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Reviews

Biphasic anaphylaxis: A review of the literature and implications for emergency management

Ali Pourmand^{a,*}, Chelsea Robinson^a, Wahab Syed^a, Maryann Mazer-Amirshahi^b^a Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States^b Department of Emergency Medicine, MedStar Washington Hospital Center, Washington, DC, Georgetown University School of Medicine, Washington, DC, United States

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ABSTRACT

Background: The biphasic reaction is a feared complication of anaphylaxis management in the emergency department (ED). The traditional recommended ED observation time is 4–6 h after complete resolution of symptoms for every anaphylaxis patient. However, there has been great controversy regarding whether this standard of care is evidence-based.

Methods: Articles were selected using a PubMed, MEDLINE search for the keywords “biphasic anaphylaxis”, yielding 155 articles. Articles were filtered by English language, and the keyword biphasic in the title. Case reports and case series were excluded, narrowing to 33 articles. Then, articles were filtered by relevance to the ED setting, and studies conducted in outpatient clinic settings were excluded, narrowing the search to 16 articles. All remaining articles were reviewed and findings were discussed.

Results: The reported mean time to onset between the resolution of initial anaphylaxis and biphasic reaction ranges widely by study from 1 to 72 h with the majority of studies reporting the mean time to onset >8 h. A delay between anaphylaxis symptom onset and administration of epinephrine of 60–190 min was reported to correlate with biphasic anaphylaxis in three studies. Anaphylaxis requiring >1 dose of epinephrine to achieve symptom resolution was also reported to correlate with biphasic reactions in two studies. No definitive conclusions about the role of corticosteroids in preventing biphasic reactions can be made at this time however; a couple small studies have shown that they may decrease the incidence of biphasic reactions. Additional risk factors correlated with biphasic reaction vary widely between studies and the generalizability of these risk factors is questionable.

Conclusions: There is a need for further research to identify true risk factors associated with biphasic anaphylaxis and to clearly define the role of corticosteroids in biphasic reactions. However, given the low incidence and rare mortality of biphasic reactions, patients who receive epinephrine within one hour of symptom onset and who respond to epinephrine with rapid and complete symptom resolution can probably be discharged from the ED with careful return precautions and education without the need for prolonged observation.

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* Corresponding author at: Department of Emergency Medicine, George Washington University, Medical Center, 2120 I St., Washington, DC 20037, United States.
E-mail address: pourmand@gwu.edu (A. Pourmand).

1. Introduction

Definitions of anaphylaxis vary widely and there is no universal agreement. According to the 2005 National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network's (NIAID/FAAN) second meeting on anaphylaxis, anaphylaxis is defined as an acute onset of illness (within minutes to hours) with involvement of skin, mucosal tissue, or both with either respiratory compromise, reduced blood pressure, or symptoms of end organ damage [1]. Anaphylaxis can also be defined as at least two of the following in response to a likely allergen: skin mucosal involvement, respiratory compromise, reduced blood pressure, and persistent gastrointestinal symptoms [1]. Some important triggers for anaphylaxis include food, medications, insect venom, and heterologous sera [2]. However, many cases of anaphylaxis are idiopathic and no allergen is identified [3]. Treatment for anaphylaxis includes epinephrine as the most important first line agent with oxygenation, fluid resuscitation, and vasopressors being important considerations in supportive management [1]. Antihistamines and steroids may also play a role in ongoing management [4]. Traditionally, emergency department (ED) observation times of 4 to 6 h are recommended for patients with anaphylactic reactions [1]. The goal of this observation period is to monitor for a potential biphasic reaction with the ability to intervene in a supervised setting should a biphasic reaction occur [1].

A biphasic reaction is defined as a recurrent reaction or appearance of new symptoms after the initial allergy-related presentation without further exposure to the causative agent [5]. According to the 2005 NIAID/FAAN's second meeting on anaphylaxis, a biphasic reaction can occur in up to 20% of patients [1]. While the symposium recommended an observation period of 4–6 h, biphasic reactions have been reported to occur anywhere between 1 and 72 h after initial symptom onset [2,6] with medians ranging 4–22 h, suggesting that the majority of biphasic reactions occur outside of the recommended ED observation period. Furthermore, evidence has shown that morbidity is rare and mortality is essentially zero from biphasic reactions whether observation period in the ED was less than or >8 h [7].

The biphasic reaction was described as early as 1925 by Duke et al. [8]. However, the first prospective study to describe the biphasic reaction did not occur until 1986 [9]. This study followed a small cohort of 25 patients and concluded that the severity of the initial anaphylactic response (including cardiovascular and respiratory involvement) did not predict the likelihood of developing a biphasic reaction. Similarly, the use of corticosteroids was not found to play any role in the development of a biphasic reaction. Thus, Stark and Sullivan recommended some observation period after anaphylaxis was necessary until predictors of biphasic reaction could be more clearly defined [9].

This is likely the origin of the modern suggested ED observation period of 4 to 6 h. In this article, we have reviewed evidence regarding onset and severity of biphasic reactions and challenge the notion that a 4 to 6 h ED observation period is necessary for all patients with anaphylaxis based on lack of evidence to support this antiquated notion (Table 1).

2. Methods

To complete a review of the literature, we searched PubMed and MEDLINE databases with the following search terms: “biphasic anaphylaxis”, yielding 155 articles. Search results were further limited to English language studies, and the keyword biphasic in the title filtered. Case reports and case series were excluded, narrowing to 33 articles. Then, articles were filtered by relevance to the ED setting, and studies conducted in outpatient clinic settings were excluded, narrowing to 16 articles. All remaining articles were reviewed and findings were discussed. We reviewed the reference lists of included articles for additional studies.

2.1. Pathophysiology of the biphasic reaction

The exact pathogenesis of the biphasic reaction has yet to be elucidated; however, there are several theories about factors that may be correlated with a biphasic reaction. Until the late 1970s, it was thought that all IgE mediated responses occurred immediately after exposure to an antigen and resolved shortly thereafter [10]. However, it was later postulated that late cutaneous manifestations were also IgE mediated, rather than IgG mediated, as previously thought. Dolovich et al. and Solley et al. proved this notion to be true [11,12].

The biphasic reaction was initially thought to be attributed to inadequate treatment of the initial anaphylaxis event [13]. Some studies have supported this notion. For example, Brazil et al. as well as Alqurashi et al. described the biphasic reaction as more prevalent in patients who required more than one dose of epinephrine to treat the initial anaphylactic reaction [4,14]. Other factors that have been thought to contribute to the biphasic reaction are oral ingestion of the antigen as it allows for prolonged absorption and exposure to the antigen. However, this is unlikely to be true as biphasic reaction has been exhibited with many other types of exposures [10].

Two other mechanisms, based on murine models, have also been postulated [10]. One study found that platelet activating factor was recruited and released late, after the initial event, and was responsible for the biphasic reaction [15]. Inhibition of tumor necrosis factor may prevent the biphasic reaction, yet interestingly, elevations in tumor necrosis factor are typically not seen in patients with biphasic reactions [16]. In another murine model, gut mast cell degranulation occurred after even a single oral ingestion, leading to a biphasic reaction. However, this typically occurred 72 h after initial ingestion and would not explain why most patients experience biphasic reaction within 8 h after the initial response [10]. Thus, the pathophysiology behind the biphasic reaction and risk factors that may contribute to it are not clearly understood.

2.2. Risk factors for biphasic reaction

Evidence is controversial as to whether there are any identifiable clinical characteristics that accurately predict the biphasic reaction as many similarly conducted retrospective studies come to different conclusions. These inconsistencies make the generalizability of the findings questionable.

Stark and Sullivan conducted one of the first studies regarding the biphasic reaction in 1985 [9]. In their retrospective study of 25 patients with anaphylaxis, they concluded that recurrent or prolonged reactions were 2.8 fold more likely if the onset was 30 or more minutes after exposure to the stimulus or if the offending agent had been administered by mouth ($p < 0.03$).

A few decades later, another retrospective study found that a personal history of drug anaphylaxis was more common in patients who experienced a biphasic reaction. In 9 of 415 patients with biphasic anaphylaxis, analyses of the predictors of the biphasic reaction identified a history of drug anaphylaxis (odds ratio 14.3, 95% confidence interval 2.4–85.8) to be a contributing factor [5].

Two studies reported when the anaphylactic trigger was unknown to the patient or provider, the incidence of biphasic reaction was significantly higher. In a pooled meta-analysis, Lee et al. demonstrated that an unknown trigger and hypotension were associated with biphasic anaphylaxis [17]. Another retrospective study of 541 patients with anaphylaxis, identifying 21 (6%) of patients with biphasic reaction, biphasic reactions were associated with a history of prior anaphylaxis (OR 2.6 [95% CI: 1.1–6.4]; $P = 0.029$), unknown precipitant (OR 2.6 [95% CI: 1.1–6.2]; $P = 0.03$), symptoms of diarrhea (OR 4.5 [95% CI: 1.4–14.0]; $P = 0.024$), and wheezing (OR 2.6 [95% CI: 1.4–8.9]; $P = 0.029$) [18].

Respiratory features are also reported in some studies to be correlated with a biphasic reaction. Smit et al. demonstrated this in a study of 282 anaphylaxis patients in Hong Kong. Biphasic reactions were

Table 1
Characteristics of biphasic reaction studies

Study	Design	N	Findings	Conclusions
Douglas et al. [2]	Observational Cohort	94	In 35 outpatients in the Allergy Clinic of Madigan Army Medical Center from 1988 to 1991, 44 anaphylactic reactions were observed, and 2 reactions were biphasic. In a similar time period from 1986 to 1992, 59 inpatients with anaphylaxis were observed, 4 experienced biphasic reactions.	The incidence of biphasic reaction in this study was lower than previously published studies.
Brady et al. [3]	Retrospective Review	67	In a review of records of ED anaphylaxis patients with 2/3 of cutaneous, respiratory, or cardiovascular symptoms, 2 (3%) recurrent (biphasic) cases were found, expressed as cutaneous manifestations. The remaining 97% had a mean ED time of 4.2 h with no recurrence.	Recurrent anaphylaxis events are rare and non-life threatening, and expressed as cutaneous manifestations. Outpatient management of symptoms was adequate for the majority of anaphylaxis patients.
Brazil et al. [4]	Retrospective Review	34	In a review of 34 patients admitted over an 18-month period for observation after anaphylaxis necessitating adrenaline, 6 (18%) had biphasic reactions, and required more adrenaline vs uni-phasic patients.	Biphasic reactions occur frequently and while there are no specific features to identify these patients, increased adrenaline requirements prior to admission should be a marker for biphasic reaction.
Ko et al. [5]	Prospective Observational	655	In an observational study of 655 patients, of 415 patients treated with corticosteroids, 9 had a biphasic reaction with a median time for recurrence of 15 h, and had a higher incidence of history of drug anaphylaxis (odds ratio 14.3, 95% confidence interval 2.4–85.8).	2.2% of anaphylaxis patients requiring corticosteroids had biphasic reaction and previous history of drug anaphylaxis was a risk factor for biphasic reaction.
Lee et al. [6]	Prospective Observational Cohort	872	In an observational study of 872 visits to an academic ED, 36 were had biphasic reactions. Logistic regression analysis found that prior anaphylaxis, epinephrine administered 60 min after arrival, and unknown triggers were associated with biphasic reaction.	4.1% of ED patients with anaphylaxis had biphasic reactions, and were associated with unknown triggers, first epinephrine administration after 60 min and prior anaphylaxis.
Rohacek et al. [7]	Retrospective Review	495	Of 495 patients presenting to the ED in a 12-year period for anaphylaxis, 25 biphasic reactions were observed, including 2 that occurred the hospital stay and 1 who was transferred to the ICU. No risk factors for biphasic reactions were identified and no deaths were reported. 227 patients were observed >8 h.	Biphasic reactions were rare in prolonged or short observation periods, with no reported mortality.
Stark and Sullivan. [9]	Prospective Observational	25	Of 25 patients with anaphylaxis, 5 were found to be have biphasic reactions, and 3/5 received large doses of steroids. Biphasic reactions were associated with onset >30 min after exposure.	Biphasic reactions are common and patients should be followed closely after remission of symptoms.
Lieberman. [10]	Review Article	N/A	In a review of publications on MEDLINE published from 1970 to 2005 on anaphylaxis, incidence ranged from 1 to 20%. Risk factors identified were severity of reaction, time of onset after administration, hypotension, laryngeal edema, delay in epi administration, and too small of epinephrine dose. However, no consensus was found for risk factors.	Biphasic reactions are common and patients should be followed closely after remission of symptoms, with 8 h sufficient for most reactions. Ranges for observation have been recommended as far as 24 h.
Alquraishi et al. [14]	Retrospective Review	484	In a review of 1749 ED records from 2 pediatric academic EDs, 484 were presentations for anaphylaxis, and 71 developed biphasic reactions. Risk factors were age 6 to 9, delay in presentation to the ED longer than 90 min after the onset of the initial reaction, wide pulse pressure at triage, treatment of the initial reaction with >1 dose of epinephrine, and administration of inhaled β -agonists in the ED.	Biphasic reactions were more likely in severe anaphylaxis, and were associated with identifiable risk factors, which could be used to monitor specific patients in the ED.
Lee et al. [17]	Systematic Review	4114	In a systematic review and meta-analysis of studies prior to 2014 from MEDLINE, EMBASE, Web of Science, and Scopus, 27 observational studies were analyzed. 4114 patients with anaphylaxis and 192 patients with biphasic anaphylaxis were examined. An unknown trigger and hypotension on initial presentation were associated with increased risk, and food with decreased risk.	Clinicians should tailor observation periods for patients presenting with food triggers, unknown triggers, or hypotension on initial presentation.
Lee et al. [18]	Prospective Observational	541	Of 541 patients with anaphylaxis who presented to the ED from April 2008 to January 2013, 21 had biphasic reactions, with a median time interval of 7 h. Reactions were associated with history of anaphylaxis, unknown trigger, diarrhea, and wheezing.	Patients with identifiable risk factors of diarrhea, wheezing, prior anaphylaxis, and unknown trigger were associated with increased risk for biphasic reaction.
Smit et al. [19]	Retrospective Review	282	In a retrospective review of 282 patients presenting with anaphylaxis in a 4-year period in a Hong Kong ED, 15 biphasic reactions were reported. Of the biphasic reactions, 20% had unstable vital signs; mean time to biphasic reaction was 8 h. Respiratory features were less likely to develop biphasic reaction.	Observation of anaphylaxis patients should be prolonged due to the risk of biphasic reactions.
Lee et al. [20]	Retrospective Review	108	Retrospective review of 108 patients admitted to a children's hospital from 1985 to 1989 with anaphylaxis 6 had biphasic reactions, of which 3 required additional support with oxygen, pressors, intubation, SQ epinephrine, or continuous bronchodilators.	An increased incidence of biphasic reaction was found in patients who had a delayed administration of epinephrine.
Ellis et al. [22]	Prospective Observational	134	Of 134 ED patients in a 3-year period at a Canadian Tertiary Care center, 20 reported biphasic reactions during a 72-h window post discharge, and were found to have received less epinephrine and less corticosteroids. Average second phase onset was 10 h, ranging from 2 to 38 h.	19.4% of patients with anaphylaxis reported biphasic reactions, with an average time to onset of 10 h, and was associated with decreased epinephrine and corticosteroid use.

(continued on next page)

Table 1 (continued)

Study	Design	N	Findings	Conclusions
Vezir et al. [23]	Prospective Observational	96	In an observational study of 96 patients presenting with anaphylaxis from 2010 to 2012 in Turkey, causative agents, clinical manifestations, and treatment with recorded. Biphasic reactions were noted in 5 cases, ranging from 30 min to 9 h.	Biphasic reaction was noted in 5.2% of cases, which is lower than that reported in adult literature, and may have a lower rate in the pediatric population.
Lertnawapan and Maek-a-nantawat. [24]	Prospective Observational	208	In a observational study of 208 patients presenting with anaphylaxis from 2004 to 2008 in Thailand, 6.3% developed biphasic reactions, and had a longer period from onset of symptoms to administration of epinephrine vs uni-phasic. Longer onset of symptoms to hospital arrival times were also found in the biphasic group. Multiple regression of onset to hospital arrival and epinephrine administration was predictive of biphasic course.	Delayed administration of epinephrine was associated with biphasic anaphylactic course.
Sricharoen et al. [25]	Prospective Cohort	63	10 of 63 patients admitted to the ED with anaphylaxis in Bangkok in a 1-year period were observed with biphasic reactions. Respiratory rate and abdominal pain were significantly associated with biphasic anaphylaxis in multivariate logistic regression.	Abdominal pain and respiratory depression were significantly associated with biphasic anaphylaxis.

identified in 15 (5.3%) and it was concluded that patients with respiratory features on initial presentation were less likely to develop biphasic reactions [19]. In a retrospective study of 71 pediatric patients with biphasic reactions, Alqurashi et al. concluded that five independent predictors for biphasic reactions were found: age 6 to 9 years (OR 3.60, 95% CI: 1.5–8.58), delay in presentation to the ED longer than 90 min after the onset of the initial reaction (OR 2.58, 95% CI: 1.47–4.53), wide pulse pressure at triage (OR 2.92, 95% CI: 1.69–5.04), treatment of the initial reaction with >1 dose of epinephrine (OR 2.7, 95% CI 1.12–6.55), and administration of inhaled β -agonists in the ED (OR 2.39, 95% CI 1.24–4.62) [14].

2.3. The biphasic reaction and epinephrine

While there are no definitive conclusions, several studies have suggested that there are important factors when it comes to epinephrine administration and the likelihood of a biphasic reaction. Specifically, time from onset to administration of the first dose of epinephrine and the amount of epinephrine needed to abate the primary anaphylactic response are important predictors of biphasic reactions [14,20].

Several studies have shown that a prolonged time between onset of anaphylaxis and administration of epinephrine could be a clinical predictor for biphasic reaction. In an observational cohort study of 36 patients meeting NIAID/FAAN diagnostic criteria for biphasic reaction, first epinephrine administration >60 min after symptom onset was significantly associated with biphasic reaction with an OR of 2.29; 95% CI, 1.09–4.79 [6]. Alqurashi et al. concluded in a recent observational study that a subgroup of pediatric patients who had delays in their initial epinephrine administration were more likely to develop biphasic reactions $p = 0.01$ [14]. In another retrospective analysis by Lee and Greenes, of 108 patients admitted to a children's hospital for anaphylaxis, 6 (6%) had biphasic reactions. Of those who had a biphasic reaction, the median time from the onset of symptoms to the initial administration of subcutaneous epinephrine was 190 min, versus 48 min for those without a biphasic reaction. These patients otherwise did not differ significantly in the incidence of initial epinephrine use or initial corticosteroid use [20].

In addition to time to epinephrine administration, multiple studies have reported that patients who experience biphasic reaction may need higher initial doses of epinephrine to abate their symptoms. Alqurashi et al. also reported that biphasic anaphylaxis appears to be associated with severe initial symptoms requiring epinephrine re-dosing. In a retrospective study by Alqurashi et al., of 71 pediatric patients with biphasic reaction, it was found that treatment of the initial anaphylactic reaction with more than one dose of epinephrine was associated with biphasic reaction (OR 2.7, 95% CI 1.12–6.55) [14]. In another

retrospective review of 34 patients admitted for protracted anaphylactic reactions, 6 patients (18%) developed biphasic reactions. No clinical features on initial presentation were identified to correlate with biphasic reaction; however, these patients did require significantly more epinephrine to treat their initial symptoms compared with patients experiencing only uni-phasic reactions ($p = 0.03$). Patients with uni-phasic reaction required an average of 0.6 mg epinephrine while those with biphasic reactions required an average of 1.2 mg. The difference was statistically significant. ($p = 0.03$, 95% CI: 0–1 mg). The dose of epinephrine required to treat second stage features of biphasic reactions varied between 0.4 and 1.0 mg (mean 0.5 mg) [4].

2.4. The biphasic reaction and corticosteroids

Corticosteroid administration at the onset of anaphylaxis is thought to decrease the incidence of the biphasic reaction. However, evidence in support of this notion is largely lacking. There has yet to be a randomized controlled trial studying whether corticosteroid administration has a role in preventing the biphasic reaction [21]. Therefore, data in support of corticosteroid use comes from smaller retrospective studies. The NIAID/FAAN states that there is no evidence to support that corticosteroids reduce the incidence of biphasic reaction but given their usefulness in other allergic disease, it is probably a good idea to administer them in anaphylaxis [1].

Two studies report evidence that the incidence of biphasic reaction may be decreased in patients that receive early corticosteroids. In a retrospective study of 415 anaphylaxis patients treated with corticosteroids, 9 patients (2.2%) developed biphasic reaction [5]. The incidence of biphasic reaction has been traditionally reported to range anywhere from 5.2–19.4% [22–24]. However, recent large observational retrospective studies have suggested that the true incidence might be lower, between 4 and 4.5% [6,7]. This might suggest that the incidence of biphasic reactions is lower in patients treated with corticosteroids by approximately 1.8%.

In another retrospective analysis of 507 uni-phasic (95.5%) and 25 biphasic reactions (4.5%), general characteristics of episodes with biphasic anaphylactic reactions compared with episodes with uni-phasic anaphylactic reactions were similar, except for decreased corticosteroid use (84.0% vs 97.6%, OR 0.13, 95% CI 0.04–0.5, $p = 0.005$) and H1-antagonist use (84.0% vs 98%, OR 0.10, 95% CI 0.03–0.42, $P = 0.003$) to treat the initial reaction in biphasic reactions [7].

Little evidence exists to support or refute the usefulness of corticosteroids in preventing biphasic reaction. Evidence that supports their use is derived from small retrospective studies. Further research needs to be conducted to establish a true correlative link to corticosteroids.

3. Discussion

Many characteristics of the biphasic reaction are largely not well understood. Studies disagree about the pathophysiology, the incidence, and risk factors that may be correlated with the biphasic reaction. In addition, there is a paucity of data on specific symptoms predisposing to biphasic reaction. This makes a definitive conclusion about the observation time in the ED difficult until further research is conducted.

Despite conflicting evidence, most studies find the overall incidence of biphasic reactions to be low. Older, smaller retrospective studies reported incidences of biphasic reactions as high as 21% [9,25]. However, larger more recent studies have reported the incidence to be much lower, around 4–4.5% [7,19,26]. The true incidence is also complicated by whether administration of corticosteroids was initiated upon presentation. Ko et al. reported biphasic reaction in a pediatric population to be 2.2% when all patients received corticosteroids upon initial presentation [5]. However, there is no definitive data to support or refute the efficacy of corticosteroids in decreasing the incidence of biphasic reaction [1]. It would appear that regardless of this, the overall incidence of biphasic reaction is quite low. Furthermore, clinically significant biphasic reactions are a rare occurrence. Douglass et al. reported that in a study of 59 patients with anaphylaxis, 4 experienced biphasic reactions and there were zero mortalities [2]. Rohacek et al. reported zero mortalities in a similar study, with only one of the twelve patients necessitating transfer to the intensive care unit after a biphasic reaction [7]. Lee and Greenes also report that clinically significant biphasic reactions are low as only 50% of patients with biphasic reactions had clinically significant ones [20]. Smit et al. reported the incidence of clinically significant biphasic reaction to be even lower. Their group reported only 20% of all those with biphasic reaction had unstable vital signs [19]. Thus, the incidence of biphasic reaction is low and the incidence of clinically significant biphasic reaction is even lower.

Another important consideration is time between initial presentation and the onset of the biphasic reaction. Of the studies reviewed, the shortest interval between initial anaphylaxis and biphasic reaction was a median of 4 h, reported in the pediatric population [14]. A few studies reported a median of approximately 7 to 8 h [18,19]. Others reported a median onset to biphasic reaction as much longer, between 15 and 22 h [5] [25]. However, the majority reported a wide range, with biphasic reactions occurring anywhere between 1 and 72 h [2–4,18,20]. There appears to be a wide range of reported times to onset of biphasic reaction, the majority of which are well outside the traditional ED observation period of 4 to 6 h.

Given the wide range of reported times to onset of biphasic reaction, different conclusions have been drawn about the recommended ED observation period. The NIAID/FAAN Symposium recommended that observation periods be individualized on the basis of the severity of the initial reaction, reliability of the patient, and access to care, with a reasonable observation period of 4 to 6 h. Prolonged observation times or admission is recommended for patients with severe or refractory symptoms. They state that more careful consideration should be used in patients with reactive airway disease as most fatalities associated with anaphylaxis occur in these patients [1]. This conclusion is also controversial, as Rohacek et al. concluded that no mortality was found whether patients were monitored for ≥ 8 h or for < 8 h and suggested considering discharge after complete resolution of an anaphylactic reaction [7]. Brady et al. similarly concluded that selective outpatient management for patients who respond to therapy with complete and rapid resolution of symptoms is reasonable [3].

4. Limitations

In general, studies of the risk of biphasic reaction can be separated based on timing of initiation and type of treatment, symptoms at presentation, and personal history. We found a relative paucity of high quality evidence for specific symptoms that correlated to biphasic

reaction and personal history of anaphylaxis. Inherently these factors may be assumed relevant in clinical judgment and therefore could be perceived as intuitive in decision-making regarding risk of biphasic reaction. This may be a factor in the relative lack of data and limits their utility for robust conclusions.

The evidence for corticosteroid use and epinephrine administration must be taken into account with an understanding of the pathophysiology of biphasic reaction, despite controversy over the mechanism. More severe anaphylactic reactions requiring increased epinephrine dosage or frequency suggest further aberrancy in the immunological processes leading to anaphylaxis compared to those who did not. This specific factor associated with treatment does appear to have higher quality evidence that may enable its use as a metric to assist in extrapolating risk for biphasic reaction. In regards to corticosteroid use, small retrospective studies do support their utility in decreasing the rate of biphasic reactions, but more data needs to be obtained for specific recommendations regarding their use. There has been no randomized clinical trial to date to determine whether there is a correlation between corticosteroid administration and biphasic reaction. Corticosteroids are a natural answer to ameliorate immunological phenomena, but their pathophysiological place in biphasic anaphylaxis is yet to be deduced, therefore our ability to draw conclusions is limited.

5. Conclusion

Many characteristics of biphasic anaphylaxis are still not well understood. Regardless, the incidence of clinically significant biphasic reactions is low and mortality is exceptionally rare from biphasic anaphylaxis. The onset of most biphasic reactions is beyond the traditionally recommended ED observation time of 4 to 6 h, calling this practice into question. Two important factors are the time between symptom onset and epinephrine administration as well as the amount of epinephrine needed to abate initial anaphylaxis symptoms. The notion that early corticosteroid administration can decrease the incidence of a biphasic reaction is more controversial. However, given their role in treating other allergic disease, and early evidence that they may decrease the incidence of biphasic reactions, it is most likely beneficial to continue administering corticosteroids to patients with anaphylaxis. These are all areas for future prospective study to provide better quality evidence to establish the optimal ED management of anaphylaxis.

Author disclosure statement

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