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# Biphasic Anaphylactic Reactions in Pediatrics

Joyce M. Lee, MD, and David S. Greenes, MD

**ABSTRACT.** *Objectives.* The objectives of this study were to: 1) determine the incidence of biphasic reactions in children with anaphylaxis; 2) establish what risk factors can predict progression to a biphasic reaction; and 3) assess the utility of inpatient observation for patients whose anaphylaxis appears to have resolved.

*Methods.* We performed a retrospective analysis of all children admitted to Children's Hospital inpatient service between 1985 and 1999 with acute anaphylaxis. Data were collected from the medical records regarding past medical history, presenting signs and symptoms, treatment, and hospital course. Patients were considered to have resolution of anaphylaxis if they were documented to have cessation of all symptoms and needed no therapy for at least 1 hour. Biphasic reactions were defined as a worsening of symptoms requiring new therapy after resolution of anaphylaxis. Significant biphasic reactions were defined as those requiring oxygen, vasopressors, intubation, subcutaneous epinephrine, or unscheduled bronchodilator treatments. Patients were considered to benefit from a 24-hour observation period if they had a significant biphasic reaction within 24 hours of admission.

*Results.* Of 108 anaphylactic episodes, 2 (2%) were fatal, and 1 (1%) was a protracted anaphylactic reaction. Among the remaining 105 children with resolution of anaphylaxis, 6 (6%) [95% confidence (CI): 2, 12] had biphasic reactions, of which 3 (3%) [95% CI: .6, 8] were significant. Of those who had a biphasic reaction, the median time from the onset of symptoms to the initial administration of subcutaneous epinephrine was 190 minutes, versus 48 minutes for those without a biphasic reaction. Patients with or without biphasic reactions did not differ significantly in the incidence of initial epinephrine use, initial steroid use, or serious respiratory or cardiovascular symptoms on initial presentation. Two of 105 (2%) [95% CI: .2, 7] patients clinically benefitted from a 24-hour observation period.

*Conclusions.* We found an overall incidence of biphasic reactions of 6%, and an incidence of significant biphasic reactions of 3%, among pediatric patients admitted with anaphylaxis. Delayed administration of subcutaneous epinephrine was associated with an increased incidence of biphasic reactions. Approximately 2% of patients with anaphylaxis potentially benefitted from a 24-hour period of observation after symptoms had resolved. *Pediatrics* 2000;106:762-766; *anaphylaxis, biphasic reaction, pediatric.*

ABBREVIATION. CI, 95% confidence interval.

Anaphylaxis is a systemic allergic reaction that can have serious, life-threatening consequences, and therefore requires prompt diagnosis and treatment.<sup>1,2</sup> The biphasic reaction of anaphylaxis is a recurrence of anaphylactic symptoms after an initial remission has occurred. Case series of these biphasic reactions reveal that the recurrence can be severe enough to necessitate intubation and treatment with vasopressor agents.<sup>3,4</sup> Many authors recommend, therefore, that patients with an episode of anaphylaxis be observed for 8 to 24 hours to monitor for biphasic reactions.<sup>2,5,6</sup>

A few studies assessing the rate of biphasic reactions in adults with anaphylaxis have reported rates between 5% to 20%.<sup>4,7</sup> Although there are several series of pediatric patients with anaphylaxis reported in the literature,<sup>8,9</sup> we could find no studies measuring the rate of biphasic anaphylactic reactions in children.

The objectives of this study were to: 1) determine the incidence of biphasic reactions in children with anaphylaxis; 2) identify risk factors that predict progression to a biphasic reaction; and 3) assess the utility of inpatient observation for patients whose anaphylaxis appears to have resolved.

## METHODS

We performed a retrospective analysis of all children admitted to the Children's Hospital inpatient service between 1985 and 1999 with acute anaphylaxis. Cases were identified by a search of the medical record database for all discharges with the following *International Classification of Diseases, Ninth Revision* (ICD-9) codes: 995.0-995.3 (anaphylactic shock; angioneurotic edema; unspecified adverse effect of drug, medicinal, and biological substance; or allergy, unspecified), 995.6-995.69 (anaphylactic shock due to adverse food reaction), and 999.4 (anaphylactic shock due to serum). Cases were included if they met our definition of anaphylaxis, an acute allergic reaction with involvement of at least 2 body systems: dermatologic, neurologic, gastrointestinal, respiratory, or cardiovascular. Cases were excluded if the anaphylaxis developed during hospitalization for another reason, or if the patient carried a diagnosis of chronic idiopathic anaphylaxis.

Using a standard abstraction form, one of the authors (J.M.L.), a fourth-year medical student who was not blinded to the purpose of the study, collected data from the medical records regarding past medical history, circumstances of allergen exposure, prehospital therapy, presenting signs and symptoms, treatment, and hospital course. Coding uncertainties were resolved by discussion among the authors.

Patients were considered to have *serious symptoms* if they had any of the following signs or symptoms: cyanosis, increased work of breathing, stridor, drooling, airway occlusion, wheezing, hypotension, delayed capillary refill, weak pulses, bradycardia, lethargy, diminished mental status, loss of consciousness, syncope, or seizures. Patients were considered to have *resolution of anaphylaxis*

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if they were documented to have cessation of their symptoms and needed no therapy for at least 1 hour. A *biphasic reaction* was defined as a worsening of symptoms requiring any new therapy after resolution of anaphylaxis had occurred. *Significant biphasic reactions* were those that required any of the following therapies: oxygen, intravenous vasopressor agents, intubation, subcutaneous epinephrine, or nebulized bronchodilator treatments more often than every 4 hours.

The *Statistical Package for the Social Sciences* (SPSS), version 9.0 for Windows (SPSS Inc., Chicago, IL), was used for all statistical calculations.  $\chi^2$  testing was performed for univariate analysis of the relationship between dichotomous clinical variables and the outcome variable of biphasic reactions. The unpaired *t* test was used for univariate analysis of continuous clinical predictor variables and the outcome variable of biphasic reactions. The Mann-Whitney *U* test was used for comparison of nonparametric data. Ninety-five percent confidence intervals (95% CI) were calculated for several outcomes.

## RESULTS

A total of 108 episodes of anaphylaxis were identified in 106 patients. Two (2%) cases were fatal: one was a 17-year-old with respiratory arrest after exposure to pistachios, the other was a 7-year-old with a history of multiple food allergies who had respiratory arrest after exposure to an unknown trigger. Sixty-six (61%) of the patients were male and 42 (39%) were female. Sixty-nine (64%) patients had a positive atopic history for asthma, eczema, or allergic rhinitis. The age of patients ranged from 6 months to 21 years, with a median of 8 years (Table 1).

Of 92 cases with an identified trigger, 30 (33%) patients had a prior history of allergy to the same trigger. Food was the most commonly identified trigger (Table 2). Of the 51 cases with food as trigger, 14 (27%) involved tree nuts, 12 (24%) involved peanuts, and 8 (16%) involved seafood. Other types of food implicated included fruit (3 cases), eggs (2 cases), and seeds (2 cases). The most common routes of exposure were oral in 65 (60%) cases and subcutaneous in 18 (17%) cases (Table 2). In 66 (61%) cases the setting of the initial event of anaphylaxis was not documented. The most commonly documented setting was home in 17 (16%) cases (Table 3).

There were 102 (94%) subjects who experienced respiratory symptoms. A total of 84 (78%) experienced upper airway symptoms, such as throat tightness or itchiness, drooling, stridor, or oropharyngeal swelling, and 63 (58%) experienced lower airway symptoms such as chest tightness or wheezing. Cardiovascular symptoms, which included arrhythmias, hypotension, poor capillary refill, or weak pulses were seen in 32 (30%) patients. A total of 99 (92%) patients had dermatologic symptoms, including urticaria, angioedema, flushing, or warmth. A total of 40 (37%) patients had gastrointestinal involvement,

**TABLE 1.** Demographics of the Study Subjects (N = 108)

|         | N (%)      |
|---------|------------|
| Sex     |            |
| Male    | 66 (61.1%) |
| Female  | 42 (38.9%) |
| Age     |            |
| <1 y    | 4 (3.7%)   |
| 1–5 y   | 32 (29.6%) |
| 6–11 y  | 38 (35.2%) |
| 12–21 y | 34 (31.5%) |

**TABLE 2.** Anaphylactic Trigger and Route of Exposure for All Study Subjects (N = 108)

|               | N (%)      |
|---------------|------------|
| Trigger       |            |
| Food          | 51 (47.2%) |
| Medications   | 24 (22.2%) |
| Insect bites  | 12 (11.1%) |
| Immunotherapy | 3 (2.8%)   |
| Immunizations | 1 (0.9%)   |
| Contrast dye  | 1 (0.9%)   |
| Unknown       | 16 (14.8%) |
| Route         |            |
| Oral          | 65 (60.2%) |
| Subcutaneous  | 18 (16.7%) |
| Intravenous   | 8 (7.4%)   |
| Inhaled       | 2 (1.9%)   |
| Unknown       | 15 (13.9%) |

**TABLE 3.** Setting of Anaphylactic Event (N = 108)

|                      | N (%)      |
|----------------------|------------|
| Setting              |            |
| Home                 | 17 (15.7%) |
| Doctor's office      | 6 (5.6%)   |
| Outdoors             | 6 (5.6%)   |
| Emergency department | 6 (5.6%)   |
| School               | 2 (1.9%)   |
| Radiology suite      | 2 (1.9%)   |
| Restaurant           | 1 (.9%)    |
| Relative's home      | 1 (.9%)    |
| Summer camp          | 1 (.9%)    |
| Not documented       | 66 (61.1%) |

29 (27%) had neurologic involvement, and 14 (13%) had generalized symptoms such as diaphoresis, tingling, or an impending sense of doom.

Overall, 83 (77%) cases involved serious symptoms. Among the 25 cases (23%) without serious symptoms, the most common symptoms and signs were dermatologic (88%), upper airway (72%), and other respiratory complaints (40%).

Before admission to the inpatient service, 96 (89%) patients were treated with subcutaneous epinephrine, 90 (83%) with steroids, 101 (94%) with diphenhydramine, and 14 (13%) with H<sub>1</sub> blockers. A total of 7 (7%) patients were treated with intravenous vasopressors and 7 (7%) patients were intubated.

We calculated the mean and median time for the length of hospitalization, excluding those patients with fatal reactions and excluding 1 child who remained hospitalized for other medical reasons after the initial episode of anaphylaxis. The mean length of hospitalization was  $24 \pm 21$  hours, and the median was 19 hours. The length of hospitalization ranged from 6 hours to 143 hours. The child kept for 143 hours had a protracted anaphylactic reaction.

In 76 patients we were able to ascertain the time interval from exposure to the allergen to the onset of symptoms. This time interval ranged from <1 minute to 9.7 hours. The mean time was  $31 \pm 71$  minutes, with a median of 10 minutes.

In 75 patients we were able to ascertain the time interval from onset of symptoms to the first administration of subcutaneous epinephrine. This time interval ranged from <1 minute to 17.4 hours, with a mean of  $113 \pm 176$  minutes and a median of 50

**TABLE 4.** Profile of Biphasic Anaphylactic Reactions

| Patient | Age (Years) | Sex | Trigger                       | Initial Symptoms                                                                                                                                                                                                | Initial Treatment                          |          |            | Asymptomatic Interval (Hours) | Biphasic Symptoms                                                                                           | Late Treatment |          |                     |
|---------|-------------|-----|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|----------|------------|-------------------------------|-------------------------------------------------------------------------------------------------------------|----------------|----------|---------------------|
|         |             |     |                               |                                                                                                                                                                                                                 | Epinephrine (Time to First Dose [Minutes]) | Steroids | Intubation |                               |                                                                                                             | Epinephrine    | Steroids | Intubation Pressors |
| 1       | 11          | F   | Dicloxacillin                 | Pruritis, angioedema, throat itchiness, difficulty swallowing, change in voice, stridor, chest tightness, wheezing, dyspnea, hypotension                                                                        | Yes (190)                                  | Yes      | No         | 11.4                          | Throat tightness, change in voice, stridor, increased work of breathing, chest tightness, wheezing, dyspnea | Yes            | Yes      | No                  |
| 2       | 11          | M   | Fish                          | Throat tightness, dyspnea, lacrimation, cough, abdominal pain                                                                                                                                                   | Yes (220)                                  | No       | No         | 1.3                           | Throat tightness                                                                                            | No             | Yes      | No                  |
| 3       | 1           | F   | Trimethoprim-sulfamethoxazole | Urticaria, pruritis, angioedema, tongue swelling, wheezing                                                                                                                                                      | Yes (1045)                                 | Yes      | No         | 28.4                          | Urticaria, angioedema, wheezing                                                                             | Yes            | Yes      | No                  |
| 4       | 2           | M   | Bee sting                     | Urticaria, pruritis, tongue swelling, increased work of breathing                                                                                                                                               | Yes (48)                                   | Yes      | No         | 5.9                           | Urticaria, tongue swelling                                                                                  | No             | Yes      | No                  |
| 5       | 13          | F   | Nuts                          | Urticaria, erythema, angioedema, oropharyngeal edema, throat tightness, difficulty swallowing, difficulty speaking, drooling, chest tightness, dyspnea, vomiting, abdominal pain                                | Yes (90)                                   | Yes      | No         | 5.8                           | Angioedema, stridor, increased work of breathing, dyspnea                                                   | Yes            | Yes      | Yes                 |
| 6       | 10          | M   | Bee sting                     | Urticaria, warmth, lip swelling, tongue swelling, oropharyngeal swelling, throat tightness, change in voice, difficulty swallowing, increased work of breathing, wheezing, tachycardia, impending sense of doom | Yes (Timing unknown)                       | Yes      | No         | 8.0                           | Throat itching, dyspnea                                                                                     | No             | Yes      | No                  |

minutes. The 1 case with a 17.4-hour interval involved a child who had waxing and waning symptoms for most of a day before presenting with worsening symptoms at night.

In 105 cases, resolution of initial anaphylactic symptoms was documented. In 6 (6%) [95% CI: 2, 12] of these 105 cases, a biphasic reaction occurred. Of these 6 biphasic reactions, 3 (3%) [95% CI: .6, 8] were significant. The time from the initial onset of symptoms to the onset of biphasic reaction ranged from 5.6 hours to 47.6 hours. The asymptomatic interval, which was the period from resolution of symptoms to onset of biphasic reaction, ranged from 1.3 hours to 28.4 hours. The triggers involved were medications, bee stings, and food, each in 2 cases. All of the patients with biphasic reactions had been treated with subcutaneous epinephrine for their initial phase of anaphylaxis, and 5 of 6 patients had received steroids during the initial episode.

For the patients with biphasic reactions, the symptoms and signs associated with the initial phase of anaphylaxis and with the second phase are listed in Table 4. All 6 patients had involvement of the same organ systems for their biphasic reaction as they did for their initial anaphylactic reaction. Patient 5 experienced more serious respiratory symptoms in the second phase than in the first, with new onset stridor. Only patients 1, 3, and 5 experienced serious symptoms during their biphasic reaction, for which they received subcutaneous epinephrine. Patient 5 required intubation and intravenous vasopressor agents for the biphasic reaction. All patients recovered.

Table 5 shows a comparison of presenting clinical features between those patients who did or did not develop biphasic reactions. The time interval between onset of symptoms and the initial dose of epinephrine was significantly longer for those patients who did have biphasic reactions than for those who did not ( $P = .03$  by Mann-Whitney  $U$  test). Of the 70 patients with uniphasic reactions for whom the time interval from onset of symptoms to the initial dose of epinephrine was known, 60 (86%) had an interval shorter than the median interval for patients with biphasic reactions.

No other clinical risk factors identified patients who would have biphasic reactions (Table 5). In addition to the comparisons shown in Table 5, we

sought differences in the type of allergenic trigger between patients with or without biphasic reactions. No significant differences were found.

## DISCUSSION

We report the largest series describing anaphylaxis in a pediatric population and the first study to directly address the issue of biphasic reactions in children. We found a rate of biphasic reactions of 6%, which is similar to the 5% to 7% rate described by Douglas et al<sup>7</sup> in adults, but substantially lower than the 20% rate of biphasic reactions in adults reported by Stark and Sullivan.<sup>4</sup> Our rate is also lower than the 23% rate observed by Sampson et al<sup>3</sup> in a pediatric population of 13 patients with fatal or near fatal anaphylaxis.

We found that in all cases the signs and symptoms of the biphasic reactions involved the same body systems affected initially. This is in contrast to Douglas et al,<sup>7</sup> who noted new involvement of body systems, including new onset hypotension in 1 patient and new onset wheezing in another. It is important to stress that in one of our cases, the biphasic reaction was more severe than the initial phase, similar to the findings of Douglas et al.<sup>7</sup>

The asymptomatic intervals for our patients with biphasic reactions varied from 1.3 hours to 28.4 hours. The asymptomatic intervals in our population were substantially longer than those reported by Sampson et al,<sup>3</sup> whose 3 patients with biphasic reactions had an asymptomatic period of 1 to 2 hours. However, our findings are similar to those of Douglas et al,<sup>7</sup> who report asymptomatic intervals ranging from 1 to 72 hours.

The wide range of reported asymptomatic intervals makes it difficult to determine appropriate clinical guidelines for duration of clinical observation. Most authors recommend that patients be monitored for 8 to 24 hours.<sup>2,5,6</sup> Our institution appears to comply with these recommendations, as the mean length of hospitalization for patients in our study without biphasic reactions was approximately 24 hours.

Because only 3 of our patients had serious biphasic reactions, and one happened approximately 30 hours after admission, it appears that only 2 (2%) [95% CI: 2, 12] of our 105 cases benefitted substantially from a policy of a 24-hour observation after an anaphylactic episode.

Our data do not suggest that steroids prevent biphasic reactions, as the rate of steroid use was similar in patients with and without these reactions. The lack of efficacy of steroids in preventing biphasic reactions has been reported by other researchers as well.<sup>4,10</sup> It must be noted, however, that we had limited statistical power, so our study data certainly cannot rule out the possibility that steroids provide some benefit in this setting.

Our finding of a longer interval before epinephrine administration in children with biphasic anaphylaxis is intriguing, because it is similar to the findings of Sampson et al,<sup>3</sup> who found that late administration of epinephrine was associated with a higher rate of mortality. Both our findings and those of Sampson suggest that administering epinephrine as early as

**TABLE 5.** Comparison of Patients With and Without Biphasic Reactions

|                                                   | Biphasic Reaction<br>N = 6 | No Biphasic Reaction<br>N = 99 |
|---------------------------------------------------|----------------------------|--------------------------------|
| Male gender                                       | 3 (50%)                    | 63 (63.6%)                     |
| Mean age (y)                                      | 8.0                        | 8.6                            |
| Trigger ingested orally (%)                       | 4 (66.7%)                  | 59 (59.6%)                     |
| Serious symptoms in initial phase                 | 5 (83.3%)                  | 75 (75.8%)                     |
| Epinephrine given initially                       | 6 (100%)                   | 90 (90.9%)                     |
| Median time to initial dose of epinephrine (min)* | 190                        | 48                             |
| Steroids given initially                          | 5 (83.3%)                  | 84 (84.8%)                     |

\*  $P = .03$ .

possible after the initial onset of symptoms may help prevent complications of anaphylaxis. Alternatively, it may be that patients who present later for treatment are intrinsically different in some way that makes complications more likely.

Our study suffers from the limitations of the data that are inherent in a retrospective analysis. However, we believe our retrospective study design is unlikely to affect our principal outcome measure, the incidence of biphasic reactions. Because our definition of biphasic reactions was based on the need for new medical therapy, which is carefully documented in nursing notes and physician order sheets, we think it is very unlikely that our assessment of the rate of biphasic reactions in our population is inaccurate.

A prospective study of biphasic reactions in pediatric cases of anaphylaxis would certainly be of interest. Given that pediatric anaphylaxis is such a rare event, however—with our finding only 108 hospitalized cases over a 15-year period—a prospective study with an equally large sample size will be difficult to achieve.

Another limitation of our study is that only hospitalized children were included. Many patients with anaphylaxis were likely discharged directly from the emergency department, and others may have been treated solely by their primary physicians. Yocum et al<sup>11</sup> found that only 7% of patients diagnosed with anaphylaxis were hospitalized. The rate of biphasic reactions in children discharged from the emergency department may differ from that in the cases we present.

Finally, we are limited in our ability to assess the benefit of inpatient hospitalization for our subjects. We define a beneficial hospitalization as one in which emergent medical therapies were given after admission. We cannot know for certain, however, what would have happened to these same patients, had they been discharged from the emergency department. Perhaps they would have been able to make it safely back to an emergency department in

time to be treated effectively. Only a prospective randomized trial would be able to truly compare the benefits of inpatient and outpatient monitoring.

We found an incidence of biphasic reactions of 6%, and an incidence of significant biphasic reactions of 3% among pediatric patients admitted with anaphylaxis. Delayed administration of subcutaneous epinephrine was associated with an increased incidence of biphasic reactions. Approximately 2% of patients with anaphylaxis appeared to benefit substantially from a 24-hour period of observation after symptoms had resolved.

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McNeill WH. *Plagues and Peoples.* Anchor Books; 1976

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