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 anaphylatic 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 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).

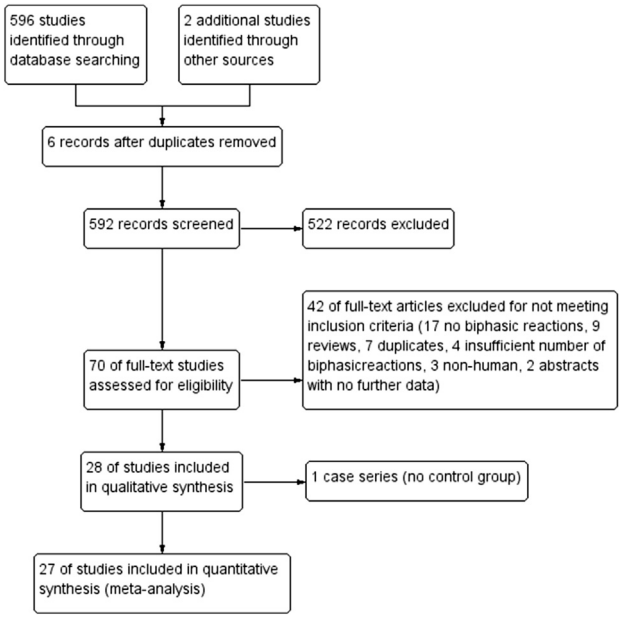

FIGURE 1. Flow diagram of the study selection process.

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 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]

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