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REVIEW

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Post-anaphylaxis observation in the ED: a decade of data challenging the traditional 24-hour rule

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Abstract

Background Biphasic anaphylaxis remains an under-recognized threat who's timing directly conflicts with conventional 2–4-hour ED observation practices.

Methods This narrative review synthesizes evidence published between 2015 and 2025, sourced from PubMed, MEDLINE, and major allergy/immunology society guidelines. A narrative synthesis was chosen due to heterogeneity in definitions and outcome reporting across studies. The analysis focuses on the evolution of risk factors, diagnostic criteria, and the performance of time-based observation strategies to inform contemporary ED disposition policies.

Key Findings Over the past decade, a paradigm shift has occurred, moving away from fixed observation durations toward risk-stratified approaches. Major practice parameters from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) now emphasize individualized observation based on the severity of the initial event. More than half of clinically significant biphasic events occur after four to six hours, indicating that traditional observation windows are insufficient for many patients. Key predictors of biphasic reactions consistently identified include a severe initial presentation (e.g., hypotension, hypoxia), the need for more than one dose of epinephrine, and a delay in initial epinephrine administration. Recent meta-analytic work has quantified the performance of observation cut-offs, demonstrating a pooled negative predictive value (NPV) of ~95% at 1 h, rising to ~97% at ≥6 h, and >98% for observation periods exceeding 8–12 h. This suggests that observation periods under 6 h may be insufficient for many patients, aligning with UK National Institute for Health and Care Excellence (NICE) guidance, which typically recommends 6–12 h of observation, particularly when risk factors are present.

Conclusion EDs should adopt risk-stratified observation pathways. A low-risk pathway (e.g., rapid and complete resolution after a single epinephrine dose, known food trigger, no cardiovascular or respiratory compromise) may permit shorter observation if coupled with a robust discharge education bundle. Conversely, a high-risk pathway (e.g., delayed or ≥2 epinephrine doses, hypotension/hypoxia, non-food/unknown trigger, or comorbidities like asthma or beta-blocker use) warrants prolonged observation (≥6 h) or hospital admission. Future research should prioritize

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prospective, multicenter ED registries to precisely document the timing of treatment-requiring relapses and further refine the dose-response relationship between observation duration and the risk of missed biphasic events, stratified by age and trigger.

Clinical trial number Not applicable.

Keywords Biphasic anaphylaxis, Emergency department, Epinephrine

Introduction

Anaphylaxis is an acute, life-threatening systemic hypersensitivity reaction that requires prompt recognition and treatment in the emergency department (ED) [1]. While intramuscular epinephrine is the cornerstone of therapy, a significant clinical conundrum remains: the management of patients after their initial symptoms have resolved. The primary challenge is that EDs routinely discharge patients earlier than evidence supports, creating a measurable safety gap. A subset of these patients will experience biphasic anaphylaxis, defined as a recurrence of symptoms hours to days after the initial episode has completely resolved, without further exposure to the inciting trigger [2]. This phenomenon, which can be as severe as or more severe than the initial reaction, poses a substantial challenge to ED disposition decisions, balancing patient safety against resource utilization, such as bed capacity and healthcare costs [3]. For a decade, clinical practice has been caught between historical convention and emerging, higher-quality evidence, creating an urgent need for a comprehensive synthesis to guide the development of rational, evidence-based observation policies.

The year 2015 marked a pivotal moment in our understanding of biphasic anaphylaxis. In real terms, standard four-hour observation would miss the majority of biphasic reactions. A systematic review and meta-analysis by Lee et al., encompassing 27 studies and 4,162 patients, provided the most robust estimates to date [4]. The study reported a pooled incidence of biphasic reactions of 4.6% and, critically, a median time to onset of 11 h (range 0.2–72 h). This finding was a direct challenge to prevailing ED practices. Many departments had conventionally adopted observation periods of 4 to 6 h, a practice rooted more in historical precedent than empirical data [5]. The Lee et al. analysis revealed that such a window would miss more than half of all biphasic events, raising serious questions about the safety of discharging patients after only a few hours of monitoring. The review also identified preliminary risk factors, noting that reactions to an unknown trigger were associated with a higher risk of a biphasic event, whereas food-induced anaphylaxis was associated with a lower risk [4]. This early evidence hinted that a "one-size-fits-all" observation period was likely inadequate, and that a more nuanced, risk-based approach was necessary.

The subsequent years saw a concerted effort to refine risk prediction. This culminated in a meaningful pivot within major US clinical practice guidelines. The 2020 Anaphylaxis Practice Parameter Update from the Joint Task Force on Practice Parameters (JTFPP), representing the AAAAI and ACAAI, formally moved away from recommending a universal observation duration. Instead, it endorsed an individualized approach, suggesting that the observation period should be guided by the severity of the initial reaction [6]. The guidelines highlighted several key risk factors for biphasic anaphylaxis, including the need for more than one dose of epinephrine, delayed administration of the initial epinephrine dose, and a history of a severe initial reaction [6, 7]. The 2023 update further solidified this stance, reinforcing that patients with severe anaphylaxis should be observed for biphasic reactions even after symptoms resolve, and that extended observation is appropriate for those requiring multiple epinephrine doses [1]. In contrast, guidance from the UK's NICE has generally retained a more structured recommendation, suggesting an observation period of 6 to 12 h after the onset of initial symptoms, especially for patients with risk factors, thereby reflecting a more cautious default position [8].

A decade after the landmark 2015 meta-analysis, the landscape of biphasic anaphylaxis management has been transformed by new data and evolving guidelines. This shift represents a considerable change in anaphylaxis disposition practice, moving away from historical conventions. However, a gap persists between high-level recommendations and their operational implementation in busy EDs. This review is necessary now to bridge that gap by translating a decade of accumulated data into actionable clinical policy. We have moved beyond simply knowing that biphasic reactions occur late; we now have quantitative metrics, such as the negative predictive value (NPV) of different observation durations, which can directly inform decision-making [9]. To date, no operationally unified, evidence-based standard exists for safe ED discharge after anaphylaxis. By synthesizing evidence on timing, risk factors, and decision-useful statistics, this review aims to equip clinicians and hospital administrators with the tools to design and implement risk-tiered observation algorithms. The goal is to move definitively beyond arbitrary, fixed-duration observation and toward

a safer, more efficient, and evidence-based standard of care for all patients recovering from anaphylaxis.

This narrative review was conducted to synthesize the evolution of evidence and clinical guidance on biphasic anaphylaxis over the last decade (January 2015 to November 2025). A literature search was performed using PubMed and MEDLINE databases with keywords including "biphasic anaphylaxis," "anaphylaxis observation," "epinephrine," and "emergency department." Inclusion criteria focused on systematic reviews, meta-analyses, large cohort studies, and major clinical practice guidelines from recognized professional bodies (e.g., AAAAI/ACAAI, NICE). The aim was to construct a cohesive narrative tracking the shift from fixed-duration observation to risk-stratified disposition strategies.

Epidemiology & natural history of biphasic anaphylaxis

Despite broad clinical awareness, biphasic anaphylaxis remains difficult to predict and frequently occurs outside standard observation windows. Biphasic anaphylaxis reactions are characterized by recurrence of anaphylactic symptoms after the initial anaphylactic resolution without the subsequent allergen exposure [10]. Epidemiological studies report that biphasic anaphylaxis occurs in a minority of cases. The incidence estimates from a large study indicated approximately 4–5% of incidence rates [4]. Despite this low incidence these reactions can be clinically important as they require additional treatment such as repeated doses of epinephrine or may lead to complications such as hypotension, airway compromise and cardiovascular instability [7]. This shows that although biphasic reactions are rare, careful monitoring is crucial for emergency management.

The temporal distribution of biphasic reactions follows the long-tailed pattern. While substantial proportions occur within a few hours after the symptoms are resolved. According to an adult emergency department cohort study, 33% of biphasic reactions occurred during 6 h of initial symptoms with severity in vital signs; however, many of patients developed biphasic reactions after discharge and then returned to the emergency department for further management [11]. This unpredictability directly undermines the logic of a universal four- to six-hour observation model. Literature review indicates mean time onset between the initial phase and a biphasic reaction usually ranges between 1 and 72 h with the majority of them reported onset greater than 8 h [5]. Such variability in the time onset emphasizes the instability of biphasic reactions and need for a substantial observation. This significant variability in onset time emphasizes the unpredictable nature of biphasic reactions and the need for substantial observation periods, as illustrated in Fig. 1.

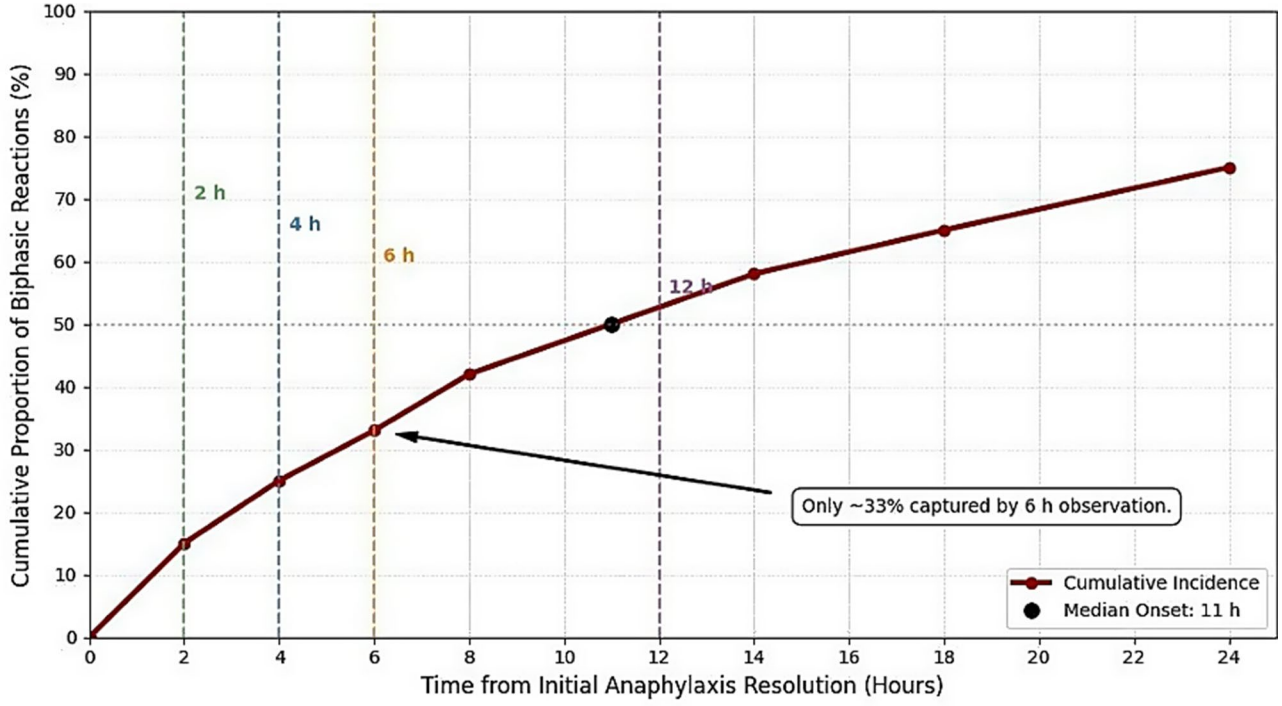

Fig. 1 Schematic time-to-event curve for biphasic reactions with overlay of typical observation windows (2, 4, 6, 12 h). The curve illustrates the cumulative incidence of biphasic reactions following the resolution of an initial anaphylactic episode, based on pooled data from 4,114 patients. The median onset time is marked at 11 h, highlighting that standard 4–6 h observation periods capture only a fraction of events (approximately 33% within 6 h). Note: This schematic figure is conceptual and derived from the narrative summary of pooled findings in the meta-analysis

Multiple studies highlighted risk factors associated with biphasic reactions such as severity of initial reaction including hypotension, hypoxia, multiorgan failure, skin problems and gastrointestinal symptoms [7]. The multiple epinephrine doses during initial treatment as well as the delayed epinephrine administration also serve as a predictor for more severe initial anaphylaxis [12]. Furthermore, trigger-type differentiation shows that foods induced anaphylaxis typically correlate with a lower likelihood of biphasic progression and these reactions resulting from nonfood allergens or any unknown biphasic risk. Other associated factors include prior history of drug allergies, allergic rhinitis respiratory or cardiovascular compromise, comorbid asthma or mast cell disorders as well as angioedema during the initial reaction [13].

Because pediatric triggers are predominantly food-related and therefore lower risk, pediatric data cannot be directly extrapolated to adults. Age and trigger specific difference indicated that pediatric anaphylaxis is more frequently induced by food allergens as indicated by study conducted in Bangkok Thailand during 2008 and 2018 among pediatric population indicates eggs, wheat and peanut in preschool children and shrimp/shellfish in school age children and adolescent cause food-induced anaphylactic reactions [14]. In contrast, adult populations more commonly experience drug and insect related triggers as indicated by ten-year retrospective study at Chiang Mai University hospital where the majority of the adults, that is 362 out of 433 (84%), accounted for anaphylactic reactions. Amongst them 18% were associated with drug induced reactions, 23% were insect stings and 47% were food allergens but were less frequent [15]. In addition to it the data extracted from an anaphylaxis registry included 11 countries with 8736 patients having monophasic whereas 435 with biphasic reactions were analyzed showed that the onset of biphasic reactions may occur due to half a life of food allergens that are present in the human gut such as milk that is absorbed more frequently than the solid. Without standardized prospective ED data, observation policies will continue to rely on incomplete evidence.

A 2023 anaphylactic update from seven different areas indicated revised diagnostic criteria for anaphylaxis, that is the serum tryptase is crucial for identification of mast cell disorders in anaphylactic reactions. The management of Anaphylaxis policies for the adult and pediatric population share the crucial concepts of immediate intramuscular adrenaline as first line treatment but it differs as per risk and trigger. For pediatric population policies focus on food allergies prevention and management with guidelines recommending age-appropriate adrenaline dosing (0.15 for infants 7.5–10 kg and 0.3 mg for older children) with at least 4 h of careful observation. The teaching strategies include emergency action plan and autoinjector as per child's weight [1]. Whereas the adult anaphylaxis policies recognized drug and insect venom as compared to food allergies. The standard adult dose of 0.5 mg adrenaline with monitoring of comorbidities in adjunct to antihistamines or corticosteroids. Both pediatric and adult policies underscore the importance of observation after the initial treatment plan to detect biphasic reactions as well as recommending centered care approaches including emergency preparedness, allergen avoidance and accurate diagnosis [1].

Guidelines & current practice (North America / Europe)

Guideline recommendations

Anaphylaxis is a severe allergic reaction that can quickly compromise breathing, circulation, or both, and sometimes recur after initial resolution (a "biphasic" reaction) [4, 6]. Given the risk and unpredictable nature of biphasic reactions, no major North American guideline endorses a fixed 2–4-hour observation period and have intentionally avoided a rigid "2-hour discharge rule." [6, 8]. Instead, they favor risk-stratified, individualized observation [6].

The 2020 joint practice parameter from the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) recommends that patients who have experienced anaphylaxis should be observed by their healthcare provider(s) until they are clinically stable. Instead, the AAAAI/ACAAI guidelines recommend that clinicians use a risk-based approach in determining the length of hospital stay or the need for follow-up observation when making treatment decisions, which can include factors such as the severity of the anaphylactic reaction, how many epinephrine doses were used during the reaction, the presence of other medical conditions the patient has, and whether the patient will be able to take care of themselves after leaving the hospital [6, 16]. These recommendations were based on very low certainty evidence [6, 16]. Similarly, the 2023 update to the AAAAI/ACAAI Practice Parameter, again emphasizes the importance of providing individualized care to patients with anaphylaxis, and provides recommendations regarding how clinicians may do so including shared decision-making, creating a plan for each patient's Epinephrine Auto-Injector (EAI), and considering comorbid conditions, such as mast cell disorders, and medication use, such as beta-blockers, when developing a plan for a patient's discharge and follow-up care [1].

The National Institute for Health and Care Excellence (NICE) Clinical Guidelines (CG134) in the UK stance remains more conservative, prioritizing extended monitoring, especially for younger patients. The NICE recommend that adults and teenagers aged 16 years and older, who have received emergency treatment for symptoms,

be monitored for 6–12 h from the time of symptom onset, based on their response to treatment [8]. On the other hand, the NICE guideline has recommended the admission of children < 16 years under pediatric care as opposed to an early discharge after a brief emergency department visit [8]. A shorter observation window may be considered only when the reaction is "controlled promptly and easily," and when robust aftercare (e.g., EAI prescription, follow-up) is assured [8]. Overall, both North American and European guidelines emphasize clinical judgment over a fixed "2-hour rule," favoring observation durations tailored to individual patient risk factors [6, 8].

Evidence on biphasic reactions & implications for observation

A key driver behind variable observation recommendations is the data on biphasic reactions. A landmark systematic review and meta-analysis by Lee et al. (2015) reported findings from 4,114 patients who experienced 192 biphasic reactions. This study also reported that the median time to onset of the second phase of a biphasic reaction was 11 h (range 0.2 to 72 h) after resolution of the first phase [4]. The authors noted that food was associated with a lower risk of biphasic reaction (OR 0.62, 95% CI 0.40–0.94), while an unknown trigger (OR 1.72, 95% CI 1.0-2.95) and initial hypotension (OR 2.18, 95% CI 1.14–4.15) were associated with an increased risk of biphasic reaction [4]. Lee et al. (2014) had previously identified factors associated with biphasic reactions when treated in the Emergency Department [17].

In a recent meta-analysis published by Kim et al. in 2019, the authors combined results from 12 studies of adult patients. They found that the NPV for biphasic reactions of 1-hour observation post-resolution is 95.0% in comparison to 6 h of observation has a 97.3% (95% CI, 95.0-98.5), the additional benefit is limited to 6 h of observation [18]. Based on these data, a 6-12-hour observation window (as per many guidelines) is a practical balance between safety and resource constraints [8, 18].

Ellis et al. (2025) conducted research regarding 138 anaphylaxis cases at a Canadian tertiary hospital. The researchers identified biphasic reaction rates of 15.94%. The second phase of the biphasic reaction occurred on average 19 h after the first episode. In comparison to the first episode, biphasic reactions were less severe; however, they were more severe than non-anaphylactic recurrence episodes. Food was a less frequent cause of biphasic reactions compared to other types of anaphylaxis. A higher proportion of biphasic reaction episodes had unknown causes. All biphasic patients required a dose of epinephrine upon arrival at the Emergency Department (ED). Several biphasic patients required multiple doses of epinephrine during their admission. Therefore, there is evidence to suggest that biphasic reactions may be associated with both delayed and/or repeated administration of epinephrine. Thus, this study provides evidence for individualized observation and treatment plans, as biphasic reactions can occur at times beyond the typical observation period and be unpredictable [10].

Biphasic reactions in pediatric populations have been studied by Short et al. (2024), who demonstrated that biphasic reactions occurred in 3.4% of the 292 children treated for anaphylaxis, occurring as far as 33 h post-discharge, which indicates that a 4-6-hour monitoring period does not preclude late biphasic reactions [19]. Biphasic anaphylaxis has also been systematically reviewed by Mack (2014), where he found that the definitions of biphasic reactions differed significantly between studies. The frequency of biphasic reactions (ranging from 7.36% to 9.07%) and the time of onset of the second phase of the reaction (ranging from 1 to 72 h) also differed significantly [20]. The variability in these time intervals makes it difficult to establish standard observation times for such reactions. It encourages the use of an individualized (risk-based) approach to monitor biphasic reactions rather than a fixed time frame. This approach aligns with the recommendations of Lee et al. (2015) and Shaker et al. (2020) for delivering personalized care [4, 6]. The heterogeneity in definitions, timing, and incidence across studies, as summarized in Table 1, argues strongly against a one-size-fits-all discharge policy and supports a move toward risk-stratified observation.

How long is "enough"? evidence synthesis on cut-offs

Observation in the emergency department (ED) after anaphylaxis is essential for patient safety because of the potential for biphasic anaphylaxis (BA), a recurrence of symptoms occurring 1–72 h after resolution of the initial episode, with some reports extending this window to 78 h [5]. The "observation cut-off" refers to the minimum duration a patient must remain asymptomatic in the ED after initial symptom resolution before discharge can be considered safe [21]. The key metric for evaluating these cut-offs is the NPV which is the probability that a patient who remains asymptomatic during the observation period will not develop a biphasic reaction after discharge.

Meta-analytic estimates demonstrate that the NPV in relation to observation period as shown in Table 2, These pooled findings quantify why extended observation reduces post-discharge risk. Current guidelines generally recommend a minimum observation period of 4–6 h after symptom resolution. However, emerging evidence suggests that biphasic reactions can occur well beyond this window. Short et al. (2024), for example, reported BA onset ranging from 10 to 33 h after initial resolution [19],

Table 1 Key studies since 2015 on biphasic anaphylaxis

Study (year)	Design / Population	Biphasic Definition	Time to Biphasic (Median / Range)	Outcomes	Limitations
Lee et al. (2015) [4]	Systematic review, 4,114 patients	Recurrence of symptoms ≤ 72 h after resolution	Median 11 h (0.2–72 h)	192 biphasic events (4.7%)	Heterogeneous definitions, mixed age groups, observational data
Kim et al. (2019) [18]	Meta-analysis, 2,890 adults	Biphasic reaction post-resolution	NPV 95% at 1 h; 97.3% at ≥ 6 h	143 biphasic reactions (4.9%)	Adults only, limited child data, variable initial treatments
Short et al. (2024) [19]	Retrospective, 292 pediatric ED	Biphasic after epinephrine therapy	6 events occurred within 2.5 h; 4 events occurred between 10–33 h post-discharge	3.4% had biphasic reaction	Single center, retrospective, limited power

These studies show that biphasic reactions frequently occur well beyond 2 h. At two hours, the miss rate for biphasic reactions remains unacceptably high for a life-threatening condition. Variability in timing and incidence argues against a one-size-fits-all "2-hour" discharge policy. Heterogeneity in age, triggers, and definitions remains a limitation, but overall trends support risk-stratified observation based on clinical factors

Table 2 Cut-off performance by observation duration

Observation Duration (post-symptom resolution)	Pooled NPV (95% CI)	Estimated Miss-Rate per 1,000 Discharged	Absolute Risk Reduction vs. 2 h per 1,000
1 h	95.0% (90.9–97.3%)	50	—
2 h	≈ 95.8%	42	Reference (0)
4 h	≈ 96.8% (95.5–97.8%)	32	10
6 h	97.3% (95.0–98.5%)	27	15
8 h	97.6% (95.5–98.8%)	24	18
> 8–12 h	> 98% (approaching 99%)	< 20	> 22

Pooled NPV, estimated miss-rate per 1,000, and absolute risk reduction vs. 2 h. (From Kim 2019 pooled estimates and narrative synthesis)

while Kim et al. (2019) recommended 6–12 h of observation based on their findings [18]. These data highlight that insufficient observation may leave patients vulnerable to delayed, potentially life-threatening recurrences. Clinical risk factors also influence the need for prolonged observation. Wolpert et al. (2022) evaluated a disposition-focused clinical decision support tool (CDST) that stratified patients into risk categories based on the severity of the initial reaction and the timeliness of epinephrine administration [22]. Risk-based discharge using this CDST improved outcomes: low-risk patients were safely discharged after shorter observation periods, whereas higher-risk patients benefited from extended monitoring. These findings reinforce the importance of integrating individual clinical risk into observation decisions rather than relying solely on fixed time thresholds.

Clinical significance of treatment-requiring events

From a clinical decision-making perspective, the true target of post-anaphylaxis observation is not merely the detection of any biphasic reaction, but specifically those biphasic events that require treatment, typically additional epinephrine, intravenous fluids, bronchodilators, corticosteroids, or airway support. These treatment-requiring biphasic reactions represent the subset with meaningful morbidity and therefore carry the greatest implications for patient safety and ED disposition planning [6]. Disposition decisions must be based on the risk of treatment-requiring recurrence, not on the occurrence of any recurrence. The literature indicate that a substantial proportion of clinically significant, treatment-requiring biphasic episodes occur beyond the commonly used 2–4-hour observation window, highlighting the insufficiency of short, uniform monitoring periods [9]. However, a major limitation in the literature is that many studies report "any biphasic reaction" as their primary outcome without distinguishing between mild, self-limited symptom recurrence and reactions that necessitate active medical intervention [2]. This lack of detail inflates biphasic incidence estimates while providing limited guidance for practical risk assessment. Therefore, for clinical relevance, ED disposition should be guided by the risk of treatment-requiring biphasic reactions rather than the occurrence of any symptom recurrence. This orientation reinforces the need for risk-stratified observation windows, longer monitoring for patients with higher clinical risk, and a cautious approach to very short universal observation policies.

The economic lens

Only risk-stratified observation is clinically defensible and economically viable. Extended observation in the ED after anaphylaxis carries important economic implications, particularly as clinicians must balance patient

safety with healthcare resource utilization. While several studies support longer observation windows (8–12 h) associated with delayed biphasic reactions [18, 23]. These benefits may not justify the added cost for patients at low clinical risk. For such individuals, prolonged monitoring may yield minimal incremental safety benefits while generating substantial and potentially unnecessary expenditures. In the United States, the average cost of ED observation for anaphylaxis has been estimated at approximately $286.92 per hour, with incremental costs ranging from $62,374 to $213,439 per additional biphasic reaction detected [9]. Shaker et al. (2019) argue that although extended observation may be appropriate for high-risk patients such as those requiring multiple epinephrine doses or presenting with severe hypotension the financial considerations must be carefully weighed against the probability of a clinically significant biphasic event [9]. When the risk of severe recurrence is elevated, the benefits of prolonged observation may outweigh these costs; however, for the average patient, the cost-benefit ratio may be unfavorable. Moreover, variability in hospital charges based on the length and setting of observation further underscores the need for targeted strategies rather than blanket policies. Evidence suggests that cost efficiencies are optimized when observation duration is aligned with an individual's clinical risk profile rather than uniformly prolonged across all patients [24].

Synthesis on observation duration

A blanket two-hour observation policy for anaphylaxis may appear operationally efficient, but evidence shows that it carries an unacceptably high risk of missed BA, particularly among patients with moderate-to-high clinical risk profiles [9]. At this early point, the negative predictive value remains insufficiently low to ensure safe discharge, meaning that a meaningful proportion of patients who experience a subsequent BA will do so after leaving the ED. This level of miss-risk is inconsistent with contemporary safety standards and undermines the purpose of post-anaphylaxis monitoring. Extending the observation period to at least six hours substantially reduces this risk. Meta-analytic data demonstrate that the probability of remaining free from a BA after discharge increases materially up to six hours, reflecting a clear safety advantage associated with longer monitoring. However, the incremental benefit of further extension begins to diminish beyond the 8–12-hour window. Although NPVs continue to rise slightly, the gains become progressively smaller relative to the additional resource investment required. This pattern indicates decreasing marginal returns with prolonged universal observation. For high-risk patients such as those with severe initial reactions, delayed epinephrine administration, or a need for multiple epinephrine doses, the extended period may still be clinically justified. For lower-risk individuals, though, the additional hours may not offer a proportionate improvement in safety.

Implementation for EDs: a risk-stratified pathway

Given the variability in timing and risk, applying these findings clinically requires a structured approach to classify patients and guide the duration of observation. Once the symptoms associated with anaphylaxis have resolved, and the patient is stable, it is possible to determine whether a patient is at "low risk" or "high risk", which would help direct both the length of time a patient needs to be observed prior to discharge, and their discharge plan [4, 18].

Some examples of the factors that would identify a patient as "low risk" in children, are rapidly resolving food-triggered events and the fact that the patient's symptoms rapidly resolve after administration of one dose of epinephrine; a food trigger that is identified as low risk; no hypotension, or hypoxia, or other evidence of multisystem involvement during treatment; no significant comorbidity (such as asthma, beta blocker use, or cardiovascular disease); and/or the patient has reliable home supervision with access to emergency medical services [10, 18]. These patients are estimated to have a < 5% chance of experiencing a biphasic reaction within the first hour of treatment, and this risk drops even lower after 6 h; thus, a mandatory minimum observation of 1 h, often extending to 3 h, is appropriate post-treatment followed by a discharge bundle including an EAI prescription and education on the proper use of this medication is considered sufficient for these patients [18].

Examples of high-risk criteria for a patient experiencing anaphylaxis would be the need for two or more epinephrine doses - the most consistent predictor of biphasic risk across all datasets - prior to symptom resolution or a slow recovery from the initial dose of epinephrine, or if the patient has symptoms of hypotension, hypoxia or other multi-systemic symptoms that may limit their ability to breathe or maintain circulation [6, 10, 16]. Other examples of high-risk criteria include anaphylaxis from an unknown or non-food trigger, asthma, heart disease, using beta blockers, mast cell disorders, or limited access to emergency services or medical support at home [6, 10, 16, 18]. Generally, these patients require observation for a minimum of 6 h. However, they are typically observed for more extended periods (e.g., six to twelve hours) or hospitalized, especially when multiple risk factors are involved, such as poor home monitoring or geographical isolation [6, 10, 16].

Several important components exist when implementing a risk-stratified anaphylaxis pathway in an ED setting. Important components of an anaphylaxis pathway include standardized order sets that address specific

criteria related to: the administration of epinephrine (dosing and frequency); the frequency of vital signs that must be monitored; the criteria used to determine whether a patient can be discharged from the ED or must remain in the ED for further evaluation; and the elements that should be included in the discharge bundle [6, 10, 16]. In addition, nursing education and protocols are crucial in identifying and treating biphasic reactions, providing adequate patient monitoring, and educating patients on how to properly administer an EAI upon discharge from the ED [16]. In addition to the above elements, it is also essential that each patient, regardless of the level of risk, receive a discharge bundle that includes: an EAI, a written plan of action, instructions for avoiding the allergen that caused the anaphylactic reaction, clear information regarding when and how to return to the ED for further treatment, and arrangements for early follow up with an Allergist [1, 10]. Establishing early follow-up with an Allergist will enable improved long-term management of the patient's allergic condition. Table 3 provides a proposed framework for a risk-stratified ED management pathway.

Anaphylactic biphasic reactions can occur at any time. While the severity of biphasic events can range from mild to more severe than the initial episode, comprehensive data on the exact percentages of severe recurrences are limited due to heterogeneity in study reporting [10]. Rates of biphasic reactions are variable and have ranged from 1% to 20%. Studies generally report that the biphasic reaction rates are between 4% and 6% [4, 10]. Biphasic reactions can also occur in what were previously considered to be low-risk patients and may occur at any time after discharge. The timing of reactions is also variable, occurring anywhere from less than one hour to as long as 72 h after initial symptoms have resolved [4, 10]. Because of this variability, it is essential to consider the following when developing your discharge plan for patients with anaphylaxis: (a) ensure that there will be access to an epinephrine auto-injector available to the patient, (b) provide patient education regarding identification and treatment of potential recurrence, and (c) educate the patient as to when they should seek additional medical evaluation.

Due to limited resources available in emergency departments, extended observation of all anaphylaxis patients would be both impractical and inefficient. Economic studies demonstrate that a risk-stratified strategy, which extends the length of observation to patients presenting with higher risk factors, is the most effective way to utilize resources while continuing to protect patient safety [6, 16]. Furthermore, when evaluating the risk of a patient for continued post-discharge safety, several factors beyond clinical stability must be considered. These include but are not limited to: (a) the reliability of the patient's home support system, (b) access to emergency services, and (c) whether or not the patient or their caregiver has the ability to administer an epinephrine auto-injector correctly and every patient must be discharged with an EAI, demonstrated proper technique, a written emergency plan, and confirmed early allergy follow-up. All of these are examples of social determinants of health that are relevant to assessing the risk for safe post-discharge care [1, 10].

Following an ED visit for anaphylaxis, ongoing care remains important. Patients will benefit by being referred to an allergist for identifying the cause of their anaphylaxis and developing a treatment plan for any potential underlying condition (such as mast cell disorder) that may exist to continue to assess and reduce their overall risk [1, 10]. Due to the lack of high certainty evidence and variability in individual risk, clinicians should also employ a shared decision-making process. As part of this process, clinicians should engage patients and their caregivers in conversations regarding the optimal length of time for an extended observation period, how to determine if they are ready for discharge, and what follow-up plans need to be made, openly discussing the risks, benefits, and uncertainties associated with each option to allow patients and their caregivers to participate in the decision making process in an informed manner [1, 6]. A comprehensive approach to managing anaphylaxis, which considers safety, practicality, and individualized

Table 3 Risk-stratified ED management pathway for anaphylaxis

Risk Tier	Observation Duration	Monitoring Requirements	Discharge Requirements
Low-risk *(e.g., rapid resolution with 1 epi dose, known food trigger, no severe features)*	1–4 h (minimum 1 h mandatory)	Monitor vitals (HR, BP, O_2 sat) and for symptom recurrence.	Standardized discharge bundle (required for all tiers): EAI prescription, comprehensive education on biphasic risk, triggers, emergency action plan, and allergy referral.
High-risk *(e.g., ≥ 2 epi doses, hypotension/hypoxia, unknown trigger, severe comorbidities)*	≥ 6 h (often 6–12 h) or admission	Continuous or frequent vitals monitoring; consider admission for persistent instability or multiple risk factors.	EAI prescription, comprehensive education, reinforced emergency plan, confirmed allergy follow-up, and consideration of social determinants of health.

This table translates evidence into practice, demonstrating that low-risk patients may be suitable for shorter observation if discharged with a robust safety plan, whereas high-risk patients require extended monitoring or hospital admission to mitigate the risk of a missed biphasic event

care, will enable clinicians to optimize emergency department management of anaphylaxis and improve long-term patient outcomes [1, 10].

Implementing such a nuanced, risk-stratified pathway presents considerable practical challenges in a busy emergency department. Barriers to successful adoption include high staff turnover, competing clinical priorities, and the generalist nature of emergency medicine, which may limit deep, specialized knowledge of anaphylaxis management. Overcoming these hurdles requires more than just clinical recommendations; it necessitates institutional commitment. Key facilitators include the integration of standardized order sets and clinical decision support tools into the electronic health record, which can automate risk assessment and guide clinicians toward appropriate observation times. Furthermore, recurrent, targeted nursing and physician education is crucial for ensuring that staff can confidently identify risk factors, manage biphasic reactions, and deliver the components of the discharge bundle effectively. Without such systemic support, the translation of evidence into consistent clinical practice is likely to remain incomplete [25–27].

Future directions & research agenda

Most current evidence on biphasic anaphylaxis comes from retrospective cohorts, such as that by Ichikawa et al. which documented the incidence and timing of biphasic reactions based on chart review rather than standardized, real-time data collection [11]. While studies of this sort provide invaluable estimates, they are inherently limited by incomplete documentation, variability in follow-up, and inability to reliably capture pre-specified risk markers such as initial severity, timing of epinephrine administration, or trigger category [28]. These limitations emphasize a pressing priority for research: the establishment of prospective, ED-based anaphylaxis registries with uniform data elements, real-time severity scoring, and pre-specified risk markers [29]. Such registries would allow for time-to-event modeling of biphasic recurrence, support external validation of risk calculators, and permit the field to move toward individualized, data-driven observation pathways.

Combining pediatric and adult data has historically masked true risk and contributed to misaligned observation standards, although the research by Ichikawa et al. provides important information about biphasic reactions in adults, its lack of patients under 18 years of age leaves a great deficiency: we still don't know how these reactions are reflected in children [11]. And this is very important, because children are not small adults: their anaphylaxis triggers, symptoms, and risks are often quite different. Foods, for instance, including peanuts and milk, are common triggers in children, whereas medication and insect stings occur with higher frequency in adults. Simply combining the data from both groups produces an average that misleadingly describes neither, a fallacy that goes by the name of ecological bias. That means that future studies should include children and consider pediatric and adult data separately from the start. Future research programs should therefore keep pediatric and adult analytic pathways separate from the outset with subsequent structured pooled analyses using age meta-regression rather than naïve aggregation. Once there is clear, separate understanding, we can carefully combine our insights using advanced statistical models designed explicitly to take age into account. Only then will we be able to construct observation guidelines that will protect children and adults alike and help all patients recover safely from anaphylaxis.

As part of the 2020 practice parameter update, a systematic review and meta-analysis were performed to inform clinical guidance on anaphylaxis management [6]. A crucial component of this evidence synthesis involved a meta-analytic dose-response analysis using a restricted cubic-spline meta-regression model. This highly advanced statistical approach was used for the purpose of characterizing the exact nonlinear relationship between the duration of patient observation and the risk of failing to identify a biphasic anaphylactic event. The model was critically adjusted for major prognostic variables, which included initial anaphylaxis severity, the need for more than one dose of epinephrine, and the anaphylaxis trigger [6]. The next-generation dose-response analyses should build on this foundation through the inclusion of IPD, harmonization of biphasic reaction definitions, and evaluation of additional spline-knot placements to more precisely identify high-risk inflection zones. Such models will directly inform adaptive observation protocols aligned with the AAAAI parameters.

Interestingly, the analysis demonstrated that increased observation time, while associated with a progressively lower risk of missing a biphasic reaction, had markedly diminished returns. The resultant number needed to monitor derived was significantly lower among high-risk patients-those with severe initial reactions or those requiring multiple epinephrine doses-pointing out that the relative cost-effectiveness of extended observation is highest in this subgroup. Such an analytical approach and resulting data are in line with the evidence and timing parameters recommended in this AAAAI practice parameter update [6].

The length of observation post-anaphylaxis should be risk-stratified, as shown by evidence from a systematic review and meta-analysis of 12 studies that had included 2,890 patients. Observing the patients for just 1 h could mean missing biphasic reactions with a risk of 5% (NPV 95%), while extending observation up to 6 h lowers it to 2.7% (NPV 97.3%) [18]. The dose–response

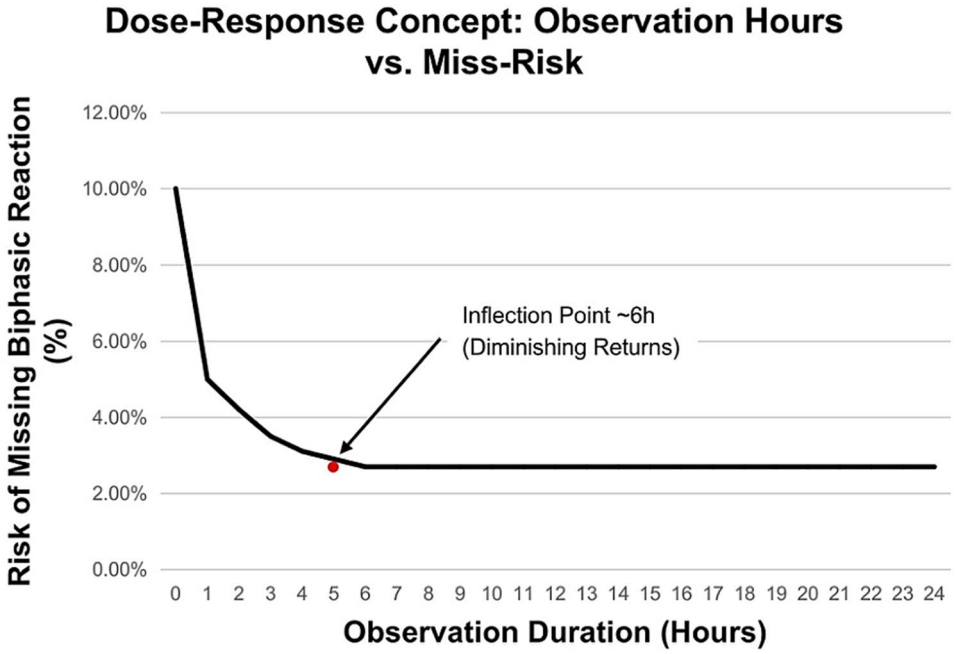

Fig. 2 Dose-response relationship between observation duration and risk of missing biphasic anaphylaxis. This conceptual graph, derived from pooled NPV trends, illustrates that the risk of missing a biphasic event decreases as observation time increases. Note the inflection point at approximately 6 h, indicating diminishing returns with further extended observation for the general anaphylaxis population

curve consistently identifies a six-hour inflection point beyond which incremental benefit diminishes. Future research should thus focus on the validation and refinement of this conceptual dose–response curve in modern populations, testing whether the inflection point varies across severity phenotypes, and evaluating whether new biomarkers—such as tryptase trajectories—can enhance predictive accuracy.

Beyond biphasic detection, future research will need to focus on patient-important outcomes such as 72-hour ED return, unplanned hospital admission, ICU transfer, and short-term mortality. Implementation-science outcomes including ED throughput, crowding metrics, and operational opportunity costs should be routinely incorporated into future trials so that observation strategies are both clinically effective and system-efficient. To enable consistent reporting of residual risk across observation windows, future practice-parameter changes and observational studies should regularly incorporate a uniform conceptual dose-response curve, as illustrated in Fig. 2, there appears to be a critical inflection point at approximately 6 h, beyond which further observation provides only marginal incremental benefit in unselected populations [18]. Future analyses should build on this foundation by incorporating individual patient data (IPD), harmonizing definitions of biphasic reactions, and evaluating additional spline-knot placements to more precisely identify high-risk inflection zones. Such models will directly inform adaptive observation protocols.

The economic evaluation by Shaker et al. (2019) provides significant insight into patient outcomes and healthcare system efficiency through the modeling of cost-effectiveness in various observation strategies following resolved anaphylaxis. This study therefore shows that routine prolonged observation-namely, 6–24 h-carries an excessively high cost per death prevented at approximately $9 million to over $44 million, thereby suggesting it is a low-value intervention for preventing mortality in unselected patient populations. Though the study does not directly measure such outcomes as 72-hour ED return rates or ICU transfers, its findings have direct implications for implementation science. Adoption of a shorter observation period of 1 h for low-risk patients might lead to significant improvements in ED throughput and a reduction in length of stay, alleviating crowding and freeing critical clinical resources for other acute needs, thereby improving overall healthcare system efficiency [9]. Future economic research should take into account dynamic risk-tiering, be customized to local cost structures, and assess hybrid models like one-hour ED observation followed by telemedicine or structured outpatient follow-up. Transforming risk-stratified paths into practical applications will require such assessments.

From a health economics perspective, extended observation should be reserved for patients whose clinical risk justifies the added resource cost. This analysis underlines the paramount importance of risk-stratified approaches and local considerations of costs. The model shows that

the cost-effectiveness of extended observation drastically depends on specific patient risk profiles and institutional cost structures. Prolonged observation becomes economically viable only in specific scenarios: notably for patients with high baseline risk of biphasic reactions (higher than 17% after 1-hour observation) or in settings with exceptionally low hourly observation costs (less than $46). This emphasizes that the economic viability of extended observation is not a given but needs to be analyzed in accordance with local operational costs and individual patient risk, strongly supporting the need for customized clinical pathways and resource allocation strategies according to these variables.

Limitations of the current evidence

Before outlining the future research agenda, it is important to acknowledge the inherent weaknesses in the current body of evidence on biphasic anaphylaxis. The majority of available data is derived from retrospective studies, which are susceptible to incomplete documentation, recall bias, and inconsistent follow-up. A significant challenge is the heterogeneity in the definition of a biphasic reaction across studies, which complicates meta-analytic efforts and leads to wide variations in reported incidence. Furthermore, many studies fail to differentiate between mild symptom recurrence and clinically significant, treatment-requiring events, limiting the practical applicability of their findings for ED disposition decisions. These limitations underscore the need for the prospective, standardized research approaches discussed below.

Conclusion

After ten years of consistent evidence, the traditional 24-hour observation period is unsupportable, the management of patients' post-anaphylaxis has undergone a profound, evidence-driven evolution over the past decade. Around 2015, the prevailing understanding was shaped by landmark meta-analytic data demonstrating that biphasic reactions were not immediate phenomena; their median onset of approximately 11 h far exceeded the brief observation periods common at the time. This foundational evidence challenged the prevailing one-size-fits-all approach and set the stage for a necessary re-evaluation of clinical practice.

In the current era (2020–2025), this re-evaluation has culminated in a clear paradigm shift. Major clinical practice guidelines from bodies like the AAAAI and ACAAI have formally moved away from recommending fixed observation times, instead championing a risk-stratified strategy based on the severity of the initial presentation. This shift is now supported by quantitative evidence. Decision and economic analyses have provided crucial metrics, such as pooled NPV, which demonstrate that extending observation from 1 to 2 h to ≥ 6 h significantly enhances safety by reducing the rate of missed biphasic events. These analyses also suggest that for many patients, observation beyond 8–12 h offers only marginal additional benefit, allowing for more rational resource allocation.

The clinical imperative is now clear: emergency departments must abandon antiquated, uniform observation policies, such as a universal "2-hour rule," which are unsupported by current evidence. The future of safe and efficient care lies in implementing structured, risk-tiered observation pathways. Low-risk patients—those with a rapid, complete response to a single dose of epinephrine and no severe features—may be suitable for shorter observation, provided they are discharged with a comprehensive education bundle. This must include clear instructions on recognizing recurrent symptoms, trigger avoidance, and correct use of an epinephrine auto-injector, as emphasized by bodies like NICE. Conversely, high-risk patients require prolonged observation (≥ 6 h) or admission.

Looking forward, the research community must focus on refining these strategies. Structured risk-tiered pathways should replace universal short observation as the minimum standard of ED care. This requires a concerted effort toward standardized reporting using consensus definitions for biphasic anaphylaxis to ensure data comparability across studies. Future prospective registries should prioritize age-stratified analyses to determine if risk and timing differ in pediatric versus adult populations thereby avoiding the ecological bias inherent in combining these distinct groups. Finally, the development and validation of clinical decision-support tools that integrate these evidence-based risk factors directly into ED workflows is a critical next step. Such tools will empower clinicians to translate a decade of research into a consistent, safer, and more efficient standard of care for every patient recovering from anaphylaxis.

Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology
ACAAI	American College of Allergy, Asthma & Immunology
AI	Artificial Intelligence
BA	Biphasic Anaphylaxis
CG	Clinical Guideline
CI	Confidence Interval
CNS	Central Nervous System
ED	Emergency Department
EAI	Epinephrine Auto-Injector
EMS	Emergency Medical Services
GI	Gastrointestinal
ICU	Intensive Care Unit
IM	Intramuscular
IV	Intravenous
IQR	Interquartile Range
JTFPP	Joint Task Force on Practice Parameters
MeSH	Medical Subject Headings
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value

OR	Odds Ratio
PICU	Pediatric Intensive Care Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROC	Receiver Operating Characteristic
RR	Relative Risk
UK	United Kingdom
US / USA	United States of America

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