

Incidence and characteristics of biphasic reactions after allergen immunotherapy

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Background: The reported incidence of biphasic anaphylactic reactions varies from 1% to 20%. Reported risk factors for biphasic reactions include a delay in epinephrine administration and a longer interval to initial improvement. To date, only 4 cases of biphasic reactions after allergen immunotherapy have been reported.

Objective: We sought to determine the incidence, clinical characteristics, and risk factors for biphasic reactions after allergen-specific immunotherapy.

Methods: Patients who were treated with epinephrine for systemic reactions after allergen immunotherapy were prospectively enrolled. Patients were assessed initially and at 24 hours by using a 31-symptom scoring system.

Results: Sixty systemic reactions occurred in 55 patients; 14 (23%) biphasic reactions were reported. Patients experiencing biphasic reactions were more likely to be female ($P = .03$) and older ($P = .01$) and require greater than 1 dose of epinephrine ($P = .001$). There was no difference between groups (biphasic vs no biphasic reaction) regarding the type of immunotherapy, current asthma, initial symptom scores, or time to symptoms, initial epinephrine, or improvement. No specific symptom predicted biphasic reactions. Biphasic reactions were significantly less severe compared with the initial reaction ($P < .001$), did not occur in children, and did not require additional epinephrine.

Conclusions: Twenty-three percent of patients requiring epinephrine for systemic reactions caused by allergen immunotherapy experienced biphasic symptoms. Patients treated promptly with epinephrine for systemic reactions should be cautioned regarding biphasic reactions; however, biphasic reactions after allergen immunotherapy were mild and did not require additional epinephrine. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Anaphylaxis, biphasic, immunotherapy

Anaphylaxis is the clinical syndrome that represents a life-threatening allergic reaction and is a well-described complication of allergen-specific immunotherapy. The risk of anaphylaxis after allergen immunotherapy has prompted experts to recommend at least a 30-minute wait time and to provide immunotherapy under the supervision of appropriately trained personnel.¹ Patients who experience anaphylaxis after allergen immunotherapy are promptly treated with epinephrine but typically can be discharged home after a period of observation. One concern after discharge is the risk for biphasic reactions. Biphasic reactions are characterized by complete clinical resolution of initial symptoms followed by onset of late-phase symptoms, usually within 8 hours.² Although the reported incidence of biphasic anaphylactic reactions varies from 1% to 20%, only 4 biphasic reactions after allergen immunotherapy have been described.³⁻⁵ The objective of this study was to prospectively follow patients who were treated for systemic reactions after allergen immunotherapy to determine the incidence and clinical characteristics of biphasic reactions.

METHODS

This study was approved by the Wilford Hall Medical Center and the Brooke Army Medical Center Institutional Review Boards. All subjects provided informed consent. Eligible subjects included any patient treated with epinephrine for a systemic allergic reaction after immunotherapy. Enrolled patients were receiving immunotherapy with aqueous extracts. After initial treatment and medical stabilization, each subject's symptoms were recorded by using a 31-symptom scoring system.⁶ Briefly, the 31 symptoms are divided into 5 main categories: general, skin, gastrointestinal, respiratory, and cardiovascular/neurologic.⁶ Patient demographics, specific therapy required, immunotherapy allergen content, time to initial symptoms, and time to epinephrine administration were recorded. Additionally, because some systemic reaction symptoms are subjective (eg, throat tightness, dyspnea, and pruritus), we measured "time to patient perception of 90% improvement" as a secondary end point. Patients were observed for 1 to 2 hours after the last dose of epinephrine. All participants reported complete resolution of symptoms before clinic discharge. Subjects were then instructed to observe and record any clinical symptoms during the next 24 hours. All subjects were telephoned at 24 hours and were queried about whether they had experienced interval symptoms. A biphasic reaction was defined as any reaction occurring after discharge from the clinic up to 24 hours after their initial symptoms; the same 31-symptom questionnaire was used for patients who experienced biphasic symptoms. Patients provided the time of onset of biphasic symptoms (defined as time elapsed from onset of initial symptoms), a subjective assessment of severity compared with their initial reaction, the duration of their symptoms, and a description of any further therapy needed.

Data management and statistical analysis were performed with SPSS 14.0 software (SPSS, Inc, Chicago, Ill). The incidence of biphasic reactions was taken to be the percentage of patients with biphasic symptoms. The Fisher exact test was used for categorical variables to assess statistical significance of

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TABLE I. Clinical demographics of enrolled patients

	No biphasic reaction (n = 46)	Biphasic reaction (n = 14)	P value
Age (y)	30 ± 16	41 ± 13	.01
Male sex	18	1	.03
Buildup phase	29	9	1.0
Duration of IT (y)	0.9 ± 1.6	2.3 ± 6.0	.15
Aeroallergen IT	33	9	.74
Current asthma	23	7	1.0
Daily antihistamine	30	11	.51
Prior systemic reaction to IT	14	4	1.0
Less than 18 years old	15	0	.01

IT, Immunotherapy.

differences in percentages of patients with biphasic reactions in different subgroups. The Student *t* test for comparing the means of 2 independent samples was used to analyze variables measured on a continuous scale (eg, age). Null hypotheses were tested against 2-directional alternatives. Descriptive statistics were used to assess the frequency and clinical characteristics of biphasic reactions. The paired *t* test was used to compare initial and biphasic symptoms. *P* values of less than .05 were considered statistically significant.

RESULTS

Immunotherapy

Participants were enrolled between September 2006 and November 2007 at 2 hospitals: Brooke Army Medical Center and Wilford Hall Medical Center, San Antonio, Texas.

During the enrollment period at Brooke Army Medical Center, a total of 10,932 immunotherapy injections were administered to 330 unique individuals (age range, 6-75 years). Thirty-four (0.31% reaction per allergy injection) reactions occurred in 31 patients at this site. Of the 34 reactions, 29 (85%) required at least 1 dose of epinephrine, and 19 (66%) of 29 were enrolled in the study. Reasons for not being enrolled were that the site investigator (K.W.) was not present and the patient was treated by another allergist or licensed provider. The incidence of systemic reactions requiring epinephrine at this site was not statistically different regarding the type of immunotherapy administered: 0.78% for Hymenoptera compared with 0.38% for aeroallergens (*P* = .32).

At Wilford Hall Medical Center, 12,796 allergen immunotherapy injections were administered to 366 unique individuals (age range, 5-76 years) during the enrollment period. Forty-four (0.34% reaction per allergy injection) reactions occurred in 39 patients. Three reactions did not require epinephrine and were not included. Forty-one reactions in 36 patients did require epinephrine, and all (100%) were included for analysis. At this site, the incidence of systemic reactions requiring epinephrine was significantly greater in patients receiving venom immunotherapy: 0.91% for Hymenoptera compared with 0.23% for aeroallergens (*P* < .0001).

Patient demographics

A total of 55 enrollees experienced 60 systemic reactions requiring epinephrine after allergen immunotherapy. The average age was 33 ± 16 years. Nineteen (32%) reactions occurred in men. Fifteen (25%) reactions occurred in children less than 18 years old. Thirty-eight (63%) reactions occurred during the buildup phase of immunotherapy. Sixty-two percent were

TABLE II. Characteristics of systemic reactions and therapy administered

	No biphasic reaction (n = 46)	Biphasic reaction (n = 14)	P value
Symptom onset (min)	28 ± 22	17 ± 14	.10
Time to epinephrine (min)	8.5 ± 13.8	8.2 ± 12.8	.94
>1 Dose of epinephrine	8	9	.001
Oral antihistamine	37	11	1.0
Oral corticosteroid	6	1	1.0
Albuterol nebulization	10	2	.71
Time to >90% improvement (min)	33 ± 37	20 ± 10	.23
Total symptom score (out of 31)	3.8 ± 2.9	4.1 ± 1.8	.67

receiving a dose from the 1:1 vol/vol vial, whereas 13% were receiving a dose from the 1:10 vol/vol vial. The average duration of immunotherapy was 1.2 ± 3.2 years. Fifty percent of participants had a history of asthma, and 68% were taking a daily second-generation antihistamine. Seventy percent of participants were receiving aeroallergen immunotherapy, and 30% were receiving venom immunotherapy (Table I).

Initial treatment

The median time from allergen immunotherapy injection to initial systemic reaction symptoms was 25 minutes (range, 1-180 minutes). The median time from onset of initial symptoms to initial epinephrine dose was 4 minutes (range, 1-82 minutes). Seventeen (28%) patients required more than 1 dose of epinephrine. In addition to epinephrine, 80% of patients received an oral antihistamine, 12% received oral corticosteroids, and 20% received a β_2 -agonist nebulization treatment. Median time to 90% subjective improvement after the initial epinephrine dose was 20 minutes (range, 2-180 minutes; Table II).

Biphasic reactions

Fourteen (23%) instances of biphasic reactions occurred in 60 systemic reactions after allergen immunotherapy (Tables III and IV). Patients who experienced biphasic reactions were more likely to be older (*P* = .01) and female (*P* = .03). There was no statistical difference between groups regarding duration of immunotherapy, current asthma, type of immunotherapy, or use of a daily antihistamine (Table I). Of the 14 biphasic reactions, 8 (57%) patients had extracutaneous symptoms, and 6 (43%) had isolated cutaneous symptoms (Table IV).

Patients having a biphasic reaction were also more likely to receive more than 1 dose of epinephrine (*P* = .001), but there was no difference between time to symptom onset, time to epinephrine dose, or additional therapy administered (ie, antihistamine, oral corticosteroid, and albuterol nebulization; Table II). There was also no difference between groups regarding time to improvement (*P* = .23) or initial symptom scores (*P* = .67, Table II). Finally, no child less than 18 years old (*n* = 15) experienced a biphasic reaction (*P* = .01).

Regarding initial symptoms, there was no specific symptom that was predictive of a biphasic reaction (Table V). Patients with initial symptoms of nasal congestion/rhinorrhea (*P* = .05) and diaphoresis (*P* = .08) were more likely to experience a biphasic

TABLE III. Profile of uniphasic immunotherapy reactions

Patient age (y)/sex	Antigen	Symptoms	TSS	Management
15/F	A	Generalized itching, rhinorrhea, chest congestion, cough, wheeze	4	EPI, OA, NEB
52/F	A	Cough	1	EPI
51/M	A	Anxiety, generalized itching, periorbital swelling, generalized urticaria/flushing	4	EPI, OA, OS
40/F	A	Cough	1	EPI
27/F	A	Chest congestion, cough	2	EPI, OA, OS
32/F	A	Generalized urticaria/flushing, nausea	2	EPI, OA
40/F	A	Chest or throat tightness, cough	2	EPI, OA
48/F	H	Anxiety, generalized urticaria/flushing	2	EPI, OA
9/M	A	Chest or throat tightness	1	EPI
24/F	A	Generalized itching, generalized urticaria/flushing, nausea, dizziness	4	EPI, OA
24/F	H	Nausea, dizziness	2	EPI
40/F	A	Generalized itching, generalized urticaria/flushing, headache	3	EPI, OA, OS
38/M	A	Generalized itching, generalized urticaria/flushing	2	EPI, OA
9/M	A	Chest or throat tightness, dyspnea	2	EPI, NEB
7/F	A	Generalized itching, generalized urticaria/flushing	2	EPI, OA, OS
52/F	A	Generalized itching, generalized urticaria/flushing, chest or throat tightness, cough	4	EPI
10/F	A	Generalized itching, generalized urticaria/flushing, cough, dyspnea	4	EPI, OA, OS, NEB
30/F	H	Generalized itching, generalized urticaria/flushing	2	EPI, OA
52/F	A	Generalized itching, generalized urticaria/flushing, chest or throat tightness	3	EPI, OA, NEB
31/F	A	Chest or throat tightness, rhinorrhea and nasal congestion, cough	3	EPI, OA, NEB
7/M	A	Anxiety, Generalized itching, generalized urticaria/flushing, periorbital swelling, chest and throat tightness, cough, wheeze, dyspnea	8	EPI, OA, NEB
29/F	A	Generalized itching, visual disturbance	2	EPI, OA
15/F	A	Anxiety, generalized itching, difficulty swallowing, dizziness, visual disturbances	5	EPI, OA
28/F	A	Generalized itching, generalized urticaria/flushing, diaphoresis	3	EPI, OA
40/M	A	Anxiety, paresthesia, weakness, nausea, chest or throat tightness, chest pain, dyspnea, dizziness, visual disturbances, pallor, hypotension	11	EPI, OA, OS, NEB
10/M	A	Anxiety, chest or throat tightness, cough, wheeze, dyspnea, dizziness	6	EPI, OA, NEB
26/F	H	Generalized itching, generalized urticaria/flushing	2	EPI, OA
28/M	H	Sense of impending doom, generalized urticaria/flushing, dizziness	3	EPI, OA
7/F	H	Generalized itching, generalized urticaria/flushing, periorbital edema	3	EPI, OA
48/M	H	Generalized itching, generalized urticaria/flushing, diaphoresis	4	EPI, OA
53/M	H	Generalized itching, cough	2	EPI, OA
19/F	H	Abdominal pain, rhinorrhea and nasal congestion, diaphoresis	3	EPI, OA
7/F	H	Anxiety, generalized itching, periorbital edema	3	EPI, OA
52/F	H	Paresthesia, generalized itching, rhinorrhea and nasal congestion	3	EPI, OA
42/M	A	Anxiety, paresthesia, sense of impending doom, generalized itching, periorbital edema, angioedema, chest and throat tightness, difficulty speaking, hoarse voice, cough, dyspnea	11	EPI, OA, NEB
16/M	A	Chest or throat tightness, rhinorrhea and nasal congestion, dyspnea	3	EPI
17/M	A	Malaise, weakness, periorbital edema, angioedema, nausea, abdominal pain, chest or throat tightness, difficulty swallowing, rhinorrhea and nasal congestion, difficulty speaking, hoarse voice, cough, wheeze, dyspnea, pallor, hypoxemia ($\text{Po}_2 < 92\%$)	16	EPI, OA
16/F	A	Generalized itching, generalized urticaria/flushing	2	EPI, OA
11/F	H	Anxiety, chest and throat tightness	2	EPI, OA
43/M	A	Malaise, cough, dyspnea, wheeze, diaphoresis	5	EPI
17/M	A	Chest or throat tightness, difficulty swallowing, rhinorrhea and nasal congestion, cough, dyspnea	5	EPI, OA, NEB
67/F	A	Generalized urticaria/flushing, cough, wheeze, dyspnea	4	EPI, OA
35/F	A	Generalized itching, generalized urticaria/flushing	2	EPI, OA
46/M	A	Malaise, generalized itching, rhinorrhea and nasal congestion, headache	4	EPI, OA
52/M	H	Anxiety, paresthesia, chest or throat tightness, rhinorrhea and nasal congestion, difficulty speaking, hoarse voice, dyspnea, headache	8	EPI
42/M	A	Generalized itching, angioedema, chest or throat tightness, difficulty swallowing, rhinorrhea and nasal congestion, hoarse voice, cough	7	EPI, OA

TSS, Total symptom score (out of possible 31); A, aeroallergen immunotherapy; EPI, epinephrine; OA, oral antihistamine; NEB, albuterol nebulization; OS, oral corticosteroid; H, Hymenoptera immunotherapy.

reaction, although this did not reach statistical significance. The median time to biphasic symptoms was 5.5 hours (range, 2-24 hours). The subjective severity of the biphasic reaction when compared with the initial reaction was 10% or less in 9 (64%) patients. Thirteen of 14 patients assessed the severity at 25% or less of their initial reaction. Total symptom scores were significantly less during the biphasic reaction (1.3 ± 0.5) compared with initial

symptom scores (4.1 ± 1.8 , $P < .001$). One patient who experienced generalized flushing and pruritus during her initial reaction described an identical reaction 3 hours later but denied any respiratory, cardiovascular, or gastrointestinal symptoms. The median duration of biphasic symptoms was 53 minutes (range, 1-480 minutes); 8 (57%) reactions lasted 1 hour or less. Three (21%) patients took an additional oral antihistamine at the onset of

TABLE IV. Profile of biphasic immunotherapy reactions (initial and biphasic symptoms)

Patient age (y)/sex	Antigen	Initial symptoms	Initial TSS	Management	Severity of biphasic reaction	Time to biphasic reaction (h)	Biphasic symptoms	Biphasic TSS	Management
66/F	H	Generalized itching, generalized urticaria/flushing, nausea, rhinorrhea and nasal congestion	4	EPI, OA	Milder	2.5	Generalized itching	1	No intervention
40/F	A	Chest or throat tightness, difficulty swallowing, rhinorrhea and nasal congestion, dizziness, diaphoresis, pallor	6	EPI, OA	Milder	7	Generalized urticaria/flushing	1	No intervention
22/F	A	Generalized itching, wheeze, dyspnea	3	EPI, OA	Milder	5	Dizziness	1	No intervention
38/F	H	Generalized itching, diaphoresis	2	EPI, OA	Milder	4.5	Generalized itching	1	No intervention
34/F	H	Generalized itching, generalized urticaria/flushing, rhinorrhea and nasal congestion, cough	4	EPI, OA	Milder	5	Malaise	1	No intervention
53/F	H	Anxiety, generalized itching, generalized urticaria/flushing, dyspnea, dizziness	5	EPI, OA	Milder	3	Generalized itching	1	OA
50/M	A	Anxiety, sense of impending doom, chest or throat tightness, rhinorrhea and nasal congestion, wheeze, dyspnea	6	EPI, NEB	Milder	16	Chest or throat tightness	1	NEB
47/F	A	Generalized itching, periorbital edema, angioedema, nausea, chest or throat tightness, rhinorrhea and nasal congestion, cough, dyspnea	8	EPI, OA, NEB	Milder	2	Dyspnea	1	NEB
55/F	A	Rhinorrhea and nasal congestion	1	EPI, OA	Milder	4	Rhinorrhea and nasal congestion	1	No intervention
36/F	A	Periorbital edema, generalized urticaria/flushing, rhinorrhea and nasal congestion, cough	4	EPI	Milder	24	Periorbital edema	1	OA
31/F	A	Generalized itching, chest or throat tightness, dizziness, diaphoresis	4	EPI	Milder	7.5	Chest or throat tightness, dizziness	2	No intervention
54/F	A	Chest or throat tightness, cough, dyspnea, wheeze	4	EPI, OA	Milder	12	Cough, wheeze	2	NEB
45/F	A	Generalized itching, generalized urticaria/flushing	2	EPI, OA	Similar	3	Generalized itching, generalized urticaria/flushing	2	OA
25/F	H	Generalized itching, generalized urticaria/flushing, periorbital edema, rhinorrhea and nasal congestion, diaphoresis	5	EPI, OA, OS	Milder	5	Weakness, generalized itching	2	No intervention

TSS, Total symptom score (out of 31); H, Hymenoptera immunotherapy; EPI, epinephrine; OA, oral antihistamine; A, aeroallergen immunotherapy; NEB, albuterol nebulization; OS, oral corticosteroid.

biphasic symptoms, whereas 3 (21%) others used their β_2 -agonist rescue inhaler. No patient required epinephrine or believed symptoms were severe enough to warrant a trip to the emergency department.

DISCUSSION

This is the first study, to our knowledge, that prospectively examined the incidence and clinical characteristics of biphasic reactions after allergen immunotherapy. The term *biphasic*

TABLE V. Symptoms reported during initial systemic reaction*

	No biphasic reaction (n = 46)	Biphasic reaction (n = 14)	P value
Anxiety	11	2	.71
Paresthesia	4	0	.56
Malaise	3	0	1.0
Weakness	2	0	1.0
Feeling of impending doom	2	1	.56
Generalized itching	25	9	.56
Periorbital edema	6	3	.42
Generalized urticaria/erythema	20	6	1.0
Angioedema	3	1	1.0
Chest or throat tightness	17	5	1.0
Chest pain	1	0	1.0
Abdominal pain	2	0	1.0
Nausea	5	2	.66
Difficulty swallowing	4	1	1.0
Nasal congestion or rhinorrhea	11	8	.05
Difficulty speaking	3	0	1.0
Hoarse voice	4	1	1.0
Cough	16	4	.76
Wheeze	6	3	.42
Dyspnea	12	4	1.0
Dizziness	6	3	.42
Visual disturbance	3	0	1.0
Diaphoresis	4	4	.08
Pallor	2	1	.56
Headache	3	0	1.0

*No patient experienced collapse, confusion, stridor, incontinence, diarrhea, or vomiting.

anaphylaxis was first coined in a case series published by Popa and Lerner³ in 1984. Since then, multiple retrospective and prospective evaluations have been performed regarding the incidence of biphasic reactions, but there are only 4 reported instances of biphasic reactions after allergen immunotherapy.³⁻⁵ Popa and Lerner³ reported the first case after rye grass immunotherapy. Douglas et al⁴ reported 2 adults who experienced biphasic reactions after aeroallergen immunotherapy, an incidence of 5% (2/44). Finally, Ellis and Day⁵ report 1 adult experiencing a biphasic reaction after immunotherapy that was managed at home with a self-administered oral antihistamine.

In this study there were several interesting and significant observations. First, the overall incidence of biphasic reactions in patients experiencing systemic reactions after allergen immunotherapy was 23%, which was similar to that seen in other large anaphylaxis cohort studies.^{5,7} However, this incidence was much higher than the 5% incidence observed in the only reported cohort of patients receiving allergen immunotherapy⁴; this difference can perhaps be explained by the prospective nature of the current study because the definitions of anaphylaxis and biphasic reactions were similar.

Douglas et al⁴ suggested that “early intervention” with epinephrine might decrease the risk for biphasic reactions, a finding that our study did not support. Of note, the majority of patients in that study only had cutaneous symptoms before initial treatment. Lee and Greenes⁸ described that a delay to epinephrine was a risk factor for biphasic reactions in patients presenting to the emergency department with acute anaphylaxis. However, in our study 56 (93%) of 60 reactions occurred while patients were still in the clinic’s waiting area, resulting in a mean time to epinephrine administration for all patients of 8.3 ± 13.5 minutes. Thus the

prompt administration of epinephrine resulted in an inability to conclude whether delays in epinephrine administration increased the risk for biphasic reactions. Another significant finding was the observation that women and older individuals were more likely to experience biphasic reactions, a finding that has not previously been described. Additionally, although 25% of enrolled patients were less than 18 years old, none experienced a biphasic reaction.

We observed that patients who required greater than 1 dose of epinephrine were more likely to experience biphasic reactions ($P = .001$). Two previous studies differed regarding the risk of biphasic reactions and the number of epinephrine doses.^{5,9} A retrospective review of 34 patients admitted for anaphylaxis found that patients who required more epinephrine in the initial phase (1.2 mg vs 0.6 mg) were more likely to experience biphasic symptoms.⁹ Ellis and Day⁵ observed the converse: less epinephrine increased this risk for biphasic reactions.

Although not statistically significant, patients who experienced biphasic reactions had faster improvement of initial symptoms compared with patients without biphasic reactions (20 ± 10 minutes vs 33 ± 37 minutes, $P = .23$). This finding differs from a previous observation that patients experiencing biphasic reactions took longer to improve.⁵ Finally, specific symptoms were not predictive of a biphasic reaction (Table V), which is in agreement with a recent review article that failed to define a consistent set of predictive clinical symptoms.¹⁰

There were some limitations to our study. First, biphasic reactions generally occur within 8 hours, but some patients have reported symptoms up to 72 hours later.⁴ Because patients were contacted at 24 hours, we might have missed some patients who experienced a biphasic reaction with onset later than 24 hours. However, no participants reported further problems past the initial 24 hours when queried before receiving their next allergen injection.

Second, many experts define anaphylaxis as involving systemic symptoms that are not solely cutaneous. In this study enrolled patients were determined by their treating board-certified allergist to have a clinical course concerning for anaphylaxis. Study enrollment was based on patients receiving epinephrine rather than first fulfilling the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network working group consensus anaphylaxis criteria.¹¹ In the context of allergen immunotherapy, the rapid onset of diffuse cutaneous symptoms is typically treated with epinephrine rather than waiting for further clinical deterioration. The working group states that there are “patients who present with symptoms not yet fulfilling the criteria of anaphylaxis ... in whom it would be appropriate to initiate therapy with epinephrine.”¹¹ The only other study focusing on anaphylaxis and biphasic reactions in a cohort of patients receiving allergen immunotherapy required involvement of only 1 organ system (eg, cutaneous) for a diagnosis of anaphylaxis.⁴ However, retrospectively applying patient symptoms to the current consensus definition for anaphylaxis, we determined that 29 (48%) of 60 reactions met criterion 1, whereas 3 (5%) reactions met criterion 2. Fifteen (25%) reactions were treated for cutaneous-only symptoms, whereas 12 (20%) reactions had respiratory-only symptoms before epinephrine, and 1 (2%) had gastrointestinal-only symptoms.

Another limitation is that this study was not designed to define the role of corticosteroids for the prevention of biphasic reactions. It is unclear whether corticosteroids given for the primary event can prevent or lessen the severity of late-phase reactions.¹⁰

Although we did not find a statistical difference regarding the use of oral corticosteroids in this study ($P = 1.0$), only 7 patients received oral corticosteroids.

Finally, should the criteria for immediate anaphylaxis be applied to define biphasic reactions? Although several studies have required that biphasic symptoms must meet the same criteria as the initial definition of anaphylaxis,^{5,7} others have been less strict. Brazil and MacNamara⁹ defined biphasic symptoms as the development of any “further symptoms requiring adrenaline” in patients initially successfully treated for anaphylaxis. Similarly, Lee and Greenes⁸ defined a biphasic reaction as any “worsening of symptoms requiring any new therapy after resolution of anaphylaxis had occurred.”⁸ Although Douglas et al⁴ did require that biphasic reactions meet the same criteria as the initial anaphylaxis, their requirement of only 1 involved organ system has obvious limitations. Finally, Smit et al¹² defined biphasic reactions as “any reaction occurring after initial treatment and complete resolution of symptoms.” Because there is no consensus definition for biphasic reactions, we classified reactions as biphasic if any of the 31 symptoms described in the initial survey were experienced within 24 hours. Of the 14 biphasic reactions, 8 (57%) patients had extracutaneous symptoms, whereas 6 (43%) had isolated cutaneous symptoms.

We were reassured to find that all but 1 patient who experienced a biphasic reaction had significantly less severe symptoms; a 45-year-old woman was treated with epinephrine 90 minutes after her buildup aeroallergen injection for symptoms of generalized pruritus and urticaria. Her initial symptoms cleared within 35 minutes, but identical symptoms recurred 3 hours later. Our results contrast with previous observations that the biphasic reaction can be more severe than the initial reaction.^{4,7,8} Although some patients required an additional oral antihistamine or β_2 -agonist inhaler, no patient required epinephrine or went to the emergency department. In general, our practice is to provide self-injectable epinephrine to patients receiving venom immunotherapy or to those who experience a delayed (>30 minutes) reaction to immunotherapy. A recent survey found that 37% of allergists routinely provide patients epinephrine for up to 6 hours after immunotherapy.¹³ Although recent recommendations include providing self-injectable epinephrine and an Anaphylaxis Emergency Action Plan for any patient experiencing anaphylaxis, this study supports not routinely providing self-injectable epinephrine for patients who are successfully treated in the clinic for allergen-specific immunotherapy-induced anaphylactic reactions.

In conclusion, this study provides insight into the clinical characteristics of biphasic reactions after allergen immunother-

apy-induced systemic reactions. We observed a 23% incidence of biphasic reactions. Women, older patients, and patients requiring more than 1 dose of epinephrine were more likely to experience biphasic reactions; however, biphasic reactions tended to be mild and self-limited.

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Clinical implications: Biphasic reactions occurred in 23% of reactions treated with epinephrine for allergen immunotherapy-induced systemic reactions. Biphasic reactions are mild, tend to be self-limited, and have not required additional epinephrine.

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