
Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients

Anne K. Ellis, MD, FRCPC, and James H. Day, MD, FRCPC

Background: Although it is known that anaphylaxis can follow a biphasic course, reports of its incidence are conflicting. Furthermore, little is known about predictors of biphasic reactivity.

Objective: To describe the incidence and characteristics of biphasic anaphylaxis occurring in a Canadian tertiary care center.

Methods: All patients with emergency department visits and inpatients given a diagnosis of “allergic reaction” or “anaphylaxis” during a 3-year period were evaluated. Patients were contacted within 72 hours to establish symptoms and determine the presence of biphasic reactivity. A full medical record review ensued, and uniphasic and biphasic cases were compared using the Mann-Whitney *U* test for continuous data and the χ^2 and Fisher exact tests for ordinal data.

Results: A total of 134 patients with anaphylaxis were identified; complete follow-up was obtained for 103 patients. Twenty patients (19.4%) experienced confirmed biphasic reactivity. Average time to onset of the second phase was 10 hours (range, 2–38 hours); 8 patients (40.0%) had their second phase occur more than 10 hours after the initial reaction. The clinical presentations and histories of uniphasic and biphasic reactors were similar. Time to resolution of initial symptoms was significantly longer for biphasic reactors (112 vs 133 minutes; $P = .03$). Differences in management were noted: biphasic reactors received less epinephrine ($P = .048$) and tended to receive less corticosteroid ($P = .06$).

Conclusions: Biphasic reactivity occurred with an incidence of 19.4%, consistent with first descriptions. The second-phase onset was 10 hours on average, but it occurred as late as 38 hours. Biphasic anaphylaxis may be related, in part, to undertreatment.

Ann Allergy Asthma Immunol. 2007;98:64–69.

INTRODUCTION

Anaphylaxis is the clinical syndrome representing a life-threatening systemic allergic reaction. It results from immunologically induced mast cell and basophil mediator release after exposure to a specific antigen in previously sensitized persons.¹ A recent epidemiologic review² indicated that anaphylaxis occurs in 1.2% to 15% of the US population.

Variants of the usual monophasic anaphylaxis syndrome include late-onset anaphylaxis, biphasic anaphylaxis, and protracted anaphylaxis.³ Although biphasic reactions are a recognized complication, many reviews on the topic of anaphylaxis do not mention the potential for a second phase of reactivity^{4–6} or significantly downplay the possibility.⁷ Recognition of, and interest in the biphasic anaphylactic reaction is increasing, as evidenced by a recent comprehensive review by Lieberman.⁸ The incidence rate of biphasic reactions is variably reported as 1%,⁸ 2%,⁹ 5%,¹⁰ 6%,¹¹ 18%,¹² 20%,³ and 23%,¹³ with the number of cases in each of these reports ranging from 13 to 113, probably accounting for the variability. Retrospective series also tend to yield lower incidence rates owing to problems with recall bias and missed cases, whereas higher incidence rates arise from prospective evaluations.

Because the initial study by Stark and Sullivan³ described asymptomatic windows of 1 to 8 hours, this is the time frame often quoted in the medical literature, with some researchers reporting a smaller window of 1 to 3 hours^{14,15} based on another evaluation.¹³ However, a case report was published in 1997 of a patient from Kingston, Ontario, whose second phase of anaphylactic reactivity occurred almost 25 hours after the initial onset of symptoms.¹⁶ Subsequently, 2 other case series have been published documenting the onset of second-phase reactivity after asymptomatic windows of 23,¹² 28,¹¹ and 29¹² hours.

No consistent clinical features have yet been identified to be predictive of a second phase. One study¹¹ found that patients with biphasic reactions had a significantly longer median time to administration of the initial epinephrine dose. Other studies concluded that the amount of epinephrine required to stabilize initial symptoms,¹² oral route of antigen exposure,³ and a slower onset of initial symptoms³ were predictors. It is difficult to draw conclusions from the various case series that have been published to date, particularly regarding the paucity of prospective evaluations, with the likely effect of underestimating the true incidence of biphasic reactivity.

The objective of this study was to prospectively evaluate cases of anaphylaxis seen in Kingston during a 3-year period. Referrals were received from the emergency departments (EDs) at Kingston General Hospital and Hotel Dieu Hospital and from inpatient services in Kingston General Hospital.

Division of Allergy and Immunology, Queen's University, Kingston, Ontario.

Received for publication March 20, 2006.

Accepted for publication in revised form August 1, 2006.

The goal was to determine the incidence, predictors, and characteristics of biphasic anaphylactic reactions.

METHODS

This study was reviewed and approved by the Queen's University and Affiliated Teaching Hospitals Health Sciences Human Research Ethics Board. All the participants gave verbal informed consent to participate. All the patient medical records from the ED with discharge diagnoses of "allergic reaction," "anaphylaxis," or any other phrase containing the word "allergy" (eg, drug allergy and food allergy) were forwarded within 24 hours to the principal investigator (A.K.E.) for review. Patients were contacted no later than 72 hours after the ED visit, and usually within less than 48 hours, to document exact symptoms, to determine whether diagnostic criteria for anaphylaxis were met, and to determine whether a biphasic reaction had occurred. Medical records were then evaluated to document physical findings (eg, visible urticaria, angioedema, decreased saturation of oxygen, and hypotension), to confirm the diagnosis, and to determine management details. The exact timing of onset and resolution of symptoms was noted through careful corroboration of ED documentation and patient interview. The "starting time" of the reaction was defined as the time of symptom onset, and the "resolution time" was defined as the time at which either the patient identified no ongoing or persistent symptoms or the treating nurses and physicians documented absent signs and symptoms. Inpatients with anaphylaxis underwent a similar review. Etiology was determined as best as possible by history; if a clear causality could not be established, the suspected antigen was classified as "unknown." If a patient had an established history of recurrent idiopathic episodes, they were classified as "idiopathic."

For this study, *anaphylaxis* was defined as per the Canadian Pediatric Surveillance Program¹⁷ as "a severe allergic reaction to any stimulus, having sudden onset and generally lasting less than 24 hours; a disorder involving at least two body systems, with multiple symptoms such as hives, flushing, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhea or shock." For a reaction to be labeled "biphasic," the second-phase reaction had to meet this same definition. Recurrence of urticaria or another rash alone was insufficient to qualify as a biphasic reaction.

Uniphasic and biphasic cases were compared regarding patient age, time to onset of symptoms, history of anaphylaxis or asthma, clinical features, management, and time to resolution of symptoms (the Mann-Whitney *U* test was used for continuous data and the Pearson χ^2 and Fisher exact tests were used for ordinal data as appropriate). Statistical analyses were completed using a software program (SPSS for Windows version 11.0; SPSS Inc, Chicago, IL).

RESULTS

A total of 134 patients with anaphylaxis were identified during a 3-year period (1999–2001). Follow-up data were successfully obtained for 103 patients. The median age of all

the patients with anaphylaxis was 33 years (range, 11 months to 79 years). Of the 103 patients with available follow-up data, 20 were biphasic (19.4%). The median age of biphasic reactors was 25 years (range, 4–73 years), compared with 35 years (range, 1.3–79 years) for uniphasic reactors ($P = .09$). Medical record review comparing patients lost to follow-up with those with complete follow-up did not reveal any ostensible differences.

A variety of antigens led to biphasic reactions, the most common being foods (35.0%) and Hymenoptera venom (25.0%). The occurrence rates of inciting antigens were not significantly different between uniphasic and biphasic reactions ($P > .25$). A detailed listing of responsible antigens is provided in Table 1.

The average time to onset of the second phase of reactivity was 10 hours (range, 2–38 hours). Eight (40.0%) of the reactions occurred more than 10 hours after the first reaction. Clinical presentations of the uniphasic and biphasic reactions were similar, with no significant differences in the expression of various manifestations. The time to onset of initial symptoms was not different ($P = .90$), and neither was the history of anaphylaxis or asthma ($P = .33$). Biphasic reactors, however, took significantly longer to achieve resolution of their initial symptoms than uniphasic reactors (133 vs 112 minutes; $P = .03$). In terms of patient management, there were no significant differences in the use of H_1 or H_2 antihistamines or β -agonists. However, biphasic reactors were administered less epinephrine ($P = .048$). In addition, there were trends toward a lower rate of corticosteroid use ($P = .07$), and the corticosteroid dose tended to be lower in those having biphasic reactions ($P = .06$). A summary of comparisons between uniphasic and biphasic reactors, including management, is given in Table 2.

Most biphasic reactions (55%) were clinically similar to the original presentation. Although many were milder (35%), a sizable proportion of second-phase reactions (40%) involved life-threatening manifestations (eg, hypotension, throat or tongue swelling; usually these symptoms were also present in the first-phase reaction), and 20% required more aggressive therapy than the original reaction to provide symptomatic control. Of interest, urticaria occurred in all second phases but not necessarily in the first phase. Details of the manifestations and management strategies of the biphasic reactions are summarized in Table 3.

A potentially useful clinical application of these data would be to identify patients prone to develop biphasic reactivity with the second phase beyond the expected 1- to 8-hour window. Thus, a secondary analysis was performed with just biphasic reactors whose second phase occurred at least 9 hours after initial resolution of symptoms. The only factor found to predict this late recurrence was an even longer time to resolution of initial symptoms, as the late biphasic reactors took 193 minutes, on average, to respond fully to treatment

Table 1. Antigens Responsible for Anaphylactic Reactions*

Antigen	Overall (N = 134)	Uniphasic (n = 83)	Biphasic (n = 20)	P value
Foods				
Nuts/peanuts	22 (16.4)	16 (19.3)	4 (20.0)	
Peanut	11 (8.2)	9 (10.8)	2 (10.0)	
Other nuts	11 (8.2)	7 (8.4)	2 (10.0)	
Seafood	12 (9.0)	6 (7.2)	1 (5.0)	
Milk	3 (2.2)	2 (2.4)	0	
Other	8 (6.0)	3 (3.6)	2 (10.0)	
Subtotal	51 (38.1)	29 (34.9)	7 (35.0)	>.99
Hymenoptera	30 (22.4)	18 (21.7)	5 (25.0)	.77
Medication				
Penicillin derivatives	3 (2.2)	1 (1.2)	1 (5.0)	
Other antibiotics	4 (3.0)	4 (4.8)	0	
NSAIDs	5 (3.7)	4 (4.8)	0	
Immunotherapy	4 (3.0)	1 (1.2)	1 (1.2)	
Other medications	6 (4.5)	5 (6.0)	0	
Subtotal	22 (16.4)	15 (18.1)	2 (10.0)	.52
Unknown/idiopathic history				
Unknown	19 (14.2)	12 (14.5)	5 (25.0)	
Idiopathic history	7 (5.2)	6 (7.2)	1 (5.0)	
Subtotal	26 (19.4)	18 (21.7)	6 (30.0)	.38
Miscellaneous (including latex)	5 (3.7)	3 (3.6)	0	>.99

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

* Data are given as number (percentage).

Table 2. Summary of Uniphasic and Biphasic Comparisons

Comparator	Uniphasic (n = 83)	Biphasic (n = 20)	P value
Age, median, y	35	25	.09
Pediatric cases (<13 y), No. (%)	7 (8.4)	3 (15.0)	.40
Females, No. (%)	39 (47.0)	9 (45.0)	.81
History of anaphylaxis, No. (%)	39 (47.0)	7 (35.0)	.56
History of asthma, No. (%)	30 (36.1)	8 (40.0)	.90
Time to onset of symptoms, median, min	15	15	.90
β -Agonist used, No. (%)	23 (27.7)	2 (10.0)	.15
Total dose, average, mg nebulized	9	7.5	.10
Epinephrine used, No. (%)	68 (81.9)	11 (55.0)	.13
Total dose, median, mg	0.39/0.32*	0.30/0.21*	.048†
H ₁ antagonist used, No. (%)	79 (95.2)	19 (95.0)	>.99
H ₂ antagonist used, No. (%)	25 (30.1)	4 (20.0)	.42
Corticosteroid used, No. (%)	46 (55.4)	7 (35.0)	.07
Prednisone equivalent dose, average	113/63*	101/31*	.06
Time to resolution, min	112	133	.03†

* Value among patients who actually received the drug/overall value.

† Significant difference between groups.

compared with 112 minutes for uniphasic reactors ($P = .006$).

Conversely, an equally useful application would be to predict which patients will not have a biphasic reaction. Analysis of the resolution time data revealed that no biphasic reactions occurred if patients responded completely to treatment in less than a half hour (specifically, the resolution times documented were 10, 15, or 20 minutes). Of similar interest and importance is that all the patients meeting this cutoff time for symptom resolution ($n = 14$)

received epinephrine for treatment of their anaphylactic reactions. These “short resolvers” were more likely to have had a history of anaphylaxis than biphasic reactors (57% vs 26%) and were slightly younger (median age, 22 years) than the biphasic group (median age, 25 years); these differences were not statistically significant. The higher rate of epinephrine use (100% vs 73%) was, however, statistically significant ($P = .03$). Patients with short resolution times differed from other uniphasic reactors in their younger age (median, 22 vs 35 years; $P = .03$).

Table 3. Profile of Biphasic Anaphylactic Reactions

Patient age, y/sex	Antigen	Biphasic manifestations	Severity of second reaction*	Time to second phase, h	Management of second phase	Management location
24/F	Unknown	SOB, wheeze, rash, urticaria, angioedema, tongue and throat swelling	Similar	20	EPI, H1A, CS	ED
16/F	Unknown	Tachycardia, SOB, rash, urticaria, angioedema, hoarseness, pruritus	Similar	10	EPI, H1A, H2A, CS, IVF	ED, subsequent admission
4/F	Hymenoptera	Tachycardia, rash, urticaria, angioedema	Similar	4	EPI, H1A, CS	ED, subsequent admission
32/M	Hymenoptera	Rash, urticaria, light-headed, pruritus	Milder	12.5	H1A	Home (self-treated)
47/M	Peach	SOB, urticaria, angioedema, mouth and throat swelling, pruritus	Similar to more severe	2	EPI, H1A	ED
24/M	Hymenoptera	SOB, urticaria, pruritus	Similar	3	EPI, CS, H2A, IVF	ED
73/M	Penicillin	SOB, wheeze, hypotension, rash, urticaria, pruritus	Similar	38	EPI, BD, CS	Inpatient
47/M	Shrimp	Rash, urticaria, angioedema, abdominal pain, pruritus	Similar	2.5	EPI, H1A	ED
18/F	Peanut	Tachycardia, wheeze, rash, urticaria, angioedema, pruritus	Similar to more severe	21	EPI, H1A, H2A, CS, BD, IVF	ED
31/F	Unknown	Urticaria, angioedema, throat swelling, pruritus	Milder	8	H1A	ED
4/M	Hymenoptera	Tachycardia, urticaria, angioedema, tongue and throat swelling, light-headed, N/V	More severe	5	CS, H1A	ED, subsequent admission
13/M	Unknown	Rash, urticaria, mouth and throat swelling, pruritus	Milder	12	CS	ED
19/M	Unknown	Tachycardia, SOB, rash, urticaria, mouth and throat swelling, N/V, abdominal pain, diarrhea, pruritus	More severe	3	EPI, H1A, H2A, CS, IVF	ED, subsequent admission
36/M	Nuts	SOB, wheeze, rash, mouth swelling, pruritus	Milder	2	H1A	ED
25/F	Tangerine	SOB, rash, urticaria, angioedema, throat swelling, pruritus	Similar	22	H1A	ED
38/F	Nuts	Angioedema, throat swelling, hoarseness, paresthesia, pruritus	Similar	6	H1A	Family physician's office
36/M	Idiopathic history	SOB, rash, urticaria, angioedema, pruritus	Milder	9	EPI, H1A, H2A, CS	ED
55/F	Hymenoptera	SOB, rash, urticaria, angioedema, paresthesia, pruritus	Milder	10	EPI, H2A, CS, IVF	ED
19/F	Immunotherapy	SOB, rash, urticaria, angioedema, pruritus	Milder	1.5	H1A	Home (self-treated)
7/M	Unknown	Rash, urticaria, angioedema, paresthesia, pruritus	Similar	9.5	CS	ED

Abbreviations: BD, bronchodilators; CS, corticosteroids; ED, emergency department; EPI, epinephrine; H1A, H₁ antagonist; H2A, H₂ antagonist; IVF, intravenous fluids; LOC, level of consciousness; N/V, nausea/vomiting; SOB, shortness of breath.

*Definitions: milder: symptoms/signs were fewer or not as bothersome to the patient; similar: symptoms/signs were closely approximated to the original reaction; similar to more severe: symptoms/signs were similar in nature (eg, angioedema occurred in both reactions) but were either more impressive to the patient or were treated more aggressively by the ED physician; and more severe: symptoms/signs were increased in severity and number (ie, new symptoms occurred that were not part of the original symptom complex and were life-threatening, eg, tongue and throat swelling).

DISCUSSION

Stark and Sullivan³ first described the entity of biphasic anaphylaxis in detail in a prospective study of 25 anaphylactic patients in which biphasic reactions occurred at a rate of 20%. Subsequent studies, mainly retrospective, have gener-

ated a wide range of incidences (2%–23%).^{8–13,18–20} In the present prospective study, biphasic anaphylaxis occurred at a rate of 19.4%, which is consistent with the initial study by Stark and Sullivan, and subsequent published prospective studies,¹² suggesting that retrospective evaluations may un-

derestimate the true prevalence of this entity. In this study, on average, the second phase of symptoms occurred after an asymptomatic window of 10 hours, which is longer than the frequently quoted window of 1 to 3 or 1 to 8 hours.^{3,13} In addition, the second phase was delayed beyond 10 hours in 40% of patients and beyond 20 hours in 20%. This supports findings from another study¹² that documented the onset of secondary features to be after 20 hours in one third of biphasic reactions. The possibility of a prolonged onset to the second phase was recently highlighted in a review of biphasic anaphylactic reactions by Lieberman.⁸

That second-phase reactivity was shown to occur much later than previously thought has significant implications for the clinical management of patients. Many EDs tend to observe patients after resolution of anaphylactic reactivity for no more than 2 to 6 hours. Indeed, the average duration of ED observation time in the present evaluation was 3.8 hours. The findings from this study suggest that patients treated for anaphylaxis should be monitored for 24 hours or longer. This could be accomplished either via ongoing care in the ED or, given the current constraints and overcrowding in most urban EDs, discharge into an environment with adequate supervision, easy access to emergency medical response systems, and available autoinjectable epinephrine.

Biphasic reactors in this study took significantly longer to achieve resolution of their initial symptoms. This variable has not been investigated previously, to our knowledge. Indeed, time to resolution was positively correlated with time to onset of the second phase, ie, the longer it took to achieve resolution of symptoms, the longer the asymptomatic interval if a second-phase reaction occurred. Also, patients who developed second-phase reactivity received less epinephrine and had less corticosteroid therapy (a possible explanation for the longer time to achieve symptom resolution). This presents an interesting contrast to the findings of Brazil and MacNamara,¹² who, in a short evaluation of biphasic anaphylaxis (6 patients), found that these patients required more epinephrine to ameliorate their initial symptoms than those having only uniphasic reactions. This may, in fact, represent a similarity in the biphasic population in that if some of our patients had been treated more aggressively with increased doses of epinephrine, time to resolution would not have been so protracted. The study by Lee et al¹¹ of pediatric biphasic reactions demonstrated an association between delay in administration of epinephrine and the presence of biphasic reactivity. This, too, is in keeping with the association between biphasic reactivity and undertreatment with epinephrine. In particular, this fits with the finding of the protective effect of rapid resolution of symptoms after treatment with epinephrine in the present study.

Corticosteroids are given to prevent or minimize biphasic and protracted reactions; this study presents data to partially support this rationale, because fewer biphasic reactors received corticosteroids (35% vs 55%), and, when treated, lower doses (31 vs 63 prednisone equivalents) were prescribed. Nevertheless, 7 (35%) of 20 biphasic reactions oc-

curred despite the administration of corticosteroids. The aforementioned findings of lower epinephrine dosages and decreased corticosteroid use in biphasic reactors vs uniphasic reactors raises the possibility that biphasic reactivity may be partly related to symptomatic breakthrough of medication coverage as a result of undertreatment of the first episode.

The converse of the finding that a longer time to resolution predicted an increased risk of biphasic reactivity would be that a shorter time to resolution may predict an absent second-phase response. This is suggested by the data in that the incidence of biphasic reactivity was 0% in patients who responded to treatment in less than (but not equal to) a half hour. All of these patients received epinephrine in their management strategy, underscoring the importance of this lifesaving therapy not only to produce prompt resolution of symptoms but perhaps also to prevent recurrence of reactivity. No single time to resolution of symptoms universally predicted the occurrence of a second phase.

In terms of the clinical presentation of biphasic vs uniphasic anaphylaxis, the features were similar, with no statistically significant differences in the incidence rates of the various manifestations. Thus, the reason for these patients receiving, on average, less epinephrine is unclear beyond the treating physician's discretion, although one possibility may be that there was a slightly higher incidence of biphasic reactivity among pediatric patients in this study, some of whom received lesser doses. There was no significant difference in the rate of β -agonist use between uniphasic and biphasic reactors. Neither were there any differences in causation, ie, uniphasic and biphasic reactions occurred as frequently in response to Hymenoptera stings and other nonoral allergens. Because foods and medications accounted for only 45% of the biphasic reactions, biphasic reactivity cannot be attributed to secondary absorption of antigen alone.

Most biphasic reactions were clinically similar to the original presentation. Although many were milder, a considerable proportion of second-phase reactions (40%) involved life-threatening manifestations, eg, hypotension or throat and tongue swelling (usually also present in the first-phase reaction), and 20% required more aggressive therapy than the original reaction to control symptoms. Urticaria was a universal manifestation in the second-phase reactions, although not always occurring in the first phase (Table 3).

A potential diagnostic possibility in patients who experience their biphasic reactions more than 20 hours after the initial event is antigen reexposure rather than true biphasic reactivity. In this study, cases were carefully reviewed to exclude this possibility. One patient, in whom the second-phase onset time was 38 hours, experienced anaphylactic reactivity to intravenous penicillin G, followed by no further doses of this medication. Two other cases of late-onset second-phase reactions were due to foods, raising the possibility of secondary reabsorption of antigen, but this is unlikely given the delayed time frame (ie, secondary absorption would have to have occurred approximately 20 hours or more after initial ingestion). In the final case of very-late-onset recur-

rence, no identifiable cause was found, so a repeated exposure cannot be fully excluded. She was observed in the ED for 7 hours, discharged to her mother's care, did not return to the environment of her original reaction, and had not consumed any foods or medications afterward aside from the antihistamine and prednisone prescribed by the ED physician within the hour before the recurrence of symptoms. Protracted anaphylaxis, where symptoms persisted beyond 24 hours despite aggressive therapy, did not occur in this series, and neither were there any fatalities.

In conclusion, biphasic anaphylaxis is a well-recognized clinical entity, but conflicting reports exist of its true incidence, characteristics, and predictors. This study showed that biphasic reactivity, which was independent of inciting antigen, occurred in almost 20% of anaphylactic reactions. The onset of the second phase of symptoms was longer than the generally accepted time of 1 to 8 hours, at an average asymptomatic interval of 10 hours, with a sizable portion experiencing their second phase considerably later (ie, >20 hours). Those who developed a second phase were somewhat longer in achieving resolution of initial symptoms, particularly when the second phase was very late. Those who achieved early resolution of symptoms within half an hour of onset consistently received epinephrine, which seemed to protect against the onset of biphasic reactivity. Based on these findings and on differences noted in management, the occurrence of biphasic anaphylaxis may be related in part to undertreatment of the initial presentation with epinephrine and corticosteroids.

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Requests for reprints should be addressed to:
 Anne K. Ellis, MD
 c/o Division of Allergy and Immunology
 McMaster University
 1200 Main St W
 HSC 3V48
 Hamilton, Ontario, Canada L8N 3Z5
 E-mail: ellis.anne@gmail.com