sensible. Furthermore, the present data provide a clear description of the time of onset and nature of pediatric biphasic reactions.

Nevertheless, this is a retrospective study and inherently subject to several limitations. Because of the study design, the authors cannot confidently eliminate the possibility of loss to follow-up. Some patients could have developed biphasic reactions after ED discharge but did not return to the ED. This could have resulted in an underestimation of the actual biphasic reaction rate. They also did not account for potential anaphylaxis triggers. A recent study from Germany reported that 18% of children have aggravating factors for their anaphylaxis, such as coexisting infection, psychological stress, and menses.⁴⁷ These triggers are believed to increase the inflammatory response.^{1,48,49} However, it is not clear whether these factors increase the risk of severe anaphylaxis and, ultimately,

of biphasic reactions. A prospective study design and data collection is an ideal research method to overcome these limitations in the future.

Although multiple anaphylaxis severity scores exist in the literature, these scores are not well validated in the pediatric population. In addition, most of these scores consist of subjective indicators. Applying any of those scores to these retrospectively collected data could result in differential misclassification and measurement error.

Future Implications

Children with severe initial reactions appear more likely to develop biphasic reactions and, in particular, could benefit from a prolonged period of observation. This period should be individualized and based primarily on the degree of severity of the initial anaphylactic reaction. In addition, children who present to the ED with seemingly mild anaphylaxis manifestations might need prolonged monitoring if epinephrine treatment is not administered or is delayed. Given the relatively high sensitivity of the present predictors, children with mild anaphylaxis who do not match any of these predictors could be considered for early disposition from the ED (<6 hours timed from the onset of the anaphylactic reaction) as long as an appropriate counseling has been provided. The authors believe there is a need for large-scale prospective pediatric studies to validate these predictors and clarify the link between severity of initial anaphylaxis and the subsequent development of biphasic reactions. These studies could use the present predictors to develop a simple objective severity score that can be implemented into the clinical practice of emergency physicians. In addition, the authors have no clear clinical explanation for the susceptibility of 6- to 9-year-old children to biphasic reactions. Therefore, the underlying biological mechanism behind this association needs to be explored by future research.

The effect of steroids in the treatment of severe anaphylaxis or prevention of biphasic reactions has never been proved.^{50–53} The present findings concurred with several reports from the literature about the lack of efficacy of systemic steroids in preventing biphasic reactions.^{11,19,23–26,29–31,33} Although the findings from the recent trial by de Silva et al⁵⁴ raise concerns about the safety of steroids in preventing anaphylaxis, more robust evidence from a prospective randomized clinical trial is needed to specifically address the safety and efficacy of systemic steroids in preventing biphasic reactions in children.

In conclusion, biphasic reactions are relatively common in children with anaphylaxis and seem to be associated with the severity of the initial anaphylactic reactions. The authors identified 5 clinical predictors that could be used to identify patients who would benefit from prolonged ED monitoring and enable better use of ED resources. However, physicians should be cautious applying these clinical prediction rules before their validation in a large prospective study.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.05.013>.

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eTable 1

Univariate correlation with biphasic reaction for variables from history for 484 anaphylaxis episodes

Characteristics	Biphasic (n = 71)	Uniphasic (n = 413)	P value
Demographics			
Age (y), median (IQR)	6 (2.7–10.1)	4.7 (1.9–11.2)	.40
Age range (y), n (%)			.03
<2	11 (15.5)	107 (25.9)	
2–5	24 (33.8)	128 (31)	
6–9	18 (25.4)	54 (13.1)	
10–13	10 (14.1)	54 (13.1)	
≥14	8 (11.3)	70 (16.9)	
Boys, n (%)	51 (71.8)	263 (63.7)	.23
Allergy history, n (%)			
Food	49 (69)	244 (59.1)	.11
Environmental	9 (12.7)	63 (15.3)	.72
Drugs	6 (8.5)	38 (9.2)	1
Medical history, n (%)			
Carry epinephrine auto-injector	39 (54.9)	197 (47.7)	.30
Anaphylactic reaction	24 (33.8)	132 (32)	.78
Biphasic allergic reaction	2 (2.8)	11 (2.7)	.50
Asthma	32 (45.1)	178 (43.1)	.88
Atopic dermatitis	29 (40.8)	158 (38.3)	.69
Allergic rhinitis	3 (4.2)	20 (4.8)	.63
Causative agents of current anaphylactic episode, n (%)			
Food (total)	47 (66.2)	291 (70.5)	.49
Peanut	18 (25.4)	113 (27.4)	.77
Tree nut	12 (16.9)	70 (16.9)	1
Milk	5 (7)	22 (5.3)	.57
Egg	5 (7)	23 (5.6)	.58
Seafood	4 (5.6)	22 (5.3)	1
Drugs and medications	3 (4.2)	8 (1.9)	.21
Exercise	1 (1.4)	8 (1.9)	1
Bee sting	1 (1.4)	7 (1.7)	1
Unspecified	15 (21.1)	67 (16.2)	.31
Settings of current anaphylactic episode, n (%)			
Home	50 (70.4)	281 (68)	.78
Restaurant	5 (7)	44 (10.7)	.52
Outdoor	2 (2.8)	29 (7)	.29
School/daycare	10 (14.1)	31 (7.2)	.17
Unspecified	4 (5.6)	28 (6.8)	1

Abbreviation: IQR, interquartile range.

eTable 2

Univariate correlation with biphasic reaction for variables from physical examination for 484 anaphylaxis episodes

Variable	Biphasic (n = 71)	Uniphasic (n = 413)	P value
Triage vital signs, n (%)			
Tachycardia ^a	25 (35.2)	124 (30.2)	.39
Tachypnea ^b	15 (21.1)	81 (19.6)	.77
Hypotension ^c	1 (1.4)	3 (0.8)	.49
Wide pulse pressure ^d	32 (46)	112 (29.5)	.01
Oxygen saturation <95%	2 (3)	8 (2)	.65
Clinical manifestations, n (%)			
Cutaneous	69 (97.2)	402 (97.3)	1
Respiratory	64 (90.1)	343 (83.1)	.16
Cardiac	25 (35.2)	149 (36.1)	.73
Gastrointestinal	33 (46.5)	185 (44.8)	.79
Number of systems involved, n (%)			
2	36 (50.7)	211 (51.1)	.15
3	24 (33.8)	158 (38.3)	
4	11 (15.5)	44 (10.6)	

^aDefined according to Pediatric Advanced Life Support guidelines³⁶: awake heart rate >190 beats/min for 3 months to 2 years of age, >140 beats/min for 3 to 10 years, and >100 beats/min for older than 10 years.

^bDefined according to Pediatric Advanced Life Support guidelines³⁶: respiratory rate >60 breaths/min for younger than 1 year, >40 breaths/min for 1 to 3 years, >34 breaths/min for 4 to 5 years, >30 breaths/min for 6 to 12 years, and >16 breaths/min for 13 to 18 years.

^cDefined according to Pediatric Advanced Life Support guidelines³⁶: systolic blood pressure <70 mmHg for 1 to 12 months of age, <70 mmHg + (age in years × 2) for 1 to 10 years, and <90 mmHg for older than 10 years.

^dDefined as a diastolic blood pressure lower than or equal to half the systolic blood pressure.³⁶

eTable 3Univariate correlation with biphasic reaction for variables from therapy administered for 484 anaphylaxis episodes^a

Variable	Biphasic (n = 71)	Uniphasic (n = 413)	P value
Oxygen in ED, n (%)	8 (11.3)	17 (4.1)	.02
Bag mask ventilation/oral airway, n (%)	2 (1.4)	0	1
Intubation, n (%)	1 (0.2)	0	1
Epinephrine			
Administered, n (%)	55 (77.5)	254 (61.5)	.01
Number of doses, mean (SD) ^b	1.13 (0.34)	1.10 (0.34)	.56
>1 dose administered, n (%)	10 (14.1)	27 (6.5)	.03
Total dose administered (mg), median (IQR)	0.25 (0.15–0.3)	0.20 (0.15–0.3)	.01
Route of administration, n (%)			
Intramuscular	54 (98)	247 (97)	1
Subcutaneous	1 (2)	7 (3)	
Setting of first administered dose, n (%)			
Scene of reaction by caregiver	24 (43.6)	105 (41.3)	.79
During transport by EMS paramedics	5 (9.1)	18 (7.1)	
ED	26 (47.3)	131 (51.6)	
Time (min) from onset of reaction to first dose, median (IQR)	64 (25–175)	59 (25–105)	.35
Inhaled β -agonists in ED, n (%)	23 (32.4)	78 (18.8)	.02
H ₁ antihistamine			
Administered, n (%)	59 (83.1)	337 (81.6)	.87
Total dose administered (mg/kg), mean (SD)	0.80 (0.47)	0.78 (0.51)	.76
H ₂ antihistamine in ED			
Administered, n (%)	14 (19.7)	67 (16.2)	.49
Total dose administered (mg/kg), mean (SD)	1.7 (0.9)	2 (1.2)	.48
Time (min) from onset of reaction to first dose, median (IQR)	126 (99–184)	120 (79–180)	.51
Systemic steroids in ED			
Administered, n (%)	43 (60.6)	209 (50.6)	.13
Total dose administered (mg/kg), median (IQR) ^c	1.55 (1–2.2)	1.85 (1–2.2)	.99
Time (min) from onset of reaction to first dose, median (IQR)	120 (87–256)	125 (85–205)	.93
Formulation, n (%)			
Dexamethasone	18 (41.9)	114 (54.5)	.30
Hydrocortisone	4 (9.3)	17 (8.1)	
Methylprednisolone	9 (20.9)	24 (11.5)	
Prednisolone	12 (27.9)	54 (25.8)	
Intravenous fluid in ED			
Administered, n (%)	21 (30)	30 (7.3)	<.001
Total dose administered (mL/kg), median (IQR)	18.8 (14.4–20)	12.6 (6.4–20)	.11

Abbreviations: ED, emergency department; EMS, emergency medical services; IQR, interquartile range.

^aTherapies administered for initial anaphylactic reaction.^bSD of mean.^cAll steroid doses converted to prednisolone equivalent dose (1 mg of dexamethasone = 6.67 mg prednisolone; 1 mg of methylprednisolone = 1.25 mg f prednisolone; 1 mg f hydrocortisone = 0.25 mg of prednisolone).