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Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis

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ABSTRACT

Background: Epidemiologic data regarding biphasic reactions in children with anaphylaxis are sparse.
Objective: To investigate the incidence and clinical predictors of biphasic reactions in children presenting to the emergency department (ED) with anaphylaxis.
Methods: A health records review of ED visits at 2 large Canadian academic pediatric EDs was conducted. All visits that satisfied anaphylaxis diagnostic criteria of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network were included. Predictors of biphasic reaction were analyzed using univariate and multiple logistic regression analyses.
Results: Of 1,749 ED records reviewed, 484 visits met the study inclusion criteria. Seventy-one patients (14.7%) developed biphasic reactions. The median age was 6 years (interquartile range 2.7–10.1) and 51 (71.8%) were boys. Forty-nine of the 71 (69%) delayed reactions involved respiratory and/or cardiovascular manifestations and 35 (49%) were treated with epinephrine. Five independent predictors for biphasic reactions were found: age 6 to 9 years (odds ratio [OR] 3.60, 95% confidence interval [CI] 1.5–8.58), delay in presentation to the ED longer than 90 minutes after the onset of the initial reaction (OR 2.58, 95% CI 1.47–4.53), wide pulse pressure at triage (OR 2.92, 95% CI 1.69–5.04), treatment of the initial reaction with more than 1 dose of epinephrine (OR 2.7, 95% CI 1.12–6.55), and administration of inhaled β-agonists in the ED (OR 2.39, 95% CI 1.24–4.62).
Conclusion: Biphasic reactions seem to be associated with the severity of the initial anaphylactic reactions. We identified clinical predictors that could ultimately be used to identify patients who would benefit from prolonged ED monitoring and enable better utilization of ED resources.

Introduction

Anaphylaxis is a severe hypersensitivity reaction that is rapid in onset and can result in death.[1] The true pediatric population-based prevalence of anaphylaxis from all triggers is unknown.[1,2] Several studies have shown that anaphylaxis is under-recognized by patients and caregivers and underdiagnosed by health professionals.[3] Despite this, the rate of occurrence appears to be globally increasing, particularly in children.[4–7] Anaphylactic reactions account for approximately 2 to 4 per 1,000 pediatric emergency department (ED) visits in North America.[8–10]

The pattern of an anaphylactic reaction can be uniphasic, biphasic (also called *delayed* or *late phase*), or refractory in nature.[11] Owing to concerns about potentially fatal biphasic reactions,[12] most guidelines recommend a prolonged period of observation and monitoring after treatment of the initial reaction. The dilemma that most emergency physicians encounter is identifying the optimum duration of this observation.[13] Guidelines vary considerably in their recommendations: some suggest anywhere from 6 to 24 hours and others provide no specific time.[1,2,14,15] This lack of consensus about the duration of observation originates from a lack of strong and validated clinical predictors for this phenomenon.

In light of increasing ED crowding in recent years, the lack of predictors of biphasic reactions, coupled with the growing evidence suggesting an increased rate of anaphylaxis among children in the past decade, may have a detrimental impact on the quality of care provided to this vulnerable population. The available literature

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on the epidemiology and predictors of a biphasic reaction in children is very sparse. This dearth of data is reflected in the recent report from the National Institute of Allergy and Infectious Diseases[16] and in the updated World Allergy Organization anaphylaxis guidelines, published in 2013.[17] These guidelines identified significant knowledge gaps in the incidence and treatment of biphasic reactions and recommended further research. Therefore, the primary objective of this study was to investigate the incidence and predictive factors of biphasic reactions in children with anaphylaxis.

Methods

Study Design and Setting

A health record review was conducted of patients who presented to the ED with anaphylaxis during the calendar year 2010. The study was conducted at 2 pediatric tertiary care centers in Ontario, Canada: the Children's Hospital of Eastern Ontario in Ottawa and the Hospital for Sick Children in Toronto. The Children's Hospital of Eastern Ontario is the only pediatric center in Ottawa with approximately 70,000 annual ED visits. The Hospital for Sick Children is the primary care pediatric hospital for the downtown core of Toronto and has approximately 60,000 ED visits annually. The research ethics boards at the 2 sites approved this study.

Selection of Participants

Patients were identified using the hospitals' health record databases. The ED charts of patients whose primary or secondary diagnoses matched any of the *International Classification of Diseases, Tenth Revision* codes were reviewed. These search codes included, but were not limited to, "anaphylactic shock due to shell fish (crustaceans)" (T78.01), "anaphylactic shock due to other fish" (T78.02), "anaphylactic shock due to fruits and vegetables" (T78.03), "anaphylactic shock due to tree nuts and seeds" (T78.04), "anaphylactic shock due to milk and dairy products" (T78.06), "anaphylactic shock due to eggs" (T78.07), "anaphylactic shock due to other food products" (T78.08), "anaphylactic shock due to unspecified food products" (T78.09), "other adverse food reactions, not classified elsewhere" (T78.1), "anaphylactic shock, unspecified" (T78.2), and "allergy, unspecified" (T78.4). Patients younger than 18 years and whose ED visits met the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis were included in the study.[18]

Patient encounters were excluded if any of the following criteria were met: allergic event did not match the strict 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network anaphylaxis diagnostic criteria; anaphylaxis that occurred in the context of a suicide attempt or intoxication; anaphylaxis episode confounded by other medical diagnoses, such as food poisoning or mastocytosis; anaphylaxis that occurred during an outpatient clinic visit or inpatient hospitalization; or anaphylaxis episodes in which the trigger, symptoms, or treatments of the reaction were not documented.

Data Abstraction and Processing

A standard paper data extraction form was developed, piloted, and agreed to by the authors. Nursing triage notes and nursing monitoring sheets were used in addition to data from each patient's ED record as primary sources for data regarding the time of events, such as drug administration or a change in a patient's clinical status. The ambulance call report was used to supplement or confirm historical data about all anaphylactic episodes attended by the emergency medical services personnel. When available, this report was used as the main source of data regarding prehospital reaction management at the scene and during transport to the hospital. For patients with anaphylaxis to a new allergen who were referred to an allergy specialist by the emergency physician, the consultation note from the allergist, when available, was used to document the relevant trigger.

Data were abstracted from 4 main categories of variables: history, physical examination, prehospital and ED treatments and interventions, and ED monitoring period and subsequent visits. The authors chose the variables to be assessed a priori based on data from reports in the literature.[11,12,19–34] These variables included, but were not limited to, age; sex; history of anaphylaxis and atopic diseases (such as eczema and asthma); historical details of the anaphylactic event (such as name of the allergen, if identified, and location of the allergic event); recorded vital signs at triage and clinical manifestations of the episode; and epinephrine, systemic steroid, and antihistamine treatments for the anaphylactic reaction before and after ED presentation. In addition, the following variables were abstracted if the patient developed a biphasic reaction during monitoring in the ED after the initial anaphylactic episode or subsequently returned to ED within 72 hours from the initial ED visit: time of onset, clinical manifestations, and details of therapeutic interventions for the biphasic reaction.

Ten percent of the total ED visits were randomly selected for data extraction inter-rater agreement. One emergency physician at each site extracted data from every 10th visit as listed by the health record department. This list is sorted chronologically by date of visit and had only the medical record number and date of the ED visit matching the *International Classification of Diseases, Tenth Revision* codes specified earlier. Interobserver agreement for variables with high impact of errors related to patient eligibility, development of the primary outcome, and treatment of the reaction with epinephrine before and after arrival to the ED were measured using the κ-coefficient with 95% confidence intervals.

Definition and Assessment of Outcome

Emergency department visits that matched the diagnosis of anaphylaxis were divided further into 2 groups: uniphasic and biphasic. For an anaphylactic reaction to be classified as biphasic, it had to match the following criteria: (1) the initial anaphylactic reaction should be followed with a period of resolution for longer than 1 hour, during which there are no new symptoms or treatment administered; (2) this period should be followed by a second phase of new or recurrent anaphylaxis symptoms or signs not caused by antigen re-exposure; and (3) these symptoms or signs should be severe enough to require therapeutic intervention. If there were no new or recurrent symptoms or signs matching the criteria listed earlier, the reaction was considered uniphasic.

Because a biphasic reaction has been reported to occur up to 72 hours after the initial anaphylactic reaction, health records were reviewed for subsequent ED visits within this period.[11] If the patient was admitted, then the inpatient chart was reviewed. If the patient was discharged from the ED or the inpatient service (before 72 hours), then the authors searched for evidence of return visits to the ED up to 72 hours after the index visit. If a return visit occurred, then records were reviewed to determine whether the subsequent visit was related to the initial visit for the anaphylaxis episode.

Data Analysis

Data entry and analysis were performed using SPSS 20 (SPSS, Inc, Chicago, Illinois). A random 20% of the completed abstraction forms were checked for accuracy of data entry into the database. In addition, accuracy of data collection and entry was verified further by regular frequency reports and visual checks. Any queries were clarified by reviewing the original record.