

Duration of Observation for Detecting a Biphasic Reaction in Anaphylaxis: A Meta-Analysis

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Keywords

Meta-analysis · Anaphylaxis · Biphasic reaction · Observation

Abstract

Background: We conducted a meta-analysis to determine a practical observation time for detecting a biphasic reaction after resolution of the initial anaphylactic reaction. **Methods:** A systematic literature search identified studies on adult patients with anaphylaxis and a subsequent biphasic reaction due to various causes that contained sufficient data to extract outcomes. The outcomes were pooled using a random-effects model. **Results:** Twelve studies with a total of 2,890 adult patients with anaphylaxis and 143 patients with a biphasic reaction were included. In terms of the pooled negative predictive value, 1 h of observation achieved a 95.0% negative predictive value and ≥6 h of observation provided a 97.3% negative predictive value (95% CI: 95.0–98.5). The negative predictive value for a biphasic reaction increased with a longer observation time after initial anaphylaxis, and the increasing trend slowed down from 6 h of observation time. The pooled additional incidence rates of biphasic reactions per 100 person-hours after 1- and 4-h ob-

servations were 0.45 (95% CI: 0.20–1.04) and 0.41 (95% CI: 0.19–0.87), respectively. After >8–12 h of postanaphylactic observation, the negative predictive value reached >98%, while the additional incidence per 100 person-hours was <0.10. **Conclusions:** An observation time of ≥6 h after resolution of an initial anaphylaxis symptom can exclude recurrence of a secondary reaction in >95% of patients. Although longer observation periods resulted in the detection of more biphasic reactions, 6–12 h of observation time would be practical, supporting current relevant guidelines.

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Introduction

Anaphylaxis is a life-threatening allergic reaction with a sudden onset after exposure to an offending substance [1, 2]. Most of the patients with anaphylaxis experience a single episode with an unexpected occurrence, followed by symptomatic escalation and subsequent complete res-

T.-H.K. and S.H.Y. contributed equally to this work.
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olution, particularly after the provision of appropriate management. However, some anaphylactic reactions may recur hours after the initial resolution; this pattern is referred to as a biphasic reaction. A biphasic reaction is typically defined as the recurrence of anaphylaxis within 72 h of the initial anaphylactic event without reexposure to the trigger, with an incidence of $\leq 20\%$ among patients with anaphylaxis [3–5].

Concerning the biphasic reaction, it is generally recommended to sufficiently observe patients having anaphylaxis after resolution of the initial anaphylaxis to appropriately detect and take action against the occurrence of a secondary reaction. The postanaphylactic observation times recommended in the current guidelines vary, ranging from 4 h [6, 7] to 24 h [8, 9], largely based on experts' opinions rather than critical review. Thus, we conducted a meta-analysis to gauge a practical duration of observation for detecting a biphasic reaction after resolution of the initial anaphylaxis.

Materials and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [10]. We utilized the results of the systematic literature search on biphasic reactions through January 2014 conducted by Lee et al. [5]. Additionally, two authors (T.-H.K. and S.H.Y.) independently extended the search through September 2017 in Ovid-MEDLINE, Ovid-Embase, and the Web of Science databases, using the same search strategy [5]. The search was supplemented by screening references in the retrieved articles and review articles.

We applied the following inclusion criteria to determine eligibility: (a) adult study populations consisting of ≥ 5 patients with anaphylaxis due to various causes; (b) a subset of patients having a subsequent biphasic reaction; and (c) sufficient data described in detail to extract outcomes about the onset time of initial anaphylaxis and the time interval to the subsequent second reaction for each patient with a biphasic reaction. We excluded studies dealing with procedure-related iatrogenic anaphylaxis (such as due to a skin prick test, a food challenge test, or immunotherapy) and studies on pediatric patients. Conference abstracts, review articles, editorials, case reports, and guidelines for management as well as non-English publications were excluded.

Two authors (T.-H.K. and S.H.Y.) independently performed the data extraction from the included studies. The Newcastle-Ottawa Scale was used for assessing the quality of observational cohort studies [11]. A consensus was reached via discussion.

We introduced two outcomes into this meta-analysis: (1) the negative predictive value (NPV) regarding biphasic anaphylaxis and (2) the incidence of biphasic anaphylaxis during each follow-up interval. A longer postanaphylactic observation may lead to the detection of more biphasic reactions (higher NPV), but this may be accompanied by an unnecessarily long observation period for patients without biphasic reactions (lower incidence of biphasic anaphylaxis). We hypothesized that the meta-analytic evaluation

of those two outcomes could estimate the duration of observation for detecting a biphasic reaction as the posttreatment observation period lengthened (1, 4, 6, 8, 12, 24, and 48 h).

We calculated the NPV at each follow-up interval regarding a biphasic reaction as the number of patients without biphasic anaphylaxis until 48 h of observation divided by the number of patients without biphasic anaphylaxis during the specific observation period for each study. The incidence of biphasic anaphylaxis was calculated per 100 person-hours of observation [12], and 95% CIs were also calculated, assuming that the number of cases observed followed a Poisson distribution. For each follow-up interval, logit-transformed NPVs and log-transformed incidence rates were pooled using a random-effects model [13]. The pooled estimates and 95% CIs were back-transformed to the original scale. To assess heterogeneity across individual studies, the I^2 statistic was calculated as follows:

$$I^2 = \frac{\hat{\tau}^2}{\hat{\tau}^2 + \hat{\sigma}^2} \times 100\%,$$

where $\hat{\tau}^2$ and $\hat{\sigma}^2$ imply the true heterogeneity and sampling error, respectively. The analyses were conducted using the “metafor” package in R3.3.2.

Results

Of the 175 studies identified during the initial database search and the 27 studies from Lee et al. [5], 12 were ultimately included in our analysis [3, 4, 12, 14–22] (Fig. 1).

The included studies encompassed a total of 2,890 adult patients with anaphylaxis and 143 patients with a biphasic reaction. The number of patients with anaphylaxis ranged from 25 to 539 (Table 1). The percentage of patients with a biphasic reaction ranged from 0.4 to 20.0% (median: 6.5%). The median duration between initial anaphylaxis resolution and the secondary reaction ranged from 1.75 to 17 h. When assessed by the Newcastle-Ottawa Scale, the included studies scored relatively well across categories for quality of observational cohort studies (median: 6.5 points, out of 9 points in total) (Table 2).

In terms of the pooled NPV, 1 h of observation achieved a 95.0% NPV (95% CI: 90.9–97.3; $I^2 = 0.91$) and ≥ 6 h of observation provided the 2.5% lower limit of the 95% CI equal to 95% (pooled NPV: 97.3%; 95% CI: 95.0–98.5; $I^2 = 0.83$) (Fig. 2a). As the postanaphylactic observation period increased, so did the NPV for a biphasic reaction, but at a slower rate: NPV at 8 h, 97.6% (95% CI: 95.5–98.8; $I^2 = 0.83$); NPV at 12 h, 98.2% (95% CI: 96.7–99.1; $I^2 = 0.75$); NPV at 24 h, 98.2% (95% CI: 96.7–99.1; $I^2 = 0.0$); and NPV at 48 h, 99.9% (95% CI: 99.7–100.0; $I^2 = 0.0$).

The pooled additional incidence rates per 100 person-hours after 1- and 4-h observations were 0.45 (95% CI: 0.20–1.04; $I^2 = 0.50$) and 0.41 (95% CI: 0.19–0.87; $I^2 = 0.78$),

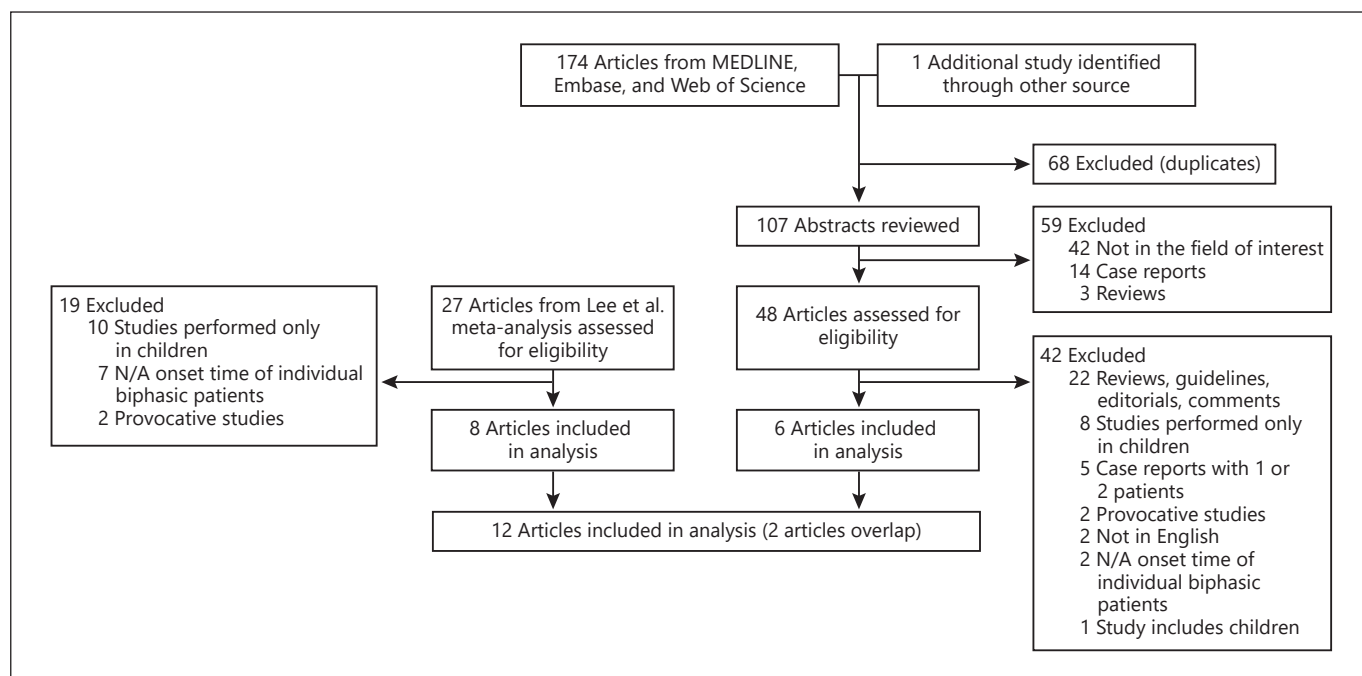


Fig. 1. Flow diagram of the literature search.

Table 1. Summary of the included studies on a biphasic reaction in adult patients with anaphylaxis

Source	Causative agent	Patients for meta-analysis, ¹ n	Mean age (range), years	Biphasic events, n (%)	Time interval from initial anaphylaxis resolution to the secondary reaction ²
Stark and Sullivan [14], 1986	Drug, ICM, food, unknown	25	41 (17–71)	5 (20.0)	4/4.3 (1–8)
Douglas et al. [15], 1994	Drug, food	53 (6)	38 (19–81)	4 (7.5)	24/30 (1–72)
Brady et al. [16], 1997	Insect bite	67	30.2/NI	2 (3.0)	33/33 (26–40)
Brazil and MacNamara [17], 1998	Insect bite, drug, food	34	Range 16–81	6 (17.6)	15.4/16.3 (4.5–29.5)
Ellis and Day [18], 2007	NI	93 (10)	NI	17 (18.3)	9/10.7 (1.5–38)
Brown et al. [19], 2013	Food, ICM, drug, venom, unknown	295 (25)	NI	28 (9.5)	17/4.03 (0.2–30.4)
Grunau et al. [20], 2014	NI	496	NI	2 (0.4)	1.75/1.75 (0.2–3.3)
Lee et al. [3], 2014	Food, ICM, drug, unknown	539 (2)	NI	19 (3.5)	7/16.2 (1–72)
Manivannan et al. [21], 2014	Food, drug, unknown	202	45 (29–69)	11 (5.4)	4/12.4 (1–36)
Rohacek et al. [4], 2014	Insect bite, drug, food, unknown	532	42.4	25 (4.7)	12/14.4 (1–48)
Ko et al. [22], 2015	Insect bite, drug, food, unknown	415	48.4	9 (2.2)	15/19.3 (1–45)
Kim et al. [12], 2018	ICM	139 (6)	55.8 (22–85)	15 (10.7)	4.9/7.2 (1–20.8)

ICM, iodinated contrast medium; NI, not identifiable. ¹ The number in parenthesis indicates the number of pediatric patients excluded from the original study. ² Median/mean value (range).

respectively (Fig. 2b). After >8–12 h of postanaphylactic observation, the NPV reached >98%, while the additional incidence per 100 person-hours was <0.10: incidence at 8 h, 0.106 (95% CI: 0.048–0.237; $I^2 = 0.0$); incidence at 12 h, 0.127 (95% CI: 0.052–0.312; $I^2 = 0.61$); incidence at 24 h, 0.084 (95% CI: 0.039–0.180; $I^2 = 0.71$); and incidence at 48 h, 0.023 (95% CI: 0.013–0.038; $I^2 = 0.04$).

Discussion

The time interval from initial anaphylaxis symptom resolution to the secondary reaction varied across patients who experienced a biphasic reaction and across relevant studies. Accordingly, it is challenging to suggest how long patients with anaphylaxis should be monitored

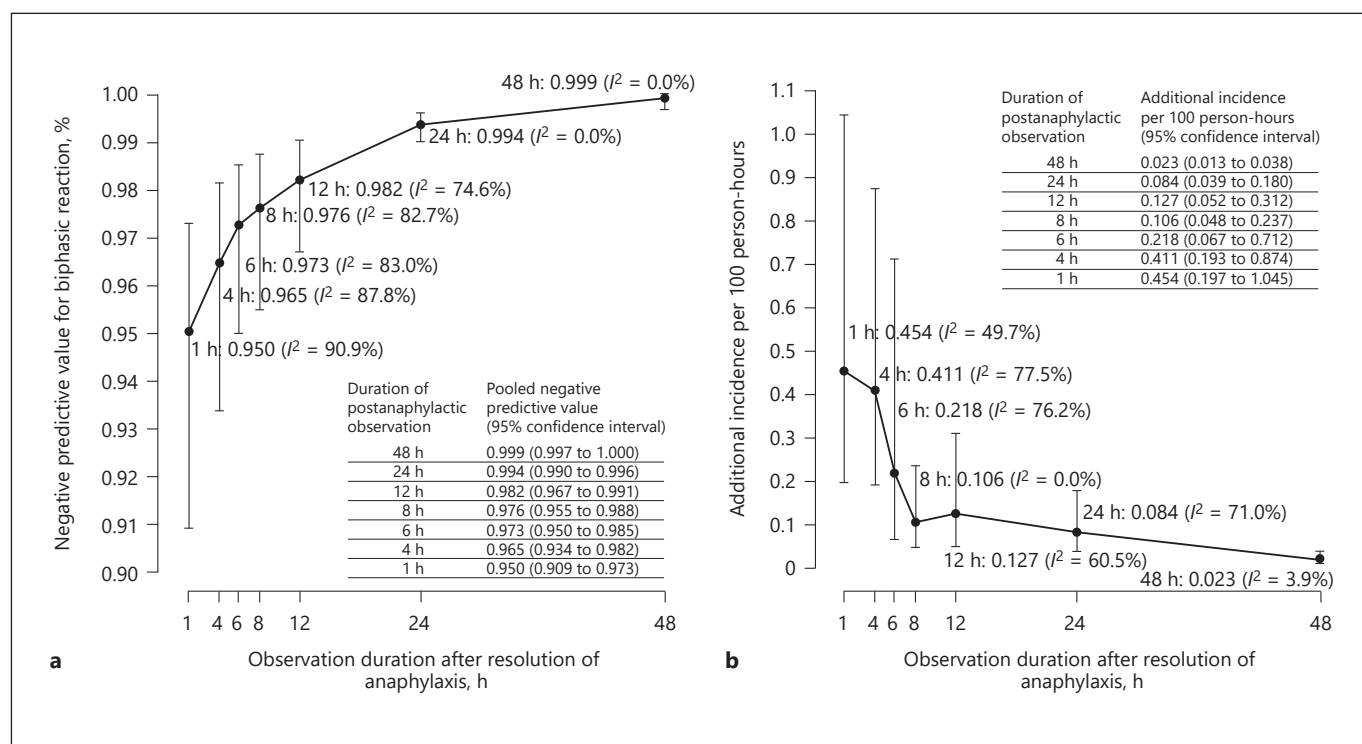


Fig. 2. Pooled negative predictive value (**a**) and additional incidence per 100 person-hours (**b**) according to the duration of postanaphylactic observation.

Table 2. Summary of the Newcastle-Ottawa Scale results for assessing the quality of the observational studies

Source	Selection (4) ¹	Comparability (2) ¹	Outcome (3) ¹
Stark and Sullivan [14], 1986	★★★★	★★	★
Douglas et al. [15], 1994	★★★★	★	★
Brady et al. [16], 1997	★★★★	★	★★★★
Brazil and MacNamara [17], 1998	★★★★	★	★
Ellis and Day [18], 2007	★★★★	★★	★
Brown et al. [19], 2013	★★★★★	★★	★★
Grunau et al. [20], 2014	★★★★	★★	★★★★
Lee et al. [3], 2014	★★★★	★	★★
Manivannan et al. [21], 2014	★★★★★	★★	★★
Rohacek et al. [4], 2014	★★★★★	★	★★★★
Ko et al. [22], 2015	★★★★★	★	★★
Kim et al. [12], 2018	★★★★	★	★★

¹The number in parenthesis indicates the maximum number of stars that can be awarded to each source (a total of 9 points).

after symptom resolution. It may be ideal to closely monitor patients with anaphylaxis as long as possible after symptom resolution. Indeed, the 48 h of postanaphylactic observation provided an NPV of 99.9% for a biphasic

reaction. However, it is impractical to boundlessly extend the duration of postanaphylactic observation due to limited resources and patient compliance. The joint task force guidelines on anaphylaxis management suggest 4–8 h of observation [9], and current guidelines in the USA [6, 7] recommend 6 h of observation, whereas the European guidelines recommend ≥ 24 h of observation [8, 9].

As the incidence of biphasic reaction was relatively low, postanaphylactic observation for 4 h achieved an NPV of 96.5%, with an additional incidence of 0.41 per 100 person-hours. Extending the observation period from 4 to 6 h, from 6 to 12 h, and from 12 to 24 h raised the NPV by approximately 1% for each extension. However, the additional incidence decreased by half at each extension. Given the relationship between the NPV and the additional incidence, a 6- to 12-h postanaphylactic observation period seems practical. This result, derived from the systematic review and meta-analysis, can serve as a rationale for the postanaphylactic observation time recommended in the current guidelines. However, the duration should be adjusted according to clinical factors such as the severity of the early-phase reaction [23], the

early administration of epinephrine [18], and inciting trigger factors [5], as well as the institutional policy and resources. Given that the severity of the secondary reaction tended to be similar to or milder than the initial anaphylaxis symptom, increasing the observation period to obtain additional NPV increases seems not to lead to any further gain in a practical sense.

Our investigation has some limitations. First, we only included studies with sufficient data about the interval between resolution of the initial anaphylaxis symptom and onset of the biphasic reaction, potentially resulting in selection bias. Second, some of the included studies defined “biphasic reaction” in an ambiguous manner. Third, we did not consider the route of exposure, dose of antigens, risk factors for biphasic reactions such as previous anaphylaxis [3], unknown triggers [3, 5], specific clinical symptoms [8, 15], and delayed or less intensive treatment [9, 18]. Future investigation may incorporate risk factors when determining the duration of postanaphylactic observation.

Taken together, an observation period of ≥ 6 h can exclude the recurrence of a secondary reaction in $>95\%$ of

patients after anaphylactic symptom resolution. Although longer observation periods resulted in the detection of more biphasic reactions, 6–12 h of postanaphylactic observation would seem practical.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

T.-H.K., S.H.Y., and S.-Y.L. designed the study; T.-H.K. and S.H.Y. searched the literature; T.-H.K., S.H.Y., and H.H. analyzed the data; T.-H.K., S.H.Y., H.H., and S.-Y.L. interpreted the data and wrote the manuscript; H.-R.K. and S.-H.C. critically reviewed the manuscript and provided insightful comments and discussion valuable for manuscript refinement.

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