

The Post-anaphylaxis Dilemma: How Long Is Long Enough to Observe a Patient after Resolution of Symptoms?

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Anaphylaxis may recur 1 to 72 hours after initial signs and symptoms apparently resolve. Reported incidence of biphasic anaphylaxis varies from 1% to 23%. Late-phase severity varies from mild to severe (rarely fatal). No evidence or expert consensus presently identifies distinguishing characteristics in the initial phase that predict a late phase. However, reports propose potential risk factors, including initial phase severity, delayed or suboptimal doses of epinephrine during initial treatment, laryngeal edema or hypotension during initial phase, delayed symptomatic onset after antigen exposure, or history of biphasic anaphylaxis. It is unclear whether systemic corticosteroids administered in the initial phase can prevent or weaken late-phase reactions. Based on available evidence, observation periods after complete resolution of uniphasic anaphylaxis should be individualized, particularly because there are no reliable predictors of biphasic anaphylaxis. A 10-hour observation period appears sufficient, but some investigators recommend 24 hours.

Introduction

Anaphylaxis is an acute and potentially lethal multisystem allergic reaction consisting of some or all of the following signs and symptoms: diffuse erythema, pruritus, urticaria and/or angioedema; bronchospasm; laryngeal edema; hypotension; and/or cardiac arrhythmias. Other symptoms can occur, such as nausea, vomiting, lightheadedness, headache, uterine and abdominal cramps, generalized warmth, feeling of impending doom, and unconsciousness. Anaphylaxis is almost unavoidable in medical practice.

The US National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) (Fairfax, VA, USA) convened two symposia during which an international and interdisciplinary group of representatives and experts from 13 professional, government, and lay organizations attempted, among other tasks, to establish clinical criteria that would improve diagnostic precision in anaphylaxis [1•]. The working definition proposed is the following: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.” The group proposed that anaphylaxis is likely to be present clinically if any one of three criteria is satisfied within minutes to hours: 1) acute onset of illness with involvement of skin, mucosal surface, or both, and at least one of the following: respiratory compromise, hypotension, or end-organ dysfunction; 2) two or more of the following occur rapidly after exposure to a likely allergen: involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; 3) hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure or decline of systolic blood pressure of greater than 30% compared to baseline [1•]. The group concluded that these criteria “are likely to capture more than 95% of cases of anaphylaxis.”

Anaphylaxis, however, occurs on a clinical continuum. Delaying treatment until the development of multiorgan symptoms is risky because the ultimate severity of an anaphylactic reaction is unpredictable at the outset [2•].

Anaphylaxis occurs in a variety of clinical scenarios. The most common culprits are foods, medications, insect stings, and allergen immunotherapy injections, but any agent capable of producing a sudden, systemic degranulation of mast cells or basophils can induce anaphylaxis [3]. The lifetime individual risk of anaphylaxis is presumed to be 1% to 3%, with a mortality rate of 1% [3], and the prevalence of anaphylaxis may be increasing [4]. Therefore, all physicians must be able to recognize and treat anaphylaxis promptly and appropriately and be able to provide recommendations to prevent future episodes.

Signs and symptoms of anaphylaxis vary, but cutaneous features (urticaria, angioedema, erythema, pruritus)

are the most common [3]. Reactions may be immediate and uniphasic, or they may be delayed in onset, biphasic (recurrent), or protracted. Up to approximately 30% of individuals with anaphylaxis may experience either protracted or biphasic reactions. Protracted anaphylaxis, which may persist up to 32 hours after treatment, is not discussed here because, by definition, treatment is continuous [5,6]. Biphasic anaphylaxis occurs in 1% to 23% of anaphylactic reactions, and symptoms may recur 1 to 72 hours (typically 8 to 10 hours) after apparent resolution of the initial phase [5,6,7••,8–12,13•,14]. The severity of the initial phase is not predictive for either biphasic or protracted anaphylaxis. Data are limited concerning the frequency with which two or more doses of epinephrine are needed to treat anaphylaxis (reports range from 16% to 36%), and multiple cofactors may be involved [15–17]. Hypotheses concerning the pathogenic mechanisms of biphasic anaphylaxis are discussed elsewhere [7••].

Because treatment continues for both uniphasic and protracted anaphylaxis until symptoms resolve, the following discussion focuses on the literature concerning biphasic anaphylaxis and its practical implications for the clinician. A literature search of Medline (January 1970 to July 2007) was conducted using the keywords *anaphylaxis*, *biphasic anaphylaxis*, and *late-phase reaction*. Cross-references were accessed when deemed appropriate.

Clinical Characteristics of Biphasic Reactions

Popa and Lerner [8] provided the first case report of three patients with biphasic anaphylaxis. Stark and Sullivan [5] subsequently reported their observations from the first prospective study of anaphylaxis in 25 consecutive patients who presented to the emergency department, five of whom had biphasic reactions occurring 1 to 8 hours after resolution of the initial event. The investigators observed that the late phase consistently shared the same major signs and symptoms as the initial phase. They also reported that recurrent reactions were more likely if symptoms developed at least 30 minutes after exposure to the stimulus or if the culprit agent had been ingested. Laryngeal edema occurred more frequently in the biphasic group (40%) than in the uniphasic group (23%), but the differences were not statistically significant. Neither Popa and Lerner [8] nor Stark and Sullivan [5] observed preventive or therapeutic benefits during the initial phase of anaphylaxis after administering high doses of corticosteroids to two of three and three of five patients, respectively. On the basis of the biphasic response and the unreliable effect of glucocorticoids on its clinical course, Stark and Sullivan [5] concluded that all patients with anaphylaxis should be observed “for several hours” after apparent recovery from acute anaphylaxis until better prognostic or avoidance measures could be developed.

Douglas et al. [9] examined anaphylaxis in both outpatient and inpatient settings in an effort to determine the frequency of biphasic reactions. Investigators noted 44

anaphylactic reactions in 35 patients who received allergen immunotherapy from 1988 to 1991, two (5%) of which were biphasic in character. Fifty-nine patients experiencing anaphylaxis from various causes were admitted to an affiliated Army medical center hospital from 1986 to 1992, four (7%) of whom had biphasic episodes. All patients admitted to the hospital had ingested the culprit agent (two had ingested shrimp and two had taken a semisynthetic penicillin). The intervals between initial and late phase ranged from 1 to 72 hours. No fatalities occurred in either the outpatient or inpatient group. Although no features clearly distinguished patients with uniphasic anaphylaxis from those with biphasic episodes, the lack of hypotension or “severe” obstruction of either the upper or lower respiratory tract seemed to favor a uniphasic response in the inpatient group. Unlike Stark and Sullivan [5], Douglas et al. [9] suggested that early administration of high-dose corticosteroids might have prevented biphasic reactions, at least in their inpatient group.

Brazil and MacNamara [10] retrospectively reviewed 34 patients admitted from the emergency department after anaphylaxis that required epinephrine. Six (18%) had biphasic episodes. The interval between phases varied from 4.5 to 29.5 hours. The investigators observed that patients who had experienced biphasic episodes did not differ clinically at initial presentation but required significantly more epinephrine to ameliorate the initial symptoms compared with patients who had uniphasic reactions (mean epinephrine dosage 1.2 mg vs 0.6 mg). The investigators concluded that all patients requiring epinephrine to control anaphylaxis should be admitted for at least 24 hours’ observation, and should be discharged only after being educated on how to recognize and treat anaphylaxis.

Brady et al. [6] retrospectively reviewed outpatient, emergency department, and hospital records over a 4.5-year period from 1991 to 1995 for anaphylaxis cases treated at a university hospital emergency department. The primary outcome criterion examined was the recurrence of symptoms within 7 days of release from the emergency department. They reviewed the state death registry and records at the primary treatment hospital and at hospitals within a 75-mile radius. Sixty-seven cases of anaphylaxis presented, of which two (3%) experienced a biphasic response (mild and limited to urticaria in each case) after Hymenoptera stings. Initial treatment for each patient consisted of epinephrine and intravenous antihistamine and steroid. One patient experienced recurrence 26 hours after release and the second at 40 hours. Brady et al. [6] concluded that recurrent anaphylactic reactions were rare and that the “recommendation calling for hospital admission for all patients with severe anaphylactic reactions that promptly respond to therapy with complete, rapid resolution must be questioned. Prolonged ED [emergency department] observation may be adequate for the patient who remains asymptomatic after initial therapy.”

Smit et al. [11] retrospectively reviewed 282 cases of adult anaphylaxis presenting to an emergency department

in Hong Kong from 1999 through 2003, of whom 15 (5.3%) had biphasic anaphylaxis. Two patients returned with tongue swelling and one returned with laryngeal edema (20% of the biphasic group). The mean time from resolution of the initial phase to recurrence was 8 hours (range, 1–23 hours). Seafood was the culprit in five cases, drugs in four, and insect bite in one. Five either had no documented culprit or the culprit was unknown. Unlike those in the report by Douglas et al. [9], patients with respiratory features on initial presentation were unlikely to develop biphasic reactions.

Lee and Greenes [12] specifically analyzed the nature and incidence of biphasic anaphylaxis occurring in children hospitalized for anaphylaxis between 1985 and 1999. Retrospective analysis of records revealed that 6 of 105 patients (6%) experienced biphasic reactions, of which four had received the culprit antigen orally (two foods and two antibiotics). The other two cases occurred after Hymenoptera stings. Of those who had a biphasic reaction, the median time from symptom onset to the initial administration of subcutaneous epinephrine was 190 minutes, compared to 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. The authors concluded that two patients (2%) clinically benefited from a 24-hour observation period.

Ellis and Day [13•] reported a prospective evaluation of emergency department and inpatient services for 134 patients identified with anaphylaxis during a 3-year period (1999–2001). Of 103 patients for whom data were available, 20 (19.4%) experienced biphasic episodes. The most common culprits were foods (35%) and Hymenoptera stings (25%). Mean time from resolution of initial phase to onset of late phase was 10 hours (range, 2–38 hours). Eight reactions (40%) occurred more than 10 hours after resolution of the initial phase of anaphylaxis; four (20%) occurred at least 20 hours after resolution. Most (55%) late-phase reactions were clinically similar to the initial phase, but 40% had life-threatening features (eg, hypotension) that were usually also present in the initial phase, and 20% required more aggressive treatment to control symptoms in the late phase than in the initial phase of anaphylaxis. The investigators' secondary analysis revealed that no biphasic reactions occurred if patients responded completely to treatment within 30 minutes. Of added interest, all these patients had received epinephrine as treatment of their anaphylaxis. Conversely, the only factor appearing to distinguish biphasic from uniphasic anaphylaxis was a greater mean time to resolution of the initial event in the biphasic group (133 minutes compared with 112 minutes in the uniphasic group). The authors concluded that the patients with biphasic responses tended to receive lesser epinephrine and corticosteroid dosages, and that these factors may partially explain how seven

(35%) of the biphasic reactions occurred despite steroid administration during the initial phase of anaphylaxis.

One biphasic anaphylaxis article thus far has reported fatalities. Sampson et al. [14] described 13 fatal and near-fatal cases of food anaphylaxis, of which all three biphasic cases (23% of this series) were fatal. The Stark and Sullivan [5] report is commonly cited for its two fatalities, which occurred in the group with protracted anaphylaxis rather than in the biphasic group.

Recommendations for Observation Periods Vary

To recapitulate, the reported incidence of biphasic anaphylaxis varies from less than 1% to a maximum of 23%. Additionally, the reported time of onset of the late phase may vary from 1 to 72 hours. One report thus far has reported fatalities. Potential risk factors include severity of the initial phase, delayed or suboptimal doses of epinephrine during initial treatment, laryngeal edema or hypotension during the initial phase, delayed symptomatic onset after antigen exposure (often a food or an insect sting), or prior history of biphasic anaphylaxis. It is unclear whether systemic corticosteroids administered in the initial phase can prevent or weaken late-phase reactions.

Several authors have suggested a 24-hour waiting period, but this appears unnecessary for most patients. No data available thus far permit accurate prediction of biphasic anaphylaxis, particularly because no investigation has clearly delineated features of anaphylaxis that would predispose an individual to biphasic rather than uniphasic anaphylaxis. Thus, not surprisingly, consensus guidelines provide considerable latitude in their recommendations for observation periods after apparent resolution of anaphylaxis [1•,18•,19–22]. Two sets are provided as examples.

On the basis of the evidence to date, the participants attending the NIAID/FAAN symposium recommended that observation periods be individualized on the basis of severity of the initial reaction, reliability of the patient, and access to care. A reasonable length of time to consider observing the post-anaphylactic patient is 4 to 6 hours for most patients, with prolonged observation times or hospital admission for those with severe or refractory symptoms. More caution should be used in patients with reactive airway disease because most fatalities associated with anaphylaxis occur in these patients [1•].

European Resuscitation Council guidelines [19] recommend that even patients with “moderate” attacks should be warned of the possibility of recurrent symptoms and, in some circumstances, kept under observation for 8 to 24 hours. “This caution is particularly applicable to:

- Severe reactions with slow onset due to idiopathic anaphylaxis;
- Reactions in severe asthmatics or with a severe asthmatic component;

- Reactions with the possibility of continuing absorption of allergen;
- Patients with a previous history of biphasic reactions.

“A patient who remains symptom-free for 4 hours after treatment may be discharged.”

Conclusions

Pending more definitive prospective, epidemiologic, and pathophysiologic studies in humans with biphasic anaphylaxis, a reasonable evidence-based recommendation appears to be that observation periods after complete resolution of uniphasic anaphylaxis should be individualized, particularly because there are no reliable predictors of biphasic anaphylaxis. An observation period of 10 hours appears sufficient for most reactions, but some investigators recommend 24 hours. Initial phases of anaphylaxis characterized by hypotension, respiratory failure or hypoxemia, repeated doses of epinephrine, poorly controlled asthma, or prior history of biphasic anaphylaxis appear to be reasonable indications for observation periods of at least 24 hours. At discharge, all patients should be provided with an epinephrine auto-injector and should receive proper instruction on self-administration in case of a subsequent episode. Patients should also have ready and prompt access to emergency medical services for transportation to the closest emergency department for treatment after injecting additional epinephrine. Further prospective studies on biphasic anaphylaxis are needed.

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Disclosure

The author has served as an anaphylaxis consultant for Verus Pharmaceuticals (San Diego, CA), and as part of the speaker's bureau on anaphylaxis for Dey, LP (Napa, CA).

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