Factors influencing emergency department observation time following anaphylaxis: a systematic review

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Abstract

Objective Anaphylaxis is a condition that warrants an observation period after symptoms resolution to detect rare but life-threatening delayed complications. There is a need for evidence to identify patients who would benefit from prolonged observation time. The purpose of this review was to identify factors that may influence the need for longer observation in the emergency department.

Methods PubMed, Embase, EBM Review, and Cochrane Library were searched using controlled vocabulary and keywords to cover all relevant data. Titles, abstract, and full text were reviewed for inclusion and exclusion criteria. Data were extracted from the included articles regarding case definitions, prognosis, treatment and time factors, and recommended observation time. Factors linked to observation time or complications were tabulated and compared between studies.

Results The search retrieved 2443 citations of which 49 were included. Twenty-one were primary studies and were used to identify factors influencing observation time or complications. Biphasic anaphylaxis was the only adverse event that warranted prolonged observation. The five risk factors often associated with biphasic reactions were time to first epinephrine, history of anaphylaxis, symptom severity, number of epinephrine doses, and unknown trigger. Biphasic reactions happened mostly within the first 72 h with most severe reactions occurring earlier than the milder ones. Heterogeneity in the definition of biphasic anaphylaxis made comparisons challenging.

Conclusions Observation time should be based on the provider's best estimation of the risk of biphasic anaphylaxis, although no single factor can predict their occurrence. The identified factors will allow the development of an early discharge screening tool.

Keywords Anaphylaxis · Biphasic · Observation · Emergency · Glucocorticoids · Risk factors · Prognostic factors

Résumé

Objectif L'anaphylaxie est une condition qui mérite une période d'observation après la disparition des symptômes pour détecter des complications retardées rares, mais potentiellement mortelles. Il est nécessaire de trouver des preuves pour identifier les patients qui bénéficieraient d'une période d'observation prolongée. Le but de cet examen était d'identifier les facteurs qui pourraient influencer la nécessité d'une période d'observation plus longue aux urgences.

Méthodes PubMed, Embase, EBM Review et Cochrane Library ont été recherchés au moyen d'un vocabulaire contrôlé et des mots-clés pour couvrir toutes les données pertinentes. Les titres, le résumé et le texte intégral ont été examinés pour les critères d'inclusion et d'exclusion. Les données concernant les définitions de cas, le pronostic, le traitement et la durée

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de traitement, et la période d'observation recommandée ont été extraites des articles inclus. Les facteurs liés à la période d'observation ou aux complications ont été présentés sous forme de tableau et comparés entre les études.

Résultats La recherche a permis de récupérer 2443 citations dont 49 ont été incluses. Vingt et un étaient des études primaires et ont été utilisées pour identifier les facteurs influençant la période d'observation ou les complications. L'anaphylaxie biphasique était le seul événement indésirable qui méritait une observation prolongée. Les cinq facteurs de risque souvent associés aux réactions biphasiques étaient le délai de la première épinéphrine, les antécédents d'anaphylaxie, la gravité des symptômes, le nombre de doses d'épinéphrine et le déclencheur inconnu. Les réactions biphasiques se sont produites principalement dans les 72 premières heures avec les réactions les plus graves se présentant plus tôt que les réactions plus légères. L'hétérogénéité de la définition de l'anaphylaxie biphasique a rendu les comparaisons difficiles.

Conclusions La période d'observation doit être basée sur la meilleure estimation du risque d'anaphylaxie biphasique fournie par le professionnel de la santé, bien qu'aucun facteur unique ne puisse prédire son apparition. Les facteurs identifiés permettront le développement d'un outil de dépistage pour les sorties précoces de l'hôpital.

Clinicians' capsule

What is known about the topic?

A small percentage of people with anaphylaxis experience a biphasic reaction. Long observation periods are recommended to identify them.

What did this study ask?

What are the predictors of a biphasic reaction that require extended observation periods?

What did this study find?

We identified five predictors of biphasic reaction: time to epinephrine, anaphylaxis history, symptom severity, number of epinephrine doses and unknown trigger.

Why does this study matter to clinicians?

Identifying factors associated with biphasic anaphylaxis will allow designing and testing of a decision rule for discharging patients early after anaphylaxis resolution.

allergen [4]. The prevalence of biphasic anaphylaxis varies between studies and reviews report rates from 0.4 to 21% [4, 5]. Time between initial and biphasic anaphylaxes varies greatly [5] with reported ranges from 1 to 72 h, and medians from 4 to 22 h [6–13]. Furthermore, the intensity of biphasic anaphylaxis is most often equal to or less than the initial anaphylaxis, with very few fatalities [14]. Guidelines generally recommend 4–8 h observation following symptom resolution, which is out of range for many reported biphasic anaphylaxis [5, 15]. There is no clear consensus among scientific literature on the best observation time, strategy, or criteria to discharge patients safely following anaphylaxis [14]. Additionally, the lack of formal definitions for anaphylaxis and biphasic anaphylaxis has created challenges in creating repeatable and comparable research [2].

Considering the low occurrence of biphasic anaphylaxis, few fatal events, and wide time range before biphasic anaphylaxis, the aim of this systematic review is to identify, in patients consulting the emergency department for anaphylaxis and treated with epinephrine or corticosteroid, factors associated with the need for a longer observation period following symptom resolution. A secondary aim is to assess the extent to which the definitions of anaphylaxis and biphasic anaphylaxis are uniform across studies. This systematic review sets the stage to derive and validate a clinical decision rule to safely discharge patients sooner following anaphylaxis and restrict prolonged observation to patients at higher risk of complications.

Introduction

Anaphylaxis is a life-threatening allergic reaction affecting 0.05–2% of the population [1]. It is a common consultation reason in the emergency department. As there is no absolute definition of anaphylaxis, diagnosis is often based on criteria defined by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) [2] available in Appendix Table 1. Management of acute episodes of anaphylaxis is based on the assessment of airway, breathing, circulation and consciousness of the patient, and epinephrine administration [3].

Biphasic anaphylaxis is a potential complication of anaphylaxis consisting of a relapse of symptoms after resolution of the initial anaphylaxis without re-exposure to the

Methods

The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines were used to conduct this systematic review [16]. A systematic search of the literature was conducted in July 2018 in four databases (PubMed, Embase, EBM Review, and Cochrane Library). Furthermore, two evidence-based clinical resources (UpToDate and Dynamed) and two recognized emergency medicine textbooks

(Tintinalli's Emergency Medicine 8th, Rosen's Emergency Medicine 9th) were added to explore current practice recommendations. Search strategies included controlled vocabulary and keywords to cover all relevant data and are available in Appendix Table 2. It is standard in emergency medicine to use evidence from the past 5 years. To prevent being overly restrictive, this period was doubled (January 2008 to July 9th, 2018), which also allowed for the 2006 NIAID/FAAN criteria to be adopted therefore providing better heterogeneity. The search was updated prior to publication on the same databases to cover the period from July 9th 2018 to April 7th 2020.

Eligibility criteria included a population of people consulting the emergency department for anaphylaxis and outcomes reporting either the prognostic and treatment factors influencing a biphasic anaphylaxis, adverse events that may occur in the post-anaphylaxis period and/or the observation time recommended. There were no restrictions on age or country of the population; however, only studies in French and English were selected. All types of studies were included except case studies. Only primary studies were included in the analysis of factors to avoid information duplication associated with reviews. Other designs were used for exploratory and informative purposes. A team member performed a first screening of titles and abstracts and removed all those that were evidently ineligible. The remaining articles were discussed in groups of 3–5 members to determine their eligibility.

Eligible articles were read and reviewed by the team (4–30 articles per person). The following data were extracted: study design, publication date, sample size, population characteristics (age, country, and environment), definitions of anaphylaxis and biphasic anaphylaxis, prognostic factors, adverse events (type, time of onset), observation time recommendations, and relationship between corticosteroids and biphasic anaphylaxis. For each selected article, a list of factors with statistically significant association to observation time, biphasic anaphylaxis, corticosteroid use, or occurrence of adverse events was extracted. The number of times each criterion was cited was tabulated. A second reviewer validated independently the data extraction for all articles. All disagreements were resolved through team discussions.

A bias assessment was performed for quality appraisal of the included primary studies. The studies were assessed for selection, misclassification, detection, performance, attrition, information, confounding, and reporting biases with evaluation grids based on the Cochrane Handbook for Systematic Reviews of Interventions [17]. Two reviewers evaluated each article separately and a third resolved disagreements.

Results

Search results

The selection process is presented in Fig. 1. The systematic search identified 2443 citations and 52 were selected after screening the title and abstract. These 52 articles were read in full and 40 were included in the systematic review. The main reasons for exclusion were outcomes addressed or population included. The update revealed five primary studies and four reviews. Twenty-one primary studies were included in the analysis of factor. The entire 49 articles were used to answer the definition and observation time questions.

Study characteristics

Overall, the review included 21 primary studies involving 22,707 patients (summarized in Table 1), while 28 citations were literature reviews, guidelines, or expert opinions (available in Appendix Table 3).

The 21 primary studies were conducted in the United States (10), Canada (5), Australia (2), Japan (2), South Korea (1), and Switzerland (1). Fourteen were retrospective studies, three were prospective and four combined both designs. Nine studies exclusively focused on pediatric populations, three on adult populations, while the others included all ages. Three pairs of studies [18–23] used the same patient sample and four studies [9, 24–26] contained some patient overlap, but the extent was difficult to determine.

Among the 28 remaining articles, 9 were reviews and 15 were guidelines or expert opinion papers. Five focused exclusively on pediatric populations and one on adults, while the others included all ages. Only six specified the number of patients included in their review.

Bias assessment

Overall, the quality of the studies included was good. Potential bias mainly came from mixed recruitment strategies used by several studies, which introduced differences in the way information was gathered. Table 2 summarizes the potential for bias.

Complications influencing observation time

Although the search strategy used was wide enough to capture all complications, the only one reported in the literature that warranted longer observation periods was biphasic anaphylaxis. The following sections focus on these factors, grouped by type, which may predict its occurrence.

Fig. 1 PRISMA flowchart: selection process of the included articles. *n* articles form the original research; *n* articles form the 2018–2020 update; *included in factors analysis

Prognosis factors of biphasic anaphylaxis

The numerous factors increasing the risk of biphasic anaphylaxis are presented in Table 3. The most frequent prognostic factors are severity of initial anaphylactic symptoms [6, 9, 18, 24, 27–29], multiple doses of epinephrine administered for initial anaphylaxis [6, 28, 30, 31]; delayed first epinephrine administration [6, 25, 26]; history of previous anaphylaxis [7, 9, 24, 25]; unknown trigger [9, 25] and young age [26, 30]. A similar list was created using only data from articles that reported clinically significant biphasic anaphylaxis. Ten factors were identified with five cited by multiple

studies and five cited only once. Minimal differences exist between the two lists (Table 4).

Treatment factors of biphasic anaphylaxis

The impact of glucocorticoids on risk of biphasic anaphylaxis showed important variability. Conflicting association emerges from primary studies and reviews. Sixteen reviews concluded that evidence was insufficient; ten that they have no effect on occurrence of biphasic anaphylaxis; and seven indicated a decrease in the risk of biphasic anaphylaxis. Six primary studies found no significant effect of corticosteroids.

Table 1 Characteristics of the included studies—primary studies

Author and year	Design	Number of participants	Country	Population	Definitions		Clinically significant biphasic reaction
					Anaphylaxis	Biphasic reaction	
Alqurashi [6], 2015	Retrospective	484	Canada	Pediatric	NIAID/FAAN	Resolution, anaphylaxis, therapy	Yes
Brown [27], 2013	Prospective	315	Australia	All ages	NIAID/FAAN	Deterioration	No
Rohacek [36], 2014	Retrospective	495	Switzerland	All ages	NIAID/FAAN	Resolution, allergy or anaphylaxis	Differentiate
Ko [7], 2015	Retrospective	415	South Korea	Adults	NIAID/FAAN	Resolution, anaphylaxis	Yes
Inoue [28], 2013	Retrospective	61	Japan	Pediatric	NIAID/FAAN	Resolution, allergy	No
Mehr [30], 2009	Retrospective	109	Australia	Pediatric	NIAID/FAAN	Resolution, allergy	No
Grunau [20], 2015	Retrospective	473	Canada	Adults	NIAID/FAAN	Resolution, anaphylaxis	Yes
Manivannan [44], 2009	Retrospective	208	USA	All ages	NIAID/FAAN	ND	ND
Lee [25], 2017	Retrospective and prospective	872	USA	All ages	NIAID/FAAN	Resolution, allergy or anaphylaxis	Differentiate
Michelson [45], 2015	Retrospective	10,255	USA	Pediatric	ICD-9 codes	Persistence	No
Ellis [31], 2007	Prospective	103	Canada	All ages	Canadian Pediatric Surveillance Program	Anaphylaxis	Yes
Grunau [21], 2014	Retrospective	496	Canada	Adults	NIAID/FAAN	Resolution, anaphylaxis	Yes
Lee [9], 2014	Retrospective	541	USA	All ages	NIAID/FAAN	Resolution, anaphylaxis	Yes
Campbell [24], 2015	Retrospective and prospective	582	USA	All ages	NIAID/FAAN	ND	ND
Oya [32], 2014	Retrospective	114	Japan	All ages	NIAID/FAAN	Resolution, anaphylaxis	Yes
Lee [22], 2017	Retrospective	439	USA	Pediatric	ND	ND	NA
Liu [26], 2019	Prospective	430	USA	All ages	NIAID/FAAN	Resolution, allergy or anaphylaxis	Differentiate
Dribin [19], 2020	Retrospective	603	USA	Pediatric	NIAID/FAAN	ND	ND
Dribin [18], 2019	Retrospective	665	USA	Pediatric (1–21 years)	NIAID/FAAN	Resolution, allergy	No
Gabrielli [29], 2019	Retrospective and prospective	3498	Canada	All ages	NIAID/FAAN	ND	ND
Lee [23], 2018	Retrospective and prospective	439	USA	Pediatric	Combination of multiple ICD-9 and ICD-10 Codes	ND	ND

All ages: include pediatric and adult population; NIAID/FAAN: used the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network definition [2]; Clinically significant biphasic anaphylaxis: articles with secondary reaction that fit the NIAID/FAAN definition; Differentiate: analyzed clinically significant reactions separately that the non-significant ones; Resolution: return of symptoms after complete resolution of initial symptoms with no new treatment received for 1 h; Anaphylaxis: must meet initial anaphylaxis criteria without re-exposition to the allergen; Allergy: reappearance of any allergy or anaphylaxis symptom; Therapy: Symptoms are severe enough to require therapeutic intervention; Deterioration: any worsening of reaction features with a delay; Persistence: persistence of symptoms beyond 6 h (biphasic and protracted combined); ND: not discussed

Table 2 Potential bias

Potential bias	Selection	Misclassification of participants	Loss to follow-up, withdrawal	Information	Blinding	Misclassification of outcome	Appropriate outcome measures	Missing data	Participants treated the same way	Selective reporting	Confounding factor
Article											
Alqurashi, 2015 ⁽⁶⁾	●	●	●	●	●	●	●	●	●	●	●
Brown, 2013 ⁽²⁷⁾	●	●	●	●	●	●	●	●	●	●	●
Rohacek, 2014 ⁽³⁶⁾	●	●	●	●	●	●	●	●	●	●	●
Ko, 2015 ⁽⁷⁾	●	●	●	●	●	●	●	●	●	●	●
Inoue, 2013 ⁽²⁸⁾	●	●	●	●	●	●	●	●	●	●	●
Mehr, 2009 ⁽³⁰⁾	●	●	●	●	●	●	●	●	●	●	●
Grunau, 2015 ⁽²⁰⁾	●	●	●	●	●	●	●	●	●	●	●
Manivannan, 2009 ⁽⁴⁴⁾	●	●	●	●	●	●	●	●	●	●	●
Lee, 2017 ⁽²⁵⁾	●	●	●	●	●	●	●	●	●	●	●
Michelson, 2015 ⁽⁴⁵⁾	●	●	●	●	●	●	●	●	●	●	●
Ellis, 2007 ⁽³¹⁾	●	●	●	●	●	●	●	●	●	●	●
Grunau, 2014 ⁽²¹⁾	●	●	●	●	●	●	●	●	●	●	●
Lee, 2014 ⁽⁹⁾	●	●	●	●	●	●	●	●	●	●	●
Campbell, 2015 ⁽²⁴⁾	●	●	●	●	●	●	●	●	●	●	●
Oya, 2014 ⁽³²⁾	●	●	●	●	●	●	●	●	●	●	●
Lee, 2017 ⁽²²⁾	●	●	●	●	●	●	●	●	●	●	●
Liu, 2019 ⁽²⁶⁾	●	●	●	●	●	●	●	●	●	●	●
Dribin, 2020 ⁽¹⁹⁾	●	●	●	●	●	●	●	●	●	●	●
Dribin, 2019 ⁽¹⁸⁾	●	●	●	●	●	●	●	●	●	●	●
Gabrielli, 2019 ⁽²⁹⁾	●	●	●	●	●	●	●	●	●	●	●
Lee, 2018 ⁽²³⁾	●	●	●	●	●	●	●	●	●	●	●

● = high risk of bias; ● = unclear risk of bias; ● = low risk of bias

Two showed trends that they decrease the risk of biphasic anaphylaxis [31, 32]. A recent meta-analysis concluded that glucocorticoids are not effective in reducing biphasic anaphylaxis and may increase their risk in children [1].

Timing factors of biphasic anaphylaxis

Most biphasic anaphylaxes occurred early after anaphylaxis symptoms resolution, commonly within the suggested 4–8 h observation [5, 6, 9, 33, 34]. In one study, 75% occurred within 6 h [6]. In another, however, 40% happened after 10 h [35]. Other studies reported mean or median time of occurrence varying from 3 to 15 h, with most being less than 7 h [4, 7, 9, 25, 27, 31]. Clinically significant biphasic anaphylaxes tend to occur sooner than non-significant ones with 69% occurring in less than 4 h [27], mean of 1.5 h [30], or median of 3 h [25].

Observation time recommendations

Multiple studies recommended post-anaphylaxis observation time. Four hours was most commonly suggested [21, 22, 27]. Rohacek proposed that physicians could consider discharging patients after complete resolution of the anaphylactic reaction [36]. Several studies recommended a longer observation period for patients most at risk of biphasic anaphylaxis, without specifying a time frame [6, 21, 25]. Four have suggested adjusting the observation period based on the ability to limit the consequences of a biphasic anaphylaxis in the community [9, 21, 25, 31]. Their criteria included: patient's ability to promptly recognize a biphasic anaphylaxis, availability of epinephrine auto-injectors, presence of a person at the patient's home, and easy access to a hospital.

Table 3 Prognostic, time, and treatment factors influencing risk of biphasic anaphylaxis

Author and year	Biphasic reaction description	Prognostic factors		Recommended observation time	Glucocorticoids effects
		Positive	Negative		
Alqurashi [6], 2015	Incidence: 14.7% Delay: 1–72 h 75% ≤ 6 h	None	Age 6–9 years Delayed presentation to ED (> 90 min) Wide pulse pressure at triage (diastolic blood pressure ≤ ½ systolic blood pressure) > 1 dose of epinephrine Administration of inhaled β-agonists in ED	Individualized based on severity, risk factors and delayed epinephrine administration < 6 h from onset for mild anaphylaxis without risk factors.	No effect
Brown [27], 2013	Incidence: 17% Incidence biphasic reactions requiring epinephrine: 9.2% Delay: median 1.7 h Delay biphasic reactions requiring epinephrine: 69% ≤ 4 h	None	Hypotensive reactions: older age and drug causation Hypoxemic reactions: older age, lung disease and injected agents Delayed deteriorations: lung disease and hypotension	4 h from last dose of epinephrine ≥ 10 h severe reaction	ND
Rohacek [36], 2014	Incidence: 4.7% Incidence anaphylactic biphasic reaction: 2.3%	None	None	Discharge after complete resolution of anaphylactic reaction	ND
Ko [7], 2015	Incidence: 2.2% Delay: median 15 h (1–45 h)	None	History of drug-induced anaphylaxis	ND	Biphasic incidence lower in this glucocorticoid cohort than other reported cohorts
Inoue [28], 2013	Incidence: 3.3%	None	Multiple dose of epinephrine Vomiting Syncope	24 h for children with multiple doses of epinephrine Careful observation of patients with vomiting, syncope and who received multiple doses of epinephrine	Steroids cannot completely prevent biphasic reactions, and should not prevent the concurrent use of epinephrine
Mehr [30], 2009	Incidence: 11% Presentation: milder (58%), similar (33%), more severe (9%) Delay: biphasic anaphylactic (median): 1.5 h Delay: biphasic non-anaphylactic 16 h	None	Multiple dose of epinephrine Greater total amount of epinephrine or IV fluid bolus Anaphylactic biphasic more common in younger patients	24 h if > 1 dose of adrenaline and/or a fluid bolus	No difference on biphasic reactions between those who received corticosteroid and those who did not.
Grunau [20], 2015	ND	None	None	ND	Effect uncertain, trend that not treating with steroids is not inferior to treating.

Table 3 (continued)

Author and year	Biphasic reaction description	Prognostic factors		Recommended observation time	Glucocorticoids effects
		Positive	Negative		
Manivannan [44], 2009	Incidence: 4.1% Delay: Range: 0.5–44 h Median 3 h IQR: 1–13 h Incidence non-anaphylactic biphasic: 7.5% Incidence when 3 prognostic factors absent: 1.6% Incidence when 3 prognostic factors present: 20%;	None	Risk factors for more severe reaction requiring multiple doses of epinephrine: Younger age Wheezing Cyanosis Hypotension and shock Arrhythmias Stridor and laryngeal edema Cough Nausea and vomiting Clinically significant biphasic anaphylaxes: History of anaphylaxis Unknown suspected trigger Timing of first epinephrine administration > 60 min All biphasic anaphylaxes: Unknown suspected trigger Timing of first epinephrine administration > 60 min	ND	ND
Lee [25], 2017	ND	None		Customize based on the severity of reaction, access to self-injectable epinephrine and emergency care, and risk factors for a biphasic reaction	No significant effect
Michelson [45], 2015	Incidence: 19.4% Delay: Range: 2–38 h Mean 10 h > 10 h: 40% Incidence anaphylactic biphasic reaction: 0.4% (2 cases) Delay: raw: 16 and 200 min Additional 3 biphasic anaphylactic with initial episode not meeting criteria for anaphylaxis	None	Resolution of symptoms < 30 min following treatment Larger dose of epinephrine used in initial treatment History of anaphylaxis Younger age Epinephrine use Larger dose of corticosteroid used in initial treatment	ND	Decreased length of stay Decreased need for second dose of epinephrine
Ellis [31], 2007			Longer time to resolution of initial symptoms	24 h monitoring in ED or in environment with supervision, and easy access to auto-injectable epinephrine and emergency medical response system.	Decrease the risk of a biphasic reaction (trend)

Table 3 (continued)

Author and year	Biphasic reaction description	Prognostic factors		Recommended observation time	Glucocorticoids effects
		Positive	Negative		
Grunau [21], 2014	Incidence: 4% Delay: Range: 1–72 h Median 7 h mean: 17 h 14 biphasic reaction more severe than initial reaction	None	ND	< 4 h post-resolution, past this point, added cost, and resources add very little to patient safety Extended observation justified for severe and protracted reactions Careful discussion on when to return to the ED and the importance of an epinephrine autoinjector	ND
Lee [9], 2014	Incidence: 6.1% Delay: Range: 2–36 h Median 8 h	None	History of anaphylaxis Unknown trigger Wheezing Diarrhea	6 h catch about half the biphasic reactions 24 h catch about 80% of biphasic reactions—necessary if no easy access to rapid emergency care	Not associated with biphasic reactions
Campbell [24], 2015	Incidence: 0% anaphylaxis	None	History of anaphylaxis and asthma Flushing/diaphoresis Dyspnea Wheezing None	ND	ND
Oya [32], 2014	Incidence of all biphasic: 7.2% Incidence of clinically significant biphasic: 5.1%	None		> 8 h, ideally 24 h for optimal results	Decrease the risk of a biphasic reaction (trend)
Lee [22], 2017	ND	ND	ND	4 h (same return rate as 8 h with decrease cost and admissions)	ND
Liu [26], 2019	ND	None	All biphasic anaphylaxis: Symptom onset to epinephrine Arrival by ambulance Clinically significant biphasic anaphylaxis: Age at visit < 18 years Arrival by ambulance First epinephrine dose at ED Children with history of asthma are NOT more likely to have severe anaphylactic reactions	ND	No significant effect
Dribin [19], 2020	ND	None		ND	ND

Table 3 (continued)

Author and year	Biphasic reaction description	Prognostic factors		Recommended observation time	Glucocorticoids effects
		Positive	Negative		
Dribin [18], 2019	ND	Age < 36 months = NPV 98.3% if no wheezing + no cardiac involvement Age > 36 months = NPV 92.4% if no wheezing + no cardiac involvement + no gastrointestinal involvement	ND	ND	ND
Gabrieli [29], 2019	ND	Prehospital epinephrine reduces risk of requiring > 1 dose of epinephrine Prehospital antihistamines reduce risk of requiring > 1 dose of epinephrine	Prehospital corticosteroids increase risk of admission to ICU/hospital ward Severe reaction increases risks of admission to ICU/hospital ward, requiring > 1 dose of epinephrine and the need of IV fluids	ND	Might increase the risk of negative outcomes of anaphylaxis
Lee [23], 2018	ND	ND	ND	Reducing observation time from 8 to 4 h if no red flags resulted in 57% reduction of admissions without increases of ED revising 72 h after discharge Red flags: history of biphasic anaphylaxis or severe reaction, progression of or persistent symptoms, history of severe asthma, current asthma flare, hypotension during ED stay, > 1 epinephrine dose, fluid bolus required	ND

ICU intensive-care unit, ND not discussed, IQR interquartile range, NPV negative predictive value, *Italic* factors are not statistically significant but show a trend

Table 4 Factors associated with increased risk of biphasic reaction

Biphasic anaphylaxis of uncertain clinical significance	Number of article (<i>N</i> = 9)	Clinically significant biphasic anaphylaxis only	Number of articles (<i>N</i> = 6)	All biphasic anaphylaxis	Number of articles (<i>N</i> = 13)
Severity of symptoms ^a	6	Time to first epinephrine (> 60 min)	3	Severity of symptoms*	8
Time to first epinephrine (> 60 min)	2	History of anaphylaxis	3	Number of doses of epinephrine (> 1 dose)	4
Number of doses of epinephrine (> 1 dose)	2	Severity of symptoms*	2	Time to first epinephrine (> 60 min)	3
Young age	2	Number of doses of epinephrine (> 1 dose)	2	History of anaphylaxis	3
History of anaphylaxis	1	Unknown trigger	2	Young age	3
Unknown trigger	1	Time to symptoms resolution (> 30 min)	1	Unknown trigger	2
History of asthma	1	Young age	1	Arrival by ambulance	1
Arrival by ambulance	1	Arrival by ambulance	1	History of asthma	1
		Administration of β -agonists (in pediatric population)	1	Time to symptoms resolution (> 30 min)	1
		Age 6–9 years old (in pediatric population)	1	Administration of β -agonists (in pediatric population)	1
				Age 6–9 years old (in pediatric population)	1

Clinically significant biphasic anaphylaxis: articles with secondary reaction that fit the NIAID/FAAN definition. All biphasic anaphylaxis: articles not distinguishing the type of the secondary reaction only

^aSeverity of symptoms: hypotension, syncope, respiratory compromises, arrhythmia, vomiting, and diarrhea; see Table 1 to see which articles considered only clinically significant biphasic anaphylaxis

Definitions of anaphylaxis and biphasic anaphylaxis

All but one primary study used a clear definition of anaphylaxis. Seventeen studies used the NIAID/FAAN definition [2]. Fifteen studies also used a precise definition for biphasic anaphylaxis, seven considering them as the recurrence of a new anaphylaxis episode (clinically significant), five considering them the recurrence of any allergic symptoms (clinical significance uncertain), and three separating the clinically significant and non-significant biphasic anaphylaxis [25, 26, 36]. Most studies referred to the NIAID/FAAN [2] criteria to classify biphasic anaphylaxes as clinically significant. Other less restrictive or precise definitions were also noted. Biphasic anaphylaxis is generally defined as a relapse of symptoms after an asymptomatic period of 1 h or more, without further contact with the allergen [37]. Similar findings were identified in the reviews, guidelines, and expert opinions. Table 1 and Appendix Table 3 show the definitions used in the included studies.

Discussion

Interpretation of findings

Ten predicting factors of clinically significant biphasic anaphylaxis that could influence the observation time in the emergency room post-anaphylaxis were identified through this review. Only five appeared in multiple studies and could be generalizable to a wider anaphylaxis population. These five predictors (time to first epinephrine, history of anaphylaxis, symptom severity, number of epinephrine doses, and unknown trigger) should be included in future anaphylaxis studies. The symptom severity factor appeared several times as a poor prognosis indicator, but its description is the one that varied the most between studies. Frequently mentioned symptoms included hypotension, syncope, respiratory compromises (dyspnea, hypoxemia, wheezing, or stridor), arrhythmia, vomiting, and diarrhea. Recent reviews have retained the majority of these criteria, but none included them all [5, 39]. The most common characteristics of severity are hypotension and respiratory compromises. Thus, as

its definition is not uniform across studies, the severity of symptoms criteria should be further studied and clarified.

The use of glucocorticoids during treatment of initial anaphylaxis should not be considered as a good prognostic indicator in a clinical prediction rule, as evidenced by the heterogeneous data from primary studies included and the meta-analysis by Shaker [1].

The variability of the definitions used for anaphylaxis and biphasic anaphylaxis and their clinical significance causes heterogeneity making the search for prognostic factors arduous. To make future studies more comparable, a uniform definition of anaphylaxis and of biphasic anaphylaxis would be helpful. We recommend the commonly used and widely accepted NIAID/FAAN [2] definition for both as it is appropriate for use both in clinic and research and has increased in use since its publication.

Comparison to previous studies

Most recent reviews aim to characterize biphasic anaphylaxes and their prognostic factors exclusively [4, 5, 35, 38]. The search terms of this systematic review were wide enough to identify all factors that could influence observation time (treatment adverse effects of anaphylaxis, and community factors). However, no adverse event other than a biphasic anaphylaxis was found to be frequent or serious enough to warrant prolonged observation after the initial symptom resolution. Although the aim of this review was not identical, the results are consistent with the current literature.

Clinical implications

The list of factors in its present form should not be treated as prolonged observation criteria but rather as the first steps toward creating an early discharge tool following anaphylaxis. Shaker et al. [1] have performed a series of meta-analyses on some of those indicators which could better be used for clinical decision-making regarding observation time.

A specific observation time cannot be recommended based on the results and might prove not to be the best course of action. Kim [38] suggested that 6–12 h observation has a negative predictive value of 98.3%. Based on this data, Shaker [40] modeled the cost associated with longer observation period and concluded that extended observations are not cost-effective. However, the decision to discharge a patient post-anaphylaxis does not solely depend on the risks of biphasic anaphylaxis but also on the consequences an anaphylactic reaction would have on the patient in the community. Thus, a patient's ability to promptly recognize the symptoms of a biphasic anaphylaxis, the availability of epinephrine auto-injectors, and the patient's distance from a

hospital for 72 h after discharge are factors to be taken into account by the treating physician.

Research implications

This systematic review in its present form cannot be used for clinical decision-making, but has important implications for research. The identification of multiple potential risk factors for a biphasic anaphylaxis opens the door to experimental studies to create a clinical decision rule that could discriminate patients at low risk for a clinically significant biphasic anaphylaxis. A reliable rule for early discharge after anaphylaxis could minimize the number of out-of-hospital biphasic anaphylaxis while decreasing the cost associated with keeping people with low risk of adverse events under observation. Lee [25] used this strategy and found that the absence of 3 criteria (history of anaphylaxis, unknown trigger, and time to first epinephrine) reduced the risk of clinically significant biphasic anaphylaxis from 4.1 to 1.6%. In the most recent guideline, Shaker [1] suggested a number needed to monitor of 41 when the initial anaphylaxis was “severe” and 13 when it required multiple doses of epinephrine. Adding other relevant factors could increase the predictive value of a rule.

Limitations

All studies have limitations and ours is no exception. First, preliminary article selection was undertaken by a single author. Moreover, the fact that different study types were included and the variability of the definitions did not allow for pooling to draw larger conclusions. It is possible that duplication of data happened as eligible primary studies may have also been included in reviews. However, because no pooling was performed, this method ensured that no relevant information was overlooked. Additionally, most studies were observational and included very little personal, environmental, and social factors; therefore, no conclusions could be derived on those topics despite their importance for clinical decision-making. Finally, the strength of our results obviously depends on the quality of the studies included. The bias analysis was included for this reason and identified few important biases.

Conclusion

This systematic review was designed to inform the creation of a clinical decision rule. The identified risk factors will be tested through a retrospective charts review and prospective data collection in the next phases of the project to derive and validate a clinical decision rule to predict the non-occurrence

of a clinically significant biphasic anaphylaxis. A clinically relevant, statistically solid and well-defined rule will help clinicians determine which patient can safely be considered for early discharge following anaphylaxis.

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Author contributions AP and DS designed the search strategy. DS queried databases and made the articles' selection with consultation of the other authors when necessary. All authors contributed to the data extraction process. VB reviewed the data extracted from all articles. VB, DS, and AP made the bias assessment. DS took the lead in writing the manuscript with support from VB and AP. All authors discussed the results, provided critical feedback, and helped shape the research, analysis, and manuscript. SL was the principal investigator and supervised the project. All authors provided their permission to publish the manuscript.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

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