Would You Recognize This Patient's Biphasic Anaphylaxis?

Not all life-threatening allergic reactions unfold immediately. Using a case example, the authors explain how to be prepared for those with a latent phase of hours to days.

By Peter A. Cuniowski, MD, and Curtis J. Hunter, MD, FACEP

Anaphylaxis is a systemic allergic reaction involving multiple organ systems. Because it can have life-threatening consequences, it requires immediate recognition and treatment. Anaphylaxis results from the immunologically induced release of mast cell or basophile mediators (or both) after exposure to a specific antigen through a mechanism involving immunoglobulin E (IgE). The reaction is usually triggered by exposure to insect venoms, foods, medications, or rubber latex. Exercise-induced anaphylaxis and idiopathic anaphylaxis can also occur, but they are mediated by different mechanisms. Anaphylactoid reactions are typically triggered by opiates, nonsteroidal anti-inflammatory drugs, and radiocontrast agents; they are clinically indistinguishable from anaphylaxis, but they are not IgE mediated.

Variants of the typical anaphylactic reaction include delayed-onset anaphylaxis, protracted anaphylaxis, and biphasic anaphylaxis. This article will focus on biphasic anaphylaxis, including its incidence, pathophysiology, possible predictors, and treatment.

Dr. Cuniowski is an attending physician and **Dr. Hunter** is the chief in the department of emergency medicine at Brooke Army Medical Center, San Antonio Uniformed Services Health Education Consortium, in San Antonio, Texas.

PATIENT PRESENTATION

A 38-year-old man presented to the emergency department for evaluation of pain and swelling in his nose. He reported that about 24 hours earlier, he had been stung by a bee inside his left nostril. Within minutes he experienced facial and throat swelling, so he administered 0.3 mg of epinephrine intramuscularly into his anterior thigh. (The epinephrine had been prescribed after a previous bee sting.) His symptoms resolved in a few minutes and he was asymptomatic until about six hours later, when he began to develop mild throat swelling and dyspnea. He again administered 0.3 mg of IM epinephrine, and those symptoms completely resolved in a few minutes.

>>FAST TRACK<<

On arrival in the emergency department, the patient did not complain of facial or throat swelling, dyspnea, wheezing, or urticaria.

On arrival in the emergency department, the patient did not complain of facial or throat swelling,

dyspnea, wheezing, or urticaria. At triage, his vital signs were: heart rate, 90; blood pressure, 123/85; temperature, 98.6°F; respiratory rate, 18, with an oxygen saturation of 99% on room air.

The patient waited four hours before being seen by a physician. During the physician's interview, he again denied any throat swelling or dyspnea, and his vital signs were relatively unchanged from those recorded at the initial triage. He denied taking any medications and had no known medication allergies. His previous medical history was unremarkable except for an anaphylactic reaction to a bee sting approximately one year before. He said that during that episode, he was asymptomatic for 36 hours, but then developed severe respiratory distress and was admitted to the hospital, where he was intubated and spent four days in the ICU.

On examination, the left lateral portion of the patient's nose had significant edema and erythema and was tender to palpation, but no fluctuance was palpated and no stinger or venom sac was seen inside the nostril. There was no edema of the tongue, pharynx, or neck. On auscultation of the lungs, there was good air movement and no wheezing. No urticaria was noted on skin examination, and the remainder of the physical examination was normal. The patient was given oral prednisone and diphenhydramine. A peripheral intravenous line was placed and cimetidine, morphine, and one liter of crystalloid solution were infused.

Approximately one hour after being seen by the emergency physician, while in the emergency department's observational unit, the patient complained of difficulty breathing, dysphagia, and throat swelling. Examination revealed moderate edema of the tongue and posterior pharynx, inspiratory stridor, and bilateral expiratory wheezing. Repeat vital signs were: heart rate, 105; blood pressure, 125/88; respiratory rate, 28, with an oxygen saturation of 92% on room air. The patient was immediately given 0.3 mg of subcutaneous epinephrine and an albuterol/atrovent nebulizer treatment, followed by a racemic epinephrine nebulizer treatment. When he became more tachypneic and was unable to speak, an intravenous epinephrine drip was started at 3 µg/minute.

An awake nasal intubation was attempted, but the endotracheal tube could not be passed through either nostril because of the significant edema of the patient's nose. So topical anesthetics were applied to the posterior pharynx, and an awake oral fiberoptic intubation was attempted. This was also unsuccessful because of significant edema of the epiglottis. In view of this, a cricothyrotomy kit was obtained and the patient's neck was prepared.

After the patient was given succinylcholine and etomidate, a rapid-sequence intubation was successfully performed by the anesthesiologist. Direct laryngoscopy revealed significant edema of the epiglottis and vocal cords, and a 6-mm endotracheal tube was passed into the trachea with moderate difficulty. During the procedure, the patient's blood pressure remained stable and his oxygen saturation stabilized at 90% on 15 liters of supplemental oxygen.

This patient obviously had biphasic anaphylaxis, although his initial presentation was atypical. He was placed on a ventilator and admitted to the medical ICU. He remained intubated for about 12 hours and then was weaned from the ventilator and extubated. He stayed in the hospital for another 24 hours and remained asymptomatic. On day three, he was discharged with a three-day regimen of oral prednisone, diphenhydramine, and ranitidine, as well as a 14-day course of clindamycin for the cellulitis that had developed at the site of the bee sting.

EPIDEMIOLOGY OF ANAPHYLAXIS

The incidence of anaphylaxis in the United States ranges from 1% to 15% of all allergic reactions. Most of these reactions are managed in the emergency department and account for approximately 400,000 visits per year. Among emergency department patients, insect stings cause up to 59% of acute allergic reactions. Insects of the order Hymenoptera, which includes ants, bees, hornets, wasps, and yellow jackets, have a stinging apparatus at the end of their abdominal segment and inject venom (consisting of various peptides and proteins) that is capable of inducing vasoactive responses.

>>FAST TRACK<<

The endotracheal tube could not be passed through either nostril because of the significant edema of the patient's nose.

Hymenoptera stings are believed to provoke anaphylactic reactions in 0.4% to 5% of the U.S. population, causing 40 to 100 deaths per year. Many experts believe the true mortality rate is much higher. Most of these deaths occur in people with a history of Hymenoptera envenomation, who

Possible Predictors of Biphasic Anaphylaxis

- history of biphasic anaphylactic reaction
- delay in onset of more than 30 minutes between exposure to antigen and appearance of symptoms during initial reaction
- hypotension or laryngeal edema during initial reaction
- oral or ingested route of exposure to antigen
- beta blocker being taken by patient
- delay in administration of epinephrine during treatment of initial response
- inadequate dose of epinephrine to treat initial reaction
- low total dose of epinephrine given
- no corticosteroids or inadequate dose given during treatment of initial reaction
- delay in resolution of initial symptoms despite adequate treatment

develop specific IgE antibodies to various venom components. However, most people only have a localized reaction to hymenoptera stings, consisting of redness, swelling, tenderness, and pain at the envenomation site that usually develops within minutes and resolves within hours.

ATYPICAL ANAPHYLACTIC REACTIONS

Symptoms of anaphylaxis are generally monophasic, occurring within minutes of exposure to the allergen and resolving quickly once appropriate treatment is initiated. Of particular concern to emergency physicians are patients, like the one described in the case study, who experience variants of the typical anaphylactic reaction.

>>FAST TRACK**<<**

The recurrence of symptoms can be severe enough to cause airway compromise, profound hypotension, and even death.

In delayed-onset anaphylaxis, a time lag occurs between initial exposure to the inciting agent and development of clinical symptoms. The time to onset of symptoms can vary from 15 to 30 minutes to several hours. Protracted anaphylaxis occurs when symptoms last longer than 24 hours and are only minimally responsive to aggressive therapy. This type of anaphylaxis is frequently associated with profound hypotension and has a poor prognosis.

The case study in this article describes biphasic anaphylaxis, the recurrence of anaphylactic symptoms at some point after initial symptoms resolve. Case reports of biphasic reactions demonstrate that the recurrence of symptoms can be severe enough to cause airway compromise, profound hypotension, and even death. Recently, there has been a renewed interest in the recognition and prevention of this potentially life-threatening phenomenon.

Many hypotheses exist about the pathophysiology of biphasic reactions. One theory suggests that the recurrence of symptoms is not a true biphasic reaction but rather a recurrence of a protracted initial response that was temporarily interrupted by treatment modalities. Other theories suggest that the response may result from one of the following: a biphasic wave of histamine release from mast cells without subsequent antigen exposure, activation of secondary inflammatory pathways resulting from mediators released during the initial event, or synthesis of late-phase mediators from mast and other cells. The exact mechanism remains unknown, but it is probably a combination of these three theories.

DURATION OF LATENT PHASE

The reported incidence of biphasic reactions ranges from 1% to 23% of all anaphylactic reactions and consists mostly of case reports and retrospective chart reviews. This is probably an underestimate. In 1986, Stark and Sullivan performed the first prospective study of anaphylaxis in 25 consecutive patients. They found a 20% incidence of biphasic reactions, with an asymptomatic latent phase ranging from one to eight hours after the initial reaction. This is the time frame most often quoted in the medical literature for average time to onset of second-phase reactivity. However, other authors have reported latent periods ranging from as short as 1 to 3 hours to as long as 30 to 38 hours following the initial onset of symptoms, with one case report documenting a latent period of 72 hours. In a prospective study of 103 patients, Ellis and Day found that 40% experienced late-phase reactions that were delayed more than 10 hours, and 20% had reactions delayed beyond 20 hours.

Although no risk factors for biphasic anaphylaxis have been reported consistently, studies have found possible predictors. Several of these are related to inadequate treatment during the initial phase, and some studies suggest that and certain features of the therapy itself may help predict who is at risk. Key predictors include a history of biphasic anaphylaxis, slow onset of initial symptoms, hypotension or laryngeal edema during the initial event, a delay in the initial administration of epinephrine, a low total dose of epinephrine, the need for large doses of epinephrine, a slow response to initial treatment, and oral antigen exposure. For other possible predictors, see the box opposite.

In a recent study, Ellis found that biphasic reactors took longer to achieve resolution of their initial symptoms than patients with monophasic reactions (133 versus 112 minutes; $p = 0.03$). This study also found that patients with biphasic reactions received lower total doses of epinephrine than those who did not have biphasic reactions (0.30 versus 0.39 mg; $p = 0.48$). However, even though these differences are statistically significant, their magnitude is small and their clinical significance is questionable.

In some reports, failure to administer corticosteroids appeared to increase the risk of a biphasic response, but less evidence exists to support this theory. In Ellis's study, biphasic reactors showed a trend toward a lower rate of corticosteroid use (35% versus 55.4%; $p = 0.07$) and lower doses of corticosteroids (31 mg versus 63 mg; $p = 0.06$), but these differences were not statistically significant. In other reports, administering corticosteroids seemed to make little difference in preventing a late-phase response. Although no definitive conclusion can be drawn, the data suggest that corticosteroids might have a beneficial effect in some patients.

Oral antigen exposure has also been documented as a possible predisposing factor, based on the theory that an offending agent could be absorbed through the gastrointestinal tract for several hours, causing a secondary or late-phase response. This is possible, but other mechanisms must be involved because biphasic responses have occurred with several routes of exposure, including oral, parenteral, and even inhalation.

It would be ideal if one could predict the occurrence of a biphasic reaction based on the adequacy and response to the initial therapy, but currently there are not sufficient data to do so.

TREATMENT OF BIPHASIC REACTIONS

Reports of biphasic anaphylactic reactions have shown that therapy used in late-phase reactions is similar to that used in the initial phase and usually includes epinephrine, antihistamines, and corticosteroids. No studies have evaluated specific treatments for biphasic reactions; however, when these patients receive standard anaphylaxis therapy in their initial phase, mortality rates remain low, so this treatment can be assumed to be equally effective in both types of anaphylaxis.

Ellis's 2007 prospective study of 103 patients found that those whose symptoms resolved within 30 minutes of receiving epinephrine had a 0% incidence of biphasic reactions. While this data is encouraging, none of these interventions has consistently demonstrated the ability to prevent the late-phase reaction.

The patient described earlier injected himself with one 0.3 mg dose of IM epinephrine within five minutes of exposure to the Hymenoptera venom and the onset of symptoms. He then gave himself another 0.3 mg dose approximately six hours later when he had a mild exacerbation of his symptoms. A long latent phase followed before the patient developed full-blown anaphylaxis nearly 18 hours later.

This patient had biphasic anaphylaxis, but many aspects of his presentation were unique. His initial symptoms occurred quickly, he administered epinephrine almost immediately, and he had an adequate response to the initial treatment. This presentation is not consistent with other reports, which identify the slow onset of initial symptoms, a delay in epinephrine therapy, and lack of response to epinephrine as potential risk factors for a biphasic reaction. Although the patient did not have many of these risk factors, he did have one strong predictor for a late-phase reaction—a history of a biphasic anaphylactic reaction that required intubation.

>>FAST TRACK<<

Biphasic responses have occurred with several routes of exposure, including oral, parenteral, and even inhalation.

OBSERVATION PROBLEM

The possibility of delayed or biphasic anaphylaxis has a tremendous impact on patient disposition in the emergency department. Most patients presenting with anaphylaxis are observed for two to six hours

after treatment and then discharged home. However, 20% to 25% are at risk for a recurrence of their symptoms during the next 24 to 48 hours, ranging from mild episodes not requiring further treatment to fatal events despite adequate therapy. The disparity in time intervals between resolution of the initial event and recurrence of symptoms makes it impractical to address the risk of biphasic reactions by prolonging the observation of every patient who presents with anaphylaxis.

Currently, there are no definitive clinical criteria to identify a subset of patients who are at risk for a biphasic response and need a long observation period. Patients with any of the predictors mentioned previously can be admitted to an emergency department observation unit or an inpatient ward. Or, the patient may be discharged home if he has adequate supervision, easy access to emergency medical services, and epinephrine that can be administered quickly. All patients being discharged home should be given at least three epinephrine autoinjectors (one for home, one for the car, and one to carry), advised to wear a medical alert bracelet, and given a referral to an allergist for further workup and treatment, including desensitization therapy if applicable.

Overall, it is a challenge to identify people at risk for a biphasic anaphylactic reaction. Because it is still unclear what interventions will prevent a late-phase response, it is difficult to recommend a standard observation period until the pathogenesis of the biphasic anaphylactic response is better understood. □

SUGGESTED READING

Brazil E and MacNamara AF: "Not so immediate" hypersensitivity: the danger of biphasic anaphylactic reactions. *J Accid Emerg Med* 15(4):252, 1998.

Clark S and Camargo CA Jr: Emergency treatment and prevention of insect-sting anaphylaxis. *Curr Opin Allergy Clin Immunol* 6(4):279, 2006.

Ellis AK and Day JH: Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 98(1):64, 2007.

Lieberman P: Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 95(3):217, 2005.

Stark BJ and Sullivan TJ: Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 78(1 pt 1):76, 1986.

Tole JW and Lieberman P: Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 27(2):309, 2007.