
CME review article

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Biphasic anaphylactic reactions

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Objective: To examine the impact of the second phase of a biphasic response on the required observation time after resolution of symptoms that occurred during the initial phase.

Data Sources: We performed a MEDLINE search of the literature for studies published between January 1970 and January 2005 on biphasic response using the keywords *anaphylaxis*, *biphasic anaphylaxis*, *late phase reaction*, and *early phase reaction*.

Study Selection: Prospective studies, retrospective studies, and case reports were selected for inclusion in this review.

Results: The incidence of biphasic anaphylactic reactions as described in the literature is highly variable, ranging from a low of 1% to a high of 20% of episodes. There is no clear consensus regarding distinguishing features of the primary response that predicts the occurrence of a secondary response. However, the severity of the reaction, the time of onset after administration of antigen before the occurrence of symptoms of the primary response, the presence of hypotension or laryngeal edema during the primary response, and the history of a previous biphasic reaction have all been mentioned as risk factors in various studies. The severity of the late-phase reaction is highly variable, and events have ranged from mild to severe with rare fatalities. Most late-phase reactions, however, are mild to moderate in severity. A delay in the administration of epinephrine and too small a dose of epinephrine given for the primary response have also been mentioned as risk factors. It is unclear whether corticosteroids given for the primary event can prevent or ameliorate the second reaction.

Conclusions: Biphasic responses occur with significant frequency and therefore should be taken into consideration when one considers the observation period after the initial event. An observation period of 8 hours is sufficient for most reactions, but since reactions can occur as long as 72 hours after resolution of the primary event, some authors have recommended a 24-hour waiting period.

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INTRODUCTION

Until the early to mid-1970s, all IgE-mediated responses were thought to occur shortly after exposure to antigen and resolve shortly thereafter. Thus, the term *immediate hypersensitivity* was coined to distinguish these events from those (immune complex disease and delayed hypersensitivity) with later onset and more prolonged duration. This was especially thought to be true for anaphylactic reactions.¹ However, Dolovich et al^{2,3} began to challenge this concept in the early 1970s. Based on their observations of the cutaneous reaction to allergen injection, they hypothesized that late-occurring

skin reactions, which appeared after the resolution of the immediate response, were IgE mediated. Previously, it had been assumed that such later-occurring cutaneous reactions were due to IgG and complement.⁴ Dolovich and colleagues came to this conclusion based on observations that late-occurring skin reactions appeared in the absence of any detectable evidence for a type 3 immune reaction.² More conclusively, they showed that these reactions could be passively transferred by serum using the Prausnitz-Küstner method and that anti-human IgE injected into the skin also produced both an immediate and a late-phase response.^{2,3} Solley et al⁵ further extended these observations by demonstrating that late-phase cutaneous reactions were ablated by removing IgE from serum before its injection into the skin for the purpose of transferring the cutaneous reaction using the Prausnitz-Küstner technique. These investigations radically

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affected our concept of immediate hypersensitivity. They spurred interest in the late-phase response, resulting in a bevy of investigations that evaluated this response in the respiratory tract. Such studies have revolutionized our understanding of the pathogenesis of allergic reactions and have significantly altered our approach to therapy of allergic respiratory tract disease. Nonetheless, the thought that *anaphylaxis* might exhibit a biphasic response lay fallow for a number of years. This study examines the impact of the second phase of a biphasic response on the required observation time after resolution of symptoms that occurred during the initial phase. We performed a MEDLINE search of the literature for studies published between January 1970 and January 2005 on biphasic response using the keywords *anaphylaxis*, *biphasic anaphylaxis*, *late phase reaction*, and *early phase reaction*. Prospective studies, retrospective studies, and case reports were selected for inclusion in this review.

The first case reports of biphasic anaphylactic episodes were reported by Popa and Lerner⁶ more than a decade after the original observation of Dolovich et al. It was not until 2 years later that the first prospective study to evaluate the biphasic anaphylactic reaction appeared.⁷ However, as mentioned in Popa and Lerner's article, Duke⁸ described a biphasic anaphylactic reaction as early as 1925, and 2 textbooks^{9,10} published in the early 1980s mentioned the existence of biphasic anaphylactic episodes.

CLINICAL CHARACTERISTICS OF THE BIPHASIC RESPONSE

Since Popa and Lerner's initial report, there have been a number of case reports and studies that deal with the biphasic anaphylactic reaction.¹¹⁻²⁴ These evaluations are given in Table 1.

The first prospective evaluation of biphasic anaphylactic reactions was by Stark and Sullivan,⁷ who reported anaphylactic episodes in 25 patients who presented to an emergency department. Five of their patients exhibited a biphasic reaction, occurring from 1 to 8 hours after resolution of the initial episode. They observed that recurrent or prolonged reactions were more likely to occur if laryngeal edema was present during the first phase or if the onset of the original reaction was 30 minutes or more after exposure to the offending agent. These were the only investigators to note this finding. They also noted that these reactions were more likely if the allergen had been ingested. Neither the severity of the reaction nor the treatment administered seemed to play any role whatsoever in whether a biphasic response occurred. In their patients and in those described by Popa and Lerner, corticosteroids did not seem to prevent or ameliorate the biphasic reaction. In addition, 1 of their 5 patients had experienced an anaphylactoid (to radiocontrast) rather than anaphylactic reaction. The presence of neither severe respiratory symptoms nor cardiovascular manifestations (hypotension) in the initial episode was predictive of the occurrence of a late-phase reaction.

Stark and Sullivan believed that the most salient point derived from their experience was that serious, life-endan-

gering manifestations could occur in patients successfully treated for the initial response. These events could occur 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."

Douglas and colleagues¹¹ published the next study of biphasic anaphylactic events. The authors used 2 venues: the outpatient allergy clinic where patients were receiving immunotherapy and the hospital where patients were admitted for anaphylaxis at the Madigan Army Medical Center. The allergy clinic patients were analyzed retrospectively between the years 1988 and 1991, and the inpatients were retrospectively analyzed between 1986 and 1992. There were 35 immunotherapy reactions and 59 anaphylactic admissions. Two (5%) of the patients experiencing anaphylaxis to immunotherapy exhibited a biphasic reaction. Four (7%) of the patients admitted with anaphylaxis had a biphasic response. Thus, there was an overall incidence of biphasic responses of approximately 5.8%. The patients ranged in age from 7 to 77 years. There were 4 males and 2 females. All of the patients admitted to the hospital had received allergen via the oral route (2 to β -lactam antibiotics and 2 to shrimp). There were no fatalities. In their study, the biphasic response could be less severe, equal to, or more severe than the original response. As opposed to the study by Stark and Sullivan, 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 patients with a biphasic response and those who experienced only a uniphasic reaction, the absence of hypotension seemed to favor a uniphasic event.

Douglas and colleagues therefore reported a significantly lower incidence of biphasic reactions than did Stark and Sullivan. There was no clear-cut 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."

The first and only, to date, study designed to examine specifically the incidence and nature of biphasic reactions in children was reported by Lee and Greenes,¹² who retrospectively analyzed the medical records of children admitted to the hospital with anaphylaxis between 1985 and 1999. Six patients (6%) experienced biphasic reactions. In 4 of these, the antigen was administered orally (trimethoprim-sulfamethoxazole, dicloxacillin, fish, and nuts). The other 2 were due to bee stings. Each child experienced similar symptoms. All but 1 had cutaneous manifestations. Most had wheezing and shortness of breath and some had abdominal pain. Hypotension occurred in 1 child. The time of onset of the second response, after resolution of the first reaction, was 1.3 to 28.4 hours. The authors observed that a delay in epinephrine administration predisposed patients to a biphasic response.

Table 1. Studies of Biphasic Anaphylactic Reaction

Source, y	Type of study	No. of patients with biphasic response	Incidence of biphasic reactions in study, %	Age range, y	Sex, M/F	Route of administration	Time to onset of second response after resolution of primary reaction, h	No. of fatalities	Authors' comments	Comments
Popa and Lerner, ⁶ 1984	Case report	3	NA	22-52	3/0	0 Oral, 3 parenteral	3-4	0	Observe individuals with anaphylaxis for 24 hours regardless of therapy with corticosteroids	The authors coined the term "biphasic anaphylaxis"; all of the cases were considered by the authors to be mild; all of their cases were IgE mediated
Stark and Sullivan, ⁷ 1986	Prospective analysis of emergency department visits and hospitalizations	5	20	21-67	2/3	3 Oral, 2 parenteral	1-8	0*	The authors observed that in patients 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 patients to a late-phase response; treatment with corticosteroids was not helpful in preventing a late-phase response; 1 of the 5 patients with biphasic reactions had an anaphylactoid rather than an anaphylactic response; this patient received radiocontrast; a delay of ≥ 30 minutes after antigen exposure before onset of the early phase seemed to predispose patients 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

continued

Table 1. Continued

Source, y	Type of study	No. of patients with biphasic response	Incidence of biphasic reactions in study, %	Age range, y	Sex, M/F	Route of administration	Time to onset of second response after resolution of primary reaction, h	No. of fatalities	Authors' comments	Comments
Douglas et al, ¹¹ 1994	Retrospective analysis of records from the outpatient service in patients receiving immunotherapy and records of admissions to the emergency department and hospital for anaphylaxis	6	5 in outpatient clinic; 7 for hospitalizations; 5.8 overall incidence	7-77	4/2	4 Oral, 2 parenteral	1-72	0	Authors observed that their incidence of biphasic reactions was significantly lower than that previously reported by Stark and Sullivan	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
Lee and Greenes, ¹² 2000	Retrospective analysis of admissions for anaphylaxis	6	6	1-11	3/3	4 Oral, 2 parenteral	1.3-28.4	0	A delay in administration of epinephrine might predispose patients to a biphasic response; 2% of anaphylactic episodes in their study would have benefited by an observation period of 24 hours	As opposed to the Douglas et al and Stark and Sullivan studies, 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
Brady et al, ¹³ 1997	Retrospective analysis	2	3	19-21	1/1	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 decreases in blood pressure and angioedema; both were treated with corticosteroids, epinephrine, and antihistamines

continued

Table 1. Continued

Source, y	Type of study	No. of patients with biphasic response	Incidence of biphasic reactions in study, %	Age range, y	Sex, M/F	Route of administration	Time to onset of second response after resolution of primary reaction, h	No. of fatalities	Authors' comments	Comments
Ellis and Day, ¹⁴ 2004	Prospective review of emergency department visits and admissions	20	19.4	11 mo to 79 y	11/9	7 Oral, 7 parenteral, 5 idiopathic, 1 inhalation	Average time, 10 hours; range, 2–38 hours	0	A decrease in epinephrine total dose (not incidence of administration) was associated with a biphasic response; in addition, a decrease in both 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 ⁷
Brazil and MacNamara, ¹⁵ 1998	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
Forrest-Hay et al, ¹⁶ 2003	Retrospective analysis	9	9	NG	NG	NG	8 of 9 patients had their biphasic reaction within 6 hours of resolution of the primary response, but 1 patient had a second reaction occurring 35 hours after cessation of the immediate event	0	Since 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 vs those patients with uniphasic reactions; this was true for the time of onset of treatment, the severity of the episode, and the original clinical manifestations

Abbreviations: NA, not applicable; NG, not given.

* Although there were no deaths, 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.”

The median time from the onset of symptoms to the administration of epinephrine in those patients who experienced a biphasic reaction was 190 minutes vs 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 tract symptoms between those children who experienced biphasic vs uniphasic events. There were no fatalities. Thus, the incidence in their report was lower than that reported by Stark and Sullivan⁷ but in keeping with that reported by Douglas and colleagues.¹¹ They also noted that a 24-hour observation period after the resolution of the initial symptoms would have been of value in only 2% of their 105 cases.¹²

Brady and colleagues¹³ also performed a retrospective analysis by reviewing medical records between July 1991 and December 1995 of patients seen in a university hospital emergency department. This study differed from previous evaluations in that they also sought occurrences of symptoms of anaphylaxis after discharge. To do this, they sought episodes of recurrence at the primary treatment hospital and surrounding hospitals within a radius of 75 miles from the primary institution. They looked for recurrences during a 7-day period from the time of the initial visit to their emergency facility. Sixty-seven cases of anaphylaxis presented to their emergency department during the study period. They were able to identify 2 (3% incidence) who experienced a biphasic response. In both of these, the late-phase reaction was mild, limited to urticaria. The patients required neither additional treatment nor an admission. In both patients, the reactions were to Hymenoptera stings. The manifestations of the initial reaction were similar in both and consisted of decreases in blood pressure and angioedema. Each patient at the initial reaction was treated with corticosteroids, epinephrine, and antihistamines. The second response occurred 26 to 40 hours after resolution of the first episode. The authors concluded that "recurrent anaphylactic reactions were rare, occurring in only 3% of cases and without life threat in this patient population."

The most recent series to date was performed by Ellis and Day.¹⁴ They reported a prospective evaluation of emergency department visits and inpatient admissions, identifying 134 cases of anaphylaxis during a 3-year period. One hundred three patients were available for follow-up. The mean age of their population was 33 years (range, 11 months to 79 years). Twenty patients (19.4%) had biphasic reactions. The average time to onset of the second phase after resolution of the first reaction was 10 hours, with a range of 2 to 38 hours. Of note is the fact that 8 (40%) of their patients with biphasic reactions 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 those who had only a uniphasic response. The second phase could be similar, more severe, or milder than the initial event. All patients with second-phase responses had cutaneous symptoms. They found that patients with biphasic reactions could be distinguished from those with uniphasic responses in that

the mean time of resolution of the initial event was longer in the biphasic group (133 minutes vs 112 minutes for the uniphasic group). Also, those experiencing biphasic reactions were given lesser epinephrine dosages and tended to receive lesser corticosteroid dosages. Seven of their patients had antigen administered by the oral route, 7 by the parenteral route, and 1 by inhalation. Their incidence, along with that reported by Stark and Sullivan, is the highest reported to date. The authors concluded that those patients with biphasic responses tended to have initial reactions that lasted longer and also tended to receive lesser epinephrine and corticosteroid dosages.

Brazil and MacNamara¹⁵ retrospectively analyzed 34 patients with anaphylaxis admitted to the hospital. Six (18%) of these patients had biphasic reactions. They were unable to find any clinical features on initial presentation that distinguished these patients from those with uniphasic events. However, patients with biphasic reactions required more epinephrine to ameliorate the symptoms of their early response. They therefore suggested that this increased requirement for epinephrine might be considered a marker for patients subject to developing a biphasic response. The time of onset after resolution of the initial event in their series was 4.5 to 29.5 hours. 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."

Forest-Hay and colleagues¹⁶ reported a retrospective review of 103 anaphylactic events in 91 patients admitted to an emergency department in the United Kingdom. There were 9 biphasic reactions. One of these occurred 35 hours after resolution of the first reaction. In the other 8 patients, the reoccurrence was in 6 hours or less. In 1 individual the second reaction was more severe than the first. The authors were not able to identify any distinguishing features between uniphasic and biphasic events. Specifically, there were no presenting symptoms or signs, differences in treatment, or differences in time to onset of therapy between the uniphasic and biphasic episodes. 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 articles described herein, with the exception of Popa and Lerner's initial report, were designed to specifically evaluate either in a retrospective or prospective manner the incidence and clinical characteristics of biphasic reactions. There are other publications, though not designed specifically to evaluate the biphasic response, that shed some light on biphasic reactions. These are in the form of either case reports¹⁷⁻¹⁹ or series of anaphylactic cases in general that mention biphasic reactions.^{20,21} Brady and colleagues, in addition to their series of patients who experienced biphasic responses,¹³ also reported 2 separate cases.^{17,18} In one of these,¹⁷ the initial manifestation of anaphylaxis was relatively benign, consisting 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 called 911, and shortly thereafter paramedics arrived to find an elderly man complaining of profuse itching without any obvious distress. Vital signs showed a blood pressure of 102 mm Hg by palpation, pulse of 82/min, and respiratory rate of 16/min. He had urticaria and facial edema. An intravenous line was placed, diphenhydramine was administered, and the patient was transported to the emergency department. During the 45 minutes it took to arrive at the emergency department, the symptoms resolved. At arrival, he had no complaints, presenting with a blood pressure of 110/70 mm Hg with a pulse of 80/min. However, shortly after arrival he became lethargic and his blood pressure decreased to 78/40 mm Hg, with a pulse of 70/min and a respiratory rate of 28/min. Urticarial lesions reappeared. He was treated with epinephrine, corticosteroids, and antihistamines and subsequently admitted to the hospital. His stay lasted 36 hours. Of note is the fact that he was taking a β -adrenergic blocking agent at the time of the reaction. Based on this case, the authors suggested that, in contrast to their series of anaphylactic patients noted herein,¹³ in which case the second response was mild, this patient had a more severe reaction, which the authors attributed to his previous cardiovascular status, the β -blocker that he was taking, and his age, noting that their previous series consisted for the most part of younger individuals without significant medical problems. They thus concluded that older age, previous cardiovascular disease, and the use of a β -blocker might be predisposing factors for the potential occurrence of a severe biphasic response.

Ellis and Day¹⁹ 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 that was severe and persistent enough to require admission to the pediatric intensive care unit, where she was intensively treated and observed overnight. This case is similar to that reported by Brady and Bright¹⁸ in that the second phase was far more severe than the initial event. It is also of note because of the long (20 hours) asymptomatic phase between the first and second events.

Samson et al²⁰ described a series of near-fatal or fatal anaphylactic events that occurred in young patients (age range, 2–17 years). Three of the patients who died had a biphasic episode that had appeared to improve.

Webb and associates²¹ also mentioned the biphasic reaction in a series of 593 patients conducted throughout several decades. In their series, the incidence of biphasic reactions was less than 1%. However, the frequency of biphasic reactions, in this study, was determined by patient questionnaire and not by medical record review.

In a study of idiopathic anaphylaxis in children, Hogan et al²³ reported 8 cases of anaphylaxis, 1 of which had 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 (0.15 ml) and experienced a more severe delayed event eight hours after successful treatment of the initial episode.”

Based on these studies, it is impossible to draw dogmatic conclusions regarding the incidence or distinguishing features of the initial event that would predict a biphasic response. However, the incidence appears to vary considerably, from a minimum of less than 1% to a maximum of 20% of anaphylactic episodes. In addition, the time of onset after resolution of the initial symptoms can be highly variable, ranging from a minimum of 1 hour to a maximum of 78 hours. In the published literature, we can also see that such reactions can be mild to fatal and can be less severe, equal in severity, or more severe than the original response. Only 2 investigations reported fatalities. In the study by Stark and Sullivan, there were 2 deaths of their 25 patients. These 2 patients 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 had adrenal insufficiency. One death occurred 8 days after the onset of symptoms. This was a 33-year-old woman who had received cefaclor. The other patient died after 5 hours of treatment. This was a 50-year-old man who had been given murine monoclonal anti-T3 antibody.⁷ Samson et al²⁰ also reported deaths. They reported 6 deaths in children and adolescents. Three of the 6 children and adolescents appeared to be improving before the recurrence of terminal cardiorespiratory arrest. These 3 who exhibited a biphasic response had early oral and abdominal symptoms followed by a relatively symptom-free period of 1 to 2 hours and then by respiratory symptoms and a decrease in blood pressure.

Of course, it would be desirable, based on the clinical manifestations of the initial response, to predict the occurrence of a biphasic reaction. However, no data presented so far allow us to conclusively do so. There are clues in this information, however, that give us some insight. It appears as if 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 suggest that a biphasic response is more likely. There is less evidence to suggest that the absence of corticosteroid administration might predispose patients to a biphasic response. In some instances, failure to administer corticosteroids seemed to predispose patients to such a response, but in other reports the administration of corticosteroids seemed to make little difference. Thus, no definitive conclusion can be made, but it appears that these data suggest 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 1 case report the presence of previous cardiovascular disease, the age of the patient, and the administration of β -blockers at the time of the event might predispose patients 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 biphasic responses occur when the initial episode appears within minutes of exposure to antigen. The oral route of administration of antigen appears to be an important predisposing factor. However, as noted, 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 following an anaphylactoid event. Such reactions can occur as well in episodes that are idiopathic in nature. The severity of the late-phase reaction is highly variable, and events have ranged from mild to severe with a rare fatality. Most late-phase reactions, however, are mild to moderate in severity.

Because of the wide variety of intervals between the resolution of the initial event and the reoccurrence of symptoms, it is not possible to establish an observation period that would be practical and still allow for the recurrence to occur while 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 be sufficient therefore to ensure that most severe recurrences would manifest while the patient was still under medical observation.

To our knowledge, 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. Since the fatality rate has been small, apparently standard therapy has been reasonably effective. From these observations therefore, it would appear 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 given in Table 2.

THEORIES OF PATHOGENESIS

Several potential pathogenic mechanisms have been proposed. The biphasic response was originally thought to be due to a temporarily ablated initial reaction and therefore the result of insufficient treatment.^{6,9,10} 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.⁶ However, several lines of evidence mitigate against this possibility. Histologic studies of patients who experienced fatal reactions (after protracted events) do not reveal changes similar to those noted in the respiratory tract and skin after biphasic reactions.²² The only cell to accumulate in tissues after anaphylactic episodes is the eosinophil, and often there is no cellular infiltrate.²² In addition, the interval between the first and second phases in the biphasic anaphylactic response is inconsistent with that seen in cutaneous and respiratory biphasic reactions. In the latter, the second response is characteristically noted between 2 and 8 hours after resolution of the first reaction. As noted herein, however, biphasic responses can occur as early as 1 hour after resolution of the initial event and as late as 78 hours after resolution.

It has been speculated that the oral administration of antigen, which allows for continued antigen absorption, predisposes patients to biphasic reactions. However, a review of the literature, as summarized in Table 1, clearly indicates that biphasic responses occur not only after oral but also after parenteral administration. The thought that oral administration predisposes patients to a biphasic response is based on the fact that food (or drug) could be continually absorbed through the gastrointestinal tract for a number of hours, thus accounting for a dual response. This indeed could be the case, but in view of the fact that parenteral administration can produce biphasic responses, other mechanisms must be involved. Such an effect, accounting for the biphasic responses due to parenteral administration, is highly unlikely, since biphasic responses have occurred to agents that have a relatively short half-life (eg, radiocontrast). In addition, in doc-

Table 2. Summary of the Clinical Characteristics of the Biphasic Anaphylactic Event

Maximum reported incidence is 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 similar to, less severe, 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 the occurrence of a reappearance of symptoms. These include:
Oral administration of antigen
Reaction occurring while patient taking a β -blocker
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
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:
A delay in administration of epinephrine given for the primary response
An inadequate dose of epinephrine given to treat the primary reaction
The absence of or too small a dose of corticosteroids given for the initial event

umented cases of prolonged exposure to food that resulted in delayed anaphylactic responses, the episodes are not actually biphasic but simply delayed in onset presumably due to delayed absorption, as has been demonstrated for natto (fermented soybeans) contained in poly-gamma-glutamic acid, a water-soluble biodegradable polymer that delays and perhaps prolongs absorption.²⁴

Investigators have also hypothesized, based on animal models, that biphasic reactions might be due to mediators that are synthesized and released late or recruited after the initial event. For example, in a murine model of penicillin-induced anaphylaxis, it was found that a late-occurring synthesis of platelet-activating factor was responsible for the late-phase reaction.²⁵ In this model, mast cells were not required for the development of the late-phase response. Tumor necrosis factor α inhibition resulted in ablation of the late-phase response and the late increase in platelet-activating factor. However, in the investigation by Samson and colleagues²⁰ of fatal anaphylactic events, there was no elevation of tumor necrosis factor α level in 2 patients who had experienced food-induced anaphylaxis severe enough to be admitted to the intensive care unit with bronchospasm and hypotension.

A second murine model²⁶ 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 and the characteristic inflammatory response noted in the skin and the respiratory tract discussed herein. However, in this instance, the 2-phase mast cell degranulation is somewhat different from 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 wave of degranulation would not account for biphasic responses that occur within the first 8 hours (which represent most events).

It is known that mast cell degranulation can result in the activation of other inflammatory cascades, including the complement system, clotting, and clot lysis pathways.²² During severe anaphylactic episodes, decreases in complement and evidence of activation of clotting and clot lysis have been noted in humans studied during the event.^{22,27} 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 herein relates to the suggested waiting period after successful treatment of an anaphylactic episode. Unfortunately, no definitive conclusion can be drawn from these data. However, a number of authors have suggested a 24-hour waiting period. Nonetheless, this would not be necessary for

most patients. Thus, it would be desirable for there to be established criteria identifying those patients who are at risk of a biphasic response and who would therefore benefit from a prolonged period of observation. Sadly, this is not the case. None of the investigations have clearly delineated features that distinguish patients predisposed to a biphasic response from those who experience a uniphasic reaction. It is also evident that biphasic reactions can range from mild, not requiring further therapy, to potentially fatal events. Thus, at this time we cannot definitively recommend a standard observation period after resolution of an initial reaction. Some clues, gleaned from the literature, suggest a prolonged period of observation. These clues include the severity of the first episode, 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. However, these predisposing features have been described inconsistently 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 vs uniphasic reactions. These features include the rapidity of administration of epinephrine after the initial manifestations appear, the adequacy of the dose of epinephrine at the time of administration (those receiving larger doses seem to have a lower incidence of biphasic reactions), and the early use of corticosteroids. However, none of these features have consistently been demonstrated to ablate the second reaction.

Although we have made some progress in understanding the biphasic anaphylactic response since Popa and Lerner's original article, we are yet a great distance from being able to predict those who will experience it or what will prevent it. The solutions to these clinical problems await further knowledge of the underlying pathogenesis of the biphasic anaphylactic response.

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CME Examination

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CME Test Questions

1. Which of the following statements best characterizes the biphasic anaphylactic reaction?
 - a. it does not occur later than 8 hours after the first phase
 - b. it does not occur with an anaphylactoid reaction
 - c. those 50 years or older are at increased risk of a biphasic response
 - d. females are at increased risk of a biphasic response
 - e. ingested antigen is a risk factor for a biphasic response
2. Which of the following drugs(s) has been reported to predispose patients to the occurrence of a biphasic reaction?
 - a. β -blocker
 - b. angiotensin-converting enzyme inhibitor
 - c. angiotensin receptor blocker
 - d. calcium channel blocker
 - e. α -adrenergic blocker
3. Which of the following has been shown to eliminate the biphasic response in an animal model of biphasic anaphylaxis?
 - a. anti-tumor necrosis factor α
 - b. anti-interleukin (IL) 1
 - c. anti-IL-5
 - d. anti-IL-4
 - e. anti-IL-15
4. Which of the following drugs or combination of drugs given for treatment of the initial reaction has been shown to consistently prevent the occurrence of a biphasic response?
 - a. epinephrine
 - b. diphenhydramine
 - c. corticosteroids intravenously
 - d. a combination of diphenhydramine and cimetidine
 - e. none of the above
5. Biphasic responses have been seen during reactions in which of the following instances?
 - a. due to radiocontrast
 - b. due to antibiotics
 - c. due to foods
 - d. idiopathic in nature
 - e. all of the above

Answers found on page 258.