

Biphasic Anaphylaxis: Review of Incidence, Clinical Predictors, and Observation Recommendations

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Historical review

In 1902, Portier and Richet [1] attempted prophylaxis by means of immunization of dogs to sea anemone venom. The sensitized dogs had fatal reactions to subsequent nonlethal doses of the venom, however. This unexpected adverse outcome was termed by Portier and Richet [1] as *anaphylaxis*. Although a biphasic anaphylactic reaction was described by Duke [2] in 1925 and in two textbooks published in 1983 [3,4], it was Popa and Lerner [5] who described the first case reports in 1984 and coined the term *biphasic anaphylaxis*.

In the early to mid-1970s, Dolovich and his coworkers [6,7] and Solley and colleagues [8] illustrated that late-occurring skin reactions appearing after the resolution of the immediate response may be associated with IgE. This challenged the prior concept that such late-occurring cutaneous reactions were attributable to IgG or complement. These investigations radically influenced the concept of immediate hypersensitivity and spurred interest in the late-phase response, ultimately altering our approach to allergic respiratory tract disease. Yet, not until the report by Popa and Lerner [5] did we appreciate that the pathophysiology of anaphylaxis may be expressed as a biphasic response.

Clinical characteristics of the biphasic response

There have been several biphasic anaphylactic reaction studies and case reports [9–26]. These evaluations are summarized in Table 1.

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Table 1
Biphasic anaphylaxis studies

Reference	Type of study	Subjects with biphasic response	Incidence of biphasic reactions in study (%)	Age range (years)	Gender	Route of administration	Time (hours) to onset of second response after resolution of primary reaction	Fatalities	Original authors' comments	Observations
Popa and Lerner, 1984 [5]		3	N/A	22–52	3 male, 0 female	0 oral, 3 parenteral	3.5–4	0	Observe individuals with anaphylaxis for 24 hours regardless of therapy with corticosteroids.	The authors coined the term <i>biphasic anaphylaxis</i> . All their cases were considered by the authors to be mild. All their cases were IgE mediated.
Stark and Sullivan, 1986 [26]	Prospective analysis of emergency department visits and hospitalizations	5	20%	21–67	2 male, 3 female	3 oral, 2 parenteral	1–8	0 ^a	The authors observed that in subjects with biphasic responses, there was a relatively delayed time of onset of the primary response relative to antigen exposure. They therefore questioned whether a 30-minute waiting period after administration of antigen is sufficient. They recommended an observation period “several hours after apparent recovery.”	The presence of laryngeal edema in the early response may predispose to a late-phase response. Treatment with corticosteroids was not helpful in preventing a late-phase response. One of the five subjects with biphasic reactions had an anaphylactoid rather than an anaphylactic response. This patient received radiocontrast. A delay of 30 minutes or more after antigen exposure before onset of the early phase seemed to predispose to a late-phase reaction. The presence of severe respiratory or cardiovascular symptoms (hypotension) in the initial response was not predictive of the occurrence of a late-phase reaction.

Douglas et al, 1994 [9]	Retrospective analysis of records from the outpatient immunotherapy patients and records of admissions to the emergency department and hospital for anaphylaxis	6	5% in outpatient clinic, 7% hospitalized; 5.8% overall incidence	7–77	4 male, 2 female	4 oral, 2 parenteral	1–72	0	The authors observed that their incidence of biphasic reactions was significantly lower than that previously reported by Stark and Sullivan [26].	The severity of the second reaction could be equal to, less than, or greater than the initial reaction. There was a suggestion that corticosteroids might be beneficial in preventing or reducing the severity of the late response. There was a suggestion that the absence of hypotension during the initial response might indicate that a late-phase response would be less likely to occur.
Brady et al, 1997 [11]	Retrospective analysis	2	3%	19–21	1 male, 1 female	0 oral, 2 parenteral	26–40	0	Recurrent (biphasic) responses were considered rare and non-life threatening, manifested only by urticaria in their patient population.	Both patients with recurrent reactions had hymenoptera stings and falls in blood pressure as well as angioedema. Both were treated with corticosteroids, epinephrine, and antihistamines.
Brazil and MacNamara, 1998 [13]	Retrospective review	6	18%	16–81	NG	3 oral, 3 parenteral	4.5–29.5	0	Because of the delay of 29.5 hours before the onset of the second response, the authors stated that all patients requiring adrenaline to control an anaphylactic reaction should be admitted for observation for at least 24 hours.	Although there was no clinical manifestation that distinguished those patients with biphasic reactions from those patients with a uniphasic response, the authors found that patients experiencing biphasic reactions required larger doses of epinephrine to ameliorate the initial response.

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Table 1 (continued)

Reference	Type of study	Subjects with biphasic response	Incidence of biphasic reactions in study (%)	Age range (years)	Gender	Route of administration	Time (hours) to onset of second response after resolution of primary reaction	Fatalities	Original authors' comments	Observations
Lee and Greener, 2000 [10]	Retrospective analysis of admissions for anaphylaxis	6	6%	1–11	3 male, 3 female	4 oral, 2 parenteral	1.3–28.4	0	A delay in administration of epinephrine might predispose to a biphasic response. Two percent of anaphylactic episodes in their study would have benefited from an observation period of 24 hours.	As opposed to the studies by Douglas and colleagues [9] and Stark and Sullivan [26], there were no distinguishing signs or symptoms that allowed one to predict whether or not a biphasic response might occur in regard to the incidence or severity of respiratory or cardiovascular manifestations.
Forrest-Hay et al, 2003 [14]	Retrospective analysis	9	9%	NG	NG	NG	8 of 9 reactions within 6 hours, 1 patient had a second reaction occurring at 35 hours	0	Because most patients experience a biphasic response within 8 hours of the resolution of the initial phase, an 8-hour observation period was recommended.	The authors, unlike in the other studies, were unable to detect any difference between those patients experiencing biphasic versus uniphasic reactions. This was true for the time of onset of treatment, the treatment given, the severity of the episode, and the original clinical manifestations.

Ellis and Day, 2004 [12]	Prospective review of emergency department visits and admissions	20	19.4%	11 months to 79 years	11 male, 9 female	7 oral, 7 parenteral, 5 idiopathic, 1 inhalation	2-38 (average time = 10 hours)	0	A decrease in epinephrine total dose (not incidence of administration) was associated with a biphasic response. In addition, a decrease in total dose and frequency of administration of corticosteroids was also associated with this response.	This incidence is almost identical to that described by Stark and Sullivan [26].
Smit et al, 2005 [15]	Retrospective analysis	15	5.3%	6-80 (median = 33)	10 male, 5 female	9 oral, 1 parenteral, 3 not documented, 2 unknown	1.2-22.5 (mean = 7.6)	0	The authors suggested that a "reasonable approach would be to observe those who received epinephrine and remain stable for 24 hours, and to observe all other patients for 12 hours."	The authors observed that the mean time from onset to presentation was 3 times longer in biphasic than in uniphasic patients.

Abbreviations: N/A, not applicable; NG, not given.

^a The authors commented that one of the patients "almost certainly would have died if he had not been under observation when his airway obstruction reoccurred."

Popa and Lerner [5] reported three patients who developed systemic anaphylactic symptoms after exposure to rabies vaccine, rye grass extract immunotherapy, or yellow jacket sting. These patients were treated and had improved until 3.5 to 4 hours later, when they redeveloped their anaphylactic symptoms.

The first prospective evaluation of biphasic anaphylactic reactions was by Stark and Sullivan [26], who reported anaphylactic episodes in 25 patients presenting to an emergency department. Five (20%) of these subjects exhibited a biphasic reaction, which the authors noted to be two episodes of hypotension or laryngeal edema separated by an asymptomatic interval. This asymptomatic interval after resolution of the initial episode until the onset of the biphasic reaction was 1 to 8 hours. One of these five subjects actually had a biphasic anaphylactoid reaction to radiocontrast rather than an IgE-mediated biphasic anaphylactic reaction. Stark and Sullivan [26] observed that recurrent or prolonged reactions were more likely to occur (2.8-fold) if the offending agent had been ingested or if the onset of the original reaction was 30 minutes or more after exposure to the offending agent. It was also noted that these reactions were more likely if laryngeal edema was present during the first phase. Neither the severity of the initial reaction nor the treatment administered seemed to correlate with the development of a biphasic response. In their patients, as in those reported by Popa and Lerner [5], corticosteroids did not seem to prevent or ameliorate the biphasic reaction. Neither the presence of severe respiratory symptoms nor that of cardiovascular manifestations, specifically hypotension, in the initial episode was predictive of the occurrence of a late-phase reaction.

Stark and Sullivan [26] thought that the most salient points derived from their study were that serious life-threatening manifestations could recur in patients after successful treatment of the initial response and that these events could develop anywhere from 1 to 8 hours after apparent remission of the initial manifestations. They also concluded that such biphasic responses could be reasonably common, occurring in 20% of their series. They thus made the suggestion that "until methods are developed to predict or avoid late-phase anaphylactic reactions, all patients should be observed for several hours after apparent recovery from acute anaphylaxis" [26].

The next study of biphasic anaphylactic events was by Douglas and colleagues [9]. The authors used two venues: an outpatient allergy clinic, where patients received immunotherapy, and the Madigan Army Medical Center, where patients had been admitted for anaphylaxis. The patients in the allergy clinic were retrospectively analyzed between the years 1988 and 1991, and the inpatient subjects were retrospectively analyzed between 1986 and 1992. Two (5%) of the 35 patients in the allergy clinic who experienced anaphylaxis to immunotherapy developed a biphasic reaction. Four (7%) of the 59 subjects admitted to the hospital with anaphylaxis developed a biphasic response. Thus, there was an overall incidence of biphasic responses of approximately 5.8. All the patients admitted to the hospital

had received allergen by means of the oral route (2 to β -lactam antibiotics and 2 to shrimp). In their study, the biphasic response could be less severe, similar to, or more severe than the original response. There were no fatalities. In contrast to the study by Stark and Sullivan [26], there was a suggestion that corticosteroids might be effective in minimizing the biphasic manifestations or preventing such a response. Although there were no clear-cut distinguishing features between those subjects with a biphasic response and those with only a uniphasic reaction, the absence of hypotension seemed to favor a uniphasic event. Douglas and colleagues [9] reported a significantly lower incidence of biphasic reactions than did Stark and Sullivan [26]. There was no clear explanation for this, but they postulated that, at least within the inpatient group, "early intervention...with high dose corticosteroids may have played a role in decreasing the biphasic reaction rate" [9].

The first and only study to date specifically designed to evaluate the incidence and nature of biphasic reactions in children was reported by Lee and Greenes [10], who retrospectively analyzed the charts of 108 children with anaphylaxis admitted to a children's hospital between 1985 and 1999. Of these 108 episodes, 2 were fatal and 1 was protracted. The remaining 105 cases showed resolution of the initial anaphylactic manifestations. Six (6%) of these patients experienced biphasic reactions after an asymptomatic interval ranging from 1.3 to 28.4 hours. Of the biphasic anaphylactic cases, 4 were attributed to orally administered antigens (dicloxacillin, trimethoprim-sulfamethoxazole, fish, and nuts) and 2 were caused by bee stings. Each child experienced similar symptoms. All but 1 child had cutaneous manifestations, most had wheezing and shortness of breath, and some had abdominal pain. Hypotension occurred in 1 child. As observed by the authors, a notable finding is that a delay in epinephrine administration predisposed to a biphasic response. The median time from the onset of initial symptoms to the administration of epinephrine in those subjects experiencing a biphasic reaction was 190 minutes versus only 48 minutes for those with a uniphasic episode. There were no significant differences in the frequency of epinephrine administration, corticosteroid use, or serious cardiovascular or respiratory symptoms between those children experiencing biphasic versus uniphasic events. There were no fatalities. The incidence in their report was similar to the 5.8% reported by Douglas and colleagues [9] but lower than the 20% reported by Stark and Sullivan [26]. Furthermore, the authors noted in their series that "approximately 2% of patients with anaphylaxis appeared to benefit substantially from a 24-hour period of observation after symptoms had resolved" [10].

Brady and colleagues [11] performed a retrospective analysis of patients seen in a university hospital emergency department between July 1991 and December 1995. Their study differed from previous evaluations in that they also searched for recurrences of anaphylactic symptoms after discharge when individuals presented a second time to the same primary treatment

hospital or to any other hospital within a 75 mile radius of the primary institution within a 7-day period. Of the 67 patients with anaphylaxis who presented to their emergency department, 2 (3%) experienced a biphasic response 26 and 40 hours after resolution of the initial reaction. Both patients initially presented with angioedema and falls in blood pressure after exposure to hymenoptera stings and were treated with corticosteroids, epinephrine, and antihistamines. The biphasic reactions were mild, limited to urticaria. Neither patient required additional treatment or admission. The authors concluded that "recurrent anaphylactic reactions were rare, occurring in only 3% of cases and without life threat in this patient population" [11].

Ellis and Day [12] reported a prospective evaluation of emergency department visits and inpatient admissions identifying 134 patients with anaphylaxis over a 3-year period, of whom 103 were available for follow-up. Twenty patients (19.4%) had biphasic reactions occur from 2 to 38 hours after resolution of the first reaction. Eight of those who experienced biphasic anaphylaxis (40%) had their second-phase reaction occurring more than 10 hours after resolution of the initial symptoms. The symptoms of those experiencing a second phase were similar to the symptoms of those who had only a uniphasic response. The second phase could be milder than, similar to, or more severe than the initial event. All subjects with second-phase responses had cutaneous symptoms. This 19.4% incidence was similar to that found by Stark and Sullivan [26]. Ellis and Day [12] found that patients with biphasic reactions could be distinguished from those with uniphasic reactions in that the mean time of resolution of the initial event was 133 minutes in the biphasic group versus 112 minutes in the uniphasic group. Also, the authors noted that those experiencing biphasic reactions tended to have initial reactions that lasted longer, were given less epinephrine, and tended to receive less corticosteroids.

Brazil and MacNamara [13] retrospectively analyzed 34 patients with anaphylaxis admitted to a hospital. Six (18%) of these patients had biphasic reactions occurring 4.5 to 29.5 hours after resolution of initial symptoms. These investigators were unable to find any clinical features on initial presentation that distinguished these patients from those with uniphasic events. Nevertheless, the authors observed that patients with biphasic reactions did require more epinephrine to ameliorate the symptoms of their early response; thus, they suggested that this increased requirement for epinephrine might be considered a marker for patients subject to development of a biphasic response. Because of the delay of 29.5 hours in 1 patient, the authors stated that "all patients requiring adrenaline to control an anaphylactic reaction should be admitted for observation for at least 24 hours" [13].

Forest-Hay and colleagues [14] reported a retrospective review of 103 anaphylactic events in 91 patients admitted to an emergency department in the United Kingdom. There were nine biphasic reactions. Eight of these occurred within 6 hours of resolution of the first reaction. The authors noted

that one of the biphasic reactions occurred as late as 35 hours after resolution of the first reaction, however. There were no distinguishing features between uniphasic and biphasic events in regard to presenting symptoms or signs, treatments, or time to onset of therapy. Only 1 patient had a more severe biphasic reaction than the initial reaction. The authors concluded that most biphasic responses occur within 8 hours of resolution of the initial response and that little was gained by a 24-hour waiting period. They suggested discharge, after successful response to treatment, in 8 hours.

The most recently published retrospective review, and the largest study to date reporting on biphasic anaphylaxis, was done by Smit and colleagues [15], who evaluated 282 patients with anaphylaxis who presented to the Prince of Wales Hospital Emergency Department in Hong Kong between March 1999 and February 2003. Additionally, the authors searched for presentation of these patients to other hospitals in the Hong Kong area within a 5-day period after discharge from the primary site. Fifteen (5.3%) of these 282 patients developed biphasic anaphylaxis. This study differed slightly from most previous evaluations in that it recorded the duration of time from treatment to onset of biphasic response rather than from resolution of initial symptoms to onset of biphasic response. Nevertheless, mean time until the development of biphasic symptoms was 7.6 hours, with a range of 1.2 to 22.5 hours. Cutaneous manifestations were the most common initial complaint, whereas respiratory features were much less common. Overall, 12 of the 15 biphasic reactions were mild and had similar clinical manifestations as the initial reaction. Of the remaining 3 patients, who had stable vital signs on presentation, 2 developed hypotension and 1 experienced dyspnea with oxygen saturation of 92%. There were no fatalities in this study. Of interest, one of the statistically significant features in the biphasic group is that the mean time from onset to presentation was 3 hours for biphasic patients versus 1 hour for uniphasic patients. Patients who went on to develop biphasic reactions experienced less common and pronounced respiratory features; specifically, 35% of biphasic patients complained of dyspnea versus 77% of those with uniphasic anaphylaxis. The authors reported that 4 of the biphasic patients had their reaction beyond 8 hours after treatment, including the individual with decreased oxygen saturation, which occurred 12 hours after treatment, yet all biphasic reactions occurred within 23 hours from time of treatment. Therefore, the authors concluded that “a reasonable approach would be to observe those who received epinephrine and remain stable for 24 hours, and to observe all other patients for 12 hours” [15].

Most of the articles described previously were specifically designed to assess, in a retrospective or prospective manner, the incidence and clinical characteristics of biphasic anaphylaxis. Although not designed specifically to evaluate the biphasic response, some insight into the biphasic reaction may be gleaned from case reports [16–20] and series of anaphylactic cases that note biphasic reactions [21,22].

Brady and colleagues [16] reported a case of an elderly man on a β -adrenergic blocker who experienced the relatively benign initial anaphylactic manifestations of diffuse pruritus, dizziness, dyspnea, and facial swelling "occurring after an encounter with an unidentified flying insect." After self-administering diphenhydramine (25 mg) orally, the patient placed a telephone call to "911." The paramedics arrived a short time later to find an elderly man with a complaint of profuse itching, but without any obvious distress. Vital signs revealed a blood pressure of 102 mm Hg by palpation, pulse of 82 beats per minute, and respiratory rate of 16 breaths per minute. The man had urticaria and facial edema. An intravenous line was placed, diphenhydramine was administered, and the man was transported to the emergency department. During the 45 minutes it took to arrive at the emergency department, the symptoms resolved and he had no complaint. Vital signs on presentation were a blood pressure of 110/70 mm Hg and a pulse of 80 beats per minute. Shortly after arrival, however, he became lethargic, with a blood pressure of 78/40 mm Hg, a pulse rate of 70 beats per minute, and a respiratory rate of 28 breaths per minute. Urticarial lesions reappeared. He was treated with epinephrine, corticosteroids, and antihistamines and then admitted to the hospital for a period of 36 hours. In contrast to their series of anaphylaxis in predominantly younger patients without significant medical problems in which the second response was mild, Brady and colleagues [11] attributed this patient's more severe reaction to his previous cardiovascular status, the use of a beta-blocker, and his age. They thus concluded that the factors of previous cardiovascular disease, the use of a beta-blocker, and advanced age might predispose one to the potential occurrence of a severe biphasic response.

Some of these factors were also present in the report by Cortellini and colleagues [17] of a 76-year-old atopic man with history of large local reactions to insect stings, ischemic cardiomyopathy, and hypertension treated with a calcium channel blocker. The patient experienced urticaria, erythema, and hypotension of 90/60 mm Hg approximately 10 minutes after 15 vespid stings. The patient was seen at his home 30 minutes later by an emergency doctor, who found the patient with urticaria and erythema of the back and neck. Nevertheless, the patient had unaffected respiratory function, and vital signs were blood pressure ranging from 120/70 to 130/60 mm Hg and a heart rate of 74 beats per minute. The patient received parenteral corticosteroid and antihistamine and was observed for 45 minutes; at that time, his urticaria had incompletely subsided. Approximately 40 minutes later, the patient experienced a recurrence of urticaria and angioedema of the neck and felt weak. Shortly thereafter, the patient died despite resuscitation attempts by the doctor, who had returned. The authors raise the question whether administration of epinephrine or a longer observation period would have benefited this particular patient.

Novembre and colleagues [18] reported the first biphasic anaphylactic reaction to ketorolac in the case of a 13-year-old girl. She received a second

dose of ketorolac for abdominal pain 8 hours after an initial dose; 30 minutes later, she developed urticaria and breathing difficulties. She was treated in the emergency department 20 minutes later with hydrocortisone and promethazine, and her symptoms abated within 2 hours. Sixteen hours after discharge, however, she experienced a recurrence of the urticaria and dyspnea as well as abdominal pain and hypotension, with a blood pressure of 88/46 mm Hg. She received epinephrine, steroid, and antihistamine, with resolution of symptoms. The authors later performed skin prick and intradermal testing with ketorolac, the results of which were negative. Thus, the authors noted that in this patient, the reaction to the ketorolac did not seem to be mediated by IgE.

Brady and Bright [19] reported a case of multiphasic anaphylaxis on a transcontinental air flight in which the subject experienced a more severe biphasic response than the initial reaction.

Ellis and Day [20], in addition to their series noted previously, reported a case of a 14-year-old with a severe biphasic reaction to a hymenoptera sting. Approximately 20 hours after resolution of the first phase, there was a recurrence of symptoms. The second event consisted of urticaria, pruritus, angioedema, and respiratory distress severe and persistent enough to require admission to the pediatric intensive care unit, where the patient was intensively treated and observed overnight. This case is similar to that of Brady and Bright [19] in that the second phase was far more severe than the initial event. It is also of interest because of the long 20-hour asymptomatic phase between the first and second events.

Samson and colleagues [21] described a series of young subjects, ranging in age from 2 to 17 years, who experienced near-fatal or fatal anaphylactic events. Although seeming to improve, 3 of the 13 patients in this series experienced a biphasic episode.

In a series of 593 patients conducted over several decades, Webb and colleagues [22] noted the incidence of biphasic reaction in these patients to be less than 1%. The frequency of biphasic reactions in this study was determined by patient questionnaire rather than by chart review, however.

In a study of eight cases of idiopathic anaphylaxis in children, Hogan and colleagues [23] reported one of these to have a biphasic reaction. This event occurred in a 15-year-old who had wheezing, angioedema, and hypotension, and who, as described by the authors, received an "inadequate amount of epinephrine and experienced a more severe delayed event 8 hours after successful treatment of the initial episode" [23].

Based on these studies, the extent of variability concerning biphasic reactions is apparent. The incidence of biphasic anaphylaxis ranges from less than 1% to 20% of anaphylactic episodes. The time of onset after resolution of the initial reaction ranges from 1 hour to 78 hours. The severity of the second response can be less severe, equal in severity, or more severe than the original response, thus ranging from mild to fatal.

Only two investigations reported fatalities. In a report by Stark and Sullivan [26], there were two deaths among 25 patients. The 2 patients who died did not experience a truly biphasic reaction but rather had protracted events. In one instance, the patient was taking propranolol, and in the other, the patient experienced adrenal insufficiency. One patient who died was a 33-year-old woman who had received cefaclor and died 8 days after the onset of symptoms. The other was a 50-year-old man who had been given murine monoclonal anti-T3 antibody and died after 5 hours of treatment [26]. Samson and colleagues [21] reported six deaths in children and adolescents. Three of the six children and adolescents who died seemed to be improving before the recurrence of terminal cardiorespiratory arrest. These three had early oral and abdominal symptoms, followed by a relatively symptom-free period of 1 to 2 hours, and then experienced respiratory symptoms and a fall in blood pressure.

It would be ideal to predict the occurrence of a biphasic reaction based on the clinical manifestations of the initial response. No data presented thus far allow us to do so conclusively; however, we may glean information from these studies and experiences to obtain some insight. It seems that a delay in the administration of epinephrine, an inadequate amount of epinephrine given for the first response, or the requirement of large doses of epinephrine suggests that a biphasic response is more likely. There is less evidence to suggest that the absence of corticosteroid administration might predispose to a biphasic response. In some instances, failure to administer corticosteroids seemed to predispose to such a response; however, in other reports, the administration of corticosteroids seemed to make little difference. Although no definitive conclusion can be made, the data suggest that corticosteroids might have a beneficial effect in some individuals. Although no dogmatic conclusions can be drawn from the patient's history or physical manifestations of the first event, at least in one case report, the presence of previous cardiovascular disease, the age of the patient, and the use of beta-blockers might predispose to recurrence of symptoms after an initial remission. In one study, a delay in the appearance of symptoms after exposure to antigen suggested a biphasic response, but it should be noted clearly that biphasic responses occur when the initial episode takes place within minutes of exposure to antigen. The oral route of administration of antigen seems to be an important predisposing factor. As noted, however, biphasic responses can occur after the antigen is administered parenterally or even by inhalation. Most such episodes have been anaphylactic in nature, but at least in one instance, a biphasic response occurred after an anaphylactoid event. Such reactions can also occur in episodes that are idiopathic in nature.

Because of the wide variety of time intervals between the resolution of the initial event and the reoccurrence of symptoms, it is not possible to establish a strict observation period that would be practical and still allow for the recurrence to occur while the patient is under medical observation. It seems, however, that a 24-hour observation period would benefit only a small

number of patients and that most of the severe reactions occur within a far shorter period. An 8-hour observation period might thus be sufficient to ensure that most severe recurrences would manifest while the patient was still under medical observation.

No studies have systematically evaluated therapy for the late-phase reaction. In all instances, as best can be gleaned from the literature, therapy for the late-phase reaction has been similar to that of the first phase and dictated by the manifestations and severity of the second reaction. Epinephrine, antihistamines, and corticosteroids have been the mainstay of therapy for the late-phase events, as they have been for the initial events. Because the fatality rate has been low, it is inferred that standard therapy has been reasonably effective. Therefore, from these observations, it would seem that standard therapy for anaphylaxis as would be applied to the initial phase constitutes treatment for the biphasic reaction as well.

The clinical characteristics of the biphasic responses are summarized in [Box 1](#).

Theories of biphasic pathogenesis

Several potential pathogenic mechanisms have been proposed as listed in [Box 2](#).

The biphasic response was originally thought to be attributable to a temporarily ablated initial reaction, and therefore the result of insufficient treatment [3–5]. It was later hypothesized that the biphasic anaphylactic response, like that in the skin and respiratory tract, was the result of the secondary influx of cells into the site(s) of the reaction [5]. There are several lines of evidence that mitigate against this possibility, however. Histologic studies of patients experiencing fatal reactions after protracted events do not reveal changes similar to those noted in the respiratory tract and skin after biphasic reactions [24]. The only cell to accumulate in tissues after anaphylactic episodes is the eosinophil, and there is often no cellular infiltrate [24]. Furthermore, the time interval between the first and second phases in the biphasic anaphylactic reaction is inconsistent with that seen in cutaneous and respiratory biphasic reactions, which is characteristically between 2 and 8 hours after resolution of the first reaction versus as early as 1 hour and as late as 78 hours after resolution of the initial event for biphasic anaphylaxis.

It has been speculated that the oral administration of antigen, which allows for continued antigen absorption, predisposes to biphasic reactions. A review of the literature, as summarized in [Table 1](#), clearly indicates that biphasic responses occur not only after oral but after parenteral administration, however. The thought that oral administration predisposes to a biphasic response is based on the fact that an offending agent, whether food or drug, could be continually absorbed through the gastrointestinal tract for several hours, thus accounting for a dual response. This indeed

Box 1. Biphasic anaphylaxis clinical characteristics

- Reported incidence ranges from a minimum of less than 1% to a maximum of 20%.
- Onset of recurrence of symptoms after resolution of the initial event ranges from 1 to 78 hours.
- Most second responses occur within 8 hours after resolution of the first event.
- The second response may be less severe, similar to, or more severe than the original episode.
- Fatalities can occur.
- Events can be anaphylactic or anaphylactoid.
- There are no consistently reported risk factors, but several possible features of the initial episode have been mentioned as predisposing factors for a biphasic reaction. These include the following:
 - Oral administration of antigen
 - Reaction occurring while a patient is taking a beta-blocker
 - Reaction occurring in an elderly individual with cardiovascular disease
 - Delay in onset of more than 30 minutes between the administration of antigen and the appearance of symptoms of the first event
 - Presence of hypotension or laryngeal edema during the initial event
- There is no consensus as to whether therapeutic measures affect the incidence of a delayed reaction, but some reports mention treatment differences between patients with uniphasic and biphasic events. These include the following:
 - Delay in administration of epinephrine given for the primary response
 - Inadequate dose of epinephrine given to treat the primary reaction
 - Absence of or too small a dose of corticosteroids given for the initial event

could be the case, but in view of the fact that parenteral administration can produce biphasic responses, other mechanisms must be involved. Such a depo effect, accounting for the biphasic responses attributable to parenteral administration, is highly unlikely, because biphasic responses have occurred to agents that have a relatively short half-life, such as radiocontrast. In addition, in documented cases of prolonged exposure to food resulting in delayed anaphylactic responses, the episodes are not actually biphasic but

Box 2. Hypotheses of biphasic anaphylaxis pathogenesis

- The recurrence of symptoms is not attributable to a true “biphasic reaction” but represents a recurrence of a temporarily interrupted protracted initial response attributable to appropriate but perhaps inadequate therapy.
- The biphasic response is attributable to the same mechanism that underlies the biphasic respiratory and cutaneous responses—the recruitment of cells to the site(s) of the original response, followed by degranulation of these cells and subsequent secondary release of mediators.
- The biphasic response is related simply to the continued presence of antigen with a “depo” release into the systemic circulation (eg, as perhaps could occur with prolonged absorption of an ingested antigen).
- The biphasic response is attributable to bimodal synthesis of late-phase mediators (eg, platelet activating factor) from mast cells and other cells.
- The response may be the result of a biphasic wave of histamine release from mast cells as a result of the initial exposure to antigen without subsequent exposure.
- The late response is attributable to activation of secondary inflammatory pathways (eg, complement, clotting, clot lysis) resulting from mediators released during the initial event.

simply delayed in onset presumably because of delayed absorption, as has been demonstrated for natto (fermented soybeans) contained in poly γ -glutamic acid, a water-soluble biodegradable polymer, which delays and perhaps prolongs absorption [25].

Investigators have also hypothesized, based on animal models, that biphasic reactions might be attributable to mediators that are synthesized and released late or recruited after the initial event. For example, in a murine model [27] of penicillin-induced anaphylaxis, it was found that a late-occurring synthesis of platelet-activating factor was responsible for the late-phase reaction and that mast cells were not required for this late-phase response. Of interest, in this model, tumor necrosis factor- α (TNF α) inhibition resulted in ablation of the late-phase response as well as the late increase in platelet-activating factor. In the investigation by Samson and colleagues [21] of fatal anaphylactic events, however, there was no elevation of TNF α in two patients who had experienced food-induced anaphylaxis severe enough to be admitted to the intensive care unit with bronchospasm and hypotension.

A second murine model [28] has resulted in another postulation as to the cause of the biphasic response. In this instance, mast cells in the gut underwent a biphasic degranulation response after a single oral exposure to antigen. Peak periods of mediator release occurred at 30 minutes and 72 hours after oral challenge. In addition, mast cell degranulation was followed by the appearance of an inflammatory infiltrate. These observations suggest that it is possible, when antigen is given orally, for there to be a biphasic mast cell degranulation response as well as the characteristic inflammatory response noted in the skin and the respiratory tract, as discussed previously. In this instance, however, the two-phase mast cell degranulation is somewhat different than in the human respiratory model, in which the second wave of mediated release is basophil rather than mast cell generated. In addition, the prolonged time between the first and second waves of degranulation would not account for most biphasic responses, which occur within the first 8 hours.

It is known that mast cell degranulation can result in the activation of other inflammatory cascades, such as the complement system and the clotting and clot lysis pathways [24]. During severe anaphylactic episodes in human patients, falls in complement and evidence for activation of clotting and clot lysis have been noted [24,29]. Thus, it is plausible that mediator recruitment might account for some episodes, especially those characterized by severe hypotension and shock.

Potential clinical impact

The most important clinical impact of the observations discussed previously relates to the suggested waiting period after successful treatment of an anaphylactic episode. Unfortunately, no definitive conclusion can be drawn from these data. Several authors have suggested a 24-hour waiting period, although this would not be necessary for most patients. Ideally, it would be desirable for there to be definitive clinical criteria identifying those patients who are at risk for a biphasic response, and would therefore benefit from a prolonged period of observation. Yet, none of the investigations have clearly delineated such clinical criteria. It is evident that biphasic reactions can range from mild events not requiring further therapy to fatal events despite therapy. Thus, at this time, the authors cannot definitively recommend a standard observation period after resolution of an initial reaction. Some clues gleaned from the literature do suggest a prolonged period of observation. These include the severity of the first episode, the length of time between the onset of symptoms and the initiation of therapy, the provocative agent being ingested, and a previous history of a biphasic response. These predisposing features have been described inconsistently, however, and are in no way mandates of a prolonged 24-hour observation period.

Thus, in the absence of any clear-cut criterion for prolonged observation, it becomes even more desirable to establish a therapy that would

consistently prevent the biphasic reaction. Again, the literature gives us no solace in this regard, although there are some features related to therapy that seem to distinguish those who experience biphasic versus uniphasic reactions. These include the rapidity of administration of epinephrine after the initial manifestations appear, the adequacy of the dose of epinephrine at the time of administration, and the early use of corticosteroids. None of these has consistently been demonstrated to ablate the second reaction, however.

Although we have made some progress in understanding the biphasic anaphylactic response since Popa and Lerner's original article [5], we are not yet close to being able to predict those who are going to develop a biphasic reaction nor are we close to preventing it. The solutions to these clinical problems await further knowledge of the underlying pathogenesis of the biphasic anaphylactic response.

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