

Original Article

Time of Onset and Predictors of Biphasic Anaphylactic Reactions: A Systematic Review and Meta-analysis

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What is already known about this topic? A biphasic reaction is a recurrence of symptoms after resolution of initial anaphylaxis without re-exposure to the trigger. Risk factors for biphasic reactions are difficult to study due to the uncommon occurrence.

What does this article add to our knowledge? The median time of onset of biphasic reactions was 11 hours. Initial presentation with hypotension and an unknown trigger were associated with the development of a biphasic reaction.

How does this study impact current management guidelines? Clinicians should consider these risk factors for biphasic reactions when determining the duration of monitoring after the initial anaphylactic episode.

BACKGROUND: A biphasic reaction is a potentially life-threatening recurrence of symptoms after initial resolution of anaphylaxis without re-exposure to the trigger. The infrequent nature of these reactions has made them difficult to study and predict.

OBJECTIVE: The aim of this study was to evaluate the time of onset and predictors of biphasic anaphylactic reactions.

METHOD: Original research studies that described biphasic reactions in case series or cohort studies were included. Studies that did not describe biphasic reactions and case series with less than 2 biphasic reactions were excluded. Data sources included MEDLINE, EMBASE, Web of Science, and Scopus from inception to January 2014 and bibliographies of included articles. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous variables. Inconsistency among studies was assessed with the I^2 statistic.

RESULTS: Twenty-seven observational studies that enrolled 4114 patients with anaphylaxis and 192 patients with biphasic reactions were included. The median time of symptom onset was 11 (range 0.2 to 72.0) hours. Food as the inciting trigger was

associated with decreased risk (pooled OR 0.62, 95% CI: 0.4 to 0.94, $I^2 = 0\%$) and an unknown inciting trigger with increased risk (pooled OR 1.72, 95% CI: 1.0 to 2.95, $I^2 = 61\%$). Initial presentation with hypotension (pooled OR 2.18, 95% CI: 1.14 to 4.15, $I^2 = 79\%$) was also associated with the development of a biphasic reaction.

CONCLUSION: Biphasic anaphylactic reactions were less likely among patients with food as an inciting trigger. Patients who present with hypotension or have an unknown inciting trigger may be at increased risk of a biphasic reaction. Clinicians should tailor observation periods for patients individually based on clinical characteristics. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: Systematic review; Meta-analysis; Anaphylaxis; Biphasic reactions; Hypotension

A biphasic anaphylactic reaction is defined as the recurrence of symptoms within 72 hours of the initial anaphylactic event, without re-exposure to the trigger.¹ The reported incidence of biphasic reactions ranges from 3% to 20% of patients presenting to the emergency department, allergy clinics, and inpatient ward with anaphylaxis.¹⁻⁵ Current guidelines in the United States recommend 6 hours of observation after the initial anaphylactic episode due to the risk of a biphasic reaction.⁶ However, some studies and European guideline recommend up to 24 hours of observation.^{2,7,8}

Given the relative infrequency of biphasic reactions, there is a paucity of data with which to rigorously assess potential risk factors for developing a biphasic reaction. Risk factors for biphasic reactions reported in individual studies have included pediatric patients, respiratory symptoms, hypotension, and delayed or multiple epinephrine uses.^{1-5,9} However, protective and risk factors for biphasic reactions and the effect of therapeutic agents such as steroids and epinephrine have not been consistently reported among studies. For these reasons, biphasic reactions are poorly understood.

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Abbreviations used

CIs- Confidence intervals

NOS- Newcastle-Ottawa scale

ICU- Intensive care unit

ORs- Odds ratio

We conducted a systematic review and meta-analysis to synthesize the existing literature on biphasic reactions and address the following objectives: (1) to describe the time frame in which biphasic reactions occur; (2) to investigate potential risk factors for biphasic reactions in patients with anaphylaxis; and (3) to determine whether use of steroids or epinephrine for the treatment of the initial anaphylactic episode is associated with the risk of developing a biphasic reaction.

METHODS

The reporting of this systematic review and meta-analysis is consistent with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standardized reporting guidelines.¹⁰ The review protocol was developed in January 2014 and published in April 2014 at <http://www.crd.york.ac.uk/prospero/>, registration number CRD42014009395.

Definition of biphasic reactions

We defined a biphasic anaphylactic reaction as the recurrence of symptoms within 72 hours of the initial anaphylactic event without re-exposure to the trigger. We included studies that documented reactions meeting this definition.

Eligibility criteria

We included human studies of anaphylaxis with descriptions of biphasic reactions in case series, cohort studies, and clinical trials. Studies that did not describe biphasic reactions, case series with less than 2 biphasic reactions, or cohort studies with no biphasic reactions were excluded. We excluded review articles, clinical practice guidelines, and editorials but reviewed their reference lists to identify potentially eligible primary studies.

Study design

An expert reference librarian (P.J.E.) designed and conducted a comprehensive literature search, with input from the lead authors (S.L. and R.L.C.). We searched the following databases: Ovid MEDLINE (1946 to January 2014), Ovid EMBASE (1988 to January 2014), Web of Science (inception to January 2014), and Scopus (inception to January 2014). No language restrictions were applied to the search strategy. The Medline, EMBASE, and Web of Science search strategies are included in [Appendix 1](#) (in this article's Online Repository at www.jaci-inpractice.org).

We reviewed the bibliographies of included articles to identify potentially relevant articles not identified in the electronic search strategy. Studies that did not include sufficient data to construct 2 by 2 tables for pooled analysis were included in the qualitative review but not the meta-analysis. Two reviewers (S.L. and R.L.C.) individually screened all titles and abstracts identified from the search strategy (phase I). Selection was based on potential relevance to the review and according to the predetermined inclusion and exclusion criteria.

Full articles were obtained for all titles and abstracts considered to be potentially relevant by at least one reviewer. Two reviewers (S.L. and R.L.C.), working independently, assessed the full-text articles for eligibility (phase II). Disagreements were resolved by consensus with

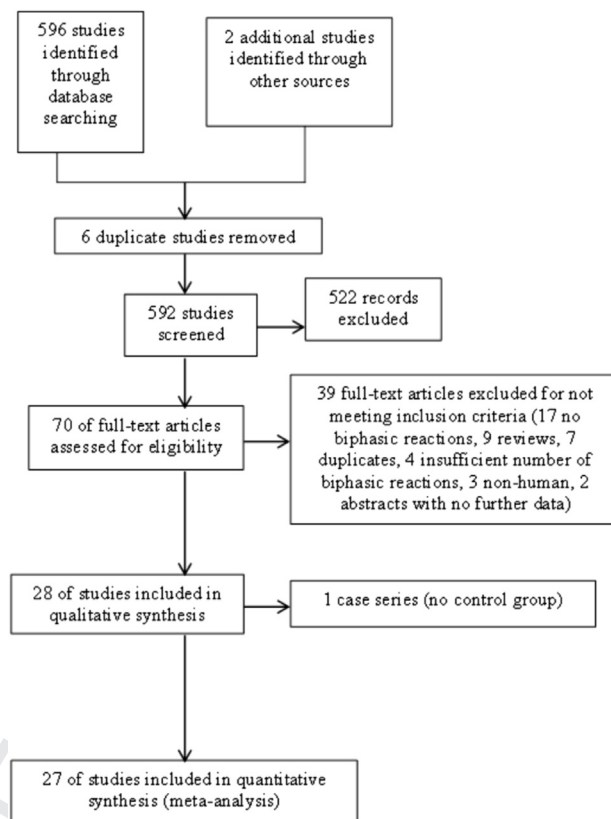


FIGURE 1. Flow diagram of the study selection process.

a third investigator (M.F.B.). Chance-adjusted agreement for full-text inclusion was assessed using Cohen's unweighted kappa with 95% confidence intervals (CIs).

We assessed the quality assessment of included studies and risk of bias using the Newcastle-Ottawa scale (NOS) for observational studies. One reviewer (S.L.) abstracted data with a standardized data abstraction form including author, year, number of patients, demographics, comorbidities, inciting trigger, past medical history, initial symptoms, and treatment for the initial episode of anaphylaxis.

We contacted the corresponding authors of included studies for unclear or missing data and confirmed the correctness of the email address by a MEDLINE search of recent articles. The initial inquiry was followed by a second inquiry by email in 2 weeks. A letter was mailed to the authors who did not have valid email address. Data were tabulated using Microsoft Office Excel 2003 (Microsoft, Redmond, Wash).

Statistical analysis

Because of anticipated clinical heterogeneity between studies (different settings, predictor variables, length of follow-up, and outcome measures), meta-analysis was restricted *a priori* to studies that contained sufficient data to construct 2 by 2 tables. Predictors were calculated using the publicly available RevMan statistical software.

(Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Using random-effects meta-analysis, we pooled the odds ratios (ORs) and estimated likelihood ratios

TABLE I. Study characteristics

Study	Setting	Study type	Patients (N)	Age by years {Mean (SD)/Median (IQR)}, Range	Female, N (%)	Biphasic events, N (%)	Time (h) to biphasic median/mean (range)
Lee et al, 2014 ⁹	ED	Cohort	541	35/NR (IQR 18-52)	320 (59)	21 (3.9)	7.0/NR (1-72)
Vezir et al, 2013 ²⁶	Peds allergy	Cohort	96	7.2/NR (SD 5.2)	35 (36.5)	5 (5.2)	2.5/4.4 (0.5-9)
Nagano et al, 2013 ²⁷	Peds ED	Cohort	345	3.0/NR Range 0.3-51	129 (37.4)	8 (2.3)	1.5/13.3 (3-28)
Liew et al, 2013 ²⁸	Peds ED/allergy	Cohort	98			4 (4.1)	
Lee et al, 2013 ¹⁶	Peds immunotherapy	Cohort	310	5 (SD 3)/NR	106 (34.2)	6 (1.9)	4.5/7.0 (2-18)
Inoue et al, 2013 ²⁹	Peds ED	Cohort	61	4.7 (SD 3.3)/NR	21 (34.4)	2 (3.3)	15/15 (12-18)
Grunau et al, 2013 ¹⁷	ED	Cohort	496	NR/38 (IQR 27-51)	264 (53.2)	2 (0.4)	1.75/1.75 (0.2-3.3)
Brown et al, 2013 ³⁰	ED	Cohort	315			2 (0.6)	5.5/5.5 (1.8-9.1)
Orhan et al, 2011 ³¹	Peds	Cohort	137	7.7 (SD 4.2)/NR	49 (35.8)	7 (5.1)	3/3.3 (1.5-6)
Lertnawapan and Maek-anantawat 2011 ²⁵	ED	Cohort	208	NR/20.7	98 (47.1)	13 (6.3)	NR/7.8 (2-13)
Calvani et al, 2011 ³²	Peds allergy	Cohort	163	NR/4 Range 0-18	52 (31.9)	3 (1.8)	
Confino-Cohen et al, 2010 ¹⁵	Immunotherapy	Cohort	76	29.1/NR Range 11-56		11 (14.5)	
Scranton et al, 2009 ¹⁴	Immunotherapy	Cohort	60	33 (SD 16)/NR	41 (68.3)	14 (23.3)	5/7.2 (2-24)
Mehr et al, 2009 ²³	Peds ED	Cohort	107	2.5/NR Range 0.2-8.8	42 (40.4)	12 (11.2)	8.8/(1.3-20.5)/NR
Jarvinen et al, 2009 ¹³	Peds immunotherapy	Cohort	50			1 (2)	
Yang et al, 2008 ³³	ED, outpatient, inpatient	Cohort	138	39.6 (SD 16.8)/NR	64 (46.4)	3 (2.2)	
Jirapongsananuruk et al, 2007 ³⁴	Inpatient	Cohort	101	23.7 (SD 21.8)/NR	48 (47.5)	5 (5)	
Ellis and Day, 2007 ²¹	ED, inpatient	Cohort	103	33/NR Range 0.9-79	48 (46.6)	20 (19.4)	NR/10 (2-38)
Poachanukoon and Paopairochanakorn, 2006 ²⁴	ED	Cohort	64	NR/26 Range 0.1-65	30 (46.9)	8 (12.5)	
Smit et al, 2005 ⁷	ED	Cohort	282	NR/28 (IQR 19-43) Range 1-91	115 (40.8)	15 (5.3)	NR/8.2 (SD 5.5)
Cianferoni et al, 2001 ³⁵	ED	Cohort	107	42 (SD 18)/NR	48 (44.9)	2 (1.9)	
Lee and Greenes, 2000 ¹	Peds inpatient	Cohort	106	8/NR Range 0.5-21		6 (5.7)	7/10 (1.3-28.4)
Brazil and MacNamara, 1998 ²	ED	Cohort	34	Range 16-81	15 (44.1)	6 (17.6)	15.4/16.3 (4.5-29.5)
Brady et al, 1997 ⁴	ED	Cohort	67	30.2/NR	33 (49.3)	2 (3)	33/33 (26-40)
Douglas et al, 1994 ³	Outpatient, inpatient	Cohort	59	Range 0.5-81	17 (28.8)	4 (6.8)	24/30 (1-72)
Sampson et al, 1992 ¹⁸	Inpatient	Case series	13	NR/13 12 (SD 4.1)/NR Range 8-17	10 (76.9)	3 (23)	
Stark and Sullivan, 1986 ⁵	NR	Cohort	25	NR/38 41/NR Range 17-71	18 (72)	5 (20)	4/4.3 (1-8)
Popa and Lerner, 1984 ¹²	NR	Case series	3	NR/47 40/NR Range 22-52	0	3 (100)	3.5/3.5 (3-4)

ED, emergency department; Peds, pediatric; NR, not reported.

Age by years was not reported by Liew et al,²⁸ Brown et al,³⁰ and Jarvinen et al.¹³ Female N(%) was not reported by Liew et al,²⁸ Brown et al,³⁰ Confino-Cohen et al,¹⁵ Jarvinen et al,¹³ Lee and Greenes.¹ Time (h) to biphasic Median/Mean (Range) was not reported by Liew et al,²⁸ Calvani et al,³² Confino-Cohen et al,¹⁵ Jarvinen et al,¹³ Yang et al,³³ Jirapongsananuruk et al,³⁴ Poachanukoon et al,²⁴ Cianferoni et al,³⁵ and Sampson et al.¹⁸

with 95% CIs for the outcomes reported in 2 or more studies. For rare events, defined as 1 to 5 events reported in an individual study, Peto's OR was calculated using a fixed-effect model. We assessed inconsistency among studies with the I^2 statistic, which

indicates the proportion of variability in study estimates due to between-study heterogeneity. I^2 values of 25%, 50%, and 75% indicate low, moderate, and high statistical heterogeneity, respectively.¹¹

TABLE II. Data synthesis for candidate risk factors for biphasic reactions

Outcome or subgroup	Studies	Participants	Sensitivity (95% CI)	Specificity (95% CI)	Effect estimate (OR, 95% CI)
Prior anaphylaxis	2	637	0.35 [0.17, 0.56]	0.77 [0.73, 0.80]	1.85 [0.74, 4.64]
Asthma	9	1673	0.29 [0.20, 0.39]	0.76 [0.73, 0.78]	1.12 [0.69, 1.80]
Food as an inciting trigger	16	2667	0.34 [0.25, 0.43]	0.54 [0.52, 0.56]	0.62 [0.40, 0.94]*
Medication as an inciting trigger	16	2567	0.25 [0.18, 0.34]	0.76 [0.74, 0.78]	1.20 [0.75, 1.92]
Venom as an inciting trigger	13	2226	0.16 [0.09, 0.24]	0.89 [0.87, 0.90]	1.11 [0.61, 2.03]
Unknown inciting trigger	16	2670	0.20 [0.14, 0.29]	0.85 [0.84, 0.87]	1.72 [1.00, 2.95]*
Initial symptom wheezing	11	1982	0.27 [0.18, 0.38]	0.69 [0.67, 0.71]	0.83 [0.51, 1.36]
Initial symptom dyspnea	11	1921	0.50 [0.39, 0.62]	0.42 [0.40, 0.44]	0.91 [0.56, 1.49]
Initial symptom hypotension	12	1987	0.32 [0.22, 0.45]	0.84 [0.82, 0.85]	2.18 [1.14, 4.15]*
Initial symptom angioedema	10	1994	0.46 [0.35, 0.57]	0.51 [0.49, 0.53]	0.79 [0.46, 1.33]
Initial symptom diarrhea	6	1217	0.11 [0.04, 0.23]	0.94 [0.92, 0.95]	2.53 [0.80, 7.97]
Initial symptom rash/urticaria	11	2030	0.70 [0.59, 0.79]	0.31 [0.29, 0.33]	1.35 [0.82, 2.23]
Treatment with epinephrine	16	2758	0.61 [0.53, 0.70]	0.34 [0.33, 0.36]	0.91 [0.60, 1.40]
Treatment with steroid	17	3134	0.80 [0.72, 0.86]	0.44 [0.42, 0.45]	1.52 [0.96, 2.43]

OR, odds ratio; CI, confidence interval.

Statistical method: Peto's odds ratio, 95% confidence interval.

*Statistically significant.

Sensitivity analysis

To demonstrate the robustness of our findings and to estimate any potential bias introduced by assumptions made in the process of conducting the review, we conducted sensitivity analyses. Sensitivity analysis is a repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear. We planned *a priori* sensitivity analyses that consisted of acute care setting (outpatient, emergency department, and inpatient excluding immunotherapy), pediatric studies, and studies determined to be at moderate risk of bias excluding those at high risk.

RESULTS

Selection process

Figure 1 shows the study selection process. The search strategy identified 596 studies. Two additional studies were identified from hand searching the reference lists of included studies. Among these, 6 were duplicates and 522 were not relevant to the study question and were excluded. The review of the titles and abstracts in phase I identified 70 potentially relevant studies. Articles written in Dutch or Italian were translated using online software (Google translate. Copyright Oxford University Press, USA); Spanish, Japanese, Portuguese, and Russian articles were translated by reviewers who were fluent in each language.

After the review of the 70 potentially relevant full-text studies identified in phase I, 28 articles were chosen inclusion in the systematic review (phase II). One study was a case series without a control group and therefore was included only in the qualitative analysis.¹² There were no randomized control trials. A total of 27 studies reported sufficient data to include in the meta-analysis. Interobserver agreement for phase II of the review had a kappa of 0.79 (95% CI 0.65 to 0.94). Eight discrepancies between the 2 reviewers were resolved by the third reviewer.

Characteristics of included studies

Table I displays the characteristics of the included studies. Twenty-six studies were cohort studies and 2 were case series. Ten studies included only pediatric patients. Four studies conducted at allergy clinics reported responses to an oral food

challenge or immunotherapy.¹³⁻¹⁶ The remaining 14 studies included adults or had no age restriction and were conducted in acute care outpatient or inpatient settings. Overall, there were 4162 patients with anaphylaxis and 190 patients with biphasic reactions.

Quality assessment

Appendix 2 (in this article's Online Repository at www.jaci-inpractice.org) shows the quality assessment for case control studies and cohort studies according to the NOS. The scale was used to stratify the risk of bias as moderate or high based on representativeness or case definition, selection of nonexposed cohort or representativeness, comparability, and ascertainment of exposure (categorized score of 1-2 as high, and 3-5 as moderate). Two reviewers evaluated study quality (S.L. and M.F.B.). Thirteen of the 28 with data for bias assessment were classified as moderate risk for bias and 15 as high risk of bias.

Rate, duration, and severity of biphasic reactions

The rate of a biphasic reaction among the included studies was 4.6% (95% CI 4.0 to 5.3) (Table I). Mean, median, and overall range of time to onset of biphasic reactions (for studies that provided data) were 9.9, 11, 0.2 to 72 hours, respectively (Table I). Four cohort studies reported low severity (severity defined as fatality, clinically important, or requirement for epinephrine) biphasic reactions.^{4,14,16,17} Among the studies that described individual biphasic symptoms (13 studies), at least 67.9% of the biphasic reactions included 2 or more organ systems. The overall admission rate to intensive care unit (ICU) for cohort studies (5 studies) was 6.7% (range: 0-14%). One case series reported fatal or near fatal reactions to food as the trigger.¹⁸

Inciting triggers

Food was the most common trigger for biphasic reactions (56, 40.6%), followed by medication (33, 23.9%), venom (18, 13%), and other triggers (10, 7.2%). The inciting trigger was not identified in a total of 25 (18.1%) biphasic reactions.

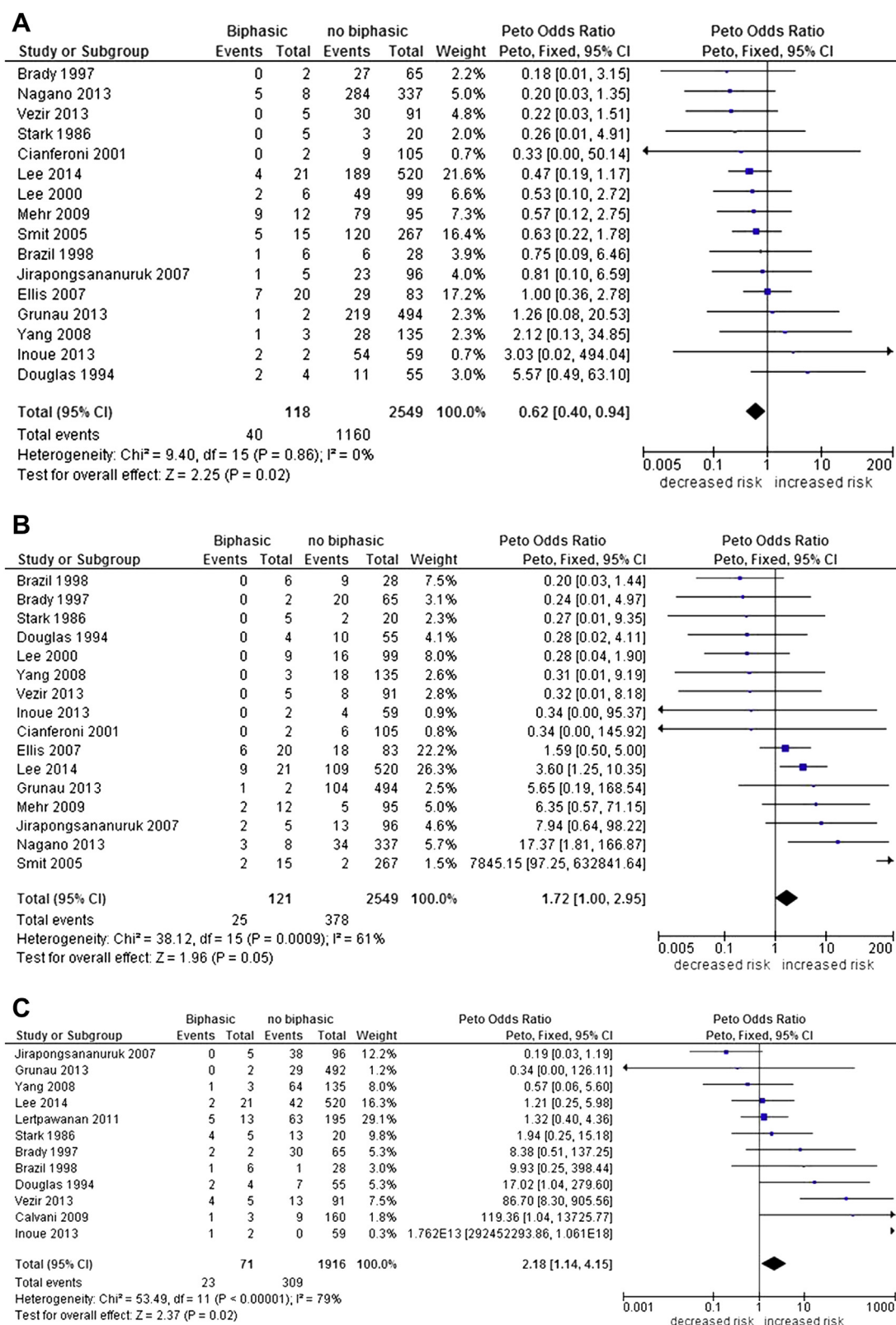


FIGURE 2. a, Association between food as the inciting trigger and biphasic reactions. b, Association between an unknown inciting trigger and biphasic reactions. c, Hypotension and risk of biphasic reactions.

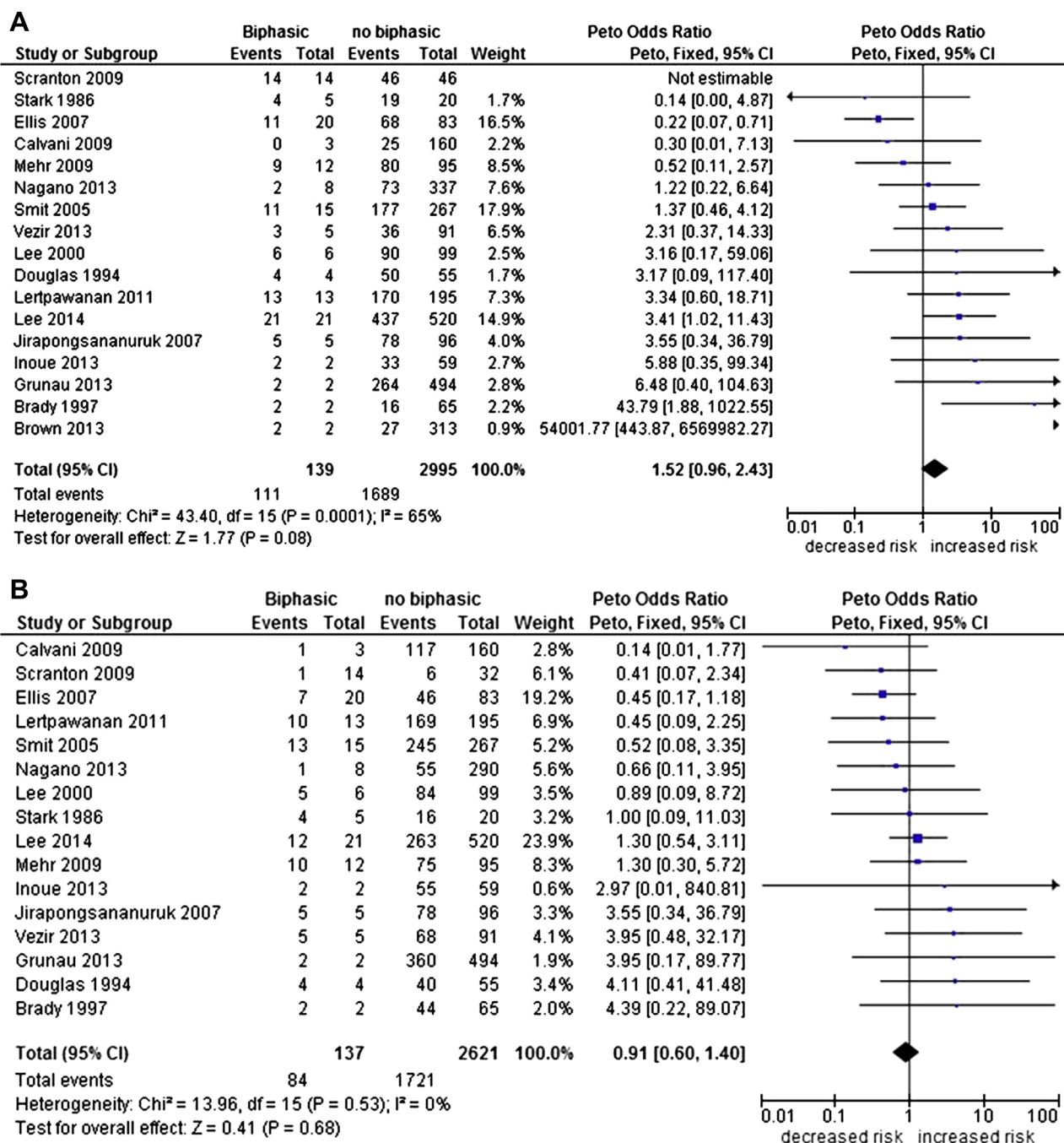


FIGURE 3. a, Steroid and risk of biphasic reactions. b, Epinephrine and risk of biphasic reactions.

Pooled candidate risk factors for a biphasic reaction

Table II shows the pooled estimates for each of the candidate risk factors for a biphasic reaction. Food as the inciting trigger was significantly negatively associated with a biphasic reaction, and an unknown inciting trigger and hypotension were significantly positively associated with a biphasic reaction. There was no significant association between a history of asthma or with treatment with epinephrine or steroids for the initial reaction with a biphasic reaction.

Figures 2(a) shows the meta-analysis and Forest plot of individual studies that evaluated food as the inciting trigger as a risk

factor for a biphasic reaction. Among the studies that reported sufficient data for meta-analysis, food as the inciting trigger was present in 16 studies with 2667 participants and was present in 40 of 118 (33.9%) biphasic reactions, 1160 of 2549 (45.5%) without biphasic reactions. Food as the inciting trigger was negatively associated with a biphasic reaction (pooled OR 0.62, 95% CI: 0.4 to 0.94, $I^2 = 0\%$). Sensitivity analysis showed that the negative association between food as the inciting trigger and a biphasic reaction remained significant in pediatric studies. Findings were not significant after synthesizing studies with moderate risk of bias indicating that the result might be affected

by bias. Immunotherapy studies did not have sufficient data for meta-analysis.

Figure 2(b) shows the meta-analysis and Forest plot for individual studies that evaluated an unknown inciting trigger as a risk factor for a biphasic reaction. An unknown inciting trigger was present in 16 studies with 2670 participants and was present in 25 of 121 (20.7%) biphasic reactions, 378 of 2549 (14.8%) without biphasic reactions. An unknown inciting trigger was positively associated with a biphasic reaction (pooled OR 1.72, 95% CI: 1.0 to 2.95, $I^2 = 61\%$). The positive association between an unknown inciting trigger and a biphasic reaction remained significant after sensitivity analyses in pediatric studies and studies at moderate risk of bias. Immunotherapy studies did not have sufficient data for meta-analysis.

Figure 2(c) shows the meta-analysis and Forest plot for individual studies that evaluated hypotension as a risk factor for a biphasic reaction. Hypotension was reported in 12 studies with 1987 participants and was present in 23 of 71 (32.4%) biphasic reactions, 309 of 1916 (16.1%) without biphasic reactions. It was associated with an increased odds of a biphasic reaction (pooled OR 2.18, 95% CI: 1.14 to 4.15, $I^2 = 79\%$). The association remained significant after sensitivity analyses for pediatrics but not for moderate risk of bias studies (data not shown), which indicates, as mentioned above, that the finding may be affected by bias. Immunotherapy studies did not have sufficient data for meta-analysis.

Figure 3(a, b) shows meta-analysis results demonstrating no significant association between steroid treatment (pooled OR 1.52, 95% CI: 0.96 to 2.43, $I^2 = 65\%$) or epinephrine (pooled OR 0.91, 95% CI: 0.6 to 1.4, $I^2 = 0$) and risk of a biphasic reaction. The findings remained insignificant in sensitivity analyses.

DISCUSSION

Statement of principal findings

In this systematic review of 4162 patients presenting with anaphylaxis, we observed a 4.6% rate of biphasic reactions. Median time between initial symptom resolution and onset of the biphasic reaction was 11 hours and ranged from 0.2 to 72 hours. The risk of a biphasic reaction was greater with an unknown inciting trigger and hypotension on presentation and less likely with food as the inciting trigger.

Strengths and limitations

The strengths of this review include its exhaustive and reproducible search strategy, inclusion of non-English studies, and the largest cumulative sample size of biphasic reactions to date. The meta-analysis estimated the strength of each association and sensitivity analyses confirmed the robustness of the results. However, there are several potential limitations to this review as well. First, biphasic reactions are rare and each study reported only a small number of biphasic reactions. There were several studies of anaphylaxis that did not report biphasic reactions; therefore, this review is prone to selection bias when estimating the rate. Second, the degree of detail reported in each of the studies with regard to patient characteristics was limited, and many were specifically focused on immunotherapy and oral food challenges rather than the general anaphylaxis population. Third, all the settings such as emergency department, outpatient clinic, and inpatient studies were included to determine the risk factors of biphasic reactions, which contributed to heterogeneity.

Fourth, the NIAID/FAAN criteria were developed in 2005, which affected case definition and increased the risk of bias for underestimating some uncommon presentations that led to biphasic reactions among studies before 2005. Fifth, it is uncertain what proportions of biphasic reactions were clinically significant. Many of the studies included very few biphasic reactions and did not include a clear definition. Sixth, many of biphasic reactions were noticed in the literature despite the absence of risk factors identified. Lastly, reviewers were not blinded to the author, institution, year, and title of manuscripts during full manuscript review due to familiarity of the literature.

Comparison with other published studies

This review suggests that many biphasic reactions occur beyond the 6 hours of observation recommended in some anaphylaxis guidelines. This is consistent with what has been reported in other studies in which a substantial proportion of biphasic reactions occur beyond 6 hours.^{3,7,9} Current guidelines in the United States recommend 6 hours of observation after the initial episode of anaphylaxis.^{6,19} However, some studies suggest 24 hours of observation.^{2,7} European guidelines recommend children with signs of hypotension or collapse to be monitored for 24 hours.⁸ Rohacek et al demonstrated that a monitoring period of less than 8 hours did not change outcomes compared with those who were monitored longer than 8 hours.²⁰ Our study results suggest that the optimal duration of observation after initial stabilization of anaphylaxis should be individualized based on patient presentation.

Pooled analyses from observational studies in this review demonstrated the rarity of ICU admission with biphasic reactions compared with the primary reaction.^{4,9,14,16,17} These findings are consistent with several previous studies that have reported that the symptoms of biphasic reactions are often less severe than symptoms that occur with the initial episode of anaphylaxis and rarely require acute intervention such as intubation, vasopressor infusion, or transfer to a higher level of care such as ICU.^{1,3,20-22} On the contrary, Sampson et al described a case series of fatal or near fatal biphasic reactions¹⁸ that occurred within 2 hours after resolution of the initial symptoms that demonstrated that biphasic reactions can be more severe than the initial reaction. A large prospective cohort study would most effectively assess the appropriate observation period after initial treatment of anaphylaxis.

Food as the inciting trigger was negatively associated with a biphasic reaction in the pooled analysis. Jarvinen et al also reported that biphasic reactions during oral food challenges were rare (2% among children).¹³ In contrast, Stark et al described that the oral route was more likely to be associated with biphasic or protracted reactions compared with parenteral exposure among 25 prospectively studied emergency department patients.⁵ However, when comparing patients with only biphasic reactions, the rate was not significantly different (25% for the oral route vs 18% for the parenteral route). Studies that were considered at high risk of bias might be affecting the data synthesis. The sensitivity analysis showed that the finding remained significant in the pediatric population but needs further verification in adults.

Having an unknown inciting trigger was associated with a biphasic reaction in the pooled analysis. A positive association between an unknown trigger and a biphasic reaction was observed in our previous study.⁹ The definition of a biphasic

anaphylactic reaction is the recurrence of anaphylaxis symptoms without re-exposure to the trigger¹; however, re-exposure to the inciting trigger is possible among patients with an unknown trigger. Although it is impossible to know for certain that the patients did not reencounter the trigger, this finding remains clinically important as these patients are at a higher risk of a recurrent reaction and this should be taken into consideration during management and the patients should be informed of the risk.

Pooled analysis showed that hypotension is a rare but significant risk factor for biphasic reactions. Significance did not remain after sensitivity analysis for risk of bias and thus must be interpreted with caution due to the increased degree of heterogeneity across studies. Hypotension has been implicated as a risk factor for biphasic reactions in previous studies,^{3,4,7,23} and our study finding is consistent with this. European guidelines recommend longer observation for pediatric patients who present with hypotension.⁸ The recommendation would be supported by our study as the association between hypotension and biphasic reactions remained significant in pediatric patients.

In our study, the association between the use of epinephrine or steroids and development of biphasic reactions was not significant. This may be because the pooled estimate (Figure 3, *a* and *b*) and confidence intervals were too wide to precisely measure the true association. Data on the use of epinephrine and steroids were available in the majority of studies; however, antihistamines are difficult to assess as they are also available as over-the-counter medications and do not require a prescription. A short-acting beta agonist was another agent often used for bronchospasm, but the effect against biphasic reactions was not clear in the literature. Other studies reported that therapeutic interventions such as steroids, antihistamines, and epinephrine may prevent biphasic reactions.^{3,21} Ellis et al reported that the biphasic reaction group received less epinephrine ($P = .048$) and possibly a lower dose of steroids ($P = .06$).²¹ Poachanukoon et al,²⁴ and Lertnawapan et al²⁵ reported an association between delayed epinephrine use and biphasic reactions. However, several other studies did not observe this association.^{1,2,4,5,7,23} Additional prospective studies are needed to determine if management with epinephrine or steroids alters the risk of a biphasic reaction.

CONCLUSIONS AND IMPLICATION FOR CLINICIANS

Biphasic reactions are uncommon and often occur beyond the 6 hours of observation recommended in some anaphylaxis guidelines. Identifying patients who are most likely to benefit from a longer period of observation is an important clinical question, and data from our meta-analysis suggest that patients with an unknown trigger or those who initially present with hypotension are at increased risk. Similarly, shorter periods of emergency department observation may be reasonable after proper instruction and prescription for epinephrine auto-injectors among patients who are at a lower risk of developing a biphasic reaction.

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APPENDIX 1. SEARCH STRATEGY

(biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR resurg* OR “late phase”) AND anaphyla* 394 PubMed

((biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR reactivat* OR resurg* OR “late phase”) AND anaphyla*) NOT MEDLINE[sb] 27 (Jan 17, 2014)
*remove mice, rats, guinea pigs 22

Remove rats & mice etc = 207

AND anaphyla*)) NOT TOPIC: (rats OR pigs OR mice OR rabbit*) 221

Scopus

(TITLE-ABS-KEY((biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR reactivat* OR resurg* OR “late phase”) AND anaphyla*) AND NOT TITLE-ABS-KEY(rats OR rabbit* OR mice OR pig*)) AND NOT (PMID(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)) 114

Ovid MEDLINE(R) 1946 to January Week 2 2014

#	Searches	Results	Search Type
1	(biphasic or phasic or multiphasic or protracted or (recur* and hours) or resurg* or reactivat* or “late phase”).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	108180	Advanced
2	1 and anaphyla*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	379	Advanced
3	..1/2 hu = y	207	

Embase 1988 to 2014 Week 02

#	Searches	Results	Search Type
1	(biphasic or phasic or multiphasic or protracted or (recur* and hours) or resurg* or reactivat* or “late phase”).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	118051	Advanced
2	1 and anaphyla*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	604	Advanced
3	1 and exp anaphylaxis/	392	Advanced
4	2 or 3	604	Advanced
5	limit 4 to human	422	

Web of Science (Jan 17, 2014)

TOPIC: (((biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR reactivat* OR resurg* OR late phase)

TITLE-ABS-KEY(“second phase” AND anaphyla* AND NOT (rats OR rabbit* OR mice OR pig*)) 23

APPENDIX 2. Quality assessment

Cohort study	Representativeness	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest not present	Comparability of cohorts	Assessment of outcome	Follow-up long enough?	Adequacy of follow-up	Risk for bias
Lee et al, 2014 ⁹	Adequate	Adequate	Adequate	Adequate	Adequate*	Potential for bias	Adequate	Adequate	Moderate
Vezir et al, 2013 ²⁶	Adequate	Adequate	Adequate	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	High
Nagano et al, 2013 ²⁷	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Moderate
Liew et al, 2013 ²⁸	Adequate	Adequate	Adequate	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	High
Lee et al, 2013 ¹⁶	Adequate	Potential for bias	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	High
Inoue et al, 2013 ²⁹	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Moderate
Grunau et al, 2013 ¹⁷	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Adequate	Moderate
Brown et al, 2013 ³⁰	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Moderate
Orhan et al, 2011 ³¹	Potential for bias	Adequate	Adequate	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	High
Lertnawapan and Maek-a-nantawat, 2011 ²⁵	Adequate	Adequate	Adequate	Adequate	Adequate*	Potential for bias	Adequate	Adequate	Moderate
Calvani et al, 2011 ³²	Potential for bias	Potential for bias	Adequate	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	High
Confino-Cohen et al, 2010 ¹⁵	Adequate	Adequate	Adequate	Potential for bias	Adequate	Potential for bias	Adequate	Adequate	Moderate
Scranton et al, 2009 ¹⁴	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Moderate
Mehr et al, 2009 ²³	Adequate	Potential for bias	Potential for bias	Adequate	Adequate*	Potential for bias	Adequate	Potential for bias	High
Jarvinen et al, 2009 ¹³	Potential for bias	Potential for bias	Potential for bias	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	Moderate
Yang et al, 2008 ³³	Potential for bias	Adequate	Potential for bias	Potential for bias	Adequate	Potential for bias	Adequate	Adequate	High
Jirapongsananuruk et al, 2007 ³⁴	Potential for bias	Potential for bias	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Moderate
Ellis and Day, 2007 ²¹	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	High
Poachanukoon and Paopairochanakorn, 2006 ²⁴	Potential for bias	Potential for bias	Potential for bias	Potential for bias	Adequate	Potential for bias	Adequate	Adequate	High
Smit et al, 2005 ⁷	Adequate	Adequate	Potential for bias	Adequate	Adequate*	Potential for bias	Adequate	Adequate	Moderate
Cianferoni et al, 2001 ³⁵	Potential for bias	Adequate	Potential for bias	Adequate	Adequate	Potential for bias	Potential for bias	Potential for bias	High
Lee and Greenes, 2000 ¹	Adequate	Adequate	Adequate	Potential for bias	Adequate	Adequate	Adequate	Adequate	High
Brazil and MacNamara, 1998 ²	Potential for bias	Potential for bias	Potential for bias	Potential for bias	Adequate	Potential for bias	Potential for bias	Potential for bias	Moderate
Brady et al, 1997 ⁴	Adequate	Potential for bias	Potential for bias	Adequate	Adequate	Potential for bias	Potential for bias	Potential for bias	High
Douglas et al, 1994 ³	Adequate	Adequate	Potential for bias	Potential for bias	Adequate	Potential for bias	Adequate	Adequate	Moderate
Stark and Sullivan, 1986 ⁵	Adequate	Adequate	Adequate	Adequate	Adequate	Potential for bias	Adequate	Potential for bias	High
Case series	Case definition	Representativeness	Selection control	Definition of controls	Comparability	Ascertainment of exposure	Method of ascertainment	Nonresponse rate	Moderate
Sampson et al, 1992 ¹⁸	Potential for bias	Potential for bias	Potential for bias	Potential for bias	Adequate	Adequate	Adequate	Adequate	High
Popa and Lerner, 1984 ¹²	Potential for bias	Potential for bias	Potential for bias	Potential for bias	Adequate	Potential for bias	Potential for bias	Potential for bias	High

ED, emergency department; Peds, pediatric population; Immunotherapy: allergy clinic immunotherapy study; PEF, peak expiratory flow.

*Comparability scores of 2.