Incidence of Clinically Important Biphasic Reactions in Emergency Department Patients With Allergic Reactions or Anaphylaxis

Brian E. Grunau, MD*; Jennifer Li, BSc; Tae Won Yi; Robert Stenstrom, MD, PhD; Eric Grafstein, MD; Matthew O. Wiens, PharmD; R. Robert Schellenberg, MD; Frank Xavier Scheuermeyer, MD, MHSc

*Corresponding Author. E-mail: briangrunau@gmail.com.

Study objective: Allergic reactions are common presentations to the emergency department (ED). An unknown proportion of patients will develop biphasic reactions, and patients are often monitored for prolonged periods to manage potential reactions. We seek to determine the incidence of clinically important biphasic reactions.

Methods: Consecutive adult patients presenting to 2 urban EDs with allergic reactions during a 5-year period were identified. Encounters were dichotomized as "anaphylaxis" or "allergic reaction" with an explicit algorithm. A comprehensive chart review was conducted on each index and all subsequent visits to detail patient presentations, comorbidities, ED management, and predefined clinically important biphasic reactions. Regional and provincial databases were linked to identify subsequent ED visits and deaths within a 7-day period. The primary outcome was the proportion of patients with a clinically important biphasic reaction, and the secondary outcome was mortality.

Results: Of 428,634 ED visits, 2,819 (0.66%) encounters were reviewed (496 anaphylactic and 2,323 allergic reactions). Overall, 185 patients had at least 1 subsequent visit for allergic symptoms. Five clinically important biphasic reactions were identified (0.18%; 95% confidence interval [CI] 0.07% to 0.44%), with 2 occurring during the ED visit and 3 postdischarge. There were no fatalities (95% CI 0% to 0.17%). In the anaphylaxis and allergic reaction groups, clinically important biphasic reactions occurred in 2 patients (0.40%; 95% CI 0.07% to 1.6%) and 3 patients (0.13%; 95% CI 0.03% to 0.41%), respectively.

Conclusion: Among ED patients with allergic reactions or anaphylaxis, clinically important biphasic reactions and fatalities are rare. Our data suggest that prolonged routine monitoring of patients whose symptoms have resolved is likely unnecessary for patient safety. [Ann Emerg Med. 2014;63:736-744.]

Please see page 737 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Emergency department (ED) patients presenting with allergic or anaphylactic reactions can have a varied clinical course from benign to fatal. Anaphylaxis affects approximately 2% of the population during their lifetime,[1] with common triggers including food, insect stings, and medications, although idiopathic anaphylaxis is also common in the ED setting.[2]

After initial treatment and clinical improvement, some patients with allergic reactions may develop a second "biphasic" reaction, which may be more severe than the initial presentation.[3] Because of concerns about possible biphasic reactions, patients are often observed in a monitored setting for 6 hours or longer; however, the benefit of this prolonged ED stay has not been demonstrated to decrease complications of biphasic reactions and incurs significant ED cost and patient inconvenience.

Importance

Although several studies have examined the incidence of biphasic reactions in ED patients, conclusions about their incidence have varied significantly, between 0.5% and 20%.[3-9] Reasons for this heterogeneity are likely due to a wide variety of definitions used for anaphylaxis and biphasic reactions. Furthermore, many biphasic reactions reported were very mild and did not satisfy definitions for anaphylaxis.[6,7] To our knowledge, to date there have been no adult ED studies examining the incidence of biphasic reactions satisfying the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network definition of anaphylaxis.[10]

Editor's Capsule Summary

What is already known on this topic

There are reports of delayed, so-called biphasic reactions after the emergency department (ED) treatment of allergy and anaphylaxis, prompting some emergency physicians to retain patients for multiple hours of monitoring.

What question this study addressed

How often do clinically important biphasic reactions occur?

What this study adds to our knowledge

In this retrospective review of 2,819 consecutive adults with allergic reaction or anaphylaxis, there were just 5 with clinically important biphasic reactions. There were no deaths or serious morbidity.

How this is relevant to clinical practice

Extended monitoring after ED treatment of allergy or anaphylaxis appears unnecessary for the majority of patients whose symptoms have resolved.

Goals of This Investigation

The objective of this study was to determine the incidence of clinically important biphasic reactions in a large cohort of ED patients, using a specified definition. We hypothesized that the incidence of clinically important biphasic reactions would be very low.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study took place at 2 urban academic teaching hospitals in Vancouver, British Columbia, Canada, affiliated with the University of British Columbia. St. Paul's Hospital is an inner-city tertiary care referral center with approximately 70,000 annual ED visits that provides a full complement of specialist services, including a 20-bed ICU and a 24-hour on-call allergist. Mount St. Joseph's Hospital is an affiliated community center with approximately 25,000 annual ED visits that offers a large general medicine service and a 6-bed ICU. The 2 study hospitals use a common comprehensive electronic medical record. All investigations, medications, consultations, and outpatient prescriptions are facilitated by the electronic physician order entry system with time-stamped digital records. For every patient encounter, emergency physicians are required to complete an electronic summary with at least 1 diagnosis, all procedures, follow-up arrangements, and outpatient prescriptions. The 2 sites are among 6 EDs in the Vancouver Coastal Health region, all of which send data to a regional database that tracks patient visits by the patient's unique provincial health number. The institutional review boards and affiliated ethics committees of Providence Health Care, the University of British Columbia, and Vancouver Coastal Health approved this study.

Selection of Participants

Patient encounters were identified from the electronic medical database if the ED discharge diagnosis code of "allergic reaction" was used. "Allergic reaction" was the sole code available to physicians to select in the ED electronic medical record for any allergy-related ED visit. There were no codes available for other similar diagnoses such as anaphylaxis, anaphylactic shock, or drug reactions. All consecutive ED visits between April 1, 2007, and March 31, 2012, were examined.

Patient encounters were excluded if any of the following criteria were met: the patient was younger than 17 years, the primary diagnosis (as coded by the treating physician) was asthma with allergic reaction coded as a secondary diagnosis, the patient left the ED immediately after registration (was not assessed by nursing staff or a physician), or the patient had a preexisting condition that was known to cause nonallergic angioedema.

Data Collection and Processing

We collected data from the electronic databases through a comprehensive chart review process designed a priori. All components of the chart were examined, including physician notes and orders, nursing notes, emergency medical services (EMS) records, prescriptions, and consultations and admission documents if applicable. Three investigators, 1 ED faculty physician and 2 medical students (BEG, JL, and TWY), systematically reviewed all study charts. All of the criteria for chart reviews stipulated by Gilbert et al[11] and Worster et al[12] were adhered to, with the exception that data abstractors were not blinded to study outcomes. However, all variables were entered before evaluation of the outcomes of anaphylaxis and biphasic reaction. Abstractors were trained on a set of 50 records. Weekly meetings were held to review data collection and resolve any disputes. In cases of conflicting data, 2 independent reviewers carefully reconsidered the entire chart and a satisfactory consensus conclusion was reached. If a variable of interest was not mentioned in any location on the ED chart, it was considered to be not applicable to the patient encounter. Missing data were noted in data collection (Table; Appendix E1, available online at http://www.annemergmed.com).

Investigators abstracted data onto a standardized Excel spreadsheet (Microsoft Excel 2011; Microsoft, Redmond, WA). The following variables were chosen a priori, with consideration of the definition of anaphylaxis[10] and consensus among the study team: patient identifiers, age, sex, dates and times the patient was in the ED and admitted to the hospital (if applicable), history of allergies or asthma, the suspected offending allergen, whether the allergen was known to the patient previously, skin involvement, mucosal tissue involvement, dyspnea, syncope, gastrointestinal symptoms, medications received by the patient before ED arrival, medications

Table. Subject characteristics and outcomes.*

Subject characteristics and outcomes	Anaphylaxis, n=496			Allergic Reactions, n=2,323		
	No. (IQR or %)	95% CI	Missing (%)	No. (IQR or %)	95% CI	Missing (%)
Demographics						
Age	38 (27–51)		0	34 (26–48)		0
Female	264 (53)		0	1,456 (63)		0
Medical history						
History of allergies	358 (72)		1 (0.2)	1,350 (58)		5 (0.2)
Medications						
Epinephrine†	266 (54)		0	483 (21)		0
Steroids‡	362 (73)		0	985 (42)		0
ED index visit, %						
Biphasic in ED	2 (0.40)	0.07–1.6	0	0	0–0.21	0
Admit	7 (1.4)	0.60–3.0	0	13 (0.6)	0.31–0.98	0
7-Day follow-up, %						
Biphasic post–ED discharge	0	0–0.96	0	3 (0.13)	0.03–0.41	0
Death in 7 days	0	0–0.96	0	0	0–0.21	0
Biphasic reactions, %						
Total	2 (0.40)	0.07–1.6	0	3 (0.13)	0.03–0.41	0

IQR, Interquartile range.
*Categorical variables are presented as number followed by percentage in parentheses. Continuous variables are represented as the median with IQR in parentheses.
†Includes intramuscular, subcutaneous, or intravenous administration by patient, EMS, or in ED.
‡Includes oral or intravenous routes administered in the ED or prescribed on discharge.

administered by EMS, medications administered in the ED, vital signs as recorded by EMS and in the ED, disposition, discharge medications, and details of subsequent visits that occurred within 7 days (see Figure 1 for definitions).

We divided patients into 2 groups: "anaphylaxis" included those satisfying the definition for anaphylaxis, and "allergic reaction" included those not satisfying it (Figure 1). The definition for anaphylaxis was adapted from the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria developed at the Second Symposium on the Definition and Management of Anaphylaxis.[10] An allergist/immunologist (RRS) and an emergency physician (BEG) selected specific physical examination signs, patient symptoms, and vital sign values a priori to fully objectify the definition of anaphylaxis (Figure 1). All ED documents were reviewed in consideration for whether the definition of anaphylaxis was satisfied. For patients who were treated with self-administered or EMS-administered epinephrine, EMS vital signs and physical examination findings were also used in determining the occurrence of anaphylaxis.

To measure interrater reliability, 5% of the index visits (139 patient encounters) were randomly selected by a random-number generator. A second reviewer who was blinded to patient outcomes reviewed these charts independently. Cohen's κ was calculated for several key variables: (1) whether the patient encounter satisfied the definition for anaphylaxis, (2) whether the encounter or subsequent encounters satisfied the definition for clinically important biphasic reaction, (3) skin involvement, (4) mucosal tissue involvement, (5) wheeze or stridor, (6) syncope, (7) gastrointestinal symptoms, and (8) the occurrence of hospital admission (see Figure 1 for definitions). There were no clinically important biphasic reactions in the random sample, and thus we proceeded to identify a second random sample with the same method; however, all clinically important biphasic reactions identified in the study were added. A second blinded reviewer evaluated all these encounters for the occurrence of a clinically important biphasic reaction in the index and subsequent visits.

To identify patients who returned to any ED in the region or died within the province within the 7-day follow-up period, study patients were linked to 2 databases, the Vancouver Coastal Health regional database and the British Columbia Vital Statistics registry (Figure 2). We performed a comprehensive chart review on all regional ED patient encounters that occurred during this follow-up period to determine whether the visit was related to allergic complaints and whether it satisfied the definitions of anaphylaxis and clinically important biphasic reaction. Three investigators (BEG, RRS, and FXS) independently reviewed all subsequent patient encounters satisfying the definition for anaphylaxis (Figure 3; Appendix E2, available online at http://www.annemergmed.com) to determine whether the definition of clinically important biphasic reaction was met. Disputes were resolved with further chart review and consensus. Further, we identified deaths of any study patients within the province during the follow-up period.

Outcome Measures

The primary outcome was the proportion of patients who had a clinically important biphasic reaction within 7 days of the index ED visit. The secondary outcome was the proportion of patients who died within 7 days. Other outcomes included length of stay, hospital admission, and return visits to the ED for allergic-related or unrelated reasons. The previously identified subgroups of anaphylaxis and allergic reaction were analyzed both separately and together.

Anaphylaxis: Any of the following three numbered criteria must be satisfied:

1. Both of the following must be satisfied:
   a. Skin or mucosal tissue involvement
   b. One of the following:
      i. Respiratory compromise
      ii. Systolic blood pressure < 90 mmHg or syncope
2. Two of the following must be satisfied after exposure to a likely allergen:
   a. Skin or mucosal tissue involvement
   b. Respiratory compromise
   c. Systolic blood pressure < 90 mmHg or syncope
   d. Gastrointestinal symptoms
3. Systolic Blood Pressure < 90 mmHg after exposure to a known allergen.

Skin Involvement: Urticaria, rash, pruritus, and swelling of the face or ears. Localized pruritus or rash which were deemed secondary to trauma or an obvious insect bite were not considered as fulfilling the definition of "skin involvement."

Mucosal tissue involvement: Swelling of lips, tongue, or pharynx.

Respiratory Compromise: Wheeze or stridor on auscultation, hypoxemia (oxygen saturation < 95%), or respiratory rate >22.

Gastrointestinal Symptoms: Abdominal pain or vomiting which is present in the ED.

Allergic Reaction: A clinical patient presentation in which the criteria for anaphylaxis was not met, however the attending physician deemed the etiology of the signs and/or symptoms secondary to allergic processes (as demonstrated by the discharge diagnosis code).

Clinically Important Biphasic Reaction: Recurrent or new signs or symptoms occurring after an initial allergy-related presentation, which satisfy the definition for anaphylaxis, without any obvious further exposure to an offending allergen. If certain signs or symptoms were present on the index visit and did not resolve or improve prior to the subsequent visit, these signs or symptoms were not considered "recurrent" or "new" and thus were not used in the classification of biphasic reaction in subsequent visits.

Figure 1. Definitions of anaphylaxis, allergic reaction, and clinically important biphasic reaction.

Primary Data Analysis

Microsoft Excel 2008 (Microsoft) was used for data entry and Statistica (StatSoft, Inc., Tulsa, OK) for analysis. Dichotomous variables were reported as percentages and 95% confidence intervals (CIs) (with continuity correction). Continuous variables were presented as means with SDs (if normally distributed) or medians with interquartile ranges (if non-normally distributed; determined by Kolmogorov-Smirnov statistic).

RESULTS

Characteristics of Study Subjects

Between April 1, 2007, and March 31, 2012, there were 428,634 ED visits to the 2 study sites; 2,995 patient encounters were identified with discharge diagnoses of allergic reaction within the records of the 2 EDs, yielding 2,819 eligible ED visits (0.66%) from 2,480 unique patients (Figure 2). The agreement for the variables of skin involvement (κ=0.93), mucosal tissue involvement (κ=0.83), wheeze or stridor (κ=0.95), syncope (κ=1.0), gastrointestinal symptoms (κ=1.0), anaphylaxis (κ=1.0), and hospital admission (κ=1.0) on the first sample of randomly selected 139 charts was excellent. The second sample of charts also revealed excellent agreement for the occurrence of clinically important biphasic reactions (κ=1.0). Twenty patients (20/2,480; 0.8%) did not have provincial health numbers, and follow-up linkages could not be ascertained.

Main Results

Characteristics of index patient encounters can be seen in the Table and Appendix E1 (available online at http://www.annemergmed.com). Overall, 2,323 patient encounters (82.4%) were classified as allergic reaction and 496 (17.6%) as anaphylaxis. There were 2 clinically important biphasic reactions (0.071%; 95% CI 0.01% to 0.28%) that occurred during index ED visits, both of which were in the anaphylaxis group. The reactions occurred at 16 and 200 minutes into the ED encounter. Median ED length of stay for nonadmitted patients in the full study group, the anaphylaxis group, and the allergic reaction group was 1.78 hours (interquartile range 1.17 to 2.85), 2.85 hours (interquartile range 1.90 to 4.23), and 1.65 hours (interquartile range 1.10 to 2.50), respectively.

The regional ED database was interrogated to identify all subsequent visits within the 7-day follow-up period. Three hundred seventeen patients (11%) had ED visits during this period, of whom 185 (6.6%) had a visit or visits relating to allergic symptoms and 142 (5.0%) had a visit or visits that were unrelated. When all signs and symptoms were included, 17 study patients (0.6%) had subsequent visits that satisfied the definition for anaphylaxis. When we evaluated for the definition of clinically important biphasic reaction, considering only recurrent or new signs or symptoms, 3 encounters (0.11%; 95% CI 0.03% to 0.34%) satisfied the definition for a biphasic reaction (Figure 3). None of these patients satisfied the definition for anaphylaxis on the index visit. These visits occurred at 28, 35, and 143 hours after the index visit presentation time. Of the 14 remaining nonbiphasic visits, 5 of these cases involved obvious recurrent exposures to allergens and

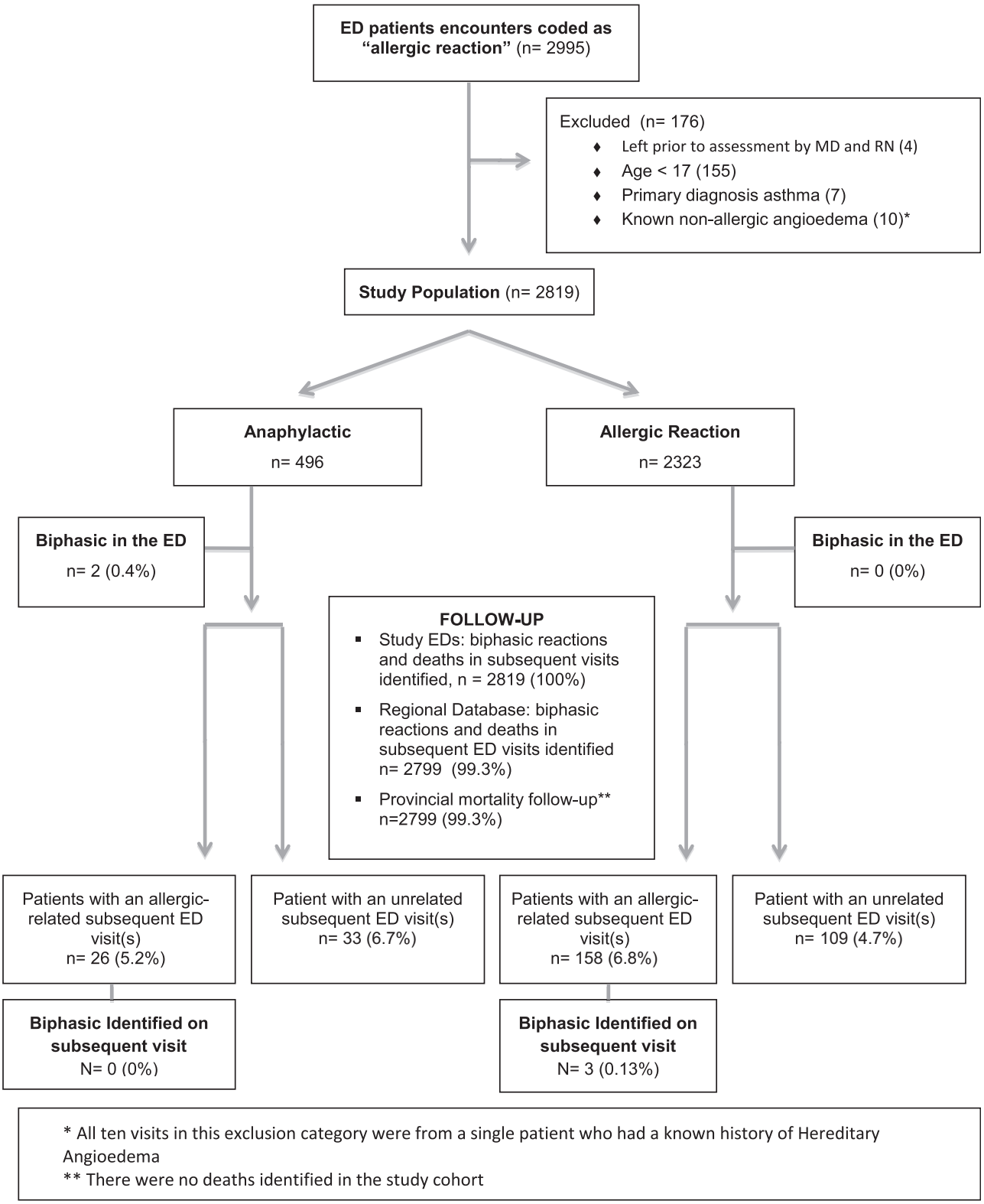

Figure 2. Flow diagram.

9 involved persistent symptoms (which were not new or recurrent). Appendix E2 (available online at http://www.annemergmed.com) illustrates clinical vignettes of all patients who satisfied the definition for anaphylaxis on a subsequent visit but did not satisfy the definition for clinically important biphasic reaction.

Index ED visits satisfying the definition of Clinically Important Biphasic Reaction

- 38-year-old male with known jackfruit allergy, presented to the ED after jackfruit ingestion with rash, mucosal swelling, dyspnea, and wheeze (anaphylaxis). He was immediately treated with epinephrine (6 minutes into ED stay) and his symptoms improved. Other treatments included salbutamol and epinephrine nebulizers, antihistamines, and hydrocortisone. Sixteen minutes into his ED stay he had acute onset of dyspnea, wheeze, and an oxygen saturation of 94%. He was again treated with epinephrine with effect.
- 37-year-old male, history of allergies to morphine, phenytoin, nuts, and bee stings, presented with rash, and wheeze thought secondary to allergic processes (anaphylaxis). He was treated with epinephrine (3 minutes into ED stay), hydrocortisone, antihistamines, and salbutamol nebulizer with improvement of signs and symptoms. At three hours and 20 minutes into his ED stay he experienced sudden onset dyspnea, wheeze, mucosal swelling, and oxygen desaturation to 94%. He was treated again with intramuscular epinephrine and nebulized epinephrine with improvement in symptoms.

Subsequent ED visits satisfying the definition of Clinically Important Biphasic Reaction

- 25-year-old male with no known allergies presented with a rash after use of cannabis (allergic reaction). He was treated with oral steroids, antihistamines, and fluids. The patient returned to the ED in six days with facial and oral angioedema, an urticarial rash, and a wheeze on auscultation. There was no clear precipitant. He stated that he had eaten nuts that day and thought this might have been a precipitant; however, he had never had reactions to nuts in the past. He was treated with epinephrine, IV steroids, and antihistamines.
- 26-year-old female with environmental allergies presented with rash of no clear precipitant, thought to be of allergic origin (allergic reaction). There were no other physical exam abnormalities and her vitals were within normal range She was treated with epinephrine (26 minutes into ED stay), anti-histamines and IV steroids. The next day she had sudden onset of urticaria and shortness of breath. On exam, she was found to have a rash, evidence of wheeze on auscultation, a respiratory rate of 24, and a systolic blood pressure of 96. She was treated with epinephrine, anti-histamines, salbutamol, and intravenous steroids.
- 28-year-old male, with history of penicillin and latex allergies, presented after playing soccer with a new soccer jersey with a thoracic and abdominal rash and knee pain (allergic reaction). He was diagnosed with a rash secondary to the soccer jersey and knee sprain. He is brought to the ED by EMS the next day with oral swelling, systolic blood pressure of 70, respiratory rate of 24, and persistent rash. He was treated effectively with epinephrine. He also received oral steroids, and antihistamines and was later discharged. The patient presented a third time to the ED later the same day with a very similar clinical picture and was treated with epinephrine and IV steroids, with resolution of symptoms.

Figure 3. Index ED visits satisfying the definition of clinically important biphasic reaction.

Overall, when the index ED visit and the 1-week follow-up were combined, there were a total of 5 (0.18%; 95% CI 0.07% to 0.44%) clinically important biphasic reactions identified. When clinically important biphasic reactions in the anaphylaxis and allergic reaction groups were examined separately, the incidence was 0.40% (95% CI 0.07% to 1.6%) and 0.13% (95% CI 0.03% to 0.41%), respectively. Linkage with the provincial British Columbia Vital Statistics Registry did not identify any deaths within 7 days (0%; 95% CI 0% to 0.17%).

LIMITATIONS

This is a retrospective medical record review and is subject to several limitations. The study sites were 2 urban Canadian EDs, and treatments and disposition may vary in different settings. There was no defined protocol for allergic reactions, and physicians managed patients in an unstructured, individualized manner, including ED treatment, investigations, length of stay, disposition, outpatient prescriptions, and follow-up. It is possible that treatment of one or various medications or other unmeasured cofounders influenced the incidence of biphasic reactions. In addition, data abstractors were not blinded to outcomes.

Patients who presented only to a primary care physician within the region or an ED out of the region within 7 days would not have been identified as having a subsequent visit or potential clinically important biphasic reaction. However, it is unlikely that primary care physicians would manage any severe reaction in a clinic setting, and most of these patients would have been re-referred to an ED. Furthermore, death of patients after migration outside the province within the follow-up period would have been missed. Twenty patients in the study cohort (0.7%) did not have a provincial health number, and thus if an adverse outcome occurred to one of these patients outside one of the study hospitals, it would have been missed.

The diagnosis of allergic reactions is based on clinical impression, which is a potential source of error. Patients with true allergic-related presentations may have been coded as other entities such "shock not otherwise specified" or "rash." Alternatively, patients may have been coded as allergic reaction when in fact the clinical presentation was the result of another cause. In attempting to identify all biphasic reactions it is possible that patients, who did not satisfy the definition for a biphasic reaction as an "obvious" reexposure to an allergen occurred, did in fact have a biphasic reaction. Also, for patients satisfying

our definition for biphasic reaction, it is possible that there was an unappreciated reexposure to an allergen, and thus the patient was identified in error as having a biphasic reaction. Finally, despite documented resolution of symptoms, the patient who was identified as having a biphasic reaction 16 minutes into the ED stay may have been experiencing persistent rather than biphasic symptoms. However, because there is no evidence to support a certain time frame in which biphasic reactions can occur, and because we sought to use an objective and reproducible definition for biphasic reactions, we classified this case as a biphasic reaction because it satisfied our criteria.

Two groups of patients were potentially mislabeled as having allergic reaction. One hundred forty-seven allergic reaction patients self-administered epinephrine before contact with the ED or EMS, and it is possible that these patients satisfied the definition for anaphylaxis before its use. However, we chose to use actual data, and patients had clinically improved because of commendable self-care. Second, there were 104 patients in the allergic reaction group who did not have all 3 vital signs (systolic blood pressure, oxygen saturation, and respiratory rate) required for the assessment of anaphylaxis recorded at least once, and they could potentially have had anaphylaxis. Although patients in both of these groups may have been misclassified as having allergic reaction instead of anaphylaxis, none of them in this subset experienced a subsequent biphasic reaction or died. Missing clinical variables relevant to the definition of anaphylaxis may have also contributed to misclassified patient encounters; however it is likely that if the variable was not mentioned in any location of the ED chart it was not applicable.

DISCUSSION

To our knowledge, this is the largest study to date examining ED allergic reactions, anaphylaxis, biphasic reactions, and allergy-related mortality. We identified 2,819 patient encounters during a 5-year period, which composed 0.66% of all ED patients. We applied an objective and reproducible definition for anaphylaxis to each study patient and identified 496 patient encounters with anaphylaxis. Clinically important biphasic reactions, which satisfied the definition for anaphylaxis with recurrent or new signs or symptoms without reexposure to an allergen, were identified through a comprehensive strategy, revealing an incidence of 0.18%. This assists clinicians by demonstrating that few patients with allergic reactions or anaphylaxis have subsequent clinically important biphasic reactions.

We sought to use a clear and objective definition for anaphylaxis and biphasic reactions. Our definition of biphasic reaction, which appears to be reliable and reproducible, sought to capture only clinically important and potentially life-threatening reactions that satisfied the definition for anaphylaxis. Rationale for this was that: (1) mild symptoms described as biphasic reactions, which are reported in some studies, would likely be considered clinically insignificant to most emergency physicians; and, (2) the comprehensive detection of all potential biphasic reactions, including those of mild severity, would likely be impossible because many of these patients would likely not return to the ED for reassessment. In investigating delayed potentially life-threatening reactions, comprehensive follow-up of subsequent ED visits and deaths is essential. We used a thorough strategy to identify all biphasic reactions and deaths among discharged and admitted patients within the 7-day follow-up period.

Allergic reactions and anaphylaxis are diagnoses that are made on clinical grounds in the acute phase because there are no reliable laboratory or other objective markers on which to rely.[13,14] Objective and reproducible definitions are essential in the identification and study of anaphylaxis. Several studies have examined the incidence of anaphylaxis; however, the definitions used have been subjective, variable, and lacking in assessments of interrater reliability.[4-7,15,16]

We based our definition of anaphylaxis on the 2006 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria,[10] which has been endorsed by international anaphylaxis guidelines.[2,17] Campbell et al[18] applied this definition along with allergist/immunologist review in a retrospective cohort of 214 ED patients with allergic reaction or anaphylaxis. They found the definition to have a sensitivity of 97% and a specificity of 82% compared with the criterion standard of a board-certified allergist/immunologist chart review adjudication. The National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network definition, however, leaves some room for interpretation in its application. For example, for the criterion "respiratory compromise," the definition offers examples of what could satisfy this (eg, hypoxemia) but does not offer specific values. In our study, we determined specific objective values a priori for each criterion in the anaphylaxis definition. This strategy proved to have excellent interrater reliability.

Little is known of the pathophysiology of biphasic reactions and, similar to issues with defining true anaphylaxis, there is no criterion standard for diagnosis. Furthermore, the time frame in which biphasic reactions may occur is unknown. Variations and the subjective nature of definitions used for determining the incidence of biphasic reactions in previous ED studies are likely a major contributor to differing results, ranging from 0.5% to 20%.[4-8,15,16] This makes comparisons of data problematic.

Three studies have examined the incidence of biphasic reactions in ED patients and performed postdischarge follow-up (essential to studies of this nature). Brady et al[7] retrospectively identified 67 ED encounters with anaphylaxis and reviewed visits of study patients to the study and surrounding hospitals within 7 days. Biphasic reactions were defined as the recurrence of allergic symptoms or signs. Two biphasic reactions were identified (3%), both in subsequent ED visits (26 and 40 hours post–ED discharge), and in both cases reactions were limited to urticaria. Smit et al[6] reviewed 282 cases of patients treated in the resuscitation room with a discharge diagnoses consistent with anaphylaxis. Local hospitals were searched for subsequent visits within 5 days; however, none were found. They reported 15 biphasic reactions (5%), defined as "any reaction occurring after the initial treatment and complete resolution of symptoms," with 12 described as mild, 2 with hypotension, and 1 with hypoxemia. Eight biphasic reactions

occurred after 8 hours and the last occurred at 23 hours. Ellis and Day[19] identified 134 ED encounters with anaphylaxis and contacted these patients (103 successfully) in the subsequent 72 hours to determine whether a biphasic reaction occurred. Biphasic and anaphylaxis definitions were the same: "a severe allergic reaction to any stimulus, having sudden onset and generally lasting less than 24 hours; a disorder involving at least 2 body systems, with multiple symptoms such as hives, flushing, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhea or shock." They reported biphasic reactions in 20 patients, with a range of 2 to 38 hours to onset, and 11 occurring at 8 hours or later. Nineteen of the reactions occurred after discharge and 3 self-treated at home. There were no deaths reported.

Previous guidelines have advocated the monitoring of patients postanaphylaxis, with recommended durations varying between 4 and 24 hours,[2,14,20] likely a testament to the uncertainty in the literature. In comparison to these recommendations, the ED length of stay in our cohort was relatively short, which appears to be appropriate. Despite differences in study methodology, the above studies are congruent with our data, demonstrating that a large proportion of biphasic reactions occurred many hours after ED discharge but resulting in no reported deaths.[6,7,19] Furthermore, the data of Smit et al[6] and Brady et al[7] are consistent with our results that severe biphasic reactions are rare. Although extended observation would be justified in patients with severe or protracted anaphylaxis, the added costs and resource use involved in routine prolonged monitoring (for example, over 4 hours) of patients whose symptoms have resolved may worsen ED crowding while likely adding little to individual patient safety. A careful discussion on when to return to the ED and the importance of an epinephrine autoinjector, however, is essential before discharge.

Previous studies have examined risk factors for the development of biphasic reactions. Although no clear predictive factor has been identified,[9] several studies have reported that longer times to intramuscular or subcutaneous epinephrine administration[4,21] and higher amounts of epinephrine administered[22-24] are associated with biphasic reactions. In our study cohort, there were 5 patients with biphasic reactions identified, 2 of whom were not treated with epinephrine on the index visit because they were not deemed to have anaphylaxis. The remaining 3 patients received epinephrine at 3, 6, and 21 minutes into their ED stay, which was rapid in comparison with treatment in previous studies.[4,21] Only 1 patient was treated with more than 1 dose of epinephrine. Because of the low incidence of clinically important biphasic reactions, we described these patients in detail (Figure 3).

To our knowledge, there have been no studies examining the incidence of biphasic reactions in patients who are not initially classified as having anaphylaxis. Three patients in our allergic reaction group (0.13%) who were not classified as having anaphylaxis on the index visit had biphasic reactions post–ED discharge and required a subsequent visit for treatment. These occurred between 28 and 143 hours after the index ED presentation. None of these patients died, however, and each was effectively re-treated in the ED and discharged.

In conclusion, clinically important biphasic reactions and fatalities are rare among ED patients with allergic reactions or anaphylaxis. Our data suggest that prolonged routine ED monitoring of patients whose symptoms have resolved is likely unnecessary for patient safety.

Supervising editor: Steven M. Green, MD

Author affiliations: From the Department of Emergency Medicine (Grunau, Stenstrom, Grafstein, Scheuermeyer), Faculty of Medicine (Li, Yi), School of Population and Public Health (Stenstrom, Wiens), and Division of Allergy and Immunology (Schellenberg), University of British Columbia, Vancouver, British Columbia, Canada; and St. Paul's Hospital, Vancouver, British Columbia, Canada (Grunau, Stenstrom, Grafstein, Schellenberg, Scheuermeyer).

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APPENDIX E1. Subject characteristics and outcomes.*

	Anaphylaxis, n=496		Allergic Reactions, n=2,323	
No. (IQR)	**n (% or IQR; 95% CI)**	**Missing (%)**	**n (% or IQR; 95% CI)**	**Missing (%)**
Demographics				
Age, y	38 (27–51)	0	34 (26–48)	0
Female	264 (53)	0	1,456 (63)	0
Medical history				
Allergies	358 (72)	1 (0.20)	1,350 (58)	0
Asthma	125 (25)	7 (1.4)	268 (12)	15 (0.65)
Precipitant				
Precipitant drug	117 (24)	0	638 (27)	0
Precipitant food	220 (44)	0	736 (32)	0
ED signs or symptoms				
Skin involvement	441 (89)	20 (4.0)	1,589 (68)	152 (6.5)
Mucosal tissue involvement	144 (29)	143 (29)	385 (17)	707 (30)
Wheeze/stridor	156 (31)	30 (6.0)	32 (1.4)	252 (11)
History of syncope	25 (5.0)	180 (37)	5 (0.22)	1,002 (43)
Gastrointestinal symptoms	62 (13)	95 (19)	23 (1.0)	909 (39)
Medications				
Epinephrine†	266 (54)	0	483 (21)	0
Steroids‡	362 (73)	0	985 (42)	0
Anti-histamines§	446 (90)	0	1,595 (69)	0
ED vital signs				
Systolic blood pressure, mm Hg	113 (104–125)	3 (0.60)	122 (111–136)	75 (3.2)
Respiratory rate, breaths/min	20 (18–24)	4 (0.81)	18 (16–20)	86 (3.7)
Oxygen saturation, %	97 (94–98)	3 (0.60)	98 (97–99)	132 (5.7)
Biphasic reactions				
Total	2 (0.40; 0.07–1.6)	0	3 (0.13; 0.03–0.41)	0
Biphasic in ED	2 (0.40; 0.07–1.6)	0	0 (0; 0–0.21)	0
Biphasic post–ED discharge	0 (0; 0–0.96)	0	3 (0.13; 0.03–0.41)	0
ED index visit				
Admit	7 (1.4; 0.60–3.0)	0	13 (0.56; 0.31–0.98)	0
7-Day follow-up				
Subsequent visit(s) for allergic symptoms	26 (5.2)	0	158 (6.8)	0
Death in 7 days	0 (0; 0–0.96)	0	0 (0; 0–0.21)	0

*Categorical variables are presented as number followed by percentage in parentheses, with CIs when appropriate. Continuous variables are represented as the median with IQR in parentheses.

†Includes subcutaneous, intramuscular, or intravenous administration routes by the patient or EMS or in the ED.

‡Includes oral or intravenous routes administered in the ED or prescribed on discharge.

§Includes oral, intramuscular, or intravenous routes administered by EMS or in the ED.

APPENDIX E2.
Subsequent ED visits satisfying the definition for anaphylaxis but not clinically important biphasic reaction.

EXCLUDED BECAUSE OF PERSISTENT SIGNS OR SYMPTOMS

- 71-year-old man with a known allergy to morphine who was undergoing treatment with piperacillin-tazobactam for empyema. He presented with a rash and wheezing on the index visit (anaphylaxis). He returned to the ED 2 days later because of persistent symptoms (none new). The cause of rash was determined to be a delayed hypersensitivity reaction.
- 62-Year-old woman with a history of multiple antibiotic allergies. She presented with a rash on the index visit that was thought to be a result of fluticasone/salmeterol (allergic reaction). The patient received a diagnosis of a COPD exacerbation on day 2 and was treated with cefuroxime. The patient had return visits to the ED on days 2, 3, and 7 for persistent rash. Oxygen saturations were persistently low (93% to 93%) on each visit, but all other vital signs were within normal ranges.
- 22-Year-old woman with a history of sulfa allergy who presented with a rash after receiving nitrofurantoin (allergic reaction). She had a syncopal episode the next day and returned to the ED. On examination, she had a persistent rash but no other abnormalities.
- 79-Year-old man with no known allergies who presented with rash, mucosal swelling, and wheeze after eating fried fish (anaphylaxis). He returned to the ED on day 2 with persistent urticaria (mucosal symptoms had resolved). He had a subsequent visit on day 4 for persistent rash. His initial RR on this visit was 32 breaths per minute, and the wheeze was again detected. He was treated with diphenhydramine and prednisone. His RR decreased to 18 during the next 105 minutes, and he was discharged.
- 28-Year-old woman with known penicillin allergy who presented with a rash of unknown precipitant (deemed of allergic origin) and tachypnea (anaphylaxis). She returned to ED again on the same day with persistent rash, and then again on day 2 with the same complaint. On the final visit, she transiently had an oxygen saturation of 92% but no respiratory or head and neck abnormalities on examination.
- 28-Year-old woman with a history of sulfa allergy who presented with a rash of unknown precipitant, thought to be of allergic origin (allergic reaction). She had a subsequent visit on day 2 with persistent rash. On this visit, she transiently had an oxygen saturation of 92%, but all other vital signs were normal and there were no respiratory or head and neck examination abnormalities.
- 56-Year-old woman with multiple drug allergies and recent myocardial infarction who presented with rash and hypoxemia after initiation of new cardiac medications (anaphylaxis). She had a subsequent visit on days 2 and 3 for persistent rash and demonstrated low oxygen saturations on each visit. She had mild lip swelling on the final visit. Niacin or clopidogrel was considered as the offending agent. (This patient accounted for 2 visits in this category.)
- 29-Year-old woman with no known allergies who presented with rash after beginning to receive minocycline (allergic reaction). She was treated again for persistent rash and oxygen saturation that was low (94%), but she had no head and neck or respiratory complaints or physical examination abnormalities. She received no treatment in the ED and was discharged, receiving an antihistamine.

EXCLUDED BECAUSE OF RECURRENT EXPOSURE TO AN ALLERGEN

- 29-Year-old man with known allergies to peanuts, several antibiotics, codeine, and bee stings who presented post–peanut exposure with a rash, tachypnea, and hypoxemia (anaphylaxis). He had a subsequent visit on day 5, with tongue swelling after reexposure to peanuts.
- 30-Year-old man with a known peanut allergy who presented after a peanut exposure with a rash (allergic reaction). He returned to the ED 3 days later immediately after exposure to pepper spray, with transient symptoms of pruritus and elevated respiratory rate that had resolved on arrival at the ED. He presented again with allergic symptoms after a repeated peanut butter exposure. (This patient accounted for 2 visits in this category.)
- 27-Year-old woman with a complex history of multiple allergies. She had multiple serial ED visits, all relating to eating the same cake and having recurrent allergic symptoms. Each visit was due to symptoms that occurred after reexposure to the cake.
- 52-Year-old man with a history of seasonal allergic rhinitis and asthma who presented with rash after eating soup and green tea (allergic reaction). He had a subsequent visit on day 7, with symptoms of rash, dyspnea, and hypoxemia after reexposure to the same allergen.