Management of Children with Anaphylaxis in the Emergency Department: Practice Pattern and Prediction of Biphasic Reactions

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ABSTRACT

This research aims to assess the practice pattern of Canadian emergency physicians for management of anaphylaxis and investigate the clinical predictors for biphasic reactions in children with anaphylaxis. We conducted two studies: a national survey and a multicenter Health Records (HR) review of emergency department visits. Of the 608 physicians surveyed, 340 (56%) responded. Overall, 211(62%) of the physicians correctly agreed that both hypothetical scenarios in the survey were consistent with anaphylaxis, and 206(61%) chose to administer epinephrine. In our HR review, we found five independent predictors of biphasic reactions: age 6-9 years (OR 3.60; 95% CI 1.5-8.58), time from onset of the anaphylactic reaction to ED presentation >90 minutes (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 reaction with >1 dose of epinephrine (OR 2.7; 95% CI 1.12-6.55), and administration of inhaled salbutamol in ED (OR 2.39; 95% CI 1.24-4.62).

EXECUTIVE SUMMARY

First Study: Diagnosis and Management of Children with Anaphylaxis: A National Survey of Emergency Physicians

Objectives: To assess the knowledge and attitudes of the Canadian emergency physicians with respect to the diagnosis and management of children with anaphylactic reactions, and to identify factors associated with correct epinephrine administration.

Methods: We conducted a national cross-sectional survey using simple random sampling. We used the membership database of the Canadian Association of Emergency Physicians as our sampling frame. Survey questions were based on two hypothetical clinical scenarios involving an infant and an adolescent having an anaphylactic reaction after ingesting peanuts. Physicians were also queried on issues related to the choice of epinephrine concentration and route of administration in anaphylaxis, confidence level demonstrating to patients the correct use of epinephrine auto-injector, and utilization of written anaphylaxis action plans upon discharge from the Emergency Department (ED). The survey was administered using modified Dillman's technique. Primary outcome measures are correct diagnosis and treatment of the anaphylactic reactions.

Results: Of the 608 surveyed members, 340 (56%) responded. The majority of respondents were male 214(63%), practiced in academic settings with primarily an adult population 155(45%) or community hospitals 149(44%). Overall, 211(62%) of the physicians correctly agreed that both clinical scenarios were consistent with anaphylaxis, and 206(61%) chose to administer epinephrine. Regarding knowledge about epinephrine administration, 280 (82%) and 287 (84%) identified correct epinephrine concentration and IM route of administration respectively. Only 148 (43%) felt confident demonstrating the correct use of epinephrine auto-injector to patients and families and only 155 (45%) provided a written anaphylaxis action plan to patients upon discharge from the ED. In comparing pediatric emergency physicians and pediatricians to adult emergency medicine physicians and family physicians, pediatric physicians were more likely to agree with the diagnosis of anaphylaxis for both scenarios (91%, 60%, and 64% respectively, p=0.02) and to treat both reactions with epinephrine (96%, 55%, and 64% respectively, p=0.002).

Conclusions: Although the majority of the Canadian emergency physicians seem to have some knowledge of pediatric anaphylaxis, a substantial proportion have knowledge gaps that may negatively impact the quality of care provided to this vulnerable population. These gaps may be mitigated through identification of barriers of adhering to the established treatment guidelines, better training and education of physicians, and further knowledge dissemination initiatives.

Second Study: Epidemiology and Clinical Predictors of Biphasic Reactions in Children with Anaphylaxis

Objectives: Biphasic reaction is the recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger. Epidemiological data regarding biphasic reactions among children is sparse. This study aims to investigate the prevalence and clinical predictors for the biphasic reaction in children presenting to the Emergency Department (ED) with anaphylaxis.

Methods: We conducted a health records review of ED visits at two large academic pediatric EDs. All visits that satisfied anaphylaxis diagnostic criteria of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) were included. We analyzed the predictors of biphasic reaction using univariate analysis and multiple logistic regression.

Results: Out of 1,749 ED records reviewed, 484 visits met study inclusion criteria. Seventy-one (14.7%) patients developed biphasic reactions. The median age was 6 years (IQR 2.7-10.1) and 51 (71.8%) were male. Forty nine of the 71 (69%) delayed reactions involved respiratory and/or cardiovascular manifestations and 35 (49%) treated with epinephrine. The majority (74.5%) of biphasic reactions occurred before ED discharge, with a median time of 4.7 hours (IQR 3.3-6 h) from onset of the initial reaction to onset of the delayed reaction. We found five independent predictors for biphasic reactions: age 6-9 years (OR 3.60; 95% CI 1.5-8.58), delay in presentation to ED of >90 min

from onset of the 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 >1 dose of epinephrine (OR 2.7; 95% CI 1.12-6.55), and administration of inhaled salbutamol in ED (OR 2.39; 95% CI 1.24-4.62).

Conclusions: In children with anaphylaxis, biphasic reactions are relatively common and often occur within 6 hours from onset of the initial reaction. Our predictors seem to indicate that biphasic reactions are associated with the severity of the initial anaphylactic reactions and could ultimately be used to identify patients who would benefit from prolonged ED monitoring. In agreement with previous literature, we found no benefit of systemic steroids in preventing biphasic reactions. Application of these findings in clinical practice may enable better utilization of ED resources.

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CHAPTER 1 INTRODUCTION

1.1 OVERVIEW OF THE THESIS RESEARCH

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.[1] The true population-based prevalence of anaphylaxis in the pediatric population 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 among children.[4–7]

The pattern of an anaphylactic reaction can be uniphasic, biphasic (also called delayed or late-phase), or refractory in nature. Biphasic reactions, defined as a recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger, can occur anywhere from 1 to 72 hours after the initial onset of symptoms. This reaction is thought to increase the risk of fatal anaphylaxis[8]. To date, there has been little work done to establish validated clinical predictors for this phenomenon, particularly among children. In addition, there is no well-established, evidence-based preventive therapeutic intervention for this potentially fatal reaction. This lack of evidence is thought to contribute considerably to the variation in the management of children with anaphylactic reactions among Canadian emergency physicians. Both the magnitude and the impact of this variation are unknown.

The first goal of this study is to explore the practice variation in the management of children with anaphylactic reactions among Canadian emergency physicians. The second goal is to investigate the epidemiology and predictive factors for the biphasic reactions in children presenting to the emergency department (ED) with anaphylaxis. The findings from this study

are essential for planning future epidemiological investigations of the incidence and risk factors of biphasic reactions, as well as to frame experimental studies exploring the efficacy of different therapeutic interventions used currently in the management of anaphylaxis.

1.2 THESIS RATIONALE

To our knowledge, there are no Canadian studies exploring the variation of practice in anaphylaxis patient management by emergency physicians. The magnitude of uptake and practice consistency with the North American guidelines for anaphylaxis management, particularly for children presenting to the ED, is also unknown. This information will help us to identify areas of discordance with the published guidelines that will require further knowledge translation efforts. This national survey portion of this study aims to answer the following question:

To what extent does significant practice variation exist in the management of children presenting with anaphylactic reactions by Canadian Emergency Physicians, despite the existence of published guidelines?

Further, given the absence of Canadian studies estimating the prevalence of pediatric ED visits caused by of anaphylaxis, we are interested in collecting data relating to children presenting to the ED with anaphylaxis, with the hopes of understanding the epidemiology of these reactions, as well as the clinical characteristics that distinguish uniphasic from biphasic reactions. The health records review part of the study aims to answer the following question:

What are the clinical predictors of biphasic reactions for children presenting to the ED with anaphylaxis?

This information is pivotal for our planned experimental study, which will look at the efficacy of antihistamines and corticosteroids in the prevention of biphasic reactions.

1.3 Description of the thesis chapters

The next chapter of this thesis will review the epidemiology of anaphylaxis in children, and the pathophysiology of its clinical manifestations. The diagnostic criteria and the challenges of establishing an anaphylaxis diagnosis in children will be briefly outlined. In the next section, we review the evidence for common anaphylaxis treatments. Then, we present a summary of the literature focusing on the current knowledge gaps for anaphylaxis diagnosis and treatment. Finally, a survey and critical review of the adult and pediatric literature describe the epidemiology and all existing risk indices available to predict biphasic anaphylactic reactions. The third chapter outlines the goals and objectives of the thesis research.

This thesis studies pediatric anaphylaxis using two different methodologies; the first being a survey and the second a health record review. Therefore, the details of each study are discussed separately. In chapter four, we describe the methodological standards used for our survey of Canadian emergency physicians regarding the diagnosis and management of pediatric anaphylaxis. More specifically, we will describe our sampling strategy; the rational for our choice of survey modes; and the methods of our questionnaire development and survey implementation. Results and

discussion of our findings are reported in two separate sections. This chapter will close with a discussion about future clinical and research implications of our survey study.

The final chapter is devoted to the health record review. In the methods section, we describe the settings and population of the study. Then, we define the primary outcome, list collected variables, and describe data analysis strategy. The results section will report the incidence of anaphylaxis in Canadian EDs, as well as the common triggers for anaphylaxis in children. The therapies given as treatment of anaphylactic episodes and their clinical outcomes will be reported. Univariate analysis results and the identified predictors of biphasic reactions from logistic regression model derivations will then be discussed. This chapter will close with a discussion about the main findings, strengths and weaknesses of the study. Comparisons will be made with reported incidences and risk factors for biphasic reactions. Finally, plans for subsequent prospective validation with a new cohort of patients will be outlined.

CHAPTER 2 BACKGROUND AND LITERATURE REVIEW

2.1 Evolution of Anaphylaxis Definition and Diagnosis

Until recently, there was no agreed upon definition of anaphylaxis. Understanding the historical evolution of the anaphylaxis definition and case diagnosis is pivotal to know the challenges and limitations of the published literature. The first Joint Task Force of Practice Parameter on anaphylaxis was published in 1998; in this report, anaphylaxis was defined as "*an immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils*".[1] Clinical anaphylaxis was defined as a generalized reaction including "pruritus, urticaria, angioedema, hypotension, wheezing, bronchospasm, nausea, vomiting, abdominal pain, diarrhea, uterine contractions, and cardiac effects. These manifestations were stated to occur either in isolation or in various combinations.[1]

Acknowledging the need for a better, consistent definition to improve the clinical recognition of anaphylaxis, the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/ FAAN) held the first "Symposium on the Definition and Management of Anaphylaxis" in 2004 where a preliminary definition was proposed.[2] In 2006, these organizations published the current established definition and diagnostic criteria for anaphylaxis.[3] The current consensus definition of anaphylaxis is "*a serious allergic reaction that is rapid in onset and might cause death*". The diagnostic clinical criteria are summarized in **Table 1**. The World Allergy Organization and the Joint Task Force Practice Parameter on anaphylaxis have adopted the listed clinical criteria for diagnosing

anaphylaxis.[4,5] Further, the American College of Emergency Physicians (ACEP) and the American Academy of Pediatrics (AAP) participated in both the creation and endorsement the NIAID/FAAN guidelines.

Table 1: Clinical Criteria for Diagnosis of Anaphylaxis Developed by the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium published in 2006*

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia).
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
b. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia).
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

a. Infants and children: low systolic BP (defined as less than 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1 to 10 years; and less than 90 mmHg from 11 to 17 years) or greater than 30% decrease in systolic BP
b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

* Adopted from Sampson et al [2]

2.2 Epidemiology of Anaphylaxis

2.2.1 General Overview

Population-based data on the incidence of anaphylaxis and its prevalence from all causes are sparse, and often imprecise.[4,6] The epidemiology of anaphylaxis has been difficult to quantify for several reasons. First, previous studies on the epidemiology and prevalence of anaphylaxis have been plagued by the lack of a consensus case definition of anaphylaxis. Second, the incorrect use of measures of disease frequency (such as incident and prevalence) by some researchers contributed to this uncertainty[9].
The issue is further complicated by symptom under-recognition by patients or caregivers and the under-diagnosis by healthcare professionals. Underreporting and miscoding are other factors contributing to the underestimation of anaphylaxis epidemiology. Of the approximately 12.4 million allergy-related emergency department visits between 1993–2004, 1 % received the diagnosis of anaphylaxis.[10] Several studies have shown that anaphylaxis is often miscoded or misclassified, with 21– 57 % of food allergy or anaphylaxis cases coded with a less specific allergy or anaphylaxis code (eg, unspecified allergy).[7,11]

2.2.2 Incidence and Epidemiological Trends:

A previous report using number of epinephrine auto-injectors (EAI) prescriptions estimated the prevalence of anaphylaxis to be as high as 2%[12] This “old” impression that anaphylaxis is uncommon has been challenged by the accumulating epidemiological data found in recent literature. Regardless of geographic area, the majority of recent studies are suggesting that the

prevalence of anaphylaxis has increased during the last decades particularly among young people[13–16]. This increase over the last decade may be as high as 350% for food-induced anaphylaxis and 230% for nonfood-induced anaphylaxis.[9,17]

Studies that used the number of epinephrine prescription estimated the incidence of anaphylaxis from all triggers as 1–5 per 1000 in France and United Kingdom (UK) and 1 per 100 in Canada.[10,18,19] Between the 1980s and 1990s, the number of epinephrine prescription in the UK increased seven-times, suggesting an increase in the rate of anaphylaxis.[18] Despite the limitations of this approach, it demonstrates a general trend in anaphylaxis frequency. Data also suggest that there has been an increase both in fatalities and in hospitalizations from anaphylaxis.[20–24]

A study by Liew and colleagues from Australia showed the hospitalization rates for anaphylaxis increased by 8.8% per year between 1994 and 2004. Children younger than the age of 5 years had the highest rates of hospital admissions for food-induced anaphylaxis (9.4 per 100,000 population), and the rate of increase in hospital admissions over time was also greatest for this age group.[21] Gupta et al reported a similar trend in the United Kingdom; the admission rate increased from 5 to 36 per million of population between 1990 and 2004.[17] During this period, the number of anaphylaxis-related admissions has increased by 700%, and those for food allergy by 500%.

2.2.3 Anaphylaxis in the Pediatric Emergency Department

To date, few epidemiological studies have primarily investigated anaphylaxis among children, and there are fewer studies conducted in an emergency department setting. As a result, data on the incidence and the trends of emergency department anaphylaxis visits over time among the pediatric population is limited. In 2006, an Australian report estimated the incidence of anaphylaxis from 1998-2001 to be 1:1000 ED visits.[25] The authors reported 57 cases of anaphylaxis matched the NIAID/ FAAN case definition. Subsequent study by de Silva et al reported 123 ED visits between 1998-2003 with a similar incidence rate.[26] More recently, Huang et al reviewed the incidence of anaphylaxis ED visits at one children's hospital in New York; they estimated an incidence of 1.8 per 1000 ED visits.[27] Epidemiological studies from Sweden and other European countries reported lower rates of pediatric ED visits than were reported in studies from Australia and the United States. [28,29]

Although the above epidemiological studies provide good insight into the overall incidence and trend of pediatric ED anaphylaxis visits, they suffer from many of the limitations discussed in section 2.2.1. In addition, the following factors limit both their interpretation and their application to the Canadian setting. First, some of these studies only reported food-induced anaphylaxis cases. Second, national variance exists in the mechanisms of reporting and in the care given to the adult versus the pediatric populations. A recent report by Hompes et al highlights this reporting variability.[30] To our knowledge, there is no published Canadian study investigating the epidemiology of anaphylaxis in the pediatric emergency setting.

2.2.4 Anaphylaxis Triggers

Foods are the most common anaphylactic reaction trigger in both adults and children. The overall prevalence of food allergy varies considerably in the literature. Self-reported or perceived food allergies tend to overestimate the prevalence compared to physician confirmed allergies. In Canada, Surveying Canadians to Assess the Prevalence of Common Food Allergies and Attitudes towards Food LAbelling and Risk (SCAAALAR) is the first Canadian-population based study designed to estimate the prevalence of food allergies.[31] The investigators conducted a cross sectional telephone survey of randomly selected households across the 10 Canadian provinces. Of the 9,667 individuals responding to this survey, the prevalence of food allergy was 7.14% in children and 6.56% in adults; this estimate was based on self-reporting.

The systematic review by Chafen et al estimated that food allergies affect between 2% and 10% of the American population.[32] Gupta et al surveyed 38,480 American children and estimated the prevalence of food allergy to be 8%, with approximately 40% of those having history of severe reactions.[33] More recently, data from the National Health Interview Survey showed that, among American children aged 0–17 years, the prevalence of food allergies increased from 3.4% from 1997– 1999 to 5.1% from 2009–2011.[34] In Australia, challenge-proven IgE-mediated food allergy affects roughly 10% of infants.[35] Data from pediatric emergency departments concur with most population-based studies and indicate that food is the most common anaphylaxis trigger, accounting for 37– 85 % of cases.[25,26] Other relatively common anaphylaxis triggers include insect bites/stings (5–13%)

and medications (5–12%).[25,26,36] Less common triggers include animals, latex, cleaning agents, environmental allergens, and exercise.

Specific Food Triggers for Anaphylaxis

Although a wide-range of foods have been reported as causes of food-induced anaphylaxis, the most commonly implicated foods worldwide are peanuts, tree nuts, milk, eggs, sesame seeds, fish, and shellfish, both in adults and children.[33,37–39] However, the individual food allergies vary between countries and cultures. Data from the SCAAALAR study indicates that milk, peanuts, and tree nuts are the most common allergies in children, and shellfish, fruits, and vegetables among adults.[40] Of children with a probable peanut and tree nut allergy, more than half reported recurrent reactions and around 90% reported moderate/severe reactions.[31] This pattern of severe reaction secondary to a peanut and tree nut allergy is reported in several developed countries and is becoming a significant public health concern.[23,30,41]

2.2.5 Anaphylaxis Risk Factors

Several studies show an association between anaphylaxis to food and the following factors: genetic predisposition (family history of allergy), gender (males in childhood), race (non-white infants), delayed infant exposure to allergenic food, low level of serum vitamin D, and low exposure to a farming environment.[42,43] A recent review by Ben-Shoshan et al provides an extensive description of these genetic, demographic, and environmental risk factors.[43] One important risk factor is asthma, which has been associated with a four-

fold increase in the risk of food allergy in children.[44] The severity of the anaphylactic reaction has been shown to be proportional to the severity of asthma.[42] Atopic dermatitis and respiratory allergies have also have been linked to risk of anaphylaxis.[44]

The recent literature focuses on identifying modifiable risk factors for an anaphylactic episode. Some studies suggest that anaphylaxis threshold may be lowered by factors that either increase the allergen uptake (ie, exercise, drugs that increase gastric pH) or enhance the inflammatory response (ie, febrile illness or non-steroidal anti-inflammatory drug use).[5,45] A recent German report from that 18% of children with anaphylaxis have aggravating factors such as exercise, drug use, coexisting infection, psychological stress, and menses.[30]

2.2.6 Economic Burden and Quality of Life

The economic costs of anaphylaxis are not limited to persons affected directly, but also to the health care system and to society as a whole. Patel et al estimated the United States spent $307 Million dollars in direct and $203 million in indirect costs on food allergy and associated anaphylaxis in 2007, for a total exceeding $500 million.[46] The mean cost of $553 per ED visit and of $4719 per hospitalization were higher than previous cost estimates for asthma: $345 and $4570 per ED visit and hospitalization, respectively.[46]

Anaphylaxis also significantly affects quality of life (QoL), which indirectly impacts economic gains. Food allergy has been shown to negatively impact parental, as well as patient, QoL. Psychological distress has been seen in children and adolescents with food allergies. [47,48]

A study of more than 1000 parents of food-allergic children in the United States found overall QoL for caregivers to be variable, although caregivers consistently reported being troubled by social limitations resulting from their child's food allergy.[49] Poor QoL was significantly more common among caregivers with more knowledge about food allergy and among those whose children had been to the emergency department for their food allergy within the preceding year, had multiple food allergies, or were allergic to specific foods (milk, egg, or wheat).[49]

Another qualitative study of Canadian families found parents experienced intense feelings of fear, paranoia, and stress as they sought to manage their child's allergy: and these feelings were equally intense during family leisure time.[50] Findings from a recent systemic review confirm the impact of anaphylaxis on these QoL parameters.[51]

2.3 Pathophysiology of Anaphylaxis

2.3.1 Immunologic Mechanism of Anaphylaxis

Anaphylaxis is most often the result of an immunologic reaction to the culprit agent, but any agent capable of producing a sudden, systemic degranulation of mast cells or basophils can produce it.[45] It may be mediated through a non-immunologic mechanism, such as exercise, or through an immunological pathway. The pathogenesis of the later is ambiguous, but findings from animal models demonstrate two distinct mechanisms that may also apply to humans. The first mechanism, the IgE-dependent reaction, primarily involving histamine release, accounts for the majority of the

anaphylactic reactions. The second mechanism is the IgE-independent reactions; this reaction is primarily mediated by either IgG or an immune complex/complement and primarily involves release of platelet activating factor (PAF). Regardless of the mechanism, the common end result of both pathways is the release of several biochemical factors that lead to the shock state.[45,52]

2.3.2 Pathophysiology of Shock

The best data about anaphylaxis pathophysiology is driven from fatal and near fatal cases, especially those recorded under monitored experimental settings. Taken together, these studies consistently showed that the respiratory and cardiovascular systems are the most common shock organs in human anaphylaxis.[51]

Respiratory effects of anaphylaxis

In their review of fatal anaphylaxis cases from United Kingdom, Pumphrey et al examined 214 anaphylactic fatalities, 196 of which cause of death could be determined.[53] Asphyxia was implicated in one-half (98 cases), of which 49 involved pulmonary inflammation, upper airway angioedema in 23, and both upper and lower airway involvement in 26. Most of those who die from food anaphylaxis have daily asthma treatment; it has been possible to establish that for some of those whose fatal asthma was triggered by food allergy and whose self-injectable epinephrine failed to save them, the dose of short-acting beta-2 agonist greatly exceeded the maximum recommended

dose. In such cases, epinephrine may no longer effectively reverse bronchospasm.[54]

Cardiovascular effects of anaphylaxis

Anaphylaxis has been shown to cause the following physiologic [55] effects:

1- Hypovolemia secondary to vascular extravasation contributing to hypotension;
2- Early arteriolar dilation manifested as a widened pulse pressure and contributing to hypotension;
3- Venodilation and blood pooling, contributing to reduced venous return and low cardiac output;
4- Relative bradycardia contributing to reduced cardiac output;
5- Impaired myocardial contractility contributing to reduced cardiac output; and
6- Early transient increase in pulmonary vascular resistance, contributing to the reduction in cardiac output by obstructing venous return to the left side of the heart.

Accumulating evidence from several experimental and observational studies support the above mechanisms. Fisher et al described the underlying mechanism for hypovolemia in a series of 205 episodes of anaphylactic shock occurring under anaesthesia. In this study, extravasation of up to 35% of effective blood volume within 10 minutes of reaction onset was evident by increases in hematocrit.[56] In a retrospective review, the postural history was known for 10 individuals who died from anaphylaxis in a nonhospital setting.[57]

Four of the 10 fatalities were associated with the assumption of an upright or sitting posture, and post-mortem findings were consistent with pulseless electrical activity attributed to reduced venous return from vasodilation and concomitant volume redistribution.

The peripheral skin-flushing, fall in diastolic blood pressure (widened pulse pressure) and tachycardia seen early in human anaphylaxis are well documented in several experimental studies.[58–60] Brown et al performed a diagnostic sting challenge on healthy adults as a subsequent study to their clinical trial of immunotherapy for ant venom. Despite normalization of heart rate after the reaction's treatment with fluid and intravenous epinephrine, the widening of pulse pressure persisted for more than 30 minutes after treatment. Furthermore, the authors observed severe bradycadia in few hypotensive reactions, requiring treatment with atropine.[58] A careful review of these reactions revealed that hypotension was preceded by a fall in diastolic blood pressure (suggesting reduced systemic vascular resistance) with tachycardia. They stated: "*in every case, the onset of hypotension was accompanied by a relative bradycardia. That is, rather than the heart rate further increasing to compensate for falling blood pressure, it fell as the blood pressure fell*".[55]

Severe reversible cardiac dysfunction associated with nonspecific electro- cardiogram changes and normal coronary arteries also has been described during human anaphylaxis. One report described two previously healthy individuals who had an anaphylactic reaction, and subsequently developed profound myocardial depression requiring intensive hemodynamic support up to 72 h.[61]

2.3.2 Clinical implications of Anaphylaxis Pathophysiology

Understanding the physiologic changes described in people with severe anaphylaxis helps in the derivation of a clinical severity scoring system and in the critical assessment of the therapeutic interventions used in anaphylaxis.

Brown et al attempted to derive a severity grading system by identifying the symptoms strongly associated with hypotension and hypoxia (O2 saturation<92%). Although this system seems to correlate well with the proportion of patients who received epinephrine as treatment for their reaction as the severity increases, there are several serious limitations that compromise its further general application, and more specifically for pediatric anaphylaxis. First, this system was developed before the publication of the NIAID/FAAN diagnostic criteria for anaphylaxis. Applying Brown's scoring system to anaphylaxis cases matching the NIAID/ FAAN diagnostic criteria will classify cases as either moderate or severe. Therefore, this system is of limited use to the pediatric population, as most cases are mild. Second, more than 75% of the population from which the system was derived were adults, again limiting the application of this grading to children who, as explained above, have many particular physiological and clinical presentations.

Several other severity-grading systems existent in the literature suffer from the above limitations. In addition, the precision of those systems is questionable, as they are based on subjective measures, with no incorporation of objective clinical indicators.

2.4 Diagnosis of Anaphylaxis in Children

Most pediatric anaphylaxis episodes occur in community settings rather than in health-care facilities.[19] The diagnosis of these episodes is commonly either made or suspected during an ED visit.[62] The correct diagnosis has serious implications for immediate management and future prevention. There is no optimal rapid, reliable, diagnostic test for anaphylaxis. The clinical diagnosis of anaphylaxis is primarily based on the diagnostic criteria described above. For a variety of reasons, the utilization and application of these clinical criteria by caregivers and health professionals have proven to be challenging, especially within the pediatric age group.[19,25,26]

Many anaphylaxis episodes in infants, children, and teens are first episodes and might not be recognized as such, especially if symptoms are mild or transient. Simon et al stated, “more than 40 differential diagnoses exist for acute anaphylactic episode”.[63] If the culprit allergen is unknown or unspecified, health professional may easily misdiagnose the allergic reaction, especially if the index of suspicion is low.

Recent studies found that roughly half of patients meeting criteria for food-induced anaphylaxis did not receive this as their discharge diagnosis.[7,11] Patients who are in shock, having stridor or difficulty breathing might not be able to describe their symptoms. Skin symptoms, such as itching, and signs, such as urticaria, or angioedema, are helpful in the diagnosis; however, cutaneous involvement is absent or unrecognized in 10–20% of anaphylaxis episodes: it can be missed if itching is not described or if the patient's skin is not fully examined. Recognition and diagnosis of anaphylaxis in infants

presents unique challenges, as they cannot describe their symptoms and may have signs difficult to interpret as they also occur in healthy infants.[64]

2.5 Management of Anaphylaxis in the ED

Treatments for anaphylaxis include epinephrine, antihistamines, corticosteroids, inhaled bronchodilators, and intravenous fluids. Epinephrine is the first-line therapy, and the single most important agent in anaphylaxis treatment.[4,5,65–67] Antihistamines and corticosteroids play a less important role and are considered to be second-line agents for the management of anaphylaxis[68].

2.5.1 First-Line treatment

Evidence-based guidelines recommend prompt administration of epinephrine as first-line treatment for an anaphylactic episode.[4,5,65–67] Timely administration of epinephrine can be life-saving as it may help slow the progression of a life-threatening reaction. **Table 2** depicts the emergency management of anaphylaxis as recommended by the World Allergy Organization (WAO) guidelines.[5] However, several studies have found that patients diagnosed with anaphylaxis are more likely to receive corticosteroids and antihistamines instead of epinephrine. [69–71]

2.5.2 Second-Line treatment

Anaphylaxis guidelines published to date differ in their recommendations for administration of second-line medications (antihistamines and corticosteroid) (**Table 3 and 4**). The evidence base for

use of these medications in the initial management of anaphylaxis - including formulation, doses, and dose regimens - is extrapolated mainly from their use in treatment of other diseases, such as urticaria (antihistamines) or acute asthma (corticosteroids).

Table 2: Emergency Management of Anaphylaxis as Recommended by the World Allergy Organization Guidelines

Basic Management of Anaphylaxis Preliminary Steps
1) Have a posted, written emergency protocol for recognition and treatment of anaphylaxis and rehearse the protocol regularly 2) Remove trigger, if possible, eg. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms 3) Assess circulation, airway, breathing, mental status, skin, and body weight (mass) promptly and simultaneously4) Call for help (resuscitation team in hospital or other healthcare setting, or emergency medical services in community setting), if available 5) Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, to a maximum of 0.5 mg (adult) or 0.3 mg (child); record the time of the dose and repeat it in 5–15 minutes, if needed; most patients respond to 1 or 2 doses 6) Place patient on the back, or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if a patient stands or sits suddenly When indicated at any time during the episode: 7) Give high flow supplemental oxygen (6-8 L/min) by face mask or oropharyngeal airway 8) Establish intravenous access using needles or catheters with wide-bore cannulae (14 or 16 gauge for adults). When indicated, give 1-2 litres of 0.9% (isotonic) saline rapidly. (eg. 5–10 mL/kg in the first 5–10 minutes to an adult; or 10 mL/kg to a child) 9) When indicated at any time, prepare to initiate cardiopulmonary resuscitation with continuous chest compressions. 10) At frequent and regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous non-invasive monitoring, if possible resuscitation with continuous chest compressions. In addition 10) At frequent and regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous non-invasive monitoring, if possible

* Adopted from the 2011 World Allergy Organization guidelines[5]

Table 3: Expert Guideline Recommendations On Antihistamines For Treatment Of Anaphylaxis

Guidelines	**H_1 Blockers**	**H_2 Blockers**
Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology, 2005[72]	Consider as second-line Diphenhydramine 1-2 mg/kg to 50 mg parenterally	Consider as second-line Ranitidine 1 mg/kg to 50 mg intravenous
National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network, 2006[3]	Second-line treatment Diphenhydramine 1-2 mg/kg to 50 mg parenterally or orally in mild cases	Second-line treatment Ranitidine or cimetidine (No dosing guidelines)
European Academy of Allergology and Clinical Immunology, 2007[73]	Recommended, options given: Chlorphenamine, cetirizine, levocetirizine, loratidine, desloratadine, fexofenadine, oxatomide	Not adequately tested in children
Resuscitation Council of the UK, 2008[65]	Recommended as second-line • Chlorphenamine dosing: >12 years: 10 mg 6 -12 years: 5 mg 6 months - 6 years: 2.5 mg < 6 months: 250 mcg/kg	Insufficient evidence to support routine use
World Allergy Organization[5]	Recommended as second-line Low sedating medication such as cetirizine, which is available generically and absorbed rapidly is preferable to a sedating H_1-antihistamine such as chlorpheniramine or diphenhydramine.	No evidence from randomized placebo-controlled trials that are free from methodological problems supports their use in treatment of this disease.

Table 4: Expert Guideline Recommendations On Corticosteroids For Treatment Of Anaphylaxis

Guidelines	**Recommendations**
Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology, 2005[72]	Consider for patients with a history of idiopathic anaphylaxis or asthma and patients severe or prolonged symptoms Intravenous glucocortico-steroids at 1-2 mg/kg/day given every 6 hours For less critical patients: oral prednisone 0.5 mg/kg
National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network, 2006[3]	Option: IV methylprednisolone at 1-2 mg/kg/dose given every 6 hours or oral prednisone 1 mg/kg for milder attacks
European Academy of Allergology and Clinical Immunology, 2007[73]	Should not be considered first-line Methylprednisolone or hydrocortisone IV options
Resuscitation Council of the UK, 2008[65]	Recommended Hydrocortisone IV or IM: >12 years of age: 200 mg 6-12 years of age: 100 mg 6 months - 6 years of age: 50 mg <6 months: 25 mg
World Allergy Organization[5]	Second line Options: Intravenous Hydrocortisone or Methylprednisolone; Oral Prednisone or Prednisolone

Current Evidence for the Use of Antihistamines in Anaphylaxis

A recent Cochrane systematic review on the use of antihistamines found no randomized or quasi-randomized controlled trials investigating H_1-antihistamines' role in anaphylaxis.[74] Concerns have been raised that administering one or more second-line medications potentially delays the prompt injection of epinephrine, the first-line treatment. H_1-antihistamines not only have no proven clinical effect on the immediate and life threatening symptoms of anaphylaxis, they could also have potentially harmful central nervous system effects, including somnolence and impairment of cognitive function. In susceptible patients, they could potentially induce fatal cardiac arrhythmias such as QT prolongation and torsade de pointes.[73,75–77] An H_2-antihistamine, administered concurrently with an H_1-antihistamine, potentially contributes to decrease in symptoms including flushing, and headache; however, H_2- antihistamines are only recommended a few anaphylaxis guidelines (**Table 3**). Although H_2-antihistamines have been studied in relation to anaphylaxis, no evidence from randomized placebo-controlled trials that are free from methodological errors support their use in anaphylaxis.[78,79]

Current evidence for Corticosteroids use in Anaphylaxis Treatment

Corticosteroids have two hypothetical effects. First is the treatment of severe or protracted anaphylaxis. Second is the prevention of biphasic reactions however, these effects have not been proven.[80] Data from fatal anaphylaxis indicates that the median time to cardiac or respiratory arrest is as follows: 5 min for drug, 15 min for venom, and 30 min for food-triggered reactions.[80] Previous studies on bioavailability showed the median time to

reach maximum serum concentration for oral hydrocortisone is approximately 1 – 2 h after administration.[81] Therefore, steroids are unlikely to prevent immediate death from anaphylaxis, or to reduce the severity of the immediate reaction. On the contrary, corticosteroids may have a detrimental effect. A recent randomized trial investigated the efficacy of premedication with steroid alone or in combination with antihistamines in the prevention of snake anti-venom induced anaphylaxis in more than1000 patients. It concluded that neither antihistamine nor hydrocortisone alone was effective in preventing serious adverse reactions. Adding antihistamines or hydrocortisone to the epinephrine (prophylactic low dose) did not increase its effectiveness. More seriously, hydrocortisone negated the effect of epinephrine and increased the risk of severe reaction.[82]

A Cochrane systematic review published on 2010,which was recently updated, failed to identify any evidence from randomized controlled trials to confirm the effectiveness of corticosteroids in the treatment of anaphylaxis in adults or children; and raised concerns that they are often inappropriately used as first-line medications in place of epinephrine.[83,84] The role of steroid in the prevention of biphasic reactions will be reviewed in section 2.5.2 of this chapter.

2.5.3 Knowledge Gaps in Anaphylaxis Diagnosis and Management

Regrettably, evidence shows anaphylaxis is often misdiagnosed and inadequately managed, regardless of the setting.[67] Epinephrine, the primary life-saving drug in anaphylaxis treatment, is infrequently used in emergency settings and is under-prescribed as a discharge medication.[69,85] In 2000, a

national surveillance of Canadian pediatricians over 18 months found only one third of reported anaphylaxis patients received epinephrine as treatment for their reactions.[86]

A recent systematic review conducted by a group of Canadian investigators identified many gaps in the clinical practice of anaphylaxis management (**Table 5**).[51,67] Lack of a proper anaphylaxis diagnosis; underuse of epinephrine as first line therapy; and inadequate discharge instructions and follow up are among the main themes identified. It should be noted that out of the fifty-nine studies included in this systematic review, only one study addressed gaps among Canadian physicians. This study, published more than ten years ago, only assessed knowledge of the correct use of epinephrine auto-injector.[87]

Table 5: Gaps of Anaphylaxis Management*****

Theme	Description	Gap
Anaphylaxis management	Lack of knowledge to identify the signs and symptoms, or correctly diagnose anaphylaxis	Patients are not diagnosed accurately Lack of awareness and adequate knowledge of anaphylaxis
	Epinephrine is not the most commonly prescribed treatment	Infrequent, inappropriate, or no use of epinephrine and low prescription of Auto-injector
Epinephrine use	Inadequate or no training provided to patients on how to use epinephrine auto-injectors	Parents of children with allergies have unmet information needs from their physicians, including not knowing the definition of anaphylaxis and the symptoms requiring epinephrine Patients receive infrequent or no instruction, demonstration, or training on how to use auto-injectors
	Epinephrine administration is inadequate or delayed	Epinephrine either not given or administration was delayed
	Physicians lack knowledge on epinephrine use	Few physicians have or know how to use an auto-injector training device In acute severe reactions, differences exist on treatment recommendations, and epinephrine is used less than other medications (e.g. steroids)
Follow-up Care	Infrequent or no referral to an allergy specialist after acute reaction	Few patients are being referred to an allergy specialist after an allergic reaction
	Patients are not given enough information about how to manage anaphylaxis	Physicians did not think that advising patients to go to the hospital after taking epinephrine was necessary Few patients with acute allergic reactions were given discharge instructions
	Patients do not have an anaphylaxis action plan	Patients do not have action plans or there is no consensus on what should be included in action plans; missing essential components or auto-injector instructions

* Adopted from Kastner et al[51]

Inadequate or Delayed Epinephrine Administration

The evidence regarding the underuse of epinephrine, as an anaphylaxis treatment, is well established from the review of fatal food allergy cases. In their review these cases in the United States between 2001 and 2006, Bock et al reported that 72% of cases did not receive timely epinephrine. The greatest number of fatalities occurred in the pediatric age group and many of those who died had not been previously hospitalized for their reactions nor did they need epinephrine.[88] The authors concluded that education among medical professionals, allowing them to diagnose food allergy, to educate patients, and to prescribe epinephrine, continues to be inadequate.

Pumphrey et al also reviewed similar cases in the United Kingdom between 1999 and 2006, reporting that 60% of cases did not receive epinephrine.[89] Over half of the deaths occurred in patients whose previous reaction had been so mild that it was unlikely a doctor would have recommended they carry an Epi-pen. This low rate of epinephrine administration among people who survived a severe reaction is similar to the Canadian report by Simons et al.[90]

Unfortunately, these gaps are not limited to physicians; they are also evident among other health professionals, such as Emergency Medical Services (EMS) paramedics, who are the first respondent to public calls about acute allergic reactions. Jacobson et al conducted a national survey of registered American EMS providers in order to assess their knowledge of anaphylaxis. Of more than 3,500 paramedics who completed the electronic survey, less than half chose epinephrine as the initial drug of choice, and

most respondents were unable to identify the correct route/location of administration.[91] Similar findings were reported by Jeong et al in their survey of EMS providers in Michigan.[92]

Confusion about Epinephrine Dosing and Route of Administration

The confusion about epinephrine administration in anaphylaxis is one of the knowledge gaps that received little attention in both the medical literature and the published guidelines. Multiple case reports of epinephrine dosing errors in patients with anaphylaxis have been published.[93–95] These reports describe inadvertent intravenous administration of a 1:1000 solution or intravenous administration of cardiac arrest dose of epinephrine. The smaller volume of medication and intramuscular administration of the 1:1000 concentrations are less common. One case series found a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration for anaphylaxis in a single ED.[95] The reason for the dosing error is likely multifactorial, but as always there is more room for error and confusion when calculating pediatric doses. The interplay between weight-based dosing and volume-based ordering is a subtle source of error.

Confusion often occurs around the medication administration route and the site. Droset et al conducted a short quality assurance survey of physicians in one UK hospital regarding their knowledge of epinephrine administration for anaphylaxis in adults. Only one third of participating physicians identified the correct route of administration, and 62% either did not know the dosage to use or chose an incorrect dose.[96,97]

Utilization of an Emergency Care Plan

The focus of anaphylaxis management has often been on the acute episode, with less attention given to the long-term management of patients at risk.[51] Each institution is recommended to have a protocol for the management of anaphylactic reactions, including a written anaphylaxis action plan provided to the patient upon discharge.[98] Anaphylaxis action plans are recommended by national and international anaphylaxis guidelines; several allergy organizations emphasize their utilization.[5,67,99] While there are currently no universally required components to an anaphylaxis action plan, it is recommended to include patient and emergency contact details; patient specific allergens/triggers and avoidance techniques; signs and symptoms of anaphylaxis; and medications prescribed including detailed instructions for the use of an epinephrine auto-injector. While there is limited evidence supporting the use of anaphylaxis action plans, a systematic review by Nurmetov et al found that these plans may reduce the frequency and severity of further reactions by improving knowledge of food avoidance techniques, improving the use of epinephrine auto-injectors and reducing anxiety.[100] However, a systematic review by Kastner et al revealing gaps in anaphylaxis management identified patients not being given an action plan, or giving a plan with missing information, was an important gap in follow up care.[51] Although the majority of anaphylaxis cases are managed in the ED[62,101], there are no previous studies that assessed the magnitude of this gap in Canada.

2.6 What do we know about the Epidemiology and Predictors of Biphasic Reactions?

A biphasic reaction is a recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger.[102,103]This reaction is thought to increase the risk of fatal anaphylaxis.[8,103] Because of concerns about biphasic reactions, most guidelines recommend a prolonged observation period and monitoring after the initial reaction treatment. The dilemma that most emergency physicians encounter is identifying the optimum duration of this period. Guideline recommendations vary considerably, with some not providing a specific time (**Table 6**). This lack of consensus about duration of observation originated from lack of strong and validated clinical predictors for this phenomenon.

In light of increased ED crowding in recent years, the lack of predictors of biphasic reactions, in spite of their growing evidence suggesting an increased prevalence of anaphylaxis over the last decade, may have detrimental impacts on the quality of care provided to these patients. The available literature on the epidemiology and the predictors of biphasic reactions is sparse. In fact, the "*true incidence of biphasic reactions and appropriate medical management to prevent or effectively treat these reactions*" was identified as a significant knowledge gap by the 2010 NIAID report.[37] Similarly, the updated 2013 World Allergy Organization anaphylaxis guidelines acknowledged the paucity of knowledge around biphasic reactions and recommended further research.[104]

Table 6: Expert Guidelines Recommendations on Duration of Observation for Patients with Anaphylaxis

Organization	Recommendations
Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology, 2005.[72]	No specific recommendations for length of observation Observation period individualized to patient
National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network, 2006.[3]	Observation time of 4-6 hours for most patients Individualize based on severity of initial reaction, access to care, reliability of patient Admission or prolonged observation of patients with refractory or severe symptoms Caution in patients with reactive airway disease
European Academy of Allergology and Clinical Immunology, 2007.[73]	No recommendations on length of observation
Resuscitation Council of the UK, 2008.[65]	At least 6 hours observation, consider up to 24 hours of observation, especially if: • Severe, idiopathic anaphylaxis with slow onset • Patient has severe asthma or a history of biphasic reactions • Possible continued allergen absorption • Difficulty responding to deterioration, including evening and night presentations and areas without access to emergency care
World Allergy Organization, 2011.[5]	Monitoring in a medically supervised setting should be individualized. Patients with moderate respiratory or cardiovascular compromise should be monitored for at least 4 hours, and if indicated, for 8–10 hours or longer Patients with severe or protracted anaphylaxis might require monitoring and interventions for days

2.6.1 Epidemiology of Biphasic Reactions

Table 7 provides a summary of all studies published addressing both the epidemiology and the predictors of biphasic reaction. Popa and Lerner reported the first case series of a biphasic reaction in 1984.[105] They described three adults who, after successful treatment of the initial anaphylactic reaction, experienced a second phase of anaphylaxis 3-4 hours after being asymptomatic. Several subsequent studies reported this incidence as being between 3% and 23%.[8,105–121]

We critically reviewed these reports and the following highlights were observed. First, the wide range of the incidence of BPR seems to be correlated with the design of the study. Most prospective studies reported a much higher incidence compare to the retrospective ones. For example, Stark and Sulivan, Ellis and Day, and more recently Scranton et al reported a prospective incidence of more than19%.[106,112,120] On the other hand, eight out of ten retrospective studies reported the incidence as approximately 10% or less (**Table 7**).

Second, the variability in the incidence may be related to the difference in definition used by various studies. The nature and severity of a biphasic reaction is either equivalent to, or milder than, the initial reaction. In other words, the nature of the second reaction can either be anaphylactic or non-anaphylactic. Earlier studies seem to use the former definition, while more recent studies appear to include any recurrence of symptoms regardless of the severity or the treatment required for these second symptoms. Furthermore, the evolution of the anaphylaxis case definition over the years may further explain the inconsistency among these studies.

Finally, the population of these studies is significantly heterogeneous. In general, studies that enrolled ED or hospitalized patients reported higher proportion of anaphylactic BPR compared to those patients enrolled from allergy clinics, where allergen immunotherapy or food challenge tests are being conducted. This basically speaks to the severity of the initial anaphylactic reactions, hence their variability in nature. This observation is well demonstrated in the study by Ellis and Day, where all biphasic reactions were anaphylactic in nature, compared to the study by Scranton et al, where they were non-anaphylactic (**Table 7**).

With all these factors in consideration, the true incidence of biphasic reaction likely lies between 10-20%.

Table7: Summary of Previous Studies on the Epidemiology and Predictors of Biphasic Reaction

Reference	Study Design	Study subjects and settings	Incidence (%)	Nature	Age (y)	Allergen trigger	Time to onset (h)*	Proposed Predictors by study authors	Comments
Popa et al, 1984[105]	Case Series	Adult 3 cases (all M)	Not applicable	A	22-52	1 immunotherapy 1 insect bite 1 rabies vaccine in patient with egg allergy	3-4	None	-One patient known for asthma -Two patients received systemic steroid treatment, and one received >1 epinephrine dose for the initial reaction
Stark et al, 1986[106]	Prospective study	Adults Inpatients and ED visits 5/25 developed BPR (3 F, 2 M)	20%	A	21-67	4 drugs (antibiotics), 1 radiocontrast media	1-8	- Anaphylaxis provoked by oral trigger -Delay of ≥30 min between exposure to trigger to development of initial reaction	-Steroid not helpful in preventing BPR - Presence of severe symptoms (hypotension, cardiac arrest, laryngeal edema, respiratory obstruction and arrest) in the initial reaction was not predictive of BPR - None of the study subjects received IM epinephrine (all received SC or IV epinephrine)
Sampson et al, 1992[8]	Case Series (of fatal and near-fatal anaphylaxis)	13 Children 3 developed fatal BPR (2 F, 1 M)	23%	A	8-15	Food (1Peanuts, 2 tree nuts)	1-2	None	-All patients with BPR had asthma - Delay in administration of first epinephrine >90 min after ingestion of allergen for all three patients
Douglas et al, 1994[107]	Retrospective chart review	Adults ED, inpatients, and outpatient allergy clinic visits 4/59 developed BPR (1 F, 3 M)	7% (among ED & hospitalized patients)	2 A, 2 NA	20-77	2 drugs, 2 food (shrimp)	1-72 (mean 30 h)	None	- No clinical features distinguished patients with UPR from BPR - Steroid not helpful in preventing BPR - 50% of patients with BPR had hypotension that required treatment with IV fluids compare to 16% of those with UPR
Brady et al, 1997[108]	Retrospective chart review	Adults ED visits 2/67 developed BPR (1 F, 31M)	3%	NA	19-21	Hymenoptera envenomation	26-40 (mean 33 h)	None	-No clinical features distinguished patients with UPR from BPR - Steroids not helpful in preventing BPR
Brazil et al, 1998[119]	Retrospective chart review	Adults, ED visits 6/34 developed BPR (1 F, 31M)	18%	A	NR	3 insect bites, 1 food (nuts), 2 drugs	4.5 to 29.5 (mean 16.3 h)	Patients with BPR required larger dosses of epinephrine to treat their initial reaction	-No clinical features distinguished patients with UPR from BPR

Reference	Study Design	Study subjects and settings	Incidence (%)	Nature	Age (y)	Allergen trigger	Time to onset (h)*	Proposed Predictors by study authors	Comments
Lee et al, 2000[121]	Retrospective chart review	Children Hospital admissions 6/105 developed BPR (3 F, 3 M)	6%	3 A, 3 NA	1-13 (<2 y=2, >10 y=4)	2 drugs, 2 food (fish, nuts), 2 bee stings	1.3 to 28.4 (mean 10.1 h)	Delay in Epinephrine administration	- 4/6 patients with BP reaction received 1st epinephrine >90 min after onset of the initial reaction - No clinical features distinguished patients with UPR from BPR - Steroids not helpful in preventing BP reaction
Smit et al, 2005[109]	Retrospective chart review	Adult and children ED visits 15/282 developed BPR (5 F, 10 M)	5.3%	3 A, 12 NA	<15 y=3 19-81y=12	5 food (seafood) 4 drugs 5 unknown 1 insect bite	1.4 to 23 (mean 8h)	Delay in presentation to ED (1h for uniphasic vs 3 h for biphasic reactors) 20% of patients with BPR had unstable vital signs on initial presentation to ED	Patients with respiratory manifestations on initial presentation were less likely to develop BP reaction
Poachanukoon et al, 2006[110]	Retrospective chart review	Adult and children Hospital admissions 8/52 developed BPR (4 F, 4 M)	15%	NR	NR	NR	NR	Time interval between the onset of initial reaction and the first epinephrine was longer for patients with BPR	-Epinephrine and steroid usage did not prevent biphasic reactions - No clinical features or allergy triggers distinguished patients with UPR from BPR
Ellis et al, 2007[120]	Prospective study	Adult and children ED visits and hospital admissions 20/103 developed BPR (9 F, 11 M)	19.4%	A	4-16y=5 18-73y=15	7 unknown 5 Hymenoptera 6 food I drug I immunotherapy	1.5-38 (mean 10h)	Patients with BP reactions received less total epinephrine dose and less systemic steroids treatment for their initial reactions	-No clinical features or allergy triggers distinguished patients with UPR from BPR - Vital signs at triage and time from onset of the initial reactions to ED presentation were not reported
Scranton et al, 2009[112]	Prospective study	Adult and children Allergy clinic 14/60 developed BPR (13 F, 1 M)	23%	NA	25-66	Immunotherapy	2 to 24 (mean 7.2h)	Patients who required > 1 dose of epinephrine treatment for the initial reaction are more likely to experience BPR	-No clinical features distinguished patients with UPR from BPR - Steroids not helpful in preventing BP reaction
Mehr et al, 2009[111]	Retrospective chart review	Children ED visits 12/109 developed BPR (4 F, 8 M)	11%	5 A, 7 NA	0.2-17 (<5 y=5, 5-10y=1, >10 y=6)	9 food 2 unknown 1 drug	1.2 to 20.5 (mean 9.5h)	Children who received >1dose of epinephrine and/or a fluid bolus for treatment of their initial anaphylactic reaction were at increased risk of developing BPR	-No clinical features or allergy triggers distinguished patients with UPR from BPR -Vital signs at triage and time from onset of the initial reactions to ED presentation were not reported

Reference	Study Design	Study subjects and settings	Incidence (%)	Nature	Age (y)	Allergen trigger	Time to onset (h)*	Proposed Predictors by study authors	Comments
Confino-Cohen et al, 2010[113]	Prospective study	Adult and children Allergy clinic 10/112 developed "subjective" BPR (7 F, 3 M)	9%	NA	14-48	Immunotherapy	3 to 24	Relatively low Peak Expiratory Flow (PEF) (regardless of asthma history) at baseline and concomitant asthma are possible risk factors for BPR	- Authors used Peak Expiratory Flow (PEF) as an objective measure. BP reaction defined as late reduction of PEF by >20% from baseline with or without subjective symptoms. 10 of 11 patients who developed BP reaction met both criteria
Lertnawapan et al, 2010 [114]	Retrospective chart review	Adult and children ED visits 13/208 developed BPR (9 F, 4 M)	6.3%	A	Median 18 y (range NR)	4 Sea food 2 Fried insect as food 2 Immunotherapy 1 Insecticide 4 Unknown	2 to 13 (mean 8h)	Median time from onset of the initial reaction to hospital arrival and to 1st epinephrine treatment were significantly longer in patient with BPR compare to those with UPR	-No clinical features or allergy triggers distinguished patients with UPR from BPR - No difference in steroid, antihistamine, or inhaled beta-agonist treatment for patients with UPR and BPR
Inoue et al, 2013[115]	Retrospective chart review	Children Inpatient and outpatient visits 2/61 developed BPR (1 F, 1 M)	3.3%	A	4- 7.5	NR	12-18	Patients who developed BPR were more likely to have experienced syncope, vomiting, and treatment with >1 dose of epinephrine for their initial reactions	- Steroids not helpful in preventing BP reaction - Syncope reported as an indicator of reduced blood pressure
Lee et al, 2013[116]	Retrospective chart review	Children Oral Food Challenge (OFC) at allergy clinic 9/614 developed BPR (13 F, 1 M)	1.5%	4A, 5 NA	0.2-17 (<5 y=5, 5-10y=3, >10y=1)	OFC to Milk, egg, and peanut	2-24	Patients with BPR were significantly more likely to have received steroids for their initial reaction. A higher percentage of biphasic reactors also appeared to have multiple organ involvement, received epinephrine, multiple doses of epinephrine, and antihistamines for their initial reactions.	
Vezir et al, 2013[118]	Prospective study	Children Allergy clinic 5/96 developed BPR (3 F, 2 M)	5.2%	NR	<5y=1 >5y=4	3 Drugs 2 Hymenoptera	0.5 to 9	All patients with BPR had received fluid replacement therapy for their initial reaction, which was severe in four of them.	-No clinical features or allergy triggers distinguished patients with UPR from BPR

*Time from onset of the initial reaction
NR=not reported, A=anaphylactic, NA=non-anaphylactic, F=female, M=male, BPR=biphasic reaction, UPR=uniphasic reaction

2.6.2 Predictors of Biphasic Reactions

Table 7 provides a summary of all studies investigating predictors of biphasic reactions. Few of those studies are specifically designed to evaluate predictors of biphasic reactions in children.

Lee and Greenes published the first report on 2000.[121] Their retrospective analysis of records between 1985 and 1999 revealed 6 of 105 patients (6%) experienced biphasic reactions, four of which had received the culprit antigen orally (two foods and two antibiotics). The other two cases occurred following hymenoptera stings. Patients with or without a biphasic reaction did not differ significantly in the incidence of initial epinephrine use; initial steroid use; or serious respiratory or cardiovascular symptoms on initial presentation. The authors observed a delay in epinephrine administration predisposed patients to an anaphylactic biphasic reaction.

Mehr et al from Australia published the second study in 2009.[111] They performed a similar review over a five-year period, between 1998 and 2003. Twelve of 102 (11%) children developed biphasic reactions, of which five were anaphylactic in nature. Compared with the first anaphylactic episode, the biphasic reaction was milder in seven cases (58%), of similar severity in four cases (33%), and more severe in one case (9%). Children developing biphasic reactions were more likely to have received more than one dose of adrenaline (58% vs. 22%, P = 0.01) and/or of a fluid bolus (42% vs. 8%, P = 0.01) than those experiencing uniphasic reactions. However, the authors stated "*It was the decision to initiate fluid resuscitation rather than the volume of fluid administered or the presence of hypotension that was a risk factor for biphasic anaphylaxis*".

Two other pediatric studies, published in 2013, investigated predictors of biphasic reactions. Inoue et al found that children in Japan who developed biphasic reaction were more likely to receive multiple doses of epinephrine as treatment for their initial reaction. However, only 2 out of 61 cases of this anaphylaxis cohort (3.3%) developed a biphasic reaction.[115] In a cohort of children who underwent an Oral Food Challenge test, Lee et al found that children who developed a biphasic reaction (1.5%) are more likely to be treated with epinephrine, receive >1 dose of epinephrine, receive systemic steroids, and involve multiple organ systems.[116] Although this study's outcomes encompassed both anaphylactic and non-anaphylactic biphasic reactions, none of these identified factors were statistically significant.

The rest of the literature on biphasic reactions following anaphylaxis has focused on either adult or mixed adult–pediatric populations, with the latter including a small number of children. Data from adult and pediatric literature add further insight about this issue. Taken together, three major factors emerge as potential reaction predictors: intrinsic factors related to allergen or patient; severity of the initial anaphylactic reaction; and the treatment parameters of the initial reaction.

Table 8 incorporates studies published to date supporting these emerging factors. This proposed model is simply an attempt to capture findings from previous literature in order to establish a scientific reference for this project. Although some of these predictors where not explicitly proposed by the authors of the original reports, a critical review of the findings from these studies support these factors indirectly.

It should be noted that some of the above studies were conducted more than a decade ago, predating a well-documented change in the overall anaphylaxis epidemiology. The largest series of biphasic reactions was reported by Ellis et al[120], which has a sample of 20 cases, raising concern about the reliability of the potential risk factors derived from those reports. In addition, most of the international guidelines providing a consensus on the definition, diagnosis, and therapy of anaphylaxis were recently published. This evolution in literature supporting the uptake and integration of these guidelines into clinical practice may have impacted the quality of care provided to patients with anaphylaxis, eventually influencing the rate and the nature of biphasic reaction.

Table 8: Identified Potential Predictors from Previous Studies

	Intrinsic factors related to the trigger or the patient	Severity of the Initial Anaphylactic reaction	Treatments of the Initial Anaphylactic reaction	
Risk factors	Oral allergen[106] History of Asthma[8,105,113] Low Peak Expiratory flow (PEF) at baseline[113] Delay of ≥30 min between exposure to trigger to development of initial reaction[106]	Hypotention[107,115] Unstable vitals[109] Syncope and Vomiting[115] (120) Multiple organ involvement[116] "Severe" reaction[118]	Treatment with >1 epinephrine dose[105,111,112,115,116,119] Less total epinephrine dose[120] Fluid bolus[111,118]	Delay in administration of first epinephrine[8,110,114,121] Delay in presentation to ED [109,114]
No effect	Respiratory manifestations [109]	Presence of severe symptoms[106]	Systemic Steroids[105–108,110,112,114–116,121]	

CHAPTER 3: OBJECTIVES

3.1 Objectives of part one (Survey)

The overall goal of this survey is to understand the knowledge and attitudes of emergency physicians across Canada, with respect to the correct management of children presenting with anaphylactic reactions. The specific objectives are:

- To describe the knowledge of correct diagnosis of pediatric anaphylactic reactions among emergency physicians
- To describe the knowledge of emergency physicians regarding the correct treatment of anaphylactic reactions with epinephrine
- To determine factors associated with correct diagnosis and treatment of anaphylaxis, as well as correct epinephrine administration
- To assess the confidence of emergency physicians in demonstrating the correct administration of epinephrine auto-injector to their patients
- To describe the practice pattern of emergency physicians in regard to utilization of written Anaphylaxis Action Plans

3.2 Objectives of part two (Health Records Review)

The overall goal of this health records review is to describe the epidemiology and management of anaphylaxis in two large pediatric emergency departments; and to investigate the incidence and predictive factors of biphasic reactions in children with anaphylactic reactions.

The **specific objectives** are:

- To determine the rate of anaphylaxis-related pediatric ED visits
- To describe therapeutic interventions provided to children with anaphylaxis in both pre-hospital and hospital settings, with a primary focus on epinephrine
- To estimate the incidence and nature of biphasic reactions
- To predict risk factors associated with biphasic reactions
- To examine the association of systemic steroids and anti-histamines with the development of biphasic reactions

CHAPTER 4 DIAGNOSIS AND MANAGEMENT OF CHILDREN WITH ANAPHYLAXIS: A NATIONAL SURVEY

4.1 METHODS

4.1.1 Overview

This section describes the procedures and methods followed for our survey. We followed the guidelines for reporting survey research methods previously summarized by Bennett et al.[122] Although the authors acknowledged that none of the checklists identified in their SUrvey Reporting GuidelinE (SURGE) report have been validated, they represent the best available evidence for transparent reporting to date.

In regards to questionnaire design, we followed a Tailored Design Method (TDM) described by Dillman et al[123]. This method involves the thoughtful planning of a survey tailored to the research question. As stated by Dillman et al " *tailored design is the development of survey procedures that create respondent trust and perception of increased rewards and reduced social costs for being a respondent*".[123] TDM goes beyond just the implementation procedure for a survey; rather, it is built on a scientific approach to reduce total survey error (sampling error, coverage error, measurement error, and non-response error), and on the social exchange theory of response, which aims to gain the respondent's trust thus increasing the benefits while decreasing participation costs.[123]

4.1.2 Sampling Strategy

Target Population: Previous research showed that the majority of pediatric anaphylaxis events are managed in the ED.[25] Therefore, we decided to target Canadian emergency physicians for this study.

Sampling Frame & Units: The Canadian Association of Emergency Physicians (CAEP) has a complete list of all of its members. The sampling unit consisted of each individual member in this frame. We used the CAEP list as our sampling frame for several reasons. First, CAEP is the largest national organization representing emergency physicians in Canada; CAEP members' credentials, geographic practice location, and practice settings vary. These features make this frame reasonably representative of the Canadian Ephysicians s population. Second, their membership list is updated annually by the CAEP administration. Around the time of the annual CAEP conference, active and new members are asked to electronically update their credentials and contact information. Having an up-to-date list is crucial for the survey implementation as described below. Finally, the research team at CAEP has conducted several successful surveys using a similar frame, making it more efficient for us, both financially and administratively, to collaborate with them on this project.

Sampling Procedure: For our sampling method, we used probability sampling through a simple random sampling model.

Eligibility Criteria: Practicing ED physicians who are Fellows of the Royal College of Physician of Canada (FRCP) or the Canadian College of Family Physicians (CCFP) will be eligible for the study.

Exclusion Criteria: Trainees and clinical fellows who are not yet a Fellow of the Royal College of Physician of Canada (FRCP) or the Canadian College of Family Physicians (CCFP) will be excluded from the study. Non-physician members such as nurses and allied health care professionals were also excluded.

4.1.3 Sample Size

The sample size was calculated through the following steps[123,124]

1. Estimating initial sample size, n_1:

$N_1 = Z^2 P(1-P)/e^2$

Where:

-Z is the level of confidence

-P is the precision of an estimated proportion

-e is the desired margin of error

The desired confidence limit is 95% of the survey estimates, but we will be satisfied if the true population proportion is within ±0.05 of the estimated based on the sample results, i.e., the required margin of error, *e*, is 0.05. Since there is no similar survey previously conducted, we will use 50% as the precision of estimated proportion, as it is more conservative and provides the largest sample size. Therefore, initial sample size will be as follows:

$n_1 = (1.96)^2 \times 0.5 \times 0.5 / (0.05)^2 = 385$ subjects

2. Adjusting the sample size to account for population size:

In 2011, the estimated total membership within CAEP was roughly 1,500 members. Adjusting the above sample size to the CAEP population results in the following sample size:

$n_2 = n_1 x\ N /\ N+n1$

= 385 x 1500 / (1500 + 385)

= 307 subjects

3. Adjusting the sample size for the effect of the sample design:

Since our sampling procedure was simple random sampling and the design effect=1, no further adjustment required for the design effect.

4. Adjusting for response rate to determine the final sample size, *n*:

The final sample size is dependent on the anticipated response rate. Based on our previous experience conducting survey research with physicians, we anticipate a response rate of 50%. The final sample size adjusted for this response rate was:

$n = n_2 / r$ = 307 / 0.5 = 615 subjects

In conclusion, 615 physicians were contacted to participate in this survey.

4.1.4 Choice of Survey Mode

Given the nature of the emergency medicine profession, we believed that a self-administered mail or online questionnaire would be most appropriate and preferable to participants, as opposed to a survey administered by interview, as it would offer respondents greater convenience

by allowing them to respond at their own pace and on their own time. Self-administration would also offer the advantage of greater administrative efficiency related to contacting the sample members and collecting their responses.[124]

The selection of a web versus mail survey requires consideration of the advantages offered by each mode. With respect to study resources, the two survey modes differ according to fixed and variable costs of development and administration. Fixed costs are those incurred regardless of the sample size, whereas variable costs are incurred when contacting sample members (i.e., in materials and time required).[125] Web surveys may have proportionally greater fixed costs incurred throughout the development and programming of a questionnaire, compared to variable costs from contacting members (e.g., by email). Mail surveys, on the other hand, often have proportionally greater variable costs incurred through printing and mailing questionnaires and reminders.[124] Although a single mode (mail survey) was initially proposed, given the lack of sufficient funding available at the time of this study and the incomplete contact information for physicians in our sample, we decided to use mixed-mode method; both web and mail survey modes were used.

Mixed mode surveys not only reduce cost, but are also advantageous in minimizing total survey error. First, it improves timelines by enabling rapid collection of responses.[123] Given the fact that some of the targeted physicians' contact addresses (mail and email) were missing, the mixed-mode survey enabled the delivery of the survey to the targeted sampling unit, thereby reducing coverage error. In addition, mixed mode survey offered the benefit of improved response rates by contacting those who may be difficult to reach via

the initial mode of data collection.[123] In their systematic review of methods to improve response rates of physician surveys, VanGeest et al found higher response rates among physicians to be associated with mix-mode surveys.[126] The 2008 report on the literature of physicians' survey, done by the American Association for Public Opinion Research (AAPOR), also emphasizes the appeal of this method as it improves response rate.[127]

4.1.5 Use of Survey Incentives

Use of incentives has been found effective in improving survey response rate, and thereby reduces non-response bias.[123,125,127,128] Even small financial incentives were found to improve physician response.[126] Dillman *et al.* recommend providing a small token cash incentive, in the range of $25 to $100, for physicians in particular, to all sample members.[123] Pre-paid cash incentives have been shown to have the largest effect on survey response rates.[123] When this is not feasible, Dillman *et al.* recommend a carefully selected material incentive.[123] A Cochrane systematic review (2009) of randomized controlled trials to increase response to paper or electronic questionnaires found that using monetary incentives increased the odds of response by more than half.[128]

We initially proposed offering all participants an unconditional, prepaid $2 dollar incentive to complete the first round of the survey. Unfortunately, because of limited funding sources available to the candidate at the time of this project, this was not possible. Instead, physicians who returned completed responses to the third and final survey round were entered into a draw to win one of twenty-five $20 Tim Horton's gift cards. This monetary

incentive was not offered for the previous two rounds conducted electronically.

4.1.6 Survey Questionnaire Development

Content of the Questionnaire

The candidate and the supervisors developed the questionnaire. First, the candidate generated the questionnaire content based on a literature review of anaphylaxis diagnosis and management by emergency care providers and the result of a recent systematic review on gaps of anaphylaxis management conducted by group of Canadian investigators.[51] Knowledge and practice gaps identified by this review are summarized in **Table 5**. The investigators subsequently rated gaps identified in their review according to clinical importance and published consensus recommendations of anaphylaxis management.[67] Items in our questionnaire are generated to cover the main three themes of gaps identified to have the highest clinical importance by the above reports.

The final survey instrument (**Appendix A-1**) included three groups of questions designed to establish: 1) physicians' demographics and practice setting; 2) two scenarios assessing emergency physicians' current knowledge of the diagnosis and the management of anaphylactic reactions in children; and 3) emergency physicians' knowledge of epinephrine administration and utilization of written anaphylaxis action plans. As this survey instrument was created de novo, several steps were taken to ensure its validity. First, the candidate developed a preliminary draft of the questionnaire, and the study authors assessed its clarity and relevance. Then, after multiple revisions by

the supervisors, a final draft was designed by the investigators and underwent pre-testing, pilot testing, and clinical sensibility assessment.

Pre-testing the Questionnaire

Once a final draft of the questionnaire was created, it was circulated among members of the Division of Emergency Medicine at the Children's Hospital of Eastern Ontario (CHEO), CHEO Research Institute (RI), and the Ottawa Hospital Research Institute (OHRI). In addition to expertise in clinical research, this team of physicians and researchers had expertise in one or more of the following areas: epidemiology, biostatistics, or survey methodology**.** The main purpose of this phase was to evaluate the questionnaire's content validity**.** The reviewers assessed the clarity of the questions posed; appropriateness of question structures and response categories; potential question-order effects; and whether additional questions should be added. Feedback from this team was important in assessing the questionnaire's face validity (whether the questionnaire appeared to measure what it intended to measure, based on the study objectives). The content and design of the survey were modified based on the team's feedback. Following this phase, the modified version of the survey was sent for pilot and clinical sensibility testing.

Clinical Sensibility Testing and Pilot Testing

To further assess the comprehensiveness, clarity, and face validity of the questionnaire, two pediatric allergy experts were invited to perform sensibility testing of the survey instrument. This testing addresses important

issues such as whether response formats are simple and easily understood; whether any items are inappropriate or redundant or missing; and the questionnaire's likelihood to address the survey objective.[129] In addition, we wanted to ensure that the clarity and lack of ambiguity of the two anaphylaxis scenarios, with the hopes of representing common clinical anaphylaxis presentations. A tool proposed by Burns et al was used for this testing (**Appendix A-2**).[129]

We conducted subsequent pilot testing of the survey by inviting ten emergency physicians (5 adult and 5 pediatric) to complete and provide feedback on the survey using the sensibility-testing tool described above (**Appendix A-2**). The respondents were asked to examine the questionnaire focusing on to its flow, salience, acceptability and administrative ease, identifying unusual; redundant; or poorly worded question stems and responses.[129] They were also asked to record the time required to complete the questionnaire. Then, the final version of the survey was revised based on responses from the physicians who completed this pilot phase

Web Development of the Questionnaire

The candidate designed the web version of the survey following design principles recommended by Dillman et al.[123] To avoid potential measurement errors caused by the mixed mode survey, the content and the design of both the online and mailed surveys were identical. As recommended by the CAEP research team, we contracted the Canadian web-survey provider FluidSurvey. Screen shots of the web-based questionnaire are shown in **Appendix A-3**. The survey was only conducted in English.

The link to the survey was included in the individualized email invitation. Users were time-stamped in the survey database. They were able to review or change their responses using the 'back' and 'next' buttons featured at the bottom of each page. The selection of one response option was enforced in the programming of closed-ended questions containing mutually exclusive response categories. However, for limited questions, respondents were allowed to choose multiple answers. The survey was programmed to progressively check question completion, as well as at the time of submission. However, respondents were still able to skip to the next page, if they choose to do so, by using "jump to" button. Although this strategy is controversial[123], it was used cautiously for a limited number of questions related to the primary outcome of the survey. We elected not to implement this feature on all the survey questions, as it has been shown to create frustration and to adversely impact the overall response rate. In addition, ethical concerns were raised about the use of this feature on web survey as it may violate the respondent's autonomy.[123]

Prior to implementation, the web survey was rigorously tested, and was completed by three members of the research team. The web-based questionnaire was tested on different browsers (MS Internet Explorer, Mozilla Firefox, Google Chrome, and Safari), and on multiple platforms (Windows XP, Vista, Windows 7, and Macintosh).

Description of the Final Web-Based Questionnaire

The final questionnaire consisted of 19 questions in four sections. There were 5 web pages in total; one for each section of the questionnaire and an additional final "thank you" page. The four sections were as follow:

1. First section: a scenario of an infant with anaphylaxis (4 questions)
2. Second section: a scenario of an adolescent with anaphylaxis (4 questions)
3. Third section: questions regarding epinephrine administration, duration of monitoring in ED after an anaphylactic event, and utilization of written AAPs (5 questions)
4. Fourth section: demographics and practice settings (6 questions)

Description of the Final Mailed Paper Questionnaire

The mailed survey package consisted of 1) a cover letter from the researchers, explaining the research goals (**Appendix A-4**); 2) a numbered survey (**Appendix A-1**); and 3) a postage-paid, preaddressed reply envelope. The survey was a four page booklet (one column per page, 2-sided), as recommended by Dillman et al.[123] As explained above, the design and the content of the paper questionnaire was identical to the online questionnaire.

4.1.7 Method for Implementation

The survey was administered using Dillman's TDM.[123] This methodology uses repeated contacts within the sampling units to maximize survey response rates while preserving the anonymity of the responders. Sending multiple contacts to potential survey respondents, such as a pre-

notification and reminders, is a very effective way to increase response rates.[130] As recommended by Dillman et al, we contacted potential participants several times. First, they received a pre-notification email informing them of the survey. Then, we sent the first and second email invitation for participation, with one reminder after each invitation**.** Finally, we approached non-respondents by sending a paper copy of the survey.

Implementation Procedure

As shown in **Table 9**, a series of up to six contacts, based on Dillman's recommendations for the implementation of mail and internet surveys, proceeded as follows: a pre-notification email sent to potential participants, mentioning that they would be receiving a survey request regarding management of pediatric anaphylaxis. The email explained the purpose of the survey, and the importance of participation. The survey invitation email containing a cover letter was emailed five days later. The link to the survey imbedded in the cover letter was unique to each participant. A thank you and reminder email was sent to all sample members one week after the first emailed request, explaining that a survey invitation had been sent, thanking those who had responded and encouraging those who had yet to do so. A second invitation email (**Appendix A-5**) was sent two weeks after the initial survey invitation email, indicating that a submitted questionnaire had not yet been received and urging the sample member to respond. To encourage participation, we highlighted the total number of responses received. This strategy has been shown to enhance participation in electronic survey.[128] Potential respondents were then emailed a second reminder thanking those

who had recently responded, urged a response from those who had not. Two weeks after this reminder, we switched to a mailed survey, including a cover letter, survey booklet, and a postage-paid preaddressed reply envelope. Conditioned incentives were only provided during this phase. As the mailed survey was sent in July when some sample members were likely to be away, the study did not close until September, when the final thank you letter was sent

Table 9: Outlines of the Survey Implementation Procedure

Procedure	**Date ***
Pre-survey announcement	May 23rd
1st email contact to complete web survey	May 28th
1st reminder	June 4th
2nd email contact to complete web survey	June 11th
2nd reminder	June 18th
3rd mail contact to complete paper survey	July 2nd
Thank-you letters with gift cards	September 3rd

***2012 Calendar year

The survey implementation system therefore incorporated a number of features to maximize the response rate. In addition, all contacts with participants included the names of the supervisors; as senior research scientists at the OHRI, Dr. Stiell and Dr. Wells served as legitimate authorities, recognizable to most CAEP members given their research activity in the field of emergency medicine. This technique has been shown to improve the response rate.[125,130] We also included the logo of the sponsoring professional institution of the investigators on the letterhead of the mailed survey.[127]

4.1.8 Statistical Methods

Database Creation and Data Entry

The candidate created the database in SPSS. Reponses from the web-based questionnaire were imported directly into this database, and the candidate manually entered responses from the mailed surveys. A 15% systematic sample of the mailed paper survey was randomly chosen for double entry and verification. Then, data was cleaned up by running frequencies of responses, checking ranges of responses, and cross-checking variable values. The analysis excluded responses from non-eligible participants.

Data Analyses

Data analysis was performed using the SPSS version 20 statistical package (SPSS; Cary, NC). Descriptive statistics were used to characterize the respondents' demographics. We used the AAPOR *Standard Definitions* guidelines to define the reported response rate.[131] Overall response rates were calculated, excluding those ineligible EPs, with a projected goal of 70% after repeated mailings. Categorical variables were summarized using frequencies and percentages, and compared using an χ^2 tests for standard dichotomous variables or a Fisher exact test for dichotomous variables, where an expected cell value was less than five. Continuous data was compared using the Student's t-test, reporting the means and standard deviations. Significance level will be determined as $P< 0.05$. Several methods have been suggested to assess non-response bias.[132] Given our inability to access the sampling frame (as per CAEP confidentiality agreement), we assessed non-

response bias by looking for differences in both characteristics and responses to the primary outcome between respondents to the web versus mailed survey. Our assumption is that respondents to mailed survey are similar to non-respondents.[133,134]

Ethical Considerations

Participation in this study entailed completing a survey questionnaire, presenting a minimal risk to sample members. In the survey cover letter (**Appendix A-4**), sample members were informed that their participation is voluntary and that they may refuse to participate or withdraw from the study at any time. Submitting the survey questionnaire was therefore regarded as implied consent to participate in the study. Participant's names did not appear on any research forms, as participant identification numbers (PINs) were used to identify the mailed survey instruments. A log book that links PINs with participant names was kept geographically separate from the study forms. All information collected was held in the strictest confidence and kept in the research office's locked cabinets. An application for an expedited review was submitted to the CHEO Research Ethics Board (REB). The study was approved (Protocol #11/140X); refer to **Appendix A-6** for the letter confirming ethics approval for this study.

4.2 Results

4.2.1 Response and Characteristics

Response Rate

All invited CAEP members were assigned final disposition codes according to the American Association for Public Opinion Research (AAPOR).[131] **Figure 1** shows the classification of the sample members into four main categories, on which the Response Rate (RR) calculations are based. Although there are no specific disposition codes in the AAPOR guidelines for the mixed survey mode, the main disposition codes are common to all single modes. Therefore, we focused on the main disposition codes. As shown in **Figure 1**, seven of the 615 respondents were subsequently determined to be ineligible after receiving their response and were excluded from the total sample, resulting in a final sample size of 608 members.

Final Disposition Codes of Surveyed Members

Category I: Returned questionnaire

Category '(I)' sample members consist of those who submitted a completed survey questionnaire, regardless of the survey mode, and are therefore considered as respondents. The criterion for "questionnaire completion" was to have provided responses to questions in the first two sections of the questionnaire, even if the rest of the questionnaire was part not completed. A total of 340 sample members met this criterion and are therefore considered respondents.

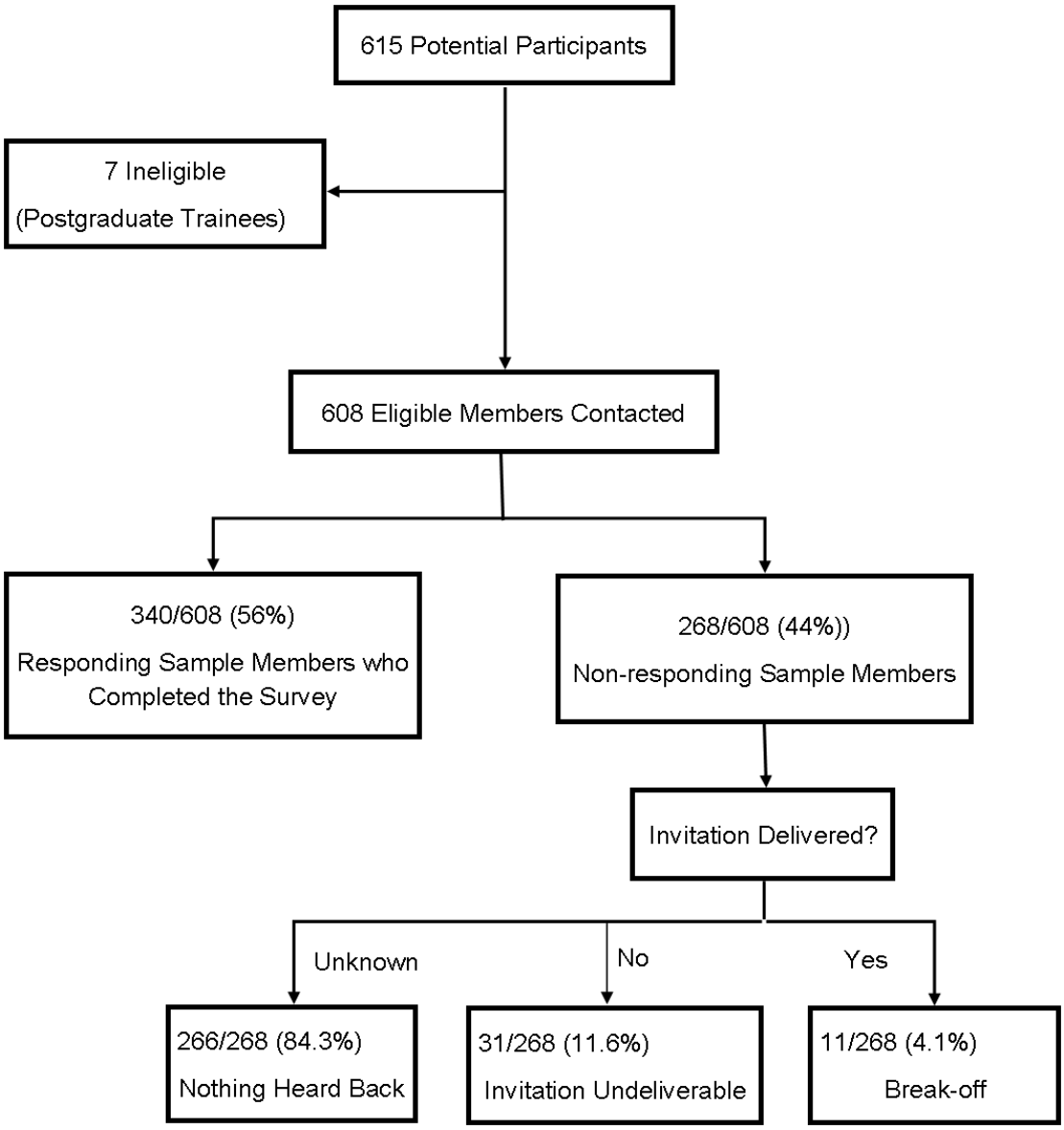


Figure 1: Flow Chart Illustrating Response Outcomes of Sample and Corresponding Disposition Categories According to AAPOR Guidelines.

Category R: Refusal or break-off

Category ‘(R)’ consists of non-responding sample members who explicitly or implicitly refused participation. Returned questionnaires that included no responses to the diagnosis and ED treatment of at least one of the scenarios were considered incomplete and excluded from the analysis. A total of 11 sample members were classified in this category.

Category U: Non-contact-invitation delivery status unknown

Category ‘(U)’ consists of 226 non-responding sample members who did not respond to any of the survey mode, thus delivery status of their survey invitations remains unknown. As we had no indicators for survey delivery problems to these members, we assumed the majority of this category received the survey by one or both modes but chose not to respond.

Category UO: Invitation to sample member returned undelivered

Category ‘(UO)’ consists of non-responding sample members whose survey was returned undelivered to both email and mail contacts. This occurred to 31 members in the study.

Response rate

The survey response rate is calculated as follows:

$$RR = \frac{I}{(I) + (R) + (U + UO)}$$

The survey response rate was 56% (340/608). This minimal response rate calculation includes sample members who completed the survey (I), over all eligible invited sample members.

4.2.2 Respondent Characteristics

Table 10 shows the characteristics of the 340 respondents, including demographics and practice setting. The majority of survey respondents were males (65%), and had been practicing longer than 5 years. More than 60% of physicians are certified by the Canadian College of Family Physicians (CCFP). Among 203 physicians who are primarily certified by the CCFP, 149 (73.4%) reported additional certification in emergency medicine. Pediatricians and Pediatric Emergency Physicians (PEMs) constituted 6.7% of survey respondents.

More than half of survey respondents reported working in academic centres, with an annual volume of greater than 60,000 ED visits. However, for approximately 25% of survey respondents, the proportion of pediatric patients in these ED was more than 25% of the total ED population.

Table 10: Demographic Characteristics and Practice Setting of Survey Respondents

Variable	N=340
Male, *n* (%)	214 (65)
Mean years of practice, range	11.4 (1-36)
Hospital settings*, *n* (%)	
Academic-primarily adult population	155 (47.1)
Academic-primarily pediatric population	20 (6.1)
Academic-mixed population	5 (1.5)
Community	149 (45.3)
Annual ED[1] patient volume*, *n* (%)	
<40,000	78 (23.7)
40,000- 59,000	86 (26.1)
≥ 60,000	165 (50.2)
Proportion of pediatric population in respondent ED**, *n* (%)	
≤ 15%	150 (45.9)
16-25%	93 (28.4)
26-35%	52 (15.9)
>35%	32 (9.8)
Highest level of postgraduate medical training*, *n* (%)	
CCFP[2]-General practice	54 (16.4)
CCFP-Emergency medicine	149 (45.3)
FRCPC[3]-Emergency medicine	100 (30.4)
FRCPC- Pediatrics/PEM[4]	22 (6.7)
Other	4 (1.2)

* Data for 11 respondents are missing

**Data for 13 respondents are missing

1 ED= Emergency Department

2 CCFP=Canadian College of Family Physicians

3 Fellowship of the Royal College of Physicians of Canada

4 PEM=Pediatric Emergency Medicine

4.2.3 Non-response analysis

We assessed for non-response bias by comparing the characteristics and responses of early and late respondents. We define early respondents as those responding to the web survey and late respondents are those responding to the mailed survey. We assume that characteristics of respondents to the last survey delivered delivery wave, by mail, were similar to the non-respondents.

There are no differences between early and late respondents regarding baseline characteristics, including hospital settings, annual ED patient volume, proportion of pediatric patient within respondent practice, years of practice, or physician's highest level of postgraduate medical training (**Table 11)**. In addition, there is no difference between early and late respondents in regard to the primary survey outcome. The proportions of respondents providing a correct diagnosis and treatment for both of the study case scenarios showed no statistically significant difference.

Table 11: Comparison of Early and Late Respondents

Variable	**Early (n=255)**	**Late (n=85)**	**p-value**
Male, *n* (%)	159 (62.3)	55 (74.7)	0.94
Mean years of practice, range	10.9 (1-36)	13.1 (1-35)	0.06
Hospital setting*, *n* (%)			
Academic	133 (52.2)	47 (55.3)	0.32
Community	111 (43.5)	38 (44.7)	
Annual ED patient volume*, *n* (%)			
<40,000	55 (21.6)	23 (27.1)	0.48
40,000- 59,000	62 (24.3)	24 (28.2)	
≥ 60,000	127 (49.8)	38 (44.7)	
Proportion of pediatric population in respondent ED*, *n* (%)			
≤ 15%	114 (44.7)	36 (42.4)	0.53
16-25%	64 (25.1)	29 (34.1)	
26-35%	40 (15.7)	14 (16.5)	
>35%	26 (10.2)	6 (7)	
Highest level of postgraduate medical training*, *n* (%)			
CCFP[1]-General practice	37 (14.5)	17 (20)	0.25
CCFP-Emergency medicine	106 (41.6)	43 (50.6)	
FRCPC[2]-Emergency medicine	78 (30.6)	22 (25.9)	
FRCPC- Pediatrics/PEM[3]	19 (7.5)	3 (3.6)	
Other	4 (1.6)	0	
First case scenario, *n* (%)			
Correct diagnosis of anaphylaxis	185 (72.5)	66 (77.6)	0.43
Correct treatment with epinephrine	173 (68.9)	61 (71.2)	0.59
Second case scenario, *n* (%)			
Correct diagnosis of anaphylaxis	179 (70.2)	61 (71.8)	0.77
Correct treatment with epinephrine	192 (75.3)	67 (78.8)	0.97

* 11 observations missing from the early group

1 CCFP=Canadian College of Family Physicians

2 Fellowship of the Royal College of Physicians of Canada

3 PEM=Pediatric Emergency Medicine

4.2.4 Diagnosis and Management of Anaphylaxis

The overall responses to the survey's clinical scenario questions are summarized in **Table 12**. Overall, more than 70% of the physicians correctly identify that children in both scenarios were having an anaphylactic reaction.

In regard to ED management, the majority of physicians agreed to administer second line adjunctive treatments more frequently than epinephrine (the primary life-saving therapy). More specifically, physicians chose the following pharmacological therapies to treat an infant with anaphylaxis: H_1-antihistamine 96.4%, H_2-antihistamine 69.3%, systemic steroids 89%, and inhaled bronchodilator 89.4%. However, 70% chose to administer only epinephrine. The proportion of physicians who chose to administer epinephrine for the second scenario of an adolescent with anaphylaxis was slightly higher (79%), however, 92% chose to administer systemic steroids and an inhaled bronchodilator. Although this scenario indicated an appropriate dose of H_1-antihistamine had been administered one hour before ED arrival, 7% of physicians chose to re-administer this same therapy.

Table 12- Responses to Questions for Two Clinical Scenarios Depicting Children Experiencing an Anaphylactic Reaction

Question	**First scenario (18 month infant with anaphylaxis) n=340**	**Second scenario (16y girl with anaphylaxis) n=329**
Scenario diagnosis, n (%)		
Anaphylactic reaction	251 (73.8)	240 (72.9)
Non-anaphylactic reaction	89 (26.2)	89 (27.1)
Management in the ED, n (%)		
Systemic epinephrine	234 (69.9)	259 (79)
H1-antihistamine	321 (96.4)	23 (7)
H2-antihistamine	233 (69.3)	255 (77.7)
Systemic steroids	284 (89)	302 (91.8)
Inhaled bronchodilator	295 (89.4)	301 (91.8)
Other *	15 (4.5)	9 (2.7)
Mean hours of observation in ED after resolution of symptoms, (SD)	4.9 (1.9)	4.7 (2)
ED disposition plan, n (%)		
Prescribe epinephrine auto-injector	252 (75)	248 (76.5)
Prescribe an oral antihistamine	283 (85.5)	296 (92.5)
Prescribe an oral steroids	210 (66.9)	236 (73.1)
Refer to an allergy specialist	231 (71.5)	207 (64.3)
Follow up with family physician	25 (7.4)	17 (5.1)
Emphasize avoidance of allergen	15 (4.5)	9 (2.7)
Explain reasons to return to ED	8 (2.4)	5 (1.5)
Provide teaching handout	7 (2.1)	3 (0.9)
Recommend Medic-Alert bracelet	2 (0.6)	3 (0.9)

*Other therapies include: oxygen, intravenous fluid, inhaled epinephrine, and inhaled steroids

Table 13- Reported Duration of ED Monitoring After Resolution of Anaphylaxis Symptoms*

Duration	n (%)
<2 h	5 (1.5)
2-4 h	127 (38.7)
5-7h	147 (44.8)
≥ 8 h	49 (14.9)

*Responses from 328 physicians

In regards to duration of ED monitoring, the mean number of observational hours reported by physicians was around five hours for both scenarios. Furthermore, when asked about their general practice patterns regarding the duration monitoring for children presenting to ED with anaphylaxis, 38.7% and 44.8% of physicians reported 2-4h and 5-7h of observation, respectively (**Table 13**). However, 14.9% of physicians would continue observation for 8h or longer after the symptoms' resolution.

For the scenario presenting an infant's first anaphylactic allergic reaction to peanuts, physicians chose to do the follow upon ED discharge: 75% prescribed epinephrine auto-injector; 71.5% referred the infant to an allergy specialist; 66.9% prescribe oral steroids; 7.4% recommended follow up with family physician; and less than 5% provided anaphylaxis or allergen-avoidance education, or explained reasons to return to ED.

On the other hand, for the parallel adolescent scenario, describing a patient with a known peanut allergy, 76.5% instructed the child to use an epinephrine auto-injector immediately for future similar reactions, 73.1% prescribed oral steroids, 64.3% referred the child to an allergist, and 5.1% recommended follow up with family physician. In addition, less than 3% of physicians chose to provide education about anaphylaxis, allergen avoidance, reasons to return to ED, or to recommend Medic-Alert bracelet.

Physicians' Knowledge of Epinephrine Treatment in Anaphylaxis and Utilization of Written Anaphylaxis Action Plans

The majority of physicians chose both the correct epinephrine concentration (1:1000) and dose (0.01mg/kg, Max of 0.3 -0.5 mg) as

treatment for anaphylaxis in children. The 1:10,000 epinephrine concentration, primarily used in cardiac arrest cases, is not recommended therapy for anaphylactic shock. Nevertheless, this concentration was chosen by 14.1% of respondents (**Table 14)**. The preferred intramuscular route of administration was chosen by 87.8% of physicians; the subcutaneous and intravenous routes were selected by 10.7% and 1.5%, respectively.

The provision of anaphylaxis education, including information on epinephrine auto-injector administration and an action plan for future reactions, are essential components of discharge instructions, especially for people who experience their first anaphylactic reaction. We assessed physicians' confidence demonstrating use of an epinephrine autoinjector (EAI) to a child or to parents; although 45.6% of physicians felt confident, 23.5% did not (**Table 14**). We also asked physicians how frequently they provided a written anaphylaxis action plan to child and parents upon discharge. More than half of the respondents reported the tool was rarely or never used, 18% used it sometimes, and only 29.4% frequently used the tool.

Table 14- Physicians Knowledge of Epinephrine Administration in Children with Anaphylaxis and Utilization of Written Anaphylaxis Action Plan

Variable	**N=328**
Epinephrine concentration, n (%)	
1:1000, (0.01mg/kg, Max of 0.3 -0.5 mg)	280 (85.9)
1:10,000, (0.01mg/kg, Max of 0.3 -0.5 mg)	35 (10.7)
1:10,000, (0.1mg/kg, Max of 1 mg)	11 (3.4)
Epinephrine administration route, n (%)	
Intramuscular	287 (87.8)
Subcutaneously	35 (10.7)
Intravenous	5 (1.5)
Confidence level in demonstrating the use of Epinephrine-autoinjector, n (%)	
Not confident	77 (23.5)
Somewhat confident	101 (30.9)
Confident	149 (45.6)
Provide child/parents with a written anaphylaxis action plan upon ED discharge, n (%)	
Never/rarely	172 (52.6)
Sometimes	59 (18)
Often/always	96 (29.4)

4.2.5 Factors Associated with Appropriate Management of Anaphylaxis and Epinephrine Administration

Table 15 summarizes factors associated with appropriate management of the survey's two hypothetical pediatric anaphylaxis cases and the knowledge appropriate epinephrine administration. Pediatricians and Pediatric Emergency Medicine (PEM) trained physicians were more likely to correctly identify the anaphylactic nature of the hypothetical scenarios than Adult Emergency and Family Physicians (90.9%, 59.8%, and 64.4% respectively, p=0.02) and subsequently treat with epinephrine (95.5%, 55.4, and 63.9% respectively, p=0.002). Furthermore, in comparison to physicians who reported ≤35% annual pediatric population encounters in their ED, physicians with a higher number of encounters were more likely to correctly identify the anaphylactic nature of the hypothetical scenarios (81.3% vs 62.8%, p=0.05) and to administer epinephrine accordingly (84.4% vs 61%, p=0.01). There was no association between the correct diagnosis or treatment of the hypothetical scenario and the type of hospital setting, ED volume, or years of practice.

In regards to knowledge of epinephrine administration, we found no association between physicians' ED settings, annual volume of patients, proportion of annual pediatric encounters in ED, training backgrounds, or years of practice and the correct choice of epinephrine concentration and dosing, or with confidence demonstrating EAI administration. However, the choice of intramuscular route for epinephrine administration was higher among ED physicians who have been practicing less than 5 years compared

to those who have been in practice for a longer period (95.6% vs 84.7%, p=0.01).

Table 15- Physician Characteristics and Management of Anaphylaxis and Epinephrine Knowledge

Characteristics	Correct diagnosis of both scenarios, n (%)	p	Correct epinephrine treatment of both scenarios, n (%)	p	Correct epinephrine concentration, n (%)	p	Correct epinephrine administration route, n (%)	p	Confidence with EAI[1] demonstration, n (%)	p
Sex										
Male	133 (62.7)	0.33	130 (61.6)	0.4	182 (85.8)	1	186 (87.7)	1	165 (77.5)	0.59
Female	78 (68.4)		76 (66.7)		98 (86)		101 (87.8)		85 (74.6)	
Hospital Setting										
Academic	120 (67.8)	0.25	109 (61.6)	0.49	154 (87)	0.53	157 (88.2)	0.87	141 (79.2)	0.24
Community	91 (61.1)		97 (65.5)		126 (84.6)		130 (87.2)		109 (73.2)	
ED volume per year										
<60,000	104 (63.8)	0.82	107 (66)	0.36	138 (84.7)	0.63	139 (85.3)	0.18	128 (78.5)	0.44
>=60,000	107 (65.6)		99 (60.7)		142 (87.1)		148 (90.2)		122 (74.4)	
Pediatric ED[2] population										
<=35%	184 (62.8)	0.05	178 (61)	0.01	249 (85)	0.28	255 (86.7)	0.15	220 (75.1)	0.13
>35%	26 (81.3)		27 (84.4)		30 (93.8)		31 (96.9)		28 (87.5)	
Highest level of postgraduate training										
CCFP[3]	130 (64.4)	0.02	129 (63.9)	0.002	175 (86.6)	0.25	179 (88.6)	0.1	151 (74.8)	0.09
FRCP[4]-EM[5]	61 (59.8)		56 (55.4)		84 (82.4)		86 (83.5)		78 (75.7)	
FRCP-Peds/PEM[6]	20 (90.9)		21 (95.5)		21 (95.5)		22 (100)		21 (95.50	
Years of practice										
< 5 years	61 (67.8)	0.52	55 (61.1)	0.7	79 (86.8)	0.86	87 (95.6)	0.01	75 (82.4)	0.15
>= 5 years	149 (63.4)		150 (64.1)		200 (85.5)		199 (84.7)		174 (74)	

Characteristics	Correct diagnosis of both scenarios, n (%)	p	Correct epinephrine treatment of both scenarios, n (%)	p	Correct epinephrine concentration, n (%)	p	Correct epinephrine administration route, n (%)	p	Confidence with EAI[1] demonstration, n (%)	p
Sex										
Male	133 (62.7)	0.33	130 (61.6)	0.4	182 (85.8)	1	186 (87.7)	1	165 (77.5)	0.59
Female	78 (68.4)		76 (66.7)		98 (86)		101 (87.8)		85 (74.6)	
Hospital Setting										
Academic	120 (67.8)	0.25	109 (61.6)	0.49	154 (87)	0.53	157 (88.2)	0.87	141 (79.2)	0.24
Community	91 (61.1)		97 (65.5)		126 (84.6)		130 (87.2)		109 (73.2)	
ED volume per year										
<60,000	104 (63.8)	0.82	107 (66)	0.36	138 (84.7)	0.63	139 (85.3)	0.18	128 (78.5)	0.44
>=60,000	107 (65.6)		99 (60.7)		142 (87.1)		148 (90.2)		122 (74.4)	
Pediatric ED[2] population										
<=35%	184 (62.8)	0.05	178 (61)	0.01	249 (85)	0.28	255 (86.7)	0.15	220 (75.1)	0.13
>35%	26 (81.3)		27 (84.4)		30 (93.8)		31 (96.9)		28 (87.5)	
Highest level of postgraduate training										
CCFP[3]	130 (64.4)	0.02	129 (63.9)	0.002	175 (86.6)	0.25	179 (88.6)	0.1	151 (74.8)	0.09
FRCP[4]-EM[5]	61 (59.8)		56 (55.4)		84 (82.4)		86 (83.5)		78 (75.7)	
FRCP-Peds/PEM[6]	20 (90.9)		21 (95.5)		21 (95.5)		22 (100)		21 (95.5)	
Years of practice										
< 5 years	61 (67.8)	0.52	55 (61.1)	0.7	79 (86.8)	0.86	87 (95.6)	0.01	75 (82.4)	0.15
>= 5 years	149 (63.4)		150 (64.1)		200 (85.5)		199 (84.7)		174 (74)	

EAI= Epinephrine auto-injector

[2] ED=Emergency Department,[3] CCFP=Canadian College of Family Physicians,[4] FRCPC=Fellowship of the Royal College of Physicians of Canada,

[5] EM=Emergency Medicine [6] Peds/PEM=Pediatrics and/or Pediatric Emergency Medicine

4.3 Discussion

4.3.1 Main Findings

Our national survey examined Canadian Emergency Physicians' (members of the Canadian Association of Emergency Physicians) practice patterns. The majority of respondents identified the correct anaphylaxis diagnosis and appropriately chose to treat with epinephrine. Despite their unproven efficacy, most physicians chose to administer adjunctive therapies, such as antihistamines and systemic steroids, in ED instead of epinephrine. In addition, these medications were as commonly prescribed for outpatient treatment as the epinephrine auto-injector . We found emergency physicians with pediatric training, or those who commonly encounter children in their practice, are more likely to correctly diagnose an anaphylactic episode in a child and to administer epinephrine.

With regard to epinephrine use, most physicians used the correct 1:1000 concentration and the intramuscular route of administration. However, physicians practicing for 5 or more years are less likely to use the intramuscular administration route. Physicians' confidence in demonstrating the use of EAI was suboptimal; roughly half of the respondents felt confident showing the technique. Although the practice of most respondents was in concordance with published guidelines for management of anaphylaxis in ED, physicians seem to lack core knowledge related to discharge planning and follow-up care. For instance, providing a written action plan or teaching handout, and arranging follow-up care from primary care providers were evidently deficient.

4.3.2 Previous Studies

Our findings are in concordance with previously identified knowledge gaps, based on the systematic literature review by Kastner et al.[51] The three major knowledge gaps identified by this review were diagnosis; management and epinephrine use; and follow-up plan (**Table 5**). Below, we discuss how our findings compare with the previous literature on these three knowledge gaps.

Diagnosis of Anaphylaxis

The relatively high proportion of correct anaphylaxis diagnoses by emergency physicians in our study contradicts available anaphylaxis data. A study by Klein and Yocum, 1995, found that 23% of patients with anaphylaxis were given an anaphylaxis diagnosis by emergency physicians.[135] Subsequent studies found that about half of patients meeting criteria for food-induced anaphylaxis did not receive a discharge diagnosis of anaphylaxis.[7,11] In addition, a case-based survey of community pediatricians in the United States found only around half of respondents could correctly recognize and treat food-induced anaphylaxis.[132] However, these studies looked data before the publication of the National Institute of Allergy and Infectious Diseases' anaphylaxis diagnostic criteria in 2006. It seems the wide adoption of better-defined diagnostic criteria and training and education of physicians is improving anaphylaxis under-diagnosis of anaphylaxis in the ED

Recent studies reviewing emergency physicians' practice found that more than 70% of allergic reaction presentations to pediatric ED were correctly diagnosed as anaphylaxis.[27,36,136] A study by Campbell et al found

approximately two-thirds of patients with an allergist's diagnosis of anaphylaxis were also given this diagnosis by emergency physicians.[137] This suggests a modest, but potentially important, increase in the recognition of anaphylaxis in ED patients. When assessed in ED setting, the diagnostic performance of the National Institute of Allergy and Infectious Diseases anaphylaxis diagnostic criteria were found to be 96.7% sensitive and 82.4% specific with a negative likelihood ratio of 0.04.[137] Nevertheless, the utilization and application of these clinical criteria by caregivers and health professionals has proven challenging, especially in the pediatric age group.[19] Until better objective diagnostic criteria or rapidly available sensitive biomarkers are developed, anaphylaxis will likely continue to be misdiagnosed in children.

Anaphylaxis management

The main knowledge gaps that our survey focused on were: the administration of systemic epinephrine in anaphylaxis; the knowledge of the correct epinephrine dose and route of administration in anaphylaxis; and the frequency of adjunctive therapy administration, such as antihistamines and corticosteroids. We will discuss now the difference between our findings and previous studies on those areas.

Epinephrine Use

In the United States, the rate of ED epinephrine administration to treat anaphylaxis has been reported as 16%.[69,70] In 2000, an 18 month national surveillance study of Canadian pediatricians found only one third of 700 reported anaphylaxis patients received epinephrine as treatment.[86] A study of

more than 2000 patients (2006-2010) with severe anaphylaxis from around sixty European cities found less than 15% of patients received systemic epinephrine.[138] The wide adoption of anaphylaxis management guidelines and improved physician's education, however, seemed to have impacted health practitioners' attitude toward epinephrine use. Approximately two-thirds of our respondents administered epinephrine in ED, which is like secondary to the wide dissemination of the anaphylaxis guidelines.[139] Similar to an anaphylaxis diagnosis, recent North American studies indicate an increasing rate of epinephrine administration, ranging between 70-80%.[26,27,36,136] Although suboptimal, this data are encouraging. It should be noted, however, that these studies looked at care provided at pediatric hospitals. There is no Canadian data on the rate of epinephrine use in the ED among children who are treated by emergency physicians in general community hospitals.

Adjunct therapies

Previous studies from both pediatric and adult literature show that epinephrine is used less commonly than antihistamines and corticosteroids in treating anaphylaxis, despite their delayed onset of action and unproven efficacy.[69–71,138] Our survey findings are consistent with these studies. In a multicentre registry of several European countries comprising more than two thousand patients with severe anaphylaxis, Grabenhenrich et al found that almost 50% received antihistamines and corticosteroids in the ED; in contrast, <15% received epinephrine. The updated European Association of Allergy and Clinical Immunology anaphylaxis guidelines classify these therapies as

"third line", and recommend against using them as an alternative to epinephrine.[99]

Intramuscular route of epinephrine

Guidelines for anaphylaxis management recommend intramuscular administration of epinephrine as a first-line intervention, because more rapid absorption and higher plasma concentrations have been shown with intramuscular than with subcutaneous delivery.[140] Except for in the case of refractory hypotensive anaphylactic shock, intravenous administration is not recommended, as it increases the risk of arrhythmia and myocardial ischemia.[93–95] Approximately 90% of our survey respondents preferred the intramuscular route; this is a relatively high rate compared to previous literature. Self-reported intramuscular epinephrine administration from previous surveys of physicians ranges between 50-70%.[141–143] Our finding that junior physicians (<5 years in practice) use intramuscular epinephrine more frequently than senior physicians (>5 years in practice) is consistent with those of Desjardin et al.[141] Grossman et al found residency training at the site of care as well as higher volumes of patients presenting with anaphylaxis is associated with the use of intramuscular epinephrine. However, we found no such correlation. In fact, our comparisons of several performance metrics of anaphylaxis management between academic and community physicians demonstrate no difference between the groups.

Epinephrine dosing errors

Epinephrine is available in multiple concentrations dependent on the recommended dosing regimen. Vials can be labeled in mass concentration (1 mg per mL) or as a ratio (1 mL of a 1/1000 or 1/10,000 solution). As such, epinephrine 10-fold error can easily occur.[144] Approximately 15% of physicians in our survey chose the cardiac arrest dose as pediatric anaphylaxis treatment. The confusion about epinephrine dosing is one of the knowledge gaps receiving little attention in the literature. Multiple reports of epinephrine dosing errors have been published.[93–95] These reports describe the inadvertent intravenous administration of either a 1:1000 solution or of the cardiac arrest dose (1:10,000). Another study showed that physicians managing acute pediatric anaphylaxis in a simulated scenario, when provided vials with mass concentration labels, gave a higher weight-based dose of epinephrine than the target dosage.[144]

Disposition Plan and Follow- up care

Provision of anaphylaxis education and arrangement of long-term care are imperative to anaphylaxis management. Previously identified gaps in follow up care included low rates of epinephrine prescriptions; physicians not providing epinephrine auto-injector instructions; patients and caregivers not being able to recognize symptoms of anaphylaxis, including unawareness of triggers to avoid, and patients and caregivers inability to manage an anaphylactic reaction, including hesitancy or difficulty with the operation of an auto-injector.[51]

In fact, a recent survey of Canadian caregivers of children who presented to ED with a first allergic reaction to food found that more than 60% of respondents felt they did not receive enough information about symptom recognition, treatment with epinephrine, and coping strategies. Consequently, many families reported high levels of anxiety resulting in the restriction of their child's activities, avoiding travel, reducing their work hours, or quitting their job.[145] Our survey findings are in concordance with some of the identified gaps, causing a significant burden on patients and caregivers.

Provision of anaphylaxis action plan

Provision of action plans upon ED discharge may reduce the frequency and severity of future reactions, improve knowledge of allergen avoidance techniques, improve epinephrine auto-injectors use and reduce anxiety.[100,136] Despite their potential impact, health professionals are found to underuse the tool.[51] More than half of survey respondents reported they never or rarely provide a written action plan upon ED discharge. A survey of 1885 anaphylaxis survivors or had been responsible for a survivor, reported that around 60% of participants did not have a plan readily available.[90] The reasons for the underutilization of action plans are not clear. It is possible that emergency physicians uninformed of their availability and/or efficacy. Individualized written anaphylaxis emergency action plan are recommended by both national and international anaphylaxis guidelines in order to mitigate some of the gaps in anaphylaxis long term care.[5,67,99]

Prescription of epinephrine auto-injector

Similar to previous studies suggesting the underprescription of the epinephrine auto-injector,[89,132] nearly 25% of our survey respondents chose not to prescribe auto-injector. This practice potentially puts large number of children at risk. Anaphylaxis is largely unpredictable; it occurs mainly in out of hospital settings and it progresses rapidly. It is thus essential that all patients at risk be provided with a self-injectable epinephrine.[146] Although the reasons for epinephrine underuse unclear, possible factors include a lack of clarity or consistency of instructions; dosing; and fear of adverse events.[70]

Patient education

Patients' education on appropriate use of the auto-injector device is equally important as several devices are in active use in Canada. Several studies indicate that, for most patients, a standard prescription and formal instruction on anaphylaxis treatment by a physician are insufficient to reach compliance with respective practical measures.[99] A survey of more than 1800 food-allergic individuals or caregivers found only 58.7 % of respondents reported receiving training from the auto-injector prescriber.[147] Auto-injector training sessions increase the likelihood of correct use by patients and caregivers.[148] Therefore, physicians and other health professionals need to maintain their skills in order to teach their patients. Unfortunately, less than half of our survey respondents felt confident demonstrating the use of auto-injectors. This finding is consistent with previous studies that have shown the competency level among physicians is generally low. Grouhi et al found only 41% of Canadian emergency physicians were able to demonstrate the correct

use of an epinephrine auto-injector, and less than 20% used a training device.[87] Another survey of 29 attending pediatricians found that only 21 % could correctly demonstrate the use of these auto-injectors.[149]

Referral to allergy specialists

Referral of a child with anaphylaxis to an allergist is an important discharge planning step.[4,99] Just one visit to an allergy clinic has been reported to improve parental knowledge of allergen avoidance, management of allergic reactions, and correct use of an auto-injector.[145,150] The proportion of physicians agreeing with the referral to an allergy specialist in our survey is significantly higher than in previous studies.[69,151] A study by Rudder et al of more than 650 children, seen at multiple emergency departments in Boston over 5 years, found only 43% were prescribed an auto-injector, and only 22% were referred to an allergist upon discharged.[39]

4.3.3 Strengths

To our knowledge, this is the first national survey exploring anaphylaxis practice patterns of Canadian emergency physicians. Although it was primarily designed to assess knowledge of pediatric anaphylaxis, many aspects are also relevant to the care of adult patients, such as epinephrine administration and discharge planning.

A second strength of this study is the assessment of emergency physicians' knowledge, whom primarily (>90%) practice in non-pediatric settings. The majority of North American children requiring emergency care are treated in general emergency departments. A report by the Institute of

Medicine found that "*the vast majority of ED visits made by children in the United States are not to children's hospitals or those with a pediatric ED, but to general hospitals, which are less likely to have pediatric expertise, equipment, and policies in place"*.[152] Similar findings are reported in Canada; roughly 15% of children who visited an ED in Ontario between 2005-2006 were seen in pediatric centres, the rest were seen in general community hospitals.[153] As many as 40% of these children do not receive evidence-based anaphylaxis treatments, and up to 20% received either unbeneficial or potentially harmful treatment.[154] Therefore, Identifying pediatric-specific knowledge gaps among this group of physicians will help bridge these potentially life-threatening gaps, eventually improving the quality of care provided to such a vulnerable population.

4.3.4 Limitations

Conducting a quality survey requires optimal minimization of sampling, coverage, non-response, and measurement errors.[125] Despite our best effort to minimize some of these errors, we cannot completely eliminate the possibility of residual errors that may bias our findings. Although the Canadian Association of Emergency Physicians is the largest national organization of emergency physicians in Canada, there is no data on the total number of emergency physicians who are not members of this organization. Non-member physicians practicing in remote or rural areas and those working part-time may not have been able to participate in the survey. This may have resulted in some coverage error. The magnitude and impact of this error is difficult to estimate since the exact number and demographics of practicing

Canadian emergency physicians is unknown. We also acknowledge the under-representation of both pediatricians and Pediatric Emergency Physicians in our survey (<10%). However, this was not our primarily targeted population. Nevertheless, comparing the performance of this population with the general and emergency family physicians through future qualitative research may provide useful insights.

Although our response rate may raise concerns for non-response bias, we do not suspect this being a serious threat to our results for two reasons. First, our sample size calculation was adjusted for this expected low response rate by doubling the sample size. Second, as demonstrated in our non-response analysis, we found no difference between early and late respondents in regard to baseline characteristics and the primary survey outcome. Kelleman and Harold suggest that nonresponse bias may be of less concern in physician surveys than in surveys of the general public, as most studies have found either no or minimal nonresponse bias.[155]

Furthermore, our response rate is similar to previous physician surveys. Flanigan et al reported these survey had a mean response rate of 54%.[127] Finally, for the purpose of our survey, both academic and community emergency physicians were equally represented.

This survey is further limited by self-reporting. Disparity between reporting and practice has been noted in other anaphylaxis studies.[156] We are unable to find published Canadian studies investigating community emergency physicians' management of pediatric anaphylaxis in order to sensibly compare data. Our identified knowledge gaps are concerning even if we assume the reported practice represent the "best", rather than the "real",

practice of emergency physicians. There is also the potential for recall bias when self-reporting the number of anaphylaxis patients seen annually.

4.3.5 Future Implications

1- Improving physician training and education

The majority of anaphylaxis cases are managed in the ED.[62,101] Therefore, we recommend educational interventions to help practicing emergency physicians maintain up-to-date knowledge and skills required for anaphylaxis management. Although our data indicates an encouraging trend in some of the anaphylaxis management practices when compared with previous literature, there is certainly an opportunity for improvement. The diagnosis and treatment principles are standard regardless of age, thus the identified gaps clearly reflect deficiency in practical training rather than in theoretical knowledge. These gaps appear to be prevalent among allergy specialists. A study by Johnson et al surveying a group of pediatricians and pediatric allergists in the United Kingdom found that, although most physicians read at least one of the anaphylaxis guidelines, there was still considerable prescribing variation of the epinephrine auto-injector, even when it was absolutely indicated.[157] Similarly, Desjardin et al surveyed a sample of Canadian allergists and non-allergists, finding around 25% of both groups underused epinephrine as treatment for a child with severe anaphylaxis.[141]

In light of our data and of previous studies, we agree with Grabenhenrich et al's proposal recommending "*a close collaboration between physicians in emergency care settings and specialized allergists to develop interventional strategies*" to address educational and training gap.[138] In

addition, there is also strategies are needed to target both undergraduate and postgraduate trainees through simulation and other educational interventions.[158,159] As our study indicates, educational programs targeting senior emergency physicians are also crucial.

We also advocate to incorporate anaphylaxis education in all Basic and Advanced Life Support courses or training modules designed by the American Heart Association and the Heart and Stroke Foundation of Canada. Current guidelines focus primarily on emergency treatment of anaphylactic shock. However, there is little focus on disposition planning and no training on epinephrine auto-injector administration techniques. In addition to the written information, aspect of post-resuscitation care should also be emphasized through hands-on simulated training. The European Association of Allergy and Clinical Immunology's updated 2014 anaphylaxis guidelines acknowledge the training gap for physicians and addressed some its challenges.[99]

2- Identification of barriers

Future research should focus on understanding barriers to both epinephrine treatment in ED and to the prescription of auto-injector through an exploration of behaviors and attitudes. The relatively low rate of ED epinephrine administration may be in part due to the high percentage of patients' self-limited reactions and the relatively low death rates from anaphylaxis. As a result, ED physicians may hesitate to administer epinephrine, due to its potential for adverse effects.[160] Among Canadian caregivers, barriers to epinephrine auto-injector use include: fear of hurting the child, of using the auto-injector incorrectly, of side effects or of bad

outcome.[161] To our knowledge, no studies explore those or other barriers. The Theory of Planned Behaviour interview technique can be a useful systematic research method in order to identify those barriers.[162]

Barriers preventing the provision of appropriate discharge education and the utilization of a written anaphylaxis action plan are should also be explored. Patient education is a process rather than a one-time event. Ideally, this process should start at the time of anaphylaxis diagnosis, and reinforced with every subsequent allergic reaction. Most patients are monitored in the ED for a prolonged period following an anaphylactic event (4-6h), which is much longer than the duration of a routine clinic visit with a primary care provider or a specialist. Furthermore, the chain of care from the ED, through community pediatrician or family physician, to an allergy specialist gives emergency physicians an excellent opportunity to initiate this education process, which has been shown to reduce patient anxiety.[145] Although several discharge checklist tools were developed by different allergy organizations to assist emergency physicians minimize this gap,[160,163] the efficacy and usability of these tools have not been robustly evaluated.

3- Dissemination of knowledge about pediatric anaphylaxis in Canadian ED

We recommend the implementation of clinical pathways for anaphylaxis management in each ED as a strategy to mitigate some of the gaps found in this survey. Clinical pathways are structured, multidisciplinary care plans used by health services to detail essential steps in the care of patients presenting with a specific clinical problem, such as anaphylaxis.[164] It

has emerged as a potentially important knowledge dissemination strategy to promote effective healthcare, patient safety, and best, evidence-based practice.[164,165] Although the evidence of the impact of an anaphylaxis clinical pathway is limited, previous studies noted improvement in adherence with management guidelines and patient safety. Implementation of an anaphylaxis clinical pathway in a Spanish pediatric ED has been shown to significantly improve epinephrine administration in the ED, epinephrine auto-injector prescription at discharge, observation in the ED, and discharge from the ED with follow-up instruction.[28] Another study found significant reduction of medication dosing error after implementing a standard anaphylaxis clinical pathway in a Canadian pediatric ED.[166]

Finally, innovative methods of pediatric anaphylaxis knowledge dissemination and of minimizing these identified gaps need to be explored. Translating Emergency Knowledge for Kids (TREKK) is an example of an organization utilizing this method. This initiative was started in 2011 as a national knowledge mobilization tool.[154] With more than 30 general emergency department partnerships across Canada, TREKK aims to support knowledge mobilization in order to bridge the research-to-practice gap for children visiting general emergency departments. This initiative is a practical tool for promoting and implementing anaphylaxis clinical pathways and written anaphylaxis action plan in general Canadian EDs.

Conclusions

Although the majority of the Canadian emergency physicians seem to have some knowledge of pediatric anaphylaxis, a substantial proportion have

knowledge gaps that may negatively impact the quality of care provided to this vulnerable population. These gaps may be mitigated through identification of barriers encountered when adhering to the established treatment guidelines; better training and education of physicians; and further knowledge dissemination initiatives.

CHAPTER 5 ANAPHYLAXIS EPIDEMIOLOGY AND PREDICTORS OF BIPHASIC REACTIONS

5.1 Methods

5.1.1 Study Design

This part of the thesis project was a health record review conducted by reviewing charts of patients presenting to the ED with anaphylaxis.

5.1.2 Study Setting

We conducted health records reviews of patients presenting to the ED with anaphylaxis over the 2010 calendar year. The study was conducted at two 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 centre in Ottawa, with approximately 70,000 annual ED visits. It also serves as the tertiary referral centre for Eastern Ontario, Western Quebec, Nunavut, and parts of Northern Ontario. The Hospital for Sick Children is the primary care pediatric hospital for the downtown core of Toronto and the tertiary pediatric referral centre for the Greater Toronto Area. It has approximately 60,000 ED visits annually.

5.1.3 Study Period

We reviewed charts of all pediatric anaphylaxis patients visiting the ED from January1st through December 31st 2010.

5.1.4 Study Population

Patients were identified using the health records database. The health records departments at both centres use the Canadian National Ambulatory Care Reporting System (NACRS); this database captures data on all patients visiting Canadian EDs. Trained health records personnel review charts of all patients visiting the ED and enter the chief compliant, the primary and the secondary diagnoses for these patients. We reviewed the emergency department charts of patients whose primary or secondary diagnoses matched any of the International Classification of Diseases (ICD) version 10 codes listed in **Appendix B-1**.

5.1.5 Inclusion Criteria:

Patients who met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis (**Table1**) were included in the study, even if their visit was not given an anaphylaxis diagnostic code. We restricted our enrolment to children <18 years of age.

5.1.6 Exclusion Criteria

Allergic episode with any one of the following characteristics were excluded:

- Allergic event not matching the strict anaphylaxis diagnostic criteria
- Anaphylaxis that occurred in context of a suicidal attempt or intoxication.
- Anaphylaxis episode confounded by other medical diagnosis, like food poisoning or mastocytosis.

- Anaphylaxis episodes where the trigger, symptoms, or treatments of the reaction were missing.
- Anaphylaxis that occurred during outpatient clinic visit or inpatient hospitalization.

5.1.7 Data Extraction

A standard paper data extraction form was developed, piloted, and agreed on by the investigators (**Appendix B-2**). The candidate extracted data at both centres. In addition to data from each patient's ED record, nursing triage notes and nursing monitoring sheets were also used as the main data sources regarding time of event such as drug administration or a change in patient's clinical status. The Ambulance Call Report was used to supplement/confirm historical data about each anaphylactic episode attended to by EMS paramedics. When available, we used this report as the main data source about pre-hospital reaction management at the scene and during transport to hospital. For patients with anaphylaxis to a new allergen and who were referred to an allergy specialist by the emergency physician, we used the consultation note from the allergist, when available, to document the allergy trigger.

Variables from History:

- Age,
- Sex,
- Weight,
- Past medical history including history of previous anaphylaxis, previous BPR, and history of atopic diseases like eczema and asthma,

- Details of treatment interventions received at the scene of the allergic reaction, including time of these interventions,
- Details of treatment interventions given by the EMS paramedics, and
- Details of the allergy event including name of the allergen, location of the event, and time of exposure to the allergen.

Variables from Examination:

- Vital signs at triage and the worst vitals recorded during the ED visit
- Details of physical findings for different body systems involvement (dermatologic, respiratory, gastrointestinal, cardiovascular, and neurologic)

Variables from Initial ED Interventions and Disposition:

- Details of non-pharmacologic/supportive interventions and the timeline,
- Details of pharmacologic interventions (including dose, route, frequency, and the time they were given) ,
- Disposition time, location (home or hospitalization), diagnosis, and instructions (including discharge medications and outpatient allergy referral)

Variables from ED Monitoring Period and Subsequent Visits:

The following variables were only abstracted if the patient developed a biphasic reaction during ED monitoring following the initial anaphylactic episode, or subsequently return to the ED within 72 h of the initial visit.

- Time of biphasic reaction onset,
- Details of clinical manifestations of the biphasic reaction, and

- Details of management interventions given for the biphasic reaction and disposition location.

Variables extracted for Inter-Observer Agreement

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 health record department. This list is sorted chronologically, by date of visit, and had only the Medical Record Number (MRN) and date of the ED visit, matching the ICD-10 codes specified above. Inter-observer agreement for variables with a high probability of error related to patient eligibility, to the development of the primary outcome, or to the treatment with epinephrine before and after arrival to ED were measured using a kappa coefficient with 95% confidence intervals.

5.1.8 Outcome Measures

The primary outcome of this study is the development of a biphasic reaction after an initial anaphylactic allergic reaction regardless of the allergen trigger.

Definition of Outcome

Biphasic reaction: For an anaphylactic reaction to be classified as biphasic it has to match the following criteria: 1) the initial anaphylactic reaction should be followed by a period of resolution for greater than one hour, during which there are no new symptoms or treatment administered; 2) subsequently, this period should be followed by a second phase of new/recurrence of anaphylaxis symptoms/signs that are not caused by antigen re-exposure; 3)

these symptoms/signs should be severe enough to require therapeutic intervention/s. If there was no recurrence of symptoms that matched all of the above criteria, the reaction was considered uniphasic. Based on the need for epinephrine treatment, we further classified the severity of the biphasic reaction as anaphylactic or non-anaphylactic in nature. Only biphasic reactions that either match the diagnostic criteria for anaphylaxis or are treated with epinephrine were classified as anaphylactic.

Outcome Assessment

Since this biphasic reaction reportedly occurs up to 72 hours after the initial reaction, the chart was reviewed for a subsequent ED visit within this time period regardless of whether patients were discharged from the ED or admitted to hospital. If the patient was admitted, the in-patient chart was reviewed. If the patient was discharged from the ED or the inpatient service (prior to 72 hours), we searched for evidence of return visits to the ED within 72 hours after the initial visit. If a return visit occurred, records were reviewed to determine if the visit was related to the initial anaphylaxis episode visit.

5.1.9 Analysis

Database Creation and Data Entry

Data entry and analysis was performed using the SPSS version 20 statistical package (SPSS; Cary, NC). The candidate created the database and entered the data from the completed paper study forms into the database. A systematic sample comprising 20% of the completed extraction forms were checked for entry accuracy by a data entry professional at CHEO's Research

Institute. The data entry accuracy was further checked by regular frequency reports and visual checks. Any queries were clarified by reviewing the original record.

Descriptive Statistics

Descriptive statistics were used to describe patient characteristics. Numbers and proportions were used as dichotomous variables. For continuous variables, means and standard deviations or medians and interquartile ranges were used as deemed appropriate. Vital signs were analyzed as categorical variables with a dichotomous outcome for two reasons. First, the study includes the entire the pediatric age range (0-18 years). The baseline physiologic respiratory and cardiovascular norm is determined by the metabolic rate, which varies across this population's age range. These physiological parameters also vary between an awake and a sleeping state. Second, a binary variable is more easily understood and more clinically relevant. As shown below, we used the American Heart Association (AHA) Pediatric Advanced Life Support (PALS) guidelines as reference cut-off points for these variables.[167] The weighted average incidence of anaphylaxis among ED visits during the study period from both centres was calculated. We also calculated other epidemiological parameters, including the proportion of patients who received epinephrine treatment for their reactions, who arrived to ED by ambulance, who developed biphasic reactions, or were admitted to hospital.

Univariate Analysis

We conducted univariate analysis to determine the association of all predictor variables with the primary dichotomous outcome (biphasic vs uniphasic reactions). The appropriate univariate technique was selected based on the type of the data. For nominal variables, chi-square or Fisher's exact test was used. An unpaired, 2-tailed student's t-test was used for univariate analysis of continuous clinical predictor variables. The Mann-Whitney U test was used to analyze correlations in nonparametric data. Only predictor variables with a p-value <0.2 were considered for the multivariate analysis.

Multivariate Analysis

We performed a logistic regression multivariate analysis to determine the independent association of factors related to the occurrence of biphasic reactions and to control for potential confounding. We aimed for a model that was clinically sensible and highly sensitive, and with reasonable specificity, if possible.

Logistic Regression:

The decision of variable selection was based on both clinical and statistical grounds. Initial logistic regression was done with variables having a p-value of <0.2 in the univariate analysis. If required, variables with more missing values were removed to make the model more robust. In order to make the model simple for clinical use without requiring complex computational aids, we divided some of the continuous variables, such as

time interval and vital signs, into categories. For variables entered in the regression model, less than three percent had missing observations. As a guide to sample size determination for a logistic regression model, the rule of 10 events per variable has been often cited in the literature, but simulations by Vittinghoff and McCulloch suggest that this rule of thumb is not, 'a well-defined bright line'.[168] Their results indicate that problems of confidence interval coverage of less 93 percent, type I error rates greater than 7 percent, and relative bias greater than 15 percent are uncommon with 5-9 EPV and still observed with 10-16 events per variable. Therefore, we limited the number of variables in our regression model to 5 events per variable. The p-value for the predictor variable to enter the model was set at 0.2 and the p-value to stay in the model was set at 0.05, or else they were removed from the model. The stepwise backward selection method was used to identify the statistically significant independent predictors. Statistical significance of independent variables was assessed using the likelihood ratio test (with a p value of < .05 as statistically significant). Regression diagnostics examining multicollinearity, influential data points, and outliers were used. For the final models developed by logistic regression, the odds ratio for the variables in the model with their 95% confidence intervals, β coefficients, and Hosmer-Lemeshow goodness of fit were calculated. We also assessed model fitness by assessing the area under the Receiver Operator Characteristic (ROC) curve.

5.1.10 Ethical Concerns

The Research Ethics Board (REB) at both sites (CHEO and the HSC) approved the study protocol prior to data collection. Copies of ethics approval documents from both sites are included in **Appendix B-3** and **B-4**. There were no ethical concerns expressed by either board. Since patients were not contacted at any stage, the ethics boards approved the project without requiring informed consent from patients. Several measures were taken to ensure maintenance of patient confidentiality. First, personal information in form of names, hospital unique number, and OHIP number were not collected. Second, An independent study number was assigned for each patient and the link between the study number and the patient identifications such as date of birth was housed separately and securely.

5.2 Results

In this part we summarize the results from the second project of the thesis. Results will be presented in two sections. The first section provides descriptive statistics and epidemiological data about pediatric anaphylaxis in the ED. The second section is devoted to the analytic data about predictors of biphasic reaction.

5.2.1 Study Flow and Inter-observer Agreement

During the study period, 1749 ED visits due to allergic symptoms were screened for potential eligibility. Of these visits, 1246 (71.2%) visits were excluded, as they did not fulfill the diagnostic criteria for anaphylaxis. **Figure 2** illustrates study flow and details of the excluded visits. Five hundred and three

visits (28.9%) met the inclusion criteria, but 19 (4%) of these then were subsequently excluded as they met the exclusion criteria. As a result, 484 of 1749 (27.6%) screened were included in the final study population.

Inter-observer agreements were calculated for appropriate inclusion of patients into the study and for variables related to the primary outcome. There was 100% agreement on the included anaphylaxis ED visits, development of biphasic reactions, and proportion of patient visits treated with epinephrine before and after ED presentation.

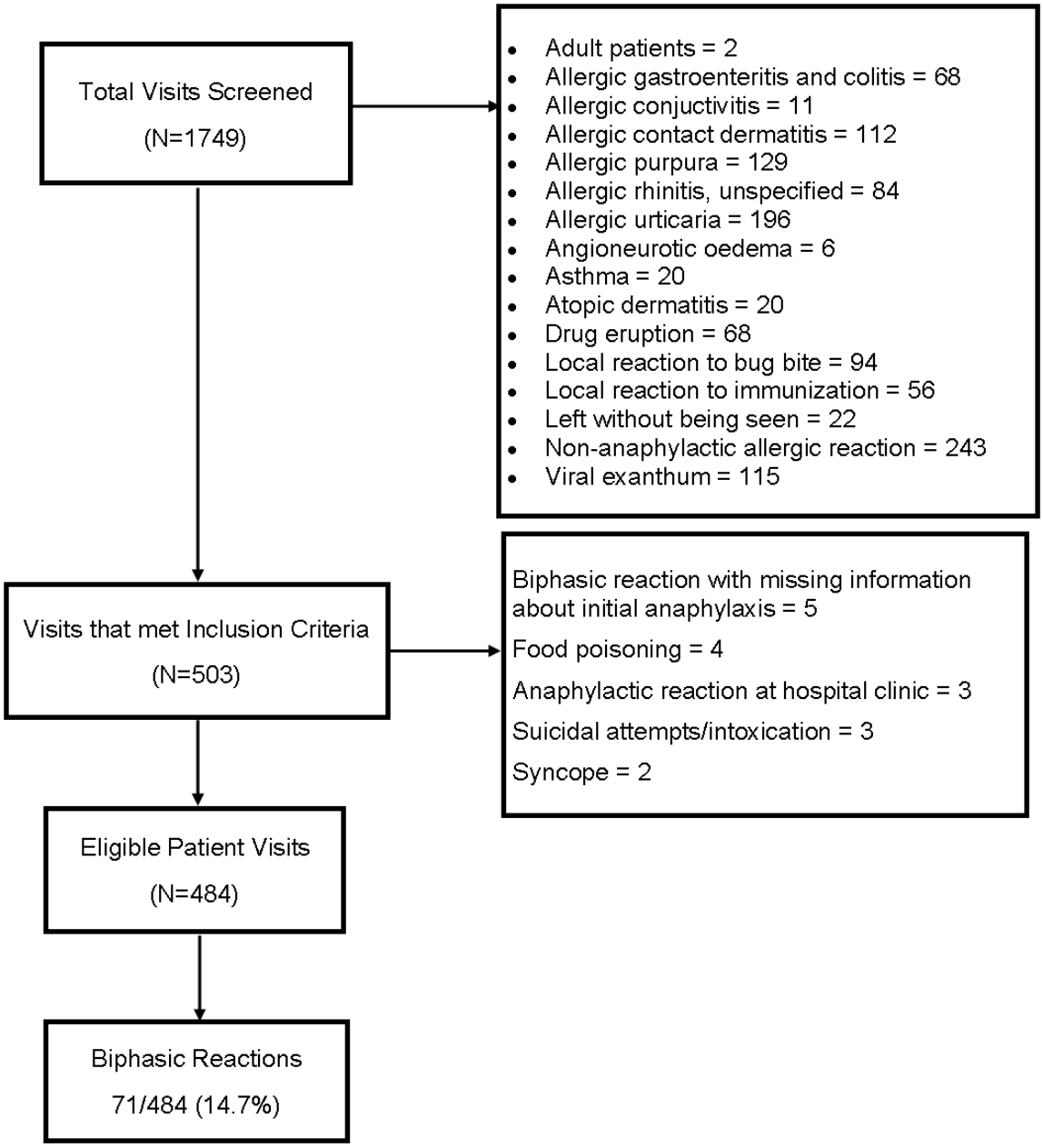


Figure 2- Flow of Study Patient Visits to the Emergency Departments

5.2.2 Characteristics of Included Patient Visits

Demographics

The 484 patient visits during the study period were from 473 patients. The cohort's median age was 4.8 years, ranging from 0.3 to 17.9 years (**Table 16**). Three hundred and fourteen (64.9%) of the total anaphylaxis episodes were in males. There was no statistically significant difference between males and females with respect to the age of presentation or the presenting clinical manifestations. Ambulance was the mode of arrival for 157 patient visits (32.4%).

Presenting Clinical Features

The predominant anaphylaxis manifestations in this cohort of 484 ED visits were: cutaneous in 471 (97.3%), respiratory in 407 (84.1%), and gastrointestinal in 218 (45%) (**Table 16**). Cardiac and neurologic features were less common, seen in 16.7% and 19.2% of visits, respectively. A summary of the triage vital signs for all included patient visits is provided on **Table 16**. Overall, tachycardia and wide pulse pressure were documented at triage on approximately one third of this cohort (**Appendix B-5**). Only 4 (0.8%) of the anaphylaxis episodes presented with hypotension

Table 16- Patient Characteristics for 484 Anaphylaxis Patient Visits

Characteristics	*N*=484
Demographics	
Age (yr), Median (IQR)*	4.8 (2.1-11.1)
Range (yr)	0.3-17.9
Male, n (%)	314 (64.9)
Hospital site, *n* (%)	
Children's Hospital of Eastern Ontario-Ottawa	322 (66.5)
The Hospital for Sick Children-Toronto	162 (33.5)
Arrival status	
Arrival by ambulance, *n*(%)	157 (32.4)
Heart rate (beats/min), mean (SD)	115.6 (26.7)
Respiratory rate (breaths/min), Median (IQR)	24 (20-30)
Systolic blood pressure (mm Hg), mean (SD)	108.1 (15.4)
Diastolic blood pressure (mm Hg), mean (SD)	64.2 (12.1)
SaO2 by oximetry, Median (IQR)	99 (98-100)
Clinical manifestation, *n* (%)	
Cutaneous	471 (97.3)
Respiratory	407 (84.1)
Gastrointestinal	218 (45)
Cardiac	81 (16.7)
Neurologic	93 (19.2)
Allergy history, *n*(%)	
Food	293 (60.5)
Environmental	72 (14.8)
Drugs	44 (9)
Other	4 (0.83)
Past history, *n* (%)	
Carry epinephrine auto-injector	236 (48.8)
Anaphylactic reaction	156 (32.1)
Intubation for anaphylactic reaction	6 (1.2)
Biphasic allergic reaction	13 (2.7)
Asthma	210 (43.4)
Allergic dermatitis	187 (38.6)
Allergic rhinitis	23 (4.8)
Causative agents of current anaphylactic episode, *n* (%)	
Food**	337 (69.7)
Drugs and medications	11 (2.3)
Exercise	9 (1.9)
Bee sting	8 (1.7)
Others	36 (7.4)
Unspecified	82 (16.9)
Settings of current anaphylactic episode, *n* (%)	
Home	331 (68.4)
Restaurant	49 (10.1)
Outdoor	31 (6.4)
School/Daycare	41 (8.5)
MD office	8 (1.7)
Other	17 (3.5)
Unspecified	6 (1.2)

*IQR=Interquartile range,

** Peanuts, tree nuts, and milk were the most common food triggers respectively

Allergic Disease

A history of a pre-existing allergic disease at presentation was common in this cohort. Asthma was the most common atopic disease, present in 210 patient visits (43.4%), followed by allergic dermatitis in 187 patient visits (38.6%) (**Table 16**). In addition, most patients in this cohort had a known history of one or more allergy triggers for their symptoms. Among reported known triggers, food was the most common type of allergen, reported by 293 (60.5%) of patient visits, followed by environmental allergens, in 72 (14.8%). In approximately 50% of these visits, patients reported carrying an epinephrine auto-injector for their confirmed allergy, and one third reported history of a previous anaphylactic reaction. Anaphylaxis episodes due to a new allergen exposure were the cause of 157 ED presentations (32.4%), and the rest were due to inadvertent exposure to a known or unspecified allergen.

Setting and allergens

Three hundred and thirty one (68.4%) of these anaphylaxis episodes occurred at home, and 41 occurred at school/daycare (8.5%) (**Table 16**). The most common allergy trigger in this cohort was food, documented in 337 patients (69.7%). Peanuts accounted for 131 (27.1%) food triggers, followed by tree nuts, 82 (16.9%); milk and dairy products. 29 (6%); eggs, 28 (5.8%); and fish or other seafood, 26 (5.4%) (**Appendix B-6**). More than 15% of the anaphylaxis events were due to unspecified culprit allergen. Only eleven (2.3%) of anaphylaxis episodes were triggered by drugs and therapeutic agents, with immunotherapy being the most common (8/11) (**Appendix B-6**).

Interestingly, all anaphylaxis episodes at community MD office were secondary to injectable immunotherapy.

Table 17- Management Received at Different Settings for 484 Anaphylaxis Patient Visits

A-At the Scene of the reaction by caregiver, *n* (%)	N=484
Epinephrine	129 (26.7)
H_1-antihistamine	162 (33.5)
Inhaled Salbutamol	30 (6.2)
B- During transport to hospital by EMS paramedics*, *n* (%)	
Oxygen	63 (13)
Oral airway/BMV**	2 (0.4)
Intubation	1 (0.2)
Epinephrine	36 (7.4)
H_1-antihistamine	34 (7.0)
Inhaled Salbutamol	13 (2.7)
Intravenous fluid	1 (0.2)
C-Emergency Department, *n* (%)	
Oxygen	25 (5.2)
Oral airway	1 (0.2)
Intubation	1 (0.2)
Epinephrine	176 (36.4)
Inhaled Salbutamol	71 (14.7)
H_1-antihistamine	295 (61)
H_2-antihistamine	81 (16.7)
Systemic steroids	252 (52.1)
Intravenous fluid	51 (10.5)

*EMS=Emergency Medical Services

****BMV=Bag and mask ventilation**

5.2.3 Management of anaphylaxis

Therapeutic interventions and management of anaphylaxis episodes at different setting are summarized in **Table 17.**

Epinephrine

Information about epinephrine administration is presented in **Table 17** and **Table 18.** Epinephrine was administered to a total of 309 (64%) members of this cohort after the onset of the initial anaphylaxis. Within this group, 301 (97.4%) epinephrine treatments were given through the recommended intramuscular route. In addition, the first dose was given in ED in 157 cases (50.8%) and the rest were given before arrival to the ED (129 (41.7%) at the scene of the reaction by patients/caregivers, and 23 (7.4%) administered by EMS paramedics. Multiple doses of epinephrine for the initial anaphylaxis were administered in 29 (6%) episodes. The median time between onset of the anaphylactic reaction and the first epinephrine treatment was 61 min (IQR=25-117). This time varies between 35 min (IQR=15-75) among those who carried epinephrine auto-injector to 89 min (IQR=55-180) among those who did not ($p<0.001$). In 157 episodes where patients were transported to the hospital by ambulance, only 88 (56%) received epinephrine before arrival. Among the 175 anaphylaxis episodes in which epinephrine was not administered, the ED discharge diagnoses were allergic reaction in 115 (65.7%), anaphylaxis in 56 (32%), and urticaria in 4 (2.3%) ($p<0.001$).

Table 18- Details of Epinephrine Treatment Administered for 484 Anaphylaxis Episodes

Number of administered Epinephrine Doses*	**n (%)**
0	175 (36.2)
1	280 (57.8)
>1	29 (6)
Time (min) to First Epinephrine**	Median (IQR)***
Among all patients (n=309)	61 (24-117)
Among patients who carry epinephrine auto-injector (n=177)	35 (16-77)
Among patients who carry no epinephrine auto-injector (n=132)	89 (54-181)
Route of first administrated dose, (n=309)	**n (%)**
Intramuscular	301 (97.4)
Subcutaneous	8 (2.6)
Settings of first administered dose, (n=309)	**n (%)**
At the scene of the reaction by patient/caregiver	129 (41.7)
During transport by EMS paramedics	23 (7.4)
In ED	157 (50.8)

* Only include epinephrine treatment for the initial anaphylaxis, epinephrine treatment administered for the biphasic reactions were not included
** Duration from onset of the reaction to first epinephrine
***** IQR=interquartile range**

Bronchodilators and Respiratory Support Therapies

Inhaled Salbutamol was the most common bronchodilator intervention, administered in 71 (14.7%) anaphylaxis events. It was administered by caregiver in 30 (6.2%) episodes, and by paramedics during transport in 13 (2.7%) episodes. Tracheal intubation, oral airway insertion, and bag and mask ventilation interventions were rarely performed for this cohort (**Table 17**)**.** Among all therapeutic interventions provided by paramedics, oxygen was the most common, administered in 63 (13%) anaphylaxis events.

Antihistamines and Systemic Steroids

H_1-antihistamines were the most frequently administered therapy in anaphylaxis, used for 396 episodes (81.8%). This treatment was received in different settings, with the majority (61%) administered in ED (**Table 17**). Systemic steroids were also administered in ED to 252 (52.1%) anaphylaxis patients. However, H_2-antihistamines were only administered during 81 (16.7%) episodes.

5.2.4 Outcome

Only 24 patient-visits (4.9%) resulted in hospital admission, three of these admissions were to the intensive care unit and the rest were to a general inpatient unit. The majorities of these admissions were uneventful and followed with discharge from hospital within 24 h. There were no fatalities among this cohort. Seventy-one of 484 initial anaphylaxis events (14.7%) were followed by the development of a biphasic reaction. The description of

patients who developed biphasic reactions is provided below and summarized in **Table 20**.

Table 19 shows the final discharge diagnosis of studied ED patient visits. Anaphylaxis (from all causes) was the most common final diagnosis in 303 patient visits (62.6%) followed by allergic reaction, in 174 patient visits (36%).

Regarding ED discharge treatment, 387 (80%) patients were prescribed EAI upon disposition from the ED. Other, less common discharge treatments include H_1-antihistamine; given for 191 (39.5%) of the episodes, and systemic steroids which was prescribed for only 79 (16.3%) patient visits. Among 157 patients with new allergy triggers, referral to an allergy specialist was arranged to 125 (79.6%) patient visits.

Table 19- Outcomes, ED Discharge Diagnoses, and Discharge Treatments for 484 Anaphylaxis Patient Visits

Outcome, *n* (%)	N=484
Developed biphasic reaction	71 (14.7)
Discharged from ED	466 (96.3)
Admitted to intensive care unit	3 (0.6)
Admitted to general pediatric ward	21 (4.3)
Referred to an allergy specialist (*n*=157)*	125 (79.6)
Discharge diagnoses, *n* (%)	
Anaphylaxis	294 (60.7)
Allergic reaction	174 (36)
Urticaria	4 (0.8)
Biphasic anaphylaxis	2 (0.4)
Exercise-induced anaphylaxis	9 (1.8)
Angioedema	1 (0.2)
Discharge treatments, *n* (%)	
Epinephrine auto-injector	387 (80)
H_1-antihistamine	191 (39.5)
Systemic steroids	79 (16.3)

*** Among 157 episodes with new allergy triggers**

5.2.5 Incidence of Anaphylaxis

During the study period, 322 anaphylaxis ED visits, among approximately 65,000 total visits, presented to the Children's Hospital of Eastern Ontario in Ottawa; 162 ED visits, among approximately 58,000 total visits, presented to the Hospital of Sick Children in Toronto. Therefore, we estimated a weighted average incidence of 3.8 anaphylaxis visits per 1000 ED presentations.

5.2.6 Characteristics of Biphasic Reactions

Biphasic reactions were noted in 71 of 484 anaphylactic reactions (14.7%). The characteristics of these reactions are summarized in **Table 20**. The median age of this group was 6 years (IQR 2.7-10.1), and 51 (64.9%) were males. In 53 of 71 delayed reactions (74.6%), the onset of the reactions occurred prior to ED discharge (during the observation period after the initial anaphylactic reactions), with median time of onset of 4.7 h (IQR 3.3-6) from onset of the initial reaction. The rest occurred after discharge from the ED with median time of onset of 18.5 h (IQR 9.2-25.2) from onset of the initial reaction, as presented in **Table 20**. Anaphylactic episodes where the biphasic reactions occurred after ED discharge were less likely to be recognized initially by ED physicians as anaphylactic reactions (50% versus 88.7%, p= 0.001), or to be treated with epinephrine in ED (61.1% versus 92.3%, p=0.01), compared to anaphylactic episodes were the biphasic reactions occurred before ED discharge.

The clinical presentations of biphasic reactions involved three major body systems (**Table 20**). According to the rate of occurrence, these

symptoms and signs represent cutaneous manifestation in 59 reactions (85.5%), respiratory manifestation in 28 (40%), and cardiac manifestation in 18 (25.7%) reactions. Although 49 of the 71 (69%) delayed reactions involved respiratory and/or cardiovascular manifestations, only 35 (49%) treated with epinephrine. The treatment interventions for the 71 biphasic reactions that were given with and without epinephrine are summarized in **Table 20.**

Table 21 shows time interval comparisons between biphasic and uniphasic groups. Compared to the uniphasic group, median time from reaction onset to ED presentation was longer in the biphasic group (96 min versus 75 min) ($p=0.03$) with longer length of ED stay (5.9 h versus 4.5h) ($p<0.001$). However, the median time from triage to MD assessment was shorter (13 min versus 24 min) ($p<0.001$) in the biphasic group.

Table 20- Characteristics of Patients who Developed Biphasic Reactions

Characteristics	*n*=71
Demographics	
Age (yr), Median (IQR)*	6 (2.7-10.1)
Age range, *n* (%)	
<2 years	11 (15.5)
2-5 years	24 (33.8)
6-9 years	18 (25.4)
10-13 years	10 (14.1)
>=14 years	8 (11.3)
Male, n (%)	51 (71.8)
Hospital site, *n* (%)	
Children's Hospital of Eastern Ontario-Ottawa	49 (69.1)
The Hospital for Sick Children-Toronto	22 (30.9)
Arrival status	
Arrival by ambulance, *n*(%)	20 (28.2)
Heart rate (beats/min), mean (SD)	117.4 (27.3)
Respiratory rate (breaths/min), mean (SD)	26.8 (7.7)
Systolic blood pressure (mm Hg), mean (SD)	108.1 (13.5)
Diastolic blood pressure (mm Hg), mean (SD)	61.7 (13.9)
SaO2 by oximetry, Median (IQ range)	99 (97-100)
Onset of the biphasic reaction, *n* (%)**	
Before ED discharge	53 (74.6)
After ED discharge	18 (25.4)
Clinical manifestations of the biphasic reaction, *n* (%)	
Cutaneous	59 (85.5)
Respiratory	28 (40)
Gastrointestinal	8 (11.3)
Cardiac	18 (25.7)
Neurologic	3 (4.2)
Treatment given in ED for the biphasic reaction, *n* (%)	
Oxygen	7 (9.8)
Epinephrine	35 (49.3)
Inhaled Salbutamol	13 (18.3)
H_1-antihistamine	47 (66.2)
H_2-antihistamine	16 (22.5)
Systemic steroids	27 (38)
Intravenous fluid	12 (16.9)
Magnesium sulfate infusion	1 (1.4)

* IQR=Interquartile range

** In relation to ED presentation for the primary anaphylactic reaction

Table 21- Time Intervals Comparison Between Biphasic and Uniphasic Episodes

Variable	Biphasic (n= 71)	Uniphasic (n= 413)	P-value
Time (min) from onset of the reaction to ED presentation, median (IQR)*	96 (53-173)	72 (51-121)	0.03
Delay in presentation to ED of >90 min from onset of the initial reaction, *n* (%)	39 (54.9)	158 (38.2)	0.01
Time (min) from triage to MD assessment, median (IQR)	13 (9-28)	24 (14-48)	<0.001
Length of ED stay (h), median (IQR)	5.9 (4.7-7.5)	4.5 (2.9-6)	<0.001
Time (h) from onset of the initial reaction to onset of biphasic reaction			
BP reaction before ED discharge, median (IQR)(n=53)	4.7 (3.3- 6)		
BP reaction after ED discharge, median (IQR)(n=18)	18.5 (9.2-25.2)		

* IQR=Interquartile range

5.2.7 Predictors of Biphasic Reactions

Univariate Analysis

Table 22 shows the univariate association of demographics and medical history variables with biphasic reactions. There was no difference between biphasic and uniphasic groups in regards to sex and to median age; however the proportion of children 6-9 years having a biphasic reaction was higher than the uniphasic (25.5% versus 13.1%) and lower among children less then two years of age (15.5% versus 25.9%) (p=0.03). Children who developed BPR were, in general, more likely to have a previous history of food allergy, compared to children in the uniphasic group (69% versus 59.1%), but this difference did not reach statistical significance. None of the other historical variables (atopic diseases, multiple allergen triggers, or locations of exposure to the culprit allergen) were associated with biphasic reactions.

The association of biphasic reactions with variables of the physical examinations is shown in **Table 23**. Among all vital signs, widened pulse pressure at initial triage presentation was the only variable associated with the BPR (p=0.01). Wide pulse pressure is defined by the 2010 PALS guidelines as diastolic blood pressure that is ≤ half of systolic blood pressure. Children who developed BPR were more likely to have respiratory symptoms (90.1% versus 83.1%) and >4 systems involvement (7% versus 2.2%) however, none of these associations were statistically significant.

Table 24 shows the association of therapeutic interventions for the initial anaphylactic reaction with the subsequent development of BPR. Overall, patients in the biphasic group received more treatment interventions

compare to patients in the uniphasic group. Children who developed BPR are more likely to receive oxygen (11.1% versus 4.1%) (p=0.02) and inhaled salbutamol (32.4% versus 18.8%) (p=0.02) in ED, compared to those with uniphasic reactions. In regards to epinephrine treatment, patients that subsequently developed biphasic reactions were more likely to receive epinephrine treatment (77.5% versus 61.5%) (p=0.01), to be treated with more than one dose of epinephrine (14.1% versus 6.5%) (p=0.03), and to receive a higher total median dose of epinephrine (0.25mg versus 0.20mg) (p=0.01). However, median time from onset of the reaction to first epinephrine, route, and settings of first dose were not statistically different between the two groups. In addition, BPR was highly associated with intravenous fluid therapy in ED compared to the uniphasic group (30% versus 7.3%) (p<0.001).

Finally, neither H_1 or H_2-antihistamines, nor steroids treatment of the initial reactions was associated with the prevention of BPR. In fact, the proportion receiving steroid therapy was higher in the biphasic group (60.6% versus 50.6%) compared to the uniphasic group. However; this difference was not statistically significant regardless of the total dose, time, or steroids formulation administered.

Table 22- Univariate Correlation with Biphasic Reactions for Variables from History for 484 Anaphylaxis Episodes

Characteristics	Biphasic (n= 71)	Uniphasic (n= 413)	P-value
Demographics			
Age (yr), Median (IQR)*	6 (2.7-10.1)	4.7 (1.9-11.2)	0.40
Age range, *n* (%) <2 years 2-5 years 6-9 years 10-13 years >=14 years	 11 (15.5) 24 (33.8) 18 (25.4) 10 (14.1) 8 (11.3)	 107 (25.9) 128 (31) 54 (13.1) 54 (13.1) 70 (16.9)	0.03
Male, n (%)	51 (71.8)	263 (63.7)	0.23
Allergy history, *n*(%)			
Food	49 (69)	244 (59.1)	0.11
Environmental	9 (12.7)	63 (15.3)	0.72
Drugs	6 (8.5)	38 (9.2)	1
Past history, *n* (%)			
Carry epinephrine auto-injector	39 (54.9)	197 (47.7)	0.30
Anaphylactic reaction	24 (33.8)	132 (32)	0.78
Biphasic allergic reaction	2 (2.8)	11 (2.7)	0.50
Asthma	32 (45.1)	178 (43.1)	0.88
Allergic dermatitis	29 (40.8)	158 (38.3)	0.69
Allergic rhinitis	3 (4.2)	20 (4.8)	0.63
Causative agents of current anaphylactic episode, *n* (%)			
Food (total) Peanut Tree nut Milk Egg Seafood	47 (66.2) 18 (25.4) 12 (16.9) 5 (7) 5 (7) 4 (5.6)	291 (70.5) 113 (27.4) 70 (16.9) 22 (5.3) 23 (5.6) 22 (5.3)	0.49 0.77 1 0.57 0.58 1
Drugs and medications	3 (4.2)	8 (1.9)	0.21
Exercise	1 (1.4)	8 (1.9)	1
Bee sting	1 (1.4)	7 (1.7)	1
Unspecified	15 (21.1)	67 (16.2)	0.31
Settings of current anaphylactic episode, *n* (%)			
Home	50 (70.4)	281 (68)	0.78
Restaurant	5 (7)	44 (10.7)	0.52
Outdoor	2 (2.8)	29 (7)	0.29
School/Daycare	10 (14.1)	31 (7.2)	0.17
Unspecified	4 (5.6)	28 (6.8)	1

* IQR=Interquartile range

Table 23- Univariate Correlation with Biphasic Reaction for Variables from Physical Examination for 484 Anaphylaxis Episodes

Variable	Biphasic (n= 71)	Uniphasic (n= 413)	P-value
Triage vital signs, *n*(%)			
Tachycardia*	25 (35.2)	124 (30.2)	0.39
Tachypnea**	15 (21.1)	81 (19.6)	0.77
Hypotension¶	1 (1.4)	3 (0.8)	0.49
Wide pulse pressure¶¶	32 (46)	112 (29.5)	0.01
Oxygen saturation <95%	2 (3)	8 (2)	0.65
Clinical manifestations, *n*(%)			
Cutaneous	69 (97.2)	402 (97.3)	1
Respiratory	64 (90.1)	343 (83.1)	0.16
Gastrointestinal	33 (46.5)	185 (44.8)	0.79
Cardiac	13 (18.3)	68 (16.5)	0.73
Neurological	12 (16.9)	81 (19.6)	0.74
Number of systems involved, *n* (%)			
2 3 4 5	36 (50.7) 24 (33.8) 6 (8.5) 5 (7)	211 (51.1) 158 (38.3) 35 (8.5) 9 (2.2)	0.15

* Defined as per Pediatric Advanced Life Support (PALS) guidelines:[167] awake heart rate>190 beat/min for age 3 months-2 years, >140 beat/min for age 3-10 years, and >100 beat/min for age>10 years.

** Defined as per PALS guidelines[167] : respiratory rate>60 breath/minute for age <1 year, >40 breath/minute for age 1-3 years, >34 breath/minute for age 4-5 years, >30 breath/minute for age 6-12 years, and >16 breath/minute for age 13-18 years.

¶ Defined as per PALS guidelines[167] : systolic blood pressure <70 mmHg for age 1-12 months, <70 mmHg +(age in yearsx2) for age 1-10 years, and <90 mmHg for age >10 years.

¶ ¶ Defined as diastolic blood pressure that is ≤half of systolic blood pressure[167]

Table 24- Univariate Correlation with Biphasic Reactions for Variables from Therapy Administered for 484 Anaphylaxis Episodes

Variable	Biphasic (n= 71)	Uniphasic (n= 413)	P-value
Oxygen in ED, *n* (%)	8 (11.3)	17 (4.1)	0.02
BMV/airway, *n* (%)	2 (1.4)	0	1
Intubation, *n* (%)	1 (0.2)	0	1
Epinephrine			
Administered, *n* (%)	55 (77.5)	254 (61.5)	0.01
Number of doses, mean (SD)*	1.13 (0.34)	1.10 (0.34)	0.56
>1 dose administered, *n* (%)	10 (14.1)	27 (6.5)	0.03
Total dose administered (mg), median (IQR)	0.25 (0.15-0.3)	0.20 (0.15-0.3)	0.01
Route of administration of 1st dose, *n* (%) Intramuscular Subcutaneous	 54 (98) 1(2)	 247 (97) 7 (3)	 1
Settings of 1st administered dose, *n* (%) Scene of the reaction by caregiver During transport by EMS paramedics ED	 24 (43.6) 5 (9.1) 26 (47.3)	 105 (41.3) 18 (7.1) 131 (51.6)	 0.79
Time (min) from onset of the reaction to 1st dose, median (IQR)	64 (25-175)	59 (25-105)	0.35
Inhaled salbutamol in ED, *n* (%)	23 (32.4)	78 (18.8)	0.02
H_1-antihistamine			
Administered, *n* (%)	59 (83.1)	337 (81.6)	0.87
Total dose administered (mg/kg), mean (SD)	0.80 (0.47)	0.78 (0.51)	0.76
H_2-antihistamine in ED			
Administered, *n* (%)	14 (19.7)	67 (16.2)	0.49
Total dose administered (mg/kg), mean (SD)	1.7 (0.9)	2 (1.2)	0.48
Time (min) from onset of the reaction to 1st dose, median (IQR)	126 (99-184)	120 (79-180)	0.51
Systemic steroids in ED			
Administered, *n* (%)	43 (60.6)	209 (50.6)	0.13
Total dose administered (mg/kg)**, median (IQR)	1.55 (1-2.2)	1.85 (1-2.2)	0.99
Time (min) from onset of the reaction to 1st dose, median (IQR)	120 (87-256)	125 (85-205)	0.93
Formulation, *n* (%) Dexamethasone Hydrocortisone Methylprednisolone Prednisolone	 18 (41.9) 4 (9.3) 9 (20.9) 12 (27.9)	 114 (54.5) 17 (8.1) 24 (11.5) 54 (25.8)	 0.30
Intravenous fluid in ED			
Administered, *n* (%)	21 (30)	30 (7.3)	<0.001
Total dose administered (ml/kg), median (IQR)	18.8 (14.4-20)	12.6 (6.4-20)	0.11

*Standard deviation of the mean

** Steroid doses converted to prednisolone equivalent (1 mg dexamethasone = 6.67 mg prednisolone; 1 mg methylprednisolone = 1.25 mg prednisolone; 1 mg hydrocortisone = 0.25 mg prednisolone)

Multivariate Logistic Regression

Model Development

The following variables with p value <0.2 in the univariate analysis were entered in the initial model:

1. “age in 5 categories”, reference level=age ≥14 years,
2. “previous history of food allergy”,
3. “wide pulse pressure at triage”,
4. “respiratory manifestations on physical exam”,
5. “number of systems involved in physical exam”,
6. "oxygen therapy in ED",
7. "epinephrine treatment", (reference level=yes)
8. “>1 dose of epinephrine treatment administered",
9. "inhaled salbutamol therapy in ED",
10. "systemic steroid administration in ED",
11. "intravenous fluid administration in ED", and
12. “time from onset of the reaction to ED presentation>90 min".

For the above categorical variables, we used a reference level=no unless otherwise specified. Instead of using the continuous variable "time from onset of the reaction to ED presentation", we created a new dummy dichotomous variable with ≥90 minutes as a cut-off point for delayed presentation to ED for two reasons. First, several previous studies showed delayed ED presentation and delayed administration of first epinephrine treatment after the onset of an anaphylactic reaction are associated with BPR. As shown in **Table 7**, most of these studies report a delay of >60-90 minutes. In addition, recent studies that investigated the role of PAF in human anaphylaxis indicate that serum PAF levels are significantly increased and

correlate directly with the severity of anaphylaxis.[169,170] This mediator peaks at 60-90 minutes from onset of the reaction.[171] Using human vascular smooth muscle cells, Vadas et al examined the effect of timing of epinephrine addition on the action of PAF and found that epinephrine was most effective when administered before stimulation with PAF, and was progressively less effective with time after PAF stimulation.[172] These cumulative lab and clinical reports, therefore, support this time cut-off point. Other variables selected in the initial model are also supported by previous studies in the literature as summarized in **Table 8**.

We assessed for co-linearity between the included variables using a Pearson correlation and found a moderate, but statistically significant correlation between 2 variables: “intravenous fluid administration in ED” and “wide pulse pressure at triage” (correlation coefficient =0.48, $p<0.001$). Therefore, we suspected that the “intravenous fluid administration in ED” variable might be a potential confounder. We ran the analysis with and without this variable and found 15% change in the maximum likelihood of the “wide pulse pressure at triage” variable between a full and reduced model. We therefore removed the “intravenous fluid administration in ED” variable from the included predictors in the regression model. Based on previous research associating asthma and BPR, we also explored the possibility of the following variables being potential confounders: “respiratory manifestations on physical exam”, “previous history of food allergy” and "inhaled salbutamol therapy in ED". We did the regression analysis with and without these predictors in the model, and noticed no significant change in the maximum likelihood of "inhaled salbutamol therapy in ED".

The standardized Pearson residual did not identify any significant outliers (cut-off point ±3 used as a reference). Also, DfBeta for each variable in the model did not identify any significant outlier or influential observations.

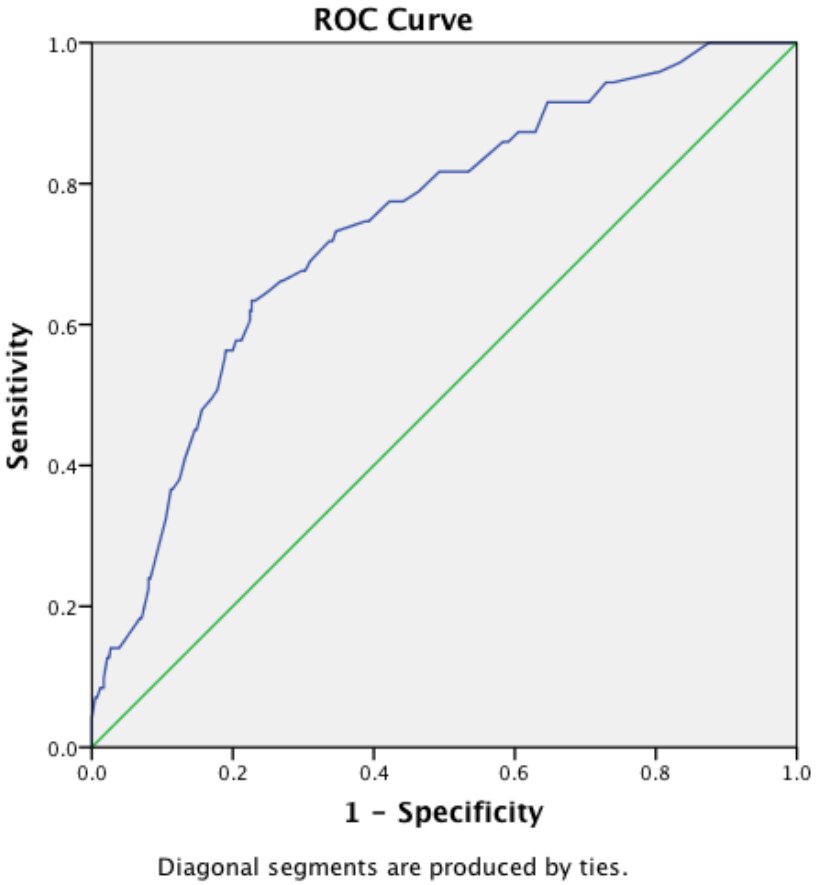
Final Logistic Regression Model

The final regression model identified the following five independent predictors of biphasic reactions: age 6-9 years (OR 3.60; 95%CI 1.5-8.58), time from onset of the anaphylactic reaction to ED presentation >90 minutes (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 reaction with >1 dose of epinephrine (OR 2.70; 95%CI 1.12-6.55), and administration of inhaled Salbutamol in ED (OR 2.39; 95%CI 1.24-4.62). **Table 25** shows the p value and β coefficient estimates for these predictors. This model was based on 481 patient visits, with no missing data. It has a sensitivity of 95.8% (95% CI 88.1-99.1%) and a specificity of 19.5% (95% CI 15.8-23.7%) in predicting a biphasic reaction after an anaphylactic episode. The p value for the Hosmer-Lemeshow goodness-of-fit is 0.697 and the area under ROC curve **Figure 3** is 0.742 (95% CI = 0.682 to 0.803) which indicate good fitting of the model.

Table 25- Independent Predictors of Biphasic Reactions as Determined by Stepwise Logistic Regression Analysis for Anaphylaxis Episodes*

Variable	β	P value	Odds Ratio	95% CI
Age 6-9 years	1.28	0.01	3.60	1.5-8.58
Time from onset of the reaction to ED presentation >90 min	0.95	0.001	2.58	1.47-4.53
Wide pulse pressure at triage	1.07	<0.001	2.92	1.69-5.04
Treatment of the reaction with >1 dose of epinephrine	0.99	0.03	2.70	1.12-6.55
Administration of inhaled Salbutamol in ED	0.87	0.01	2.39	1.24- 4.62
Intercept	-3.36	<0.001	0.04	

*Model developed for 481 patient visits without missing values



Area under ROC curve = 0.742; 95% CI = 0.682 to 0.803

Figure 3- Receiver Operating Characteristics Curve for the Final Logistic Regression Model

5.3 Discussion

5.3.1 Main Findings

Our multicentre study examined children presenting to the ED with anaphylaxis and found the incidence of anaphylaxis in Canada to be 3.8 per 1000 pediatric ED visits. Most anaphylactic reactions occurred at the patient's residence, and were triggered primarily by foods. Surprisingly, epinephrine treatment was the second most common administered therapeutic intervention, after H_1-antihistamines. Epinephrine was administered in two-third of the initial anaphylaxis episodes of this cohort, with approximately half of these treatments administered before the ED arrival. However, only around half of the anaphylaxis episodes attended to and transported to hospital by EMS paramedics received epinephrine on route.

Our main findings of a set of risk factors associated with biphasic reactions included: delay in presentation to ED of >90 minutes from onset of anaphylaxis, wide pulse pressure at triage, treatment of the anaphylactic reaction with >1 dose of epinephrine, administration of inhaled salbutamol therapy in ED, and being aged 6-9 years. Taken altogether, those predictors indicate that children with severe initial anaphylaxis are more likely to develop subsequent biphasic reactions. We also found the incidence of biphasic reaction among this population to be about 15%. Approximately three-quarters of these reactions occurred within 6 hours of the initial reaction onset. Furthermore, almost half of the biphasic reactions were anaphylactic in nature and were severe enough to be treated with epinephrine.

5.3.2 Previous Studies

Incidence of anaphylaxis in ED

Our reported incidence is consistent with the trend of increasing numbers of pediatric anaphylaxis visits over the last few years. Previous pediatric ED studies reported an incidence of 0.32-3.8 per 1000 ED visits.[25–30,36,173] It should be noted that these studies vary in the geographical location, the investigated timeline, and causative allergens (food-induced vs all triggers). Nevertheless, epidemiological studies suggest that the highest incidence of pediatric anaphylaxis is in North America. These studies reported an incidence of approximately 2-4 per 1000 pediatric ED visits.[27,36,173] Rudders et al noticed an increase in the rate of food-induced anaphylaxis presenting to a pediatric ED in Boston between 2001 and 2006 from around 1.5 to 3.8 per 1000 ED visits.[173] It is possible that this increase in incidence may simply be due to better diagnosis, resulting from the widespread implementation of the 2006 National Institute of Allergy and Infectious Disease diagnostic criteria, and from better reporting.

Epinephrine

We found a high rate of epinephrine treatment,64%, and epinephrine prescription on discharge, 80%,. Although these are substantially higher rates compared to other centres,[25,28,138] they are similar to recent reports from other North American centres.[27,136] The literature suggests that moderate-severe allergic reactions are more likely to be treated with epinephrine compared with mild reactions.[174,175] We found around two-thirds of anaphylactic episodes not treated with epinephrine were perceived as mild, hence the ED discharge

diagnosis of “allergic reaction” rather than “anaphylaxis”. It is possible that physicians based their decision for epinephrine administration on seemingly mild clinical manifestations upon ED arrival, regardless of the severity of the symptoms at onset. Up to 42% of epinephrine treatments for this cohort were administered by patients/caregivers before arrival to ED, which reflects a relatively high use of epinephrine auto-injectors compared to previous literature (24-27%).[36,146] Furthermore, the proportion of anaphylactic episodes treated with epinephrine before transport to hospital by EMS paramedics is relatively high (56%) when compared with previous studies (9-36). However, this rate is definitely suboptimal.

Adjunctive therapies

Despite their delayed onset of action and unproven efficacy, previous studies consistently showed that antihistamines and corticosteroids are more frequently used than epinephrine when treating anaphylaxis.[67-69,137] Therefore, the updated European Association of Allergy and Clinical Immunology anaphylaxis guidelines published in 2014 de-emphasized the use of these therapies by classifying them as “third line” therapies, and recommended against delaying epinephrine by the use of these medications.[97] Our finding of the epinephrine being administered in ED more than systemic steroids and H_2-antihistamines is an encouraging trend when compared with previous studies. In a multicentre registry of more than two thousand patients with severe anaphylaxis from several European countries, Grabenhenrich et al found that almost 50% recieved antihistamines and corticisteroids in the ED, however less than15% of that cohort recived epinephrine. Unfortunately,

several recent pediatric ED studies showed similar low rate of epinephrine use compared to other therapies.[26,35]

Epidemiology of biphasic reactions

There is a wide range in the previous literature's reported incidence of biphasic reactions, ranging from 3-23%.[10,11,18-33] These studies vary considerably in their design (prospective vs. retrospective); enrolled population (adults vs. children or mixed); and definition of the severity of anaphylaxis and biphasic reactions. These epidemiological factors should be carefully considered when making data comparisons. The overall incidence of biphasic reactions, approximately 15% in our study, is slightly higher than previously reported pediatric studies, 6% in the Lee and Greens study and 11% in the Mehr et al study.[23,33] These studies, however, looked at patients from more than two decades ago, a time predeceasing a documented increase in the rate and perhaps the severity of anaphylaxis.[4-7] Perhaps the nature of our cohort of children with biphasic reactions was more severe than previously reported in the literature, which could be a factor in our higher rate of biphasic reactions. The reported incidences from previous ED studies of adult or mixed pediatric and adult population are similar to our estimated incidence.[19,22,31,32,36]

Predictors of biphasic reactions

Little is known of the nature and the pathophysiology of biphasic reactions.[37] In the next few paragraphs, we will try to make sense of our predictors by comparing them with current evidence from both basic science

and clinical literature. We will discuss the association of biphasic reaction with the severity of initial anaphylaxis; delayed ED presentation and epinephrine treatment; and asthma or inhaled salbutamol for respiratory distress.

Anaphylaxis severity

The association of biphasic reactions with the severity of the initial reaction has just recently emerged as a potential mechanism. In 1992, Sampson et al reported a series of 13 children with anaphylaxis, of which three proved to be fatal.[14] Then, in 1994, Douglas et al reported a series of four adult patients with biphasic reactions, two of whom presented initially with hypotension.[13] Subsequently, Smit et al, among several other studies, reported similar findings.[22,28,31] Although these studies provide some insight into this association, the reported cases are too small to reliably predict this association. Also, the definition of "severity" among these studies is inconsistent and not based on objective scoring. Nevertheless, to date the most robust documentation of this association, incorporating immunological mediators and clinical severity scoring, was recently published by Brown et al.[37] In their prospective cohort study of adults with anaphylaxis, biphasic reactions were found to be associated with the severity of the initial reaction (particularly hypotension). The authors hypothesized that biphasic reactions are the result of a protracted inflammatory response.[37] Our identified predictors strongly support this association. We demonstrated that children with biphasic reactions had higher triage acuity score; a manifestation of anaphylactic shock with widened pulse pressure; needed multiple epinephrine treatments for their initial reaction; and had respiratory distress that required

treatment with inhaled salbutamol, when compared to those with uniphasic reactions.

Delayed epinephrine treatment

The other major factor associated with biphasic reactions is delayed epinephrine treatment for the initial reaction, or delayed ED presentation. We showed that delayed presentation to ED is a risk factor for a biphasic reaction, which is consistent with previous literature.[14,22,23,27,34] In addition, recent studies that investigated the role of platelet activating factor (PAF) in human anaphylaxis indicate that serum PAF levels are significantly increased, and correlate directly, with the severity of anaphylaxis.[37,39] This mediator peaks roughly at 60-90 minutes after the reaction onset.[40] Using human vascular smooth muscle cells, Vadas et al examined the effect of the timing of epinephrine addition on the action of PAF, and found that epinephrine was most effective when administered before stimulation with PAF but was progressively less effective with time after PAF stimulation.[41] Therefore, our subgroup analysis, combined with cumulative evidence from previous lab and clinical reports, support timely treatment with epinephrine within 90 minutes of onset of an allergic reaction.

Multiple epinephrine treatment

The association made between multiple doses of epinephrine treatments for an initial reaction with the subsequent development of biphasic reactions is consistent with several studies in the literature.[105,111,112,115,116,119] Treatment of the anaphylaxis with multiple doses of epinephrine has been

shown to correlate with severe reactions.[27,39] A recent study by Huang et al found children treated with 2 doses of epinephrine were more likely to be hospitalized and admitted to the intensive care unit than those treated with one dose.[27]

Asthma and inhaled salbutamol

Although several studies of adult patients showed asthma as a risk factor for fatal anaphylaxis and delayed reaction,[54,105,113,169] we found, as did previous pediatric studies, no association between asthma and biphasic reactions.[111,116,121] It should also be noted that treatment with inhaled salbutamol is not a proxy for asthma, as wheezing and lower airway symptoms causing respiratory distress have also been found to manifest in children and adults with anaphylaxis without underlying asthma.[29,169]

5.3.3 Strengths

To our knowledge, this is the first and largest Canadian study investigating the incidence of anaphylaxis presenting to two large pediatric hospitals. We describe, with reasonable details, many aspects of anaphylaxis management, in both pre-hospital and ED settings, with primary focus on epinephrine. Furthermore, our study presents the largest cohort of patients with biphasic reactions found in the literature. We used a standard definition of anaphylaxis and of biphasic reactions, and were able to identify clinically sensible predictors. Also, our data provides a clear description of the time, onset, and nature of pediatric biphasic reactions.

5.3.4 Limitations

We identified several limitations to our study; some related to the study design and others are secondary to the collected data and statistical analysis. The health record review is inherently subject to several limitations. Based on the study design, we are not confidently able to eliminate the possibility of missing follow up; it is possible that some patients developed biphasic reactions after discharge and did not return to ED. This may have resulted in an underestimation of the actual biphasic reaction rate, which is less concerning to us compared to overestimation. We also did not investigate the trend of anaphylaxis incidence over time. The prohibitive time and financial costs associated with such work were candidate's capacity. A prospective study design and data collection is an ideal research method to overcome these limitations in the future. Finally, multiple anaphylaxis severity scores exist in the literature. However, these scores are not well validated for use in the pediatric population. In addition, the majority of these scores consist of subjective indicators; applying any of those scores to our retrospectively collected data might result in differential misclassification and measurement error.

There are several limitations related to our collected data and statistical analysis. Despite our best effort to overcome missing data by using multiple sources, we still had missing data, especially regarding the timing of events that occurred before ED arrival. In addition, given the stress of the condition, the reported time by patients/caregivers for some variables, such as epinephrine administration before presentation to the ED, may not be accurate. Therefore, findings derived from such variables should be

interpreted with caution. Furthermore, we did not account for potential anaphylaxis triggers. A recent study from Germany reported that 18% of children have aggravating factors for their anaphylaxis, such as coexisting infection, psychological stress, and menses.[42] These aggravating factors (also called co-factors or patient risk factors) are believed to increase the inflammatory response.[1,43] This is a new concept in the field and, unfortunately, we were not able to investigate any of those triggers after completion of our data collection. It is not clear, however, if these factors increase the risk of severe anaphylaxis and ultimately, of biphasic reactions. In our analysis, we only used the traditional multiple logistic regression method for predictor derivation. Had we used another method, such as the recursive partitioning method, our analysis and ultimately derived predictors would have been more statistically robust. We did not derive risk factors scoring and sensitivity analysis because we did anticipate a large number of outcomes that would be reasonably sufficient to perform such analysis. We discussed ways to address the above limitation in the “future implications” section to follow.

5.3.5 Future Implications

The findings from this study have several implications for clinical practice and for future research.

Clinical implications

1- Not all children with anaphylaxis need to be observed for 6-8 hours

Children with severe initial reactions appear to be more likely to

develop biphasic reactions and, in particular, may benefit from a prolonged period of observation. Emergency physicians may use our predictors as a tool to objectively identify patients with potentially severe anaphylaxis who would benefit from prolonged monitoring. When identified, our findings support an observation period of at least 6 hours, timed from the onset of the initial anaphylactic reaction. Since the majority of anaphylaxis episodes in children are mild, observing all of those children in ED for 6-8 hours, as recommended by most guidelines, is unnecessary and is an inefficient patient flow strategy, as it limits departmental resources. Given the relatively high sensitivity of our predictors, children with initially mild anaphylaxis and who do not match any of our predictors could be considered for early disposition from the ED (<6 hours), as long as an appropriate counselling has been provided.

2- There is no clear benefit of systemic steroids in preventing biphasic reactions

The effect of steroids as treatment of severe anaphylaxis or as prevention of biphasic reactions has never been proven.[44–47] Although our study was not primarily designed nor powered to assess the efficacy of systemic steroids, our findings concurred with several reports from the literature about the lack of benefit of systemic steroids in preventing biphasic reactions.[13,19–21,23,25,27–29,34] Being the largest study to date examining this indication, our findings challenge the current recommendation of some international anaphylaxis guidelines, as well as the Pediatric Advanced Life Support guidelines advising the administration of systemic steroids to children in anaphylactic shock.

Research implications

1-Revised diagnostic criteria for anaphylaxis in children are needed

Although the diagnostic criteria for anaphylaxis have a reasonably high sensitivity, their practical application is undoubtedly challenging, particularly in children. Until better, objective diagnostic criteria or rapidly available, sensitive biomarkers are developed, anaphylaxis will likely continue to be misdiagnosed and undertreated. Currently, there are no child-specific criteria. Therefore, there is a need for revised clinical diagnostic criteria targeting this population that is objective and easily applied to emergency settings. We propose focusing on the respiratory and cardiovascular manifestations to drive this tool, as they are the most life-threatening systems affected by anaphylaxis, and the systems on which epinephrine is most effective. This tool may aid emergency physicians to establish an unequivocal anaphylaxis diagnosis and, ultimately increase the number of children treated appropriately.

2- Research to explore Canadian EMS paramedics' knowledge of pediatric anaphylaxis

The relatively low rate of epinephrine administration by EMS paramedics is concerning. It is difficult to make infer from non-Canadian reports, since there are significant variations in EMS provider training, not only interprovincially, but also within different regions in one province. In addition, there is substantial variation in regional protocols and scope of practices cross the different paramedic levels. Therefore, there is a need for further qualitative

research exploring Canadian EMS paramedics' knowledge of pediatric anaphylaxis. Such studies should also explore their behaviours and attitudes toward epinephrine administration for children with anaphylaxis. Findings from this will help identify need for future knowledge translation efforts. They will also guide future interventional studies, which may include continuing education and protocol changes, in order to help increase epinephrine administration frequency for anaphylactic reactions in children, thus reducing the potential of mortality and morbidity.

3- Large prospective cohort studies to validate our predictors and to develop severity scoring

Having derived clinical predictors for biphasic reactions in children with anaphylaxis, the next step in prediction methodology would be to perform a prospective validation of the predictors. Before embarking on a prospective international multicentre study to validate our predictors, we are planning to conduct a single centre prospective study at the Children's Hospital of Eastern Ontario to internally validate our identified predictors, using both logistic regression and recursive partitioning methods, and derive a risk scoring system. These studies should explore the link between severity of initial anaphylaxis and the subsequent development of biphasic reactions. These studies may use our predictors to develop a simple, objective severity score that can be implemented in emergency physicians' clinical practice. In addition, we presently have no plausible clinical explanation for the increased susceptibility of children between the ages of 6-9 years to biphasic reactions.

Therefore, the underlying biological mechanism behind this association needs to be explored by future research.

4- Experimental studies to assess the efficacy of adjunctive therapies

Although the findings from the recent trial by de Silva et al raise concerns about the safety of steroids in preventing anaphylaxis,[48] a robust evidence from a prospective randomized clinical trial is needed to specifically address the safety and efficacy of systemic steroids and H_2-antihistamines in preventing biphasic reactions in children. The primary outcome of these studies should be the development of biphasic reactions and should only enrol children treated with epinephrine for their initial anaphylaxis. A factorial design may be ideal to conduct an experimental study in order to investigate the interaction between systemic steroids and H_2-antihistamines.

Conclusions

Compared to other pediatric ED studies from different countries, our results highlight that anaphylaxis is a major health problem in Canada. We also found anaphylaxis to be commonly under-recognized by patients and caregivers. In addition, emergency physicians and EMS paramedics frequently underuse epinephrine as the first-line therapy. Revised anaphylaxis diagnostic criteria, which are objective and specific to children, are needed in order to increase the number accurate pediatric anaphylaxis diagnoses and, in turn, contribute to the appropriate ED management.

Our study clarifies the nature and epidemiology of biphasic reactions. In children with anaphylaxis, biphasic reactions are relatively common, and

often occur within 6 hours from onset of the initial reaction. We found five clinical predictors of biphasic reactions: delay in presentation to ED of >90 minutes from onset of anaphylaxis, wide pulse pressure at triage, treatment of the anaphylactic reaction with >1 dose of epinephrine, administration of inhaled salbutamol therapy in ED, and the age of the child between 6-9 years. These predictors seem to associate biphasic reactions with the severity of the initial anaphylactic reactions, and could ultimately be used to identify patients who would benefit from prolonged ED monitoring. In agreement with previous literature, our results question the role of systemic steroids in preventing biphasic reactions. Applying these findings to clinical practice may enable efficient resource utilization and improve to the overall quality of patient care provided by physicians in Canadian emergency departments.

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Appendix A-1: Anaphylaxis Survey Questionnaire

A. First Scenario:

A mother brings her 18 month old boy to your ED. He is not known for any allergies and his past medical history is unremarkable except for mild eczema. His mother states that he had a peanut butter sandwich 1 hour ago and within 30 minutes he started vomiting and crying. Triage vital signs: T 37 ^{0}C, HR 90/min, BP 96/50, RR 30/min, and O2 saturation 98% on room air. He has wheezing and mild respiratory distress. He has no skin rash.

1- The most likely diagnosis of this child is: (please choose ONE option only)

- ☐ An allergic reaction but not anaphylaxis
- ☐ An anaphylactic reaction

2- In regard to management of this child in the ED, you would administer the following: (check all that apply)

- ☐ Systemic Epinephrine
- ☐ H_1-antihistamine like Diphenhydramine (Benadryl®)
- ☐ H_2-antihistamine like Ranitidine
- ☐ Systemic corticosteroid
- ☐ Inhaled bronchodilator like Salbutamol (Ventolin®)
- ☐ Other: _____

3- <u>After resolution of symptoms</u>, please tell us for how many hours you would observe this child in the ED:

- ☐ I will observe for _____ hours

4- Upon discharge of this child from the ED, I would do the following: (check all that apply)

- ☐ Prescribe epinephrine auto-injector
- ☐ Recommend an oral antihistamine for home use as needed
- ☐ Prescribe an oral corticosteroid
- ☐ Refer this child to an allergy specialist
- ☐ Other: _____

B. Second Scenario:

A 16-year-old girl is brought to the ED because of hives and cough soon after the ingestion of a snack bar containing mixed nuts 1 hour ago. She was given Diphenhydramine (Benadryl®) 50 mg and Salbutamol MDI (Ventolin®) 2 puffs at home. She has a history of allergy to peanuts and mild asthma in the past. On arrival to the ED, she is alert and cooperative. Triage vital signs: T 37 ^{0}C, HR 100/min, BP 125/55, RR 20/min, and O2 saturation 97% on room air. She has wheezing, mild respiratory distress and generalized urticaria.

1-The most likely diagnosis of this child is: (please choose ONE option only)

- ☐ An allergic reaction but not anaphylaxis
- ☐ An anaphylactic reaction

2- In regard to management of this child in the ED, you would administer the following: (check all that apply)

- ☐ Systemic Epinephrine
- ☐ H_2-antihistamine like Ranitidine
- ☐ Systemic corticosteroid
- ☐ Inhaled bronchodilator like Salbutamol (Ventolin®)
- ☐ Other: _____

3- <u>After resolution of symptoms</u>, please tell us for how many hours you would observe this child in the ED:

- ☐ I will observe for _____ hours

4- Upon discharge of this child from the ED, I would do the following: (check all that apply)

- ☐ Advise this child to use epinephrine auto-injector immediately for similar reaction in the future.
- ☐ Recommend an oral antihistamine for home use as needed
- ☐ Prescribe an oral corticosteroid
- ☐ Refer this child to an allergy specialist
- ☐ Other: _____

C. In your daily practice for management of pediatric patients who present to the ED with an anaphylactic reaction, please tell us the following:

1- In children with an anaphylactic reaction, I usually treat the reaction with the following dose (please chose one):

- ☐ Epinephrine 1:1000, (0.01mg/kg, Max of 0.3 -0.5 mg)
- ☐ Epinephrine 1:10,000, (0.01mg/kg, Max of 0.3 -0.5 mg)
- ☐ Epinephrine 1:10,000, (0.1mg/kg, Max of 1 mg)

2- In children with an anaphylactic reaction, I usually give epinephrine through the following route of administration (please choose one):

- ☐ Intramuscular
- ☐ Intravascular
- ☐ Subcutaneously

3- In children with an anaphylactic reaction, I usually monitor in the ED after resolution of symptoms for:

- ☐ <2 h
- ☐ 2-4 h
- ☐ 5-7 h
- ☐ 8-12h
- ☐ >12 h
- ☐ Observation period should be individualized, but minimum of ___hours

4- Upon disposition of a child with an anaphylactic reaction from the ED, how commonly do you provide the parents/child with a written action plan for anaphylaxis:

- ☐ Always
- ☐ Often
- ☐ Sometimes
- ☐ Rarely
- ☐ Never

5- ***Upon disposition of a child with an anaphylactic reaction from the ED, how would you rate your confidence level in demonstrating to parents and/or a child how to use epinephrine auto-injector?***

- ☐ Not confident
- ☐ Minimally confident
- ☐ Somewhat confident
- ☐ Confident
- ☐ Very confident

D. Demographics:

What is your sex?

- ☐ Female
- ☐ Male

What is your hospital setting?

- ☐ Academic with primarily **adult** population
- ☐ Academic with primarily **pediatric** population
- ☐ Community hospital
- ☐ Other, please specify:_____

What is the volume of patients seen in your Emergency Department (ED) per year?

- ☐ <20,000
- ☐ 20,000-39,999
- ☐ 40,000-59,999
- ☐ ≥60,000

What percentage of these patients are in the pediatric age group (0-18 yrs)?

- ☐ _____ %

What is your highest level of post-graduate medical training?

- ☐ CCFP/General Practice
- ☐ CCFP-EM
- ☐ FRCP-EM
- ☐ FRCP-Pediatrics
- ☐ FRCP-Pediatric EM
- ☐ Other (please state) _____

For how many years have you been working in Emergency Medicine (Full or Part Time)?

- ☐ _____Years

That's it! Thank you for taking the time to complete this questionnaire.

If you have any questions concerning the study please contact the research team.

Again, thank you very much for your time!

Appendix A-2: Sensibility Testing Tool

The investigators request your assistance in assessing the sensibility of this questionnaire that explore the practice pattern of Canadian Emergency Physicians (EP) in management of children with anaphylaxis by answering the following questions:

1. To what extent are the questions directed at important issues pertaining to practice pattern of Canadian EP in management of children with anaphylaxis (Please circle your response)

Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

2. Are there important issues pertaining to the practice pattern that should be included in the questionnaire which have been omitted? (Please circle your response)

Crucial Gaps	Important Gaps	Minor Gaps	Minimal Gaps	Insignificant Gaps

Please identify any omissions:

---

3. To what extent are the response options provided simple and easily understood? (Please circle your response)

Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

4. To what extent are questions likely to elicit information pertaining to your experience with management of children with anaphylaxis? (Please circle your response).

Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

5. How many items are inappropriate or redundant?
(Please circle your response).

Very Many	Many	Some	Few	Hardly Any

Please identify redundant or inappropriate items:

---

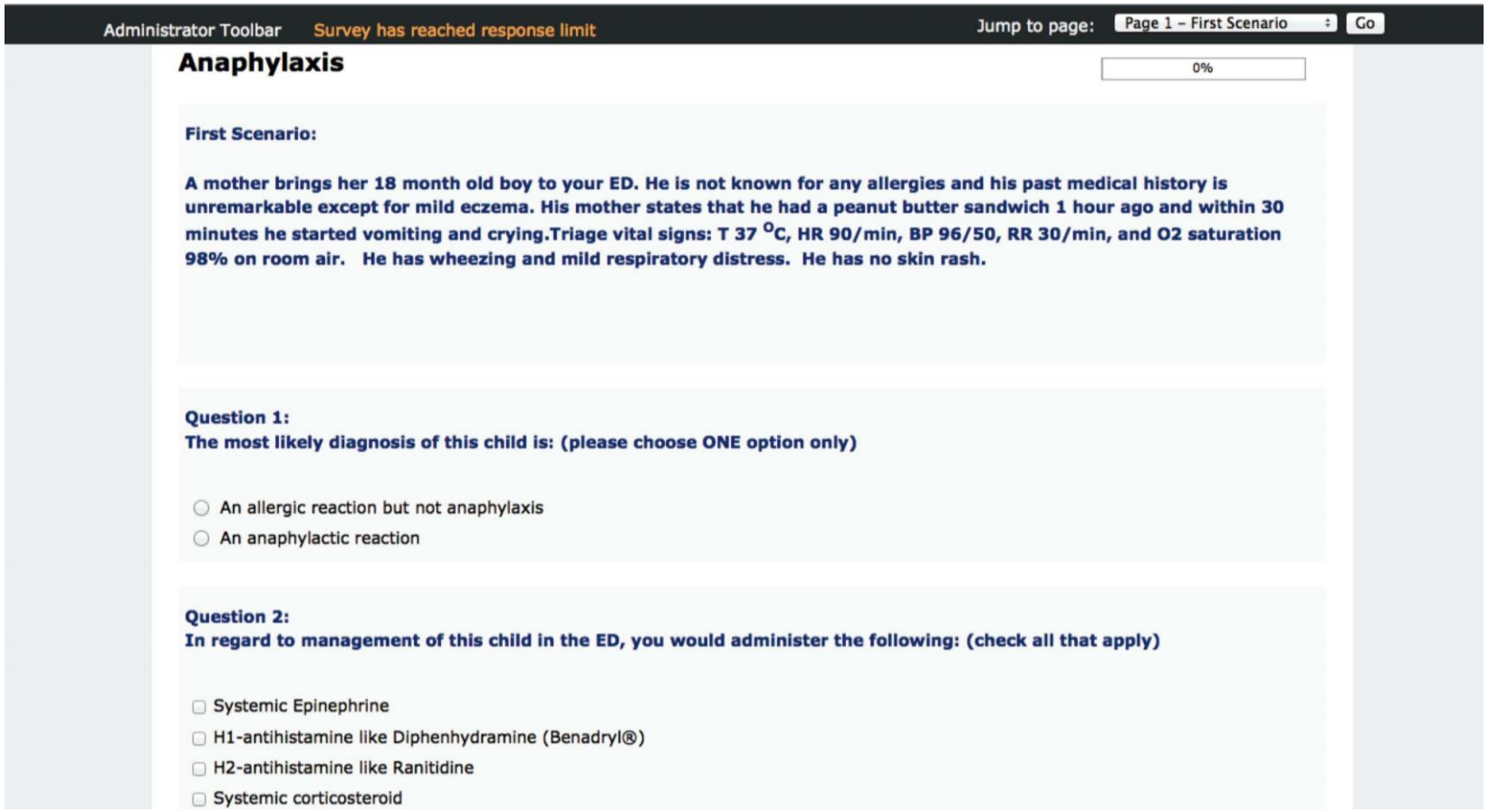
6. How likely is the questionnaire to elicit the practice pattern of Canadian EP?
(Please circle your response).

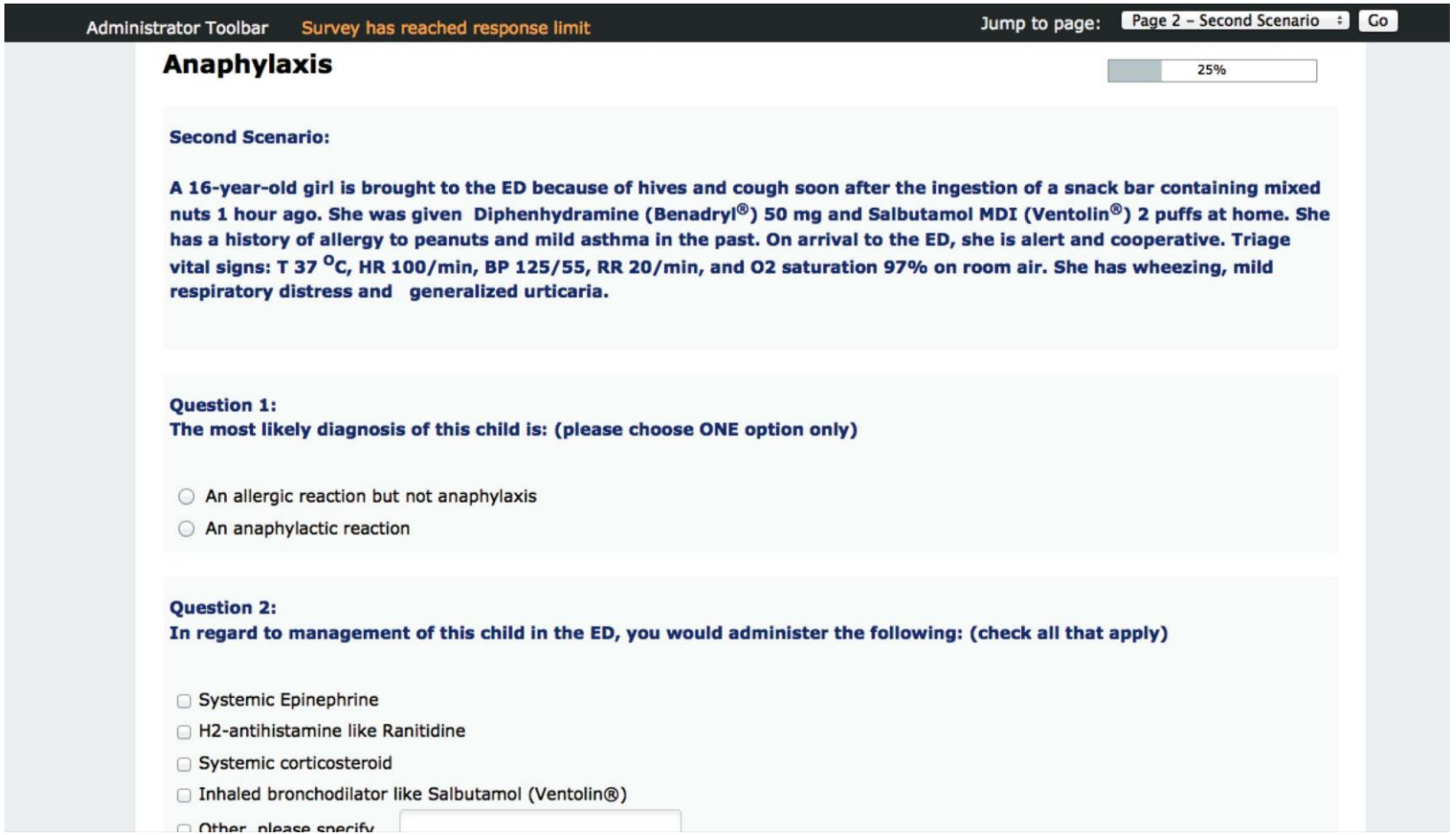
Very unlikely	Unlikely	Likely	Quite Likely	Very Likely

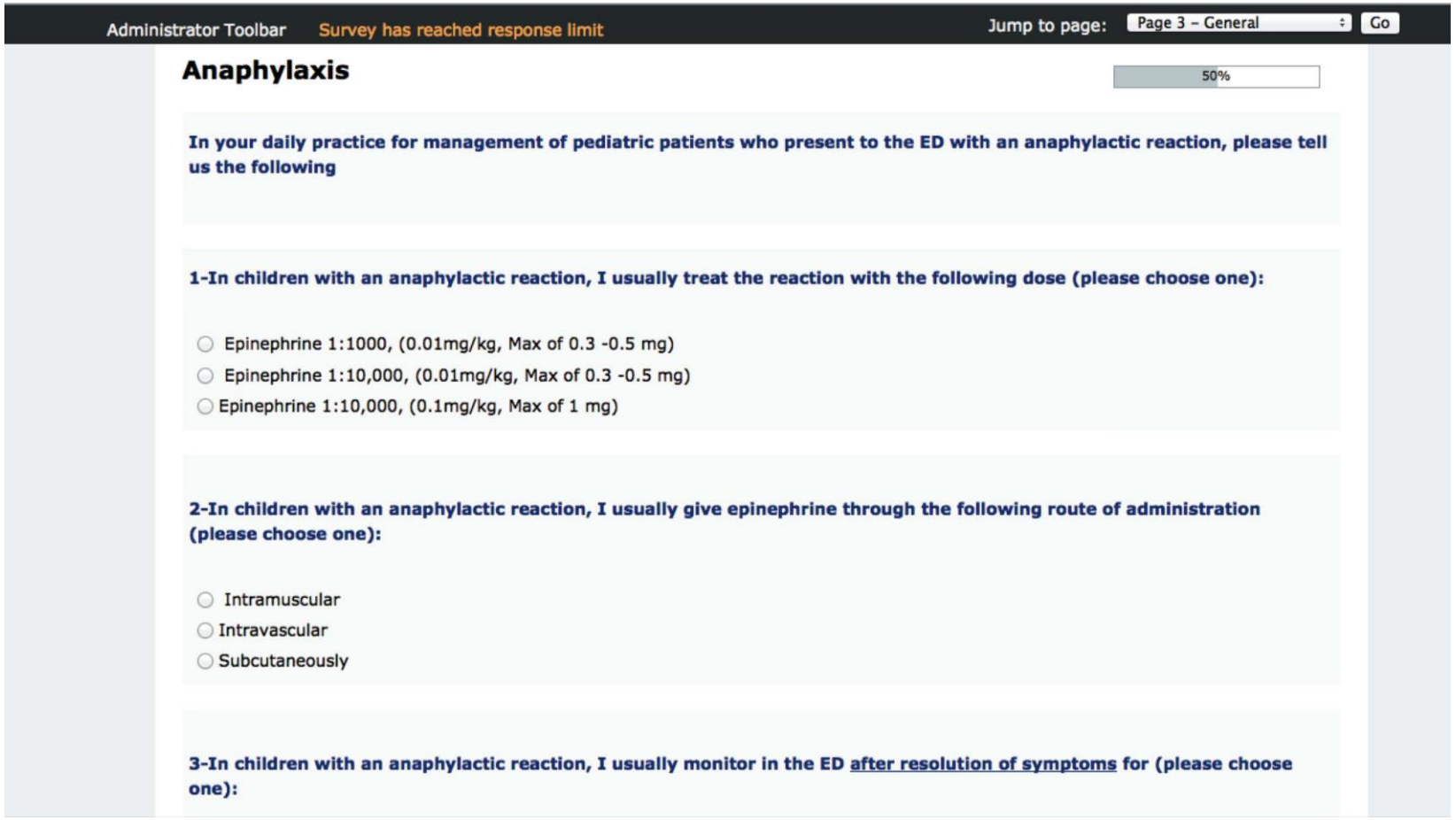
Please feel free to provide any other feedback about the survey on the space below.

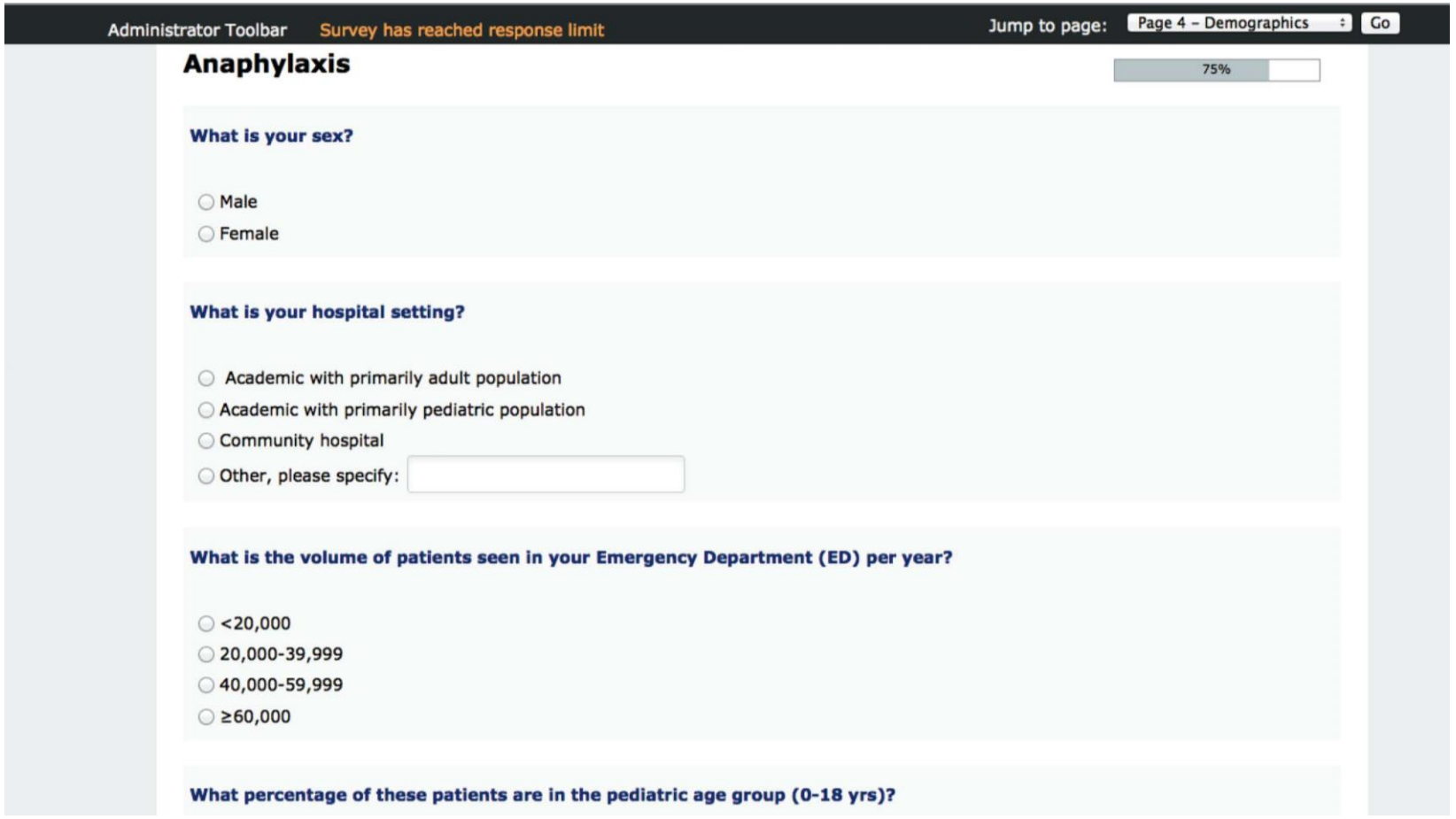
Thank you for assisting us with the sensibility testing of our questionnaire

Appendix A-3: Screen Shots of the Web Survey




Administrator Toolbar
Survey has reached response limit
Jump to page:
Page 2 – Second Scenario
Go
Anaphylaxis
25%
Second Scenario:
A 16-year-old girl is brought to the ED because of hives and cough soon after the ingestion of a snack bar containing mixed nuts 1 hour ago. She was given Diphenhydramine (Benadryl®) 50 mg and Salbutamol MDI (Ventolin®) 2 puffs at home. She has a history of allergy to peanuts and mild asthma in the past. On arrival to the ED, she is alert and cooperative. Triage vital signs: T 37 °C, HR 100/min, BP 125/55, RR 20/min, and O2 saturation 97% on room air. She has wheezing, mild respiratory distress and generalized urticaria.
Question 1:
The most likely diagnosis of this child is: (please choose ONE option only)
An allergic reaction but not anaphylaxis
An anaphylactic reaction
Question 2:
In regard to management of this child in the ED, you would administer the following: (check all that apply)
Systemic Epinephrine
H2-antihistamine like Ranitidine
Systemic corticosteroid
Inhaled bronchodilator like Salbutamol (Ventolin®)
Other, please specify


Administrator Toolbar
Survey has reached response limit
Jump to page:
Page 3 – General
Go
Anaphylaxis
50%
In your daily practice for management of pediatric patients who present to the ED with an anaphylactic reaction, please tell us the following
1-In children with an anaphylactic reaction, I usually treat the reaction with the following dose (please choose one):
Epinephrine 1:1000, (0.01mg/kg, Max of 0.3 -0.5 mg)
Epinephrine 1:10,000, (0.01mg/kg, Max of 0.3 -0.5 mg)
Epinephrine 1:10,000, (0.1mg/kg, Max of 1 mg)
2-In children with an anaphylactic reaction, I usually give epinephrine through the following route of administration (please choose one):
Intramuscular
Intravascular
Subcutaneously
3-In children with an anaphylactic reaction, I usually monitor in the ED after resolution of symptoms for (please choose one):


Administrator Toolbar
Survey has reached response limit
Jump to page:
Page 4 – Demographics
Go
Anaphylaxis
75%
What is your sex?
Male
Female
What is your hospital setting?
Academic with primarily adult population
Academic with primarily pediatric population
Community hospital
Other, please specify:
What is the volume of patients seen in your Emergency Department (ED) per year?
<20,000
20,000-39,999
40,000-59,999
≥60,000
What percentage of these patients are in the pediatric age group (0-18 yrs)?

Appendix A-4: Cover Letter of the Mailed Survey Questionnaire

Dear CAEP member,

We are writing to ask for your participation in a national survey conducted by the Emergency Department at the Children of Eastern Ontario (CHEO) and the Ottawa Hospital (TOH). We need your help in order to establish the current practice of Canadian emergency physicians regarding management of children with anaphylaxis. As a member of CAEP, your opinion on this subject is very important to us. We are extremely grateful to **more than 250 of your colleagues** that have sent us their opinion on the subject through the web version of the survey.

To our knowledge, there are no Canadian studies done to explore the variation of practice in management of pediatric patients with anaphylaxis by emergency physicians. The magnitude of uptake and practice consistency with the North American guidelines in management of anaphylaxis particularly for children presenting to the ED is also unknown. This information will help us to identify areas of discordance with the published guidelines that require further knowledge translation efforts.

The ethics board at CHEO research institute has approved this research project. Your name, email address, or any other identifying information will not be requested. In addition, all survey responses will remain completely confidential. Survey responses will only be released in aggregate forms. Your decision to complete the survey is entirely voluntary, and should you decide to complete it, your consent to participate is implied.

We ask that you please complete the enclosed survey and return it back in the enclosed envelop to our research coordinator. When your response is received, your name will be entered into a draw to win one of twenty-five $20 Tim Horton's gift cards.

We thank you in advance for your participation, as your contribution is extremely valuable.

Sincerely,

Appendix A-5: Email Reminder

Dear CAEP member,

If you have completed this survey, thank you, please disregard this reminder.

You recently received an invitation to participate in a quick national survey on management of children with anaphylaxis.

We are extremely grateful to **more than 200 of your colleagues** that have sent us their opinion on the subject.

We are kindly asking again for your collaboration as we've had no news from you...

As a member of CAEP, your opinion on this subject is very important to us.

This information will help us to explore the variation of practice among Canadian emergency physicians in management of pediatric patients with anaphylaxis. We also aim to identify areas of discordance with the published guidelines that require further knowledge translation efforts.

This is a short survey and should take only a few minutes to complete. You can access the survey through the link below:

http://app.fluidsurveys.com/surveys/walqurashi/anaphylaxis/

This research project has been approved by the ethics board at CHEO research institute. Your name, email address, or any other identifying information will not be requested. In addition, all survey responses will remain completely confidential. Survey responses will only be released in aggregate form. Your decision to complete the survey is entirely voluntary, and should you decide to complete it, your consent to participate is implied. There are no foreseeable risks to you in participating and all those that complete the survey may collectively benefit by providing a valuable resource to health care researchers and policy planners.

Should you have any difficulties with this link or any further questions or comments regarding the survey, please feel free to contact the principal investigator.

We thank you in advance for your participation, as your contribution is extremely valuable.

Appendix A-6: Research Ethics Board Approval at the Children's Hospital of Eastern Ontario of the Survey Study

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

CHEO RESEARCH ETHICS BOARD APPROVAL – DELEGATED REVIEW

Principal Investigator:
Proposal Number:
Protocol Title:
Department or PSU:
Approval date:
Valid Until:
Documents reviewed and approved:

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed under the delegated review stream, which is reserved for projects that involve no more than minimal risk to human subjects.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

- The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
- The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff).
- The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
- For all other research studies, investigators must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
- Investigators must submit an annual renewal report to the REB 30 days prior to the expiration date stated above.
- Investigators must submit a final report at the conclusion of the study.
- Investigators must provide the Board with French versions of the consent form, unless a waiver has been granted.

For complete procedures relating to these modifications, please refer to the REB website at http://www.cheori.org/about_ethics.html or contact Ethics Coordinator at

CC/sm/en 22/02/2012
c.c. CHEO RI Administration

This is an official document. Please retain the original for your file *2010 version*

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Making a difference in the lives of children and youth

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Appendix B-1: List of the ICD-10 Codes for the Health Record Review Study

D69.0	Allergic purpura
J30.1	Allergic Rhinitis due to pollen
J30.2	Other seasonal allergic rhinitis
J30.3	Other allergic rhinitis
J30.4	Allergic rhinitis, unspecified
K52.2	Allergic and dietetic gastroenteritis and colitis
L23	Allergic contact dermatitis
L50.0	Allergic urticarial
T78.00	Anaphylactic shock due to peanuts
T78.01	Anaphylactic shock due to shell fish (crustaceans)
T78.02	Anaphylactic shock due to other fish
T78.03	Anaphylactic shock due to fruits and vegetables
T78.04	Anaphylactic shock due to tree nuts and seeds
T78.05	Anaphylactic shock due to food additives
T78.06	Anaphylactic shock due to milk and daily products
T78.07	Anaphylactic shock due to eggs
T78.08	Anaphylactic shock due to other food products
T78.09	Anaphylactic shock due to unspecified food products
T78.1	Other adverse food reactions, not classified elsewhere
T78.2	Anaphylactic shock, unspecified
T78.3	Angioneurotic oedema
T78.4	Allergy, unspecified
T80.5	Anaphylactic shock due to serum
T80.6	Other serum reactions
T88.1	Other complications following immunization, not classified elsewhere
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament

Appendix B-2: Anaphylaxis Data Extraction Form

Management of Children with Anaphylaxis in the Emergency Department: Prediction of Biphasic Reaction

Participant #: 10_____

PATIENT DEMOGRAPHICS

DOB: / /

DOV: / /2010

Age (yrs) = _____

Sex [ ]M [ ]F

Weight = _____kg

PAST MEDICAL HISTORY

Known Allergy? [ ]Y [ ]N [ ] Not documented

If [Y], please list:

1- Drugs: [ ]Y [ ]N,
If [Y], please list:_____

2- Enviro: [ ]Y [ ]N,
If [Y], please list:_____

3- Food: [ ]Y [ ]N,
If [Y], please list:_____

4- Others: [ ]Y [ ]N,
If [Y], please list:_____

# of previous anaphylaxis: _____ [ ] Not documented

# of previous allergic reactions (NOT anaphylactic): _____ [ ] Not documented

Does patient carry EPIPEN? [ ]Y [ ]N

If [Y], last used? _____ [ ] Not documented

Previous intubations secondary to anaphylaxis/allergic reactions? [ ]Y [ ]N

Previous biphasic reactions? [ ]Y [ ]N [ ] Not documented

History of ANGIOEDEMA? [ ]Y [ ]N [ ] Not documented

History of ASTHMA? [ ]Y [ ]N [ ] Not documented

Please list other medical diagnoses in patient's past history:

_____

_____

Please list patient's medications:

_____

_____

HOME TREATMENT

Epi? [ ]Y [ ]N Dose & route? _____
Time Given _____

Benadryl? [ ]Y [ ]N Dose & route? _____
Time Given _____

Ventolin? [ ]Y [ ]N Dose & route? _____
Time Given _____

Other? Please specify: _____ Dose & route? _____
Time Given _____

EMS TREATMENT

Called [ ]Y [ ]N

Time of Arrival to scene: _____

Time of departure from scene: _____

Time of arrival to ED: _____

Oxygen? [ ]Y [ ]N How much (L)? _____ Time Given _____

BVM? [ ]Y [ ]N Time? _____

Oral/Nasal Airway? [ ]Y [ ]N Time? _____

Intubation? [ ]Y [ ]N Time? _____

Epi? [ ]Y [ ]N Dose & route? _____
Time Given _____

Benadryl? [ ]Y [ ]N Dose & route? _____
Time Given _____

Ventolin? [ ]Y [ ]N Dose & route? _____
Time Given _____

IV Fluids [ ]Y [ ]N Dose & route? _____
Time Given _____

Other? (specify) _____ Dose & route? _____
Time Given _____

ED CLINICAL FEATURES

Allergen(s) Involved:

_____

Setting of Exposure:

_____

Time of Exposure to allergen: _____

Time of triage: _____

Time of MD Assessment: _____

Triage vital signs:

Time: _____ Temp _____ HR _____ RR _____ BP _____ O2 Sat _____

Worst Vital Signs Recorded

Time: _____ Temp _____ HR _____ RR _____ BP _____ O2 Sat _____

Please circle clinical features:

Dermatological: [ ]Y [ ]N • Urticaria • Erythema • Pruritis • Other rash • Conjunctivitis • Facial swelling • Lip swelling • Tongue swelling • Periorbital swelling • Other (please specify): _____	**Respiratory:** [ ]Y [ ]N • Dyspnea • Wheeze • Cough • Throat swelling • Stridor • Hoarseness • Bronchospasm • Accessory muscle use • Cyanosis • Drooling • Other (please specify): _____
GI: [ ]Y [ ]N • Vomiting • Abdominal pain • Loose stools • Dysphagia • Other (please specify): _____	**Cardiovascular:** [ ]Y [ ]N • Syncope • Hypotension (sBP less than age adjusted lower limit of normal, defined as 70 + (age X 2)) • Pale
Neurologic: [ ]Y [ ]N • Dizziness/lightheadedness • Floppy • GCS < 15 or altered level of consciousness • Other (please specify): _____	

ED MANAGEMENT

Oxygen? [ ]Y [ ]N How much (L)? _____ Time: _____

BVM? [ ]Y [ ]N Time: _____

Oral/Nasal Airway? [ ]Y [ ]N Time: _____

Intubation? [ ]Y [ ]N Time: _____

Epi? [ ]Y [ ]N if [Y], dose & route? _____Time: _____

repeat doses? _____ Time: _____

total # of epi treatments? _____

Benadryl? [ ]Y [ ]N Dose & route? _____ Time : _____

Ventolin? [ ]Y [ ]N Dose & route? _____ Time : _____

Ranitidine? [ ]Y [ ]N Dose & route? _____ Time : _____

Steroids? [ ]Y [ ]N What drug given? _____

Dose & route? _____ Time : _____

IV Fluids? [ ]Y [ ]N How much (ml)? _____ Time : _____

ED DISPOSITION

Was patient **admitted** into hospital? [ ]Y [ ]N

If [Y], which service? _____

If [Y], date & time of admission? _____/_____/2010 Time: _____

Was patient **discharged home**? [ ]Y [ ]N

If [Y], date & time of discharge? _____/_____/2010 Time: _____

If [Y], was epipen prescribed? [ ]Y [ ]N
If [Y], outpatient allergist referral [ ]Y [ ]N
If [Y], please list discharge medications:

1-_____

2-_____

3-_____

4-_____

5-_____

if [Y], please list discharge instructions:

1-_____

2-_____

3-_____

4-_____

5-_____

Final Diagnosis: [ ]"Anaphylaxis"
[ ]"Allergic Reaction"
[ ]"Urticaria"
[ ]"Drug Reaction"
[ ]"Angioedema"
[ ]"Biphasic Reaction"
[ ]"Other", please specify:_____

ADVERSE EVENT

Biphasic Reaction Definition: "initial anaphylactic reaction with a period of resolution for >1h, during which there were no new symptoms or treatment administered, followed by a second phase reaction, not caused by antigen re-exposure and requiring new therapy"

1- Did patient have a biphasic reaction during ED stay? [ ]Y [ ]N

If [Y], date & time of BP reaction? _____/_____/2010 Time: _____

2- Did patient have a biphasic reaction after discharged from ED?[ ]Y [ ]N

If [Y], date & time of BP reaction? _____/_____/2010 Time: _____

Please circle clinical features:

<table>
<tr>
<td><u>Dermatological:</u> [ ]Y [ ]N
• Urticaria
• Erythema
• Pruritis
• Other rash
• Conjunctivitis
• Facial swelling
• Lip swelling
• Tongue swelling
• Periorbital swelling
• Other (please specify): _____</td>
<td><u>Respiratory:</u> [ ]Y [ ]N
• Dyspnea
• Wheeze
• Cough
• Throat swelling
• Stridor
• Hoarseness
• Bronchospasm
• Accessory muscle use
• Cyanosis
• Drooling
• Other (please specify): _____</td>
</tr>
<tr>
<td><u>GI:</u> [ ]Y [ ]N
• Vomiting
• Abdominal pain
• Loose stools
• Dysphagia
• Other (please specify): _____</td>
<td><u>Cardiovascular:</u> [ ]Y [ ]N
• Syncope
• Hypotension (sBP less than age adjusted lower limit of normal, defined as 70 + (age X 2))
• Pale</td>
</tr>
<tr>
<td colspan="2"><u>Neurologic:</u> [ ]Y [ ]N
• Dizziness/lightheadedness
• Floppy
• GCS < 15 or altered level of consciousness
• Other (please specify): _____</td>
</tr>
</table>

If 1or2 [Y], please list management for biphasic reaction:
1-_____, 2-_____, 3-_____, 4-

_____

Was this a repeat visit from previous anaphylaxis/allergic reaction? [ ]Y [ ]N
If [Y], 1-When was previous visit (date/time)?

_____
2-What was the previous diagnosis?

_____
3-Was the patient seen/treated at the same facility? [ ]Y [ ]N

Appendix B-3: Research Ethics Board Approval at the Children's Hospital of Eastern Ontario of the Health Record Review Study

RECEIVED

RESEARCH ETHICS BOARD APPLICATION FORM FOR RETROSPECTIVE CHART REVIEW AND SECONDARY ANALYSES OF CLINICAL DATA

Please submit the **original and one copy** of the application, protocol and applicable documents for review.
Please ensure that all questions are answered in full. Only complete applications will be accepted.

PROTOCOL TITLE:

Management of Children with Anaphylaxis in the Emergency Department: Prediction of Biphasic Reaction

Indicate nature of the project

☑ Retrospective ☐ Prospective secondary use of clinical data

PRIMARY CHEO SITE INVESTIGATOR:

NAME	DIVISION OR PSU	TELEPHONE	SIGNATURE
	Emergency		

SECONDARY CHEO CO-INVESTIGATORS *(use supplementary pages as required)*

NAME	DIVISION OR PSU	TELEPHONE	SIGNATURE
	Emergency		

MEMBERS OF THE RESEARCH TEAM WHO WILL HAVE ACCESS TO THE INFORMATION *(Other than those named above)*

NAME	ROLE ON THE RESEARCH TEAM	TELEPHONE	SIGNATURE

PLEASE LIST ANY CO-INVESTIGATORS WITH A PRIMARY AFFILIATION TO THE UNIVERSITY OF OTTAWA (OTHER THAN CHEO PHYSICIANS). The CHEO REB will inform the university of the outcome of its review. The University will then conduct an abridged administrative review of all projects previously approved by the

	Emergency – Civic Hospital University of Ottawa- Department of Epidemiology and Biostatistics		

RETROSPECTIVE CHART REVIEW AND SECONDARY ANALYSES OF CLINICAL DATA – CONT'D

SUMMARY OF CHART REVIEW AND SECONDARY USE OF CLINICAL DATA PROPOSALS

Please provide a brief description of the proposed research (approximately one page), which must include the following information:

1. The data abstraction form or the list of data fields to be collected should be appended to this form. Name, Date of Birth, & Full Postal Code should not be collected.
2. Any probable linkage of data (i.e., techniques used to link together records which relate to the same individual in one or more data sets). Why this is necessary and how this will be achieved?
3. Rationale and hypotheses.
4. Anticipated benefit.
5. Anticipated harms and how these will be addressed.

N.B.: It is good practice to assign a unique study number to each subject. The study number can be linked to the CHEO unique hospital number in a separate password-protected file. The study data would be held in a file in which only the study number appears. This then ensures that the study data are completely de-identified and decreases the risk of personal information becoming accessible should it be lost or stolen.

SUMMARY OF CHART REVIEW AND SECONDARY USE OF CLINICAL DATA PROPOSALS (Cont'd):

Name additional REB's who have reviewed the application and indicate the status of the review.	Approved	Disapproved	Pending (anticipated date of approval)
_____	☐	☐	☐ _____
_____	☐	☐	☐ _____
_____	☐	☐	☐ _____

FUNDING OR SPONSORING AGENCY:

☐ Study both funded and initiated by an Industry (Pharmaceutical or other), specify company name:

_____

_____

Please provide name and address of contact person: _____

_____

A fee of **$3,000.00** will be charged for the review of any research project partially or fully funded by private industry, and is applied whether the study is submitted to full board or expedited review. Consideration will be made for exemption from the review fee, on a case-by-case basis. Requests for an exemption must be made in writing to the Chair, CHEO Research Ethics Board.

Continued on the following page.

Privacy and Confidentiality Statement
In the event that a breach in privacy occurs, the investigator must immediately notify the hospital's privacy officer and the REB.

In conducting research, the investigator agrees that the personal health information (PHI) collected in this study will not:

- Be used for future projects without prior approval of the Research Ethics Board.
- Be published in such a way that could reasonably allow others to identify the patient whose personal health information is being researched.
- Be disclosed except as required or permitted by law.

General safeguards for the storage of research data:
PHI must be stored securely. Subject ID codes based on date of birth, ethnicity, hospital record number, and residency should be avoided. Variables that can be identifying of the person either alone or in combination must similarly be avoided. Instead, subjects should be coded with a study number that is not identifying of the individual. If needed, the hospital unique number can be linked to the study subject number in a separate password-protected and encrypted document. This further decreases the risk of personal information becoming accessible should the information be lost or stolen.

In addition, the following web link allows investigators to do a quick assessment of re-identification risk. The model underlying this tool is based on an analysis of the Canadian census and was developed by , Canada Research Chair in Electronic Health Information. http://www.ehealthinformation.ca/rebwizard/ca

All research records pertaining to studies that fall under Health Canada Division 5 regulations should be retained for 25 years after closure. All other studies should retain records for 5 to 7 years after the study closure, unless otherwise approved by the REB. Long term electronically stored information should be verified or validated for accessibility and correctness every 2 to 3 years.

Information stored on mobile/portable devices:
Mobile devices (e.g., laptops, USB keys, PDAs) that contain study information should be stored securely. Study data stored on these devices should be de-identified as much as possible. Electronic files stored on mobile devices should also be password-protected, and encrypted.

For additional information on the encryption and safeguarding personal health information, please refer to the guidance issued by the Ontario Information and Privacy Commissioner. http://www.ipc.on.ca/images/Resources/up-fact_12e.pdf

Data Sharing
If personal health information is to be released externally, a data sharing agreement must be signed between the health information custodian , CEO RI & scientific director; Vice-president Research, CHEO) and the external investigators. A copy of the signed data sharing agreement should be appended to this application. The REB recommends the template developed by from the Electronic Health Information Laboratory (eHIL). This template can be customized for use in different contexts.

For clinical drugs trials, the terms of data sharing are generally specified in the contract with the Sponsor. These contractual terms must be consistent with the conditions set out by the eHIL data sharing agreement.

For more information, consult the following relevant CHEO policies.
Investigators must comply with the following CHEO policies in conducting research:

Privacy and Confidentiality of Patient Personal Health Information
http://cheonet/data/1/rec_docs/12663_Admin_010_Privacy-Confidentiality_-June_15,_2010.doc

Access to and Disclosure of Patient Health Information
http://cheonet/data/1/rec_docs/3242_HREC%20067%20Access%20to%20and%20Disclosure%20of%20Patient%20Health%20Information.doc

Acceptable Use of Information Systems
http://cheonet/data/1/rec_docs/12232_IS_153_Acceptable_use_of_information_systems.pdf

Access Control to Information Systems
http://cheonet/data/1/rec_docs/12233_IS_160_Access_Control_to_Information_Systems.doc

Continued on the following page.

My signature confirms that, as Primary CHEO site investigator:

- I assume full responsibility for the research as outlined in this application.
- I will comply with the previously mentioned privacy and confidentiality conditions.
- The personal health information collected in this study will:
  1. Be used only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB.
  2. Be encoded in a way that would not be identifying of the individual. Codes based on date of birth, ethnicity, and residency will be avoided. Variables that can be identifying of the person either alone or in combination will similarly be avoided.
  3. Be stored in locked areas and access will be restricted to the names listed above. Any personal health information that leaves the site for any reason will be de-identified, password protected and encrypted. Data will be destroyed at the conclusion of the study.
  4. Not be used to contact or attempt to contact the patient whose personal health information is being researched unless CHEO first obtains the patients' express written consent,
  5. Not be published in a way that could reasonably allow others to identify the patient whose personal health information is being researched,
  6. Immediately notify the REB in writing if the investigator becomes aware of any breach of confidentiality or security.
  7. Be

Signed:

		Date:
Research Assistant	*Print Name:*	*Date:*

Unless otherwise indicated by the investigator, the CHEO REB will assume that the study will be concluded within a year of this approval date. If the investigator requires a longer activation period, an annual renewal report should be filed with the Board.

CHEO Research Ethics Board – APPROVAL

Chair's Sig __

Date: ___ __

Appendix B-4: Research Ethics Board Approval at the Hospital for Sick Children of the Health Record Review Study

SickKids
THE HOSPITAL FOR SICK CHILDREN
Research Ethics Board

RECEIVED
MAR 29 2012

Short Application for Ethical Approval of Human Subject Health Record/Database Research

1. PROJECT TITLE: Management of Children with Anaphylaxis in the Emergency Department: Prediction of Biphasic Reaction

2.PRINCIPAL INVESTIGATOR (MUST BE A PERMANENT SICKKIDS STAFF MEMBER)

Department/Division: Emergency Department
Discipline (e.g., neonatology, social work): Emergency Department
SickKids I.D. #:

CO-INVESTIGATOR(S)

Institution: CHEO
Department/Division: Emergency Department
Position (e.g., physician, fellow): Fellow
Discipline (e.g., neonatology, social work: Emergency Department
SickKids I.D. #: N/A

Name:
Signature: _____
Institution:
Department/Division:
Position (e.g., physician, fellow):
Discipline (e.g., neonatology, social work):
SickKids I.D. #:

Name:
Signature: _____
Institution:
Department/Division:
Position (e.g., physician, fellow):
Discipline (e.g., neonatology, social work):
SickKids I.D. #:

These signatures confirm that each investigator has read the proposal and agrees to conduct this study in compliance with the Tri-Council Policy Statement, the *Personal Health Information Protection Act (PHIPA, and any other applicable legislation and regulations, to adhere to the approved protocol, to apply to the Hospital For Sick Children (SickKids) Research Ethics Board (REB) for approval of amendments, report adverse events to the REB, submit annual reports and cooperate with any monitoring activities determined by the REB.*

3. OTHER RESEARCH TEAM MEMBERS WHO ARE NOT CO-INVESTIGATORS (names of individuals who will be accessing personal health information e.g., health records/Electronic Patient Charts (EPC). *Please print names (signatures not needed).*

Name(s)_____ **Position(s)** _____

4. **PRIMARY CONTACT NAME:** **Position** Staff Physician
(To whom all REB correspondenc *t surface mail will only be sent to Hospital addresses)*

EMAIL ADDRESS: ☒ **Lotus Notes** ☐ **Other** _____

5. **IS THIS PROJECT FUNDED?**

☒ **No**

☐ **Yes** a) Contract signoff may be required. Please contact Corporate Ventures at ext. 7739 to confirm.

Available Amount $_____ Funding source: _____

6. **IS THIS A MULTICENTRE STUDY?**

☐ **No**

☒ **Yes** Please contact Corporate Ventures at ext. 7739 to determine whether a contract/agreement is required.

7. **CONFLICT OF INTEREST DECLARATION BY PRINCIPAL INVESTIGATOR**

EXPLANATION

Researchers hold trust relationships with research subjects, research sponsors, SickKids, their professional bodies, and society. Researchers, SickKids, and the REB are required to identify and address actual, potential, and perceived conflicts of interest ("Conflicts of Interest") to maintain public confidence and trust, ensure the integrity of research, discharge professional obligations, and ensure accountability.

A Conflict of Interest does not necessarily imply wrongdoing, as a Conflict of Interest depends upon the circumstances, not on the character of the staff member.

A Conflict of Interest does not mean that the research cannot proceed. Many (but not all) Conflicts of Interest can be managed, but always require identification of the Conflict of Interest, disclosure to research subjects, and if required, other steps to manage the Conflict of Interest. It will be up to the REB to determine if the Conflict of Interest can be managed and if the proposed mitigation measures are adequate.

All Conflicts of Interest must be clearly identified by the Principal Investigator. The Principal Investigator is making this Declaration on behalf of himself/herself and the members of the research team (collectively referred to in the Declaration as "Researcher")

Categories of Conflict or Potential Conflict of Interest:

There are many types of Conflict of Interest which may affect the research. The Conflict of Interest may arise in relation to the Researcher or a "Related Person" to the Researcher (e.g., spouse, domestic partner, immediate family member or close acquaintance). The categories of Conflicts of Interest include the following:

(i) **Financial**

The Researcher or Related Person stands to gain financially in the undertaking or outcome of research (e.g. share ownership in study sponsor, bonus for positive test results) outside the normal compensation of the Researcher.

(ii) **Direct Status Benefit**

The Researcher or Related Person stands to gain through direct rewards in respect of his or her status (e.g. career status) in the undertaking or outcome of research (e.g. promise of promotion for successful research). It is recognized that undertaking research will usually be viewed positively in terms of enhancing career advancement. The question is whether the link between the career enhancement and the outcome of the research is so strong as to bring into question the objectivity of the Researcher or the process and outcome of the research.

(iii) **Undue Influence**

The position of the Researcher or Related Person is such that the Researcher or Related Person may exert an undue influence over the research or influence or coerce research subjects, because of his or her position or the vulnerability of the research subjects. This influence may be due to a personal or professional relationship between the affected individuals (e.g. a physician recruiting his/her own patients the subjects are to be recruited from Researcher's students or employees).

(iv) **Competing Interest**

The Researcher may be influenced to draw conclusions against the interest of the sponsor or another interested party to the study because the Researcher or a Related Person has an adversity in interest related to the research (e.g., – the Researcher has an interest in a competitor drug or product or the Researcher involved in litigation against sponsor).

DECLARATION – CONFLICT OF INTEREST

A. I have spoken with members of my research team and hereby declare that neither I nor (to the best of my knowledge) any members of my research team have an actual, potential or perceived Conflict of Interest with respect to the attached Application for Research.

☒ (check this box if applicable)

OR

I have spoken with members of my research team and have identified a Conflict(s) of Interest with respect to this application for research in the following categories and as specified below. *(Please check all boxes as appropriate and attach a separate sheet describing the conflict of interest in full detail).*

(i) Financial: ☐ Yes ☐ No Member with Conflict of Interest _____

(ii) Status: ☐ Yes ☐ No Member with Conflict of Interest _____

(iii) Undue Influence: ☐ Yes ☐ No Member with Conflict of Interest _____

(iv) Competing Interest: ☐ Yes ☐ No Member with Conflict of Interest _____

Details of Conflict of Interest:

_____

B. *(If you have checked yes to any of the items in section A above, please complete sections B and C)* I intend to manage the Conflict(s) of Interest as set out below (e.g. disclosure in consent form, declining role/position with sponsor or additional monitoring strategies such as monitoring consent). **Please note Conflicts of Interest must be disclosed on the consent form.**

_____

_____

C. I have declared all Conflicts of Interest to the Research Institute. *(If you have not disclosed the Conflicts of Interest to the Research Institute or are not obliged to declare, please explain why.)* Please attach a copy of the Research Institute approval of the Conflict(s) of Interest.

☐ Yes ☐ No ☐ N/A

D. Should a Conflict of Interest arise for me or any member of my research team during the course of the research, I shall declare this in writing to the Research Ethics Board.

☒ Yes ☐ No

E. I hereby declare that I have read this Declaration, have discussed this Declaration with the members of my research team, and that to the best of my knowledge and belief, my responses are true and complete.

Name of Principal Investigator	Signature of Principal Investigator	March 9, 2012 Date

8. PROTOCOL *(Including background, objectives, methods, and statistical analysis)*:

Rationale: Anaphylaxis is a serious allergic reaction that is rapid in onset and might cause death. The true global rate of occurrence of anaphylaxis from all triggers in the general population is unknown because of under-recognition by patients and caregivers and under-diagnosis by healthcare professionals. In addition, under-reporting, use of a variety of case definitions, use of different measures of occurrence such as incidence or prevalence, and under-coding are problemative in many epidemiologic studies. Despite this, anaphylaxis is not rare and the rate of occurrence appears to be increasing, perhaps most markedly in the younger age group.

Anaphylactic reactions may be immediate and uniphasic or they may be delay in onset, biphasic (also called late-phase). Biphasic reaction, defined as a recurrence of anaphylactic symptoms after initiatl resolution despite no further exposure to the trigger, can occur anywhere from 1 h to 72 h after the first onset of symptoms. This reaction is thought to increase the risk of fatal anaphylaxis. To date, there has been less work done to establish validated clinical predicators for this phenomenon particularly among children. In addition, there is no well-established evidence-based preventive therapeutic intervention for this potentially fatal reaction. This lack of evidence is throught to contribute considerably to the variation of practice among Canadian emergency physicians (EP) for management of children with anaphylactic reaction. The magnitude and the impact of this variation are unknown.

The main goal of this study is to investigate the prevalence and predictive factors for biphasic reaction in children presenting to the emergency department with anaphylaxis. The findings from this study are essential for planning future experimental studies exploring the efficacy of different therapeutic interventions used currently on management of anaphylaxis.

Objectives: The primary goal of this retrospective chart review is to investigate the predictive factors of biphasic reactions of children with anaphylactic reactions by comparing the demographic data, causative allergens, clinical manifestation and management of uniphasic versus biphasic reactions.

The secondary objectives are:

1. To determine the rate of anaphylactic versus non-anaphylactic biphasic reaction.
2. To collect basic epidemiological data regarding emergency department visits rate, admission rates, and fatality rate due to anaphylaxis among children in Canada.

Methods: This part of the project will be a retrospective cohort study. Potential cases of anaphylaxis will be identified from the medical record database using the International Classification of Diseases (ICD) Version 10 matching the following terms: anaphylactic shock, anaphylaxis, allergic reaction, angioedema, urticaria, food allergy, drug allergy, and insect allergy. We will enroll only children < 18 years of age. Cases not matching the strict diagnostic criteria of anaphylactic reaction (see protocol) will be excluded. We will also exclude cases of anaphylaxis that occurred during outpatient clinic visit or inpatient hospitalization. The study will be conducted in the tertiary care Emergency Departments of the Children Hospital of Eastern Ontario (CHEO) in Ottawa and the

Hospital for Sick Children (HSC) in Toronto. Charts will be reviewed over 12 months from January 1st to December 31st of the year 2010.

Ethical Considerations: Ethical approval from CHEO and HSC Research Ethic Boards will be obtained prior to data collection. Patients will not be contacted at any stage and patient confidentiality will be maintained throughout the study. An independent study number will be assigned for each patient and the link between the study number and the patient ID will be housed separately and securely. A password-protected database of the predictor variable will be created, but patient identifiers in the forms of names, address, hospital unique number, and OHIP number will be deleted from all records. Given that this is a retrospective chart review, informed consent from patients will not be necessary.

Statistical Analysis: Data entry and analysis will be performed using SPSS v. 17. Univariate data will be expressed as a percent. Chi-square testing will be performed for univariate analysis of the relationship between dichotomous clinical variables and outcome variables of biphasic reactions. The unparied t-test will be used for univariate analysis of continuous clinical predictor variables and outcome variables of biphasic reactions. The Mann-Whitney U test will be used to analyze correlations in nonparametric data. Logistic regression will be used for multivariate anlaysis to determine the independent association of factors related to the occurrence of biphasic phase of anaphylaxis. A p-value < 0.05 will be considered statistically significant.

9. **DATA COLLECTION FORM: Please attach a data collection form. Note that identifiable personal health information must not be included on data collection forms –i.e. the research subject names, initials, SickKids patient numbers, and other identifying information is strictly prohibited. Each study subject must be assigned a unique study identifier code, otherwise this application will be returned. The code-breaking information must be kept separately from the data collection files. The PI is responsible for ensuring that the code-breaking information is totally inaccessible to individuals who are not part of the research team.** *Please note that the content of the form should be adequate to answer the research questions(s).*
   Please see attached

10. **SOCIO-DEMOGRAPHIC INFORMATION: If you are planning on extracting socio-demographic information, e.g. race or ethnicity, religion, annual family income, please elaborate how this data is directly relevant to the study objectives.**
    N/A

11. **SAMPLE CHARACTERISTICS:**

    Proposed number of research subjects 1 year sample (approximately 100)

    What are the inclusive dates for the chart review? Jan 1, 2010 **to** Dec 31, 2010
    (*note: inclusive date cannot go beyond the date of application*)

12. **SECURITY AND CONFIDENTIALITY OF PERSONAL HEALTH INFORMATION AND RESEARCH DATA**
    (*Please check all steps which will be taken)*

    Are any sensitive issues raised in this study or its publication (e.g. HIV status, mental health status), which could result in harm (e.g. cause embarrassment, refusal of employment or insurance coverage, stigmatization) and therefore require subject consent?

    ☒ **No**

    ☐ **Yes**

    If yes, please specify how such consequences would be addressed:

APR 3 0 2012

☒ Identifying information de-linked

Use of study names, initials, SickKids patient numbers, and other identifying information is strictly prohibited on data collection forms, adverse event reports, and other research subject-specific documents. Subjects must be assigned a unique identification code. The code-breaking information must be kept separate from the data extraction files. It is the responsibility of the Principal Investigator to ensure that the code-breaking information is totally inaccessible to individuals who are not on the research team.

☒ Records / computers secured

Method: ☒Patients coded ☒Files/Folders password protected ☒Computer password protected
(Please provide name of password software _____)
☒Computer in locked office only
☐Other (Specify): _____

☒ Chart/Computer Access limited to research team

Method: ☒Cabinet/Office keys ONLY with research personnel
☒Computer passwords ONLY with research team
☒Other (Specify): Information will be derived from EDIS and EPC (Health Records)

15. DATA SOURCES & STORAGE

What patient information data source are you accessing?

☒ Health Records (Health Record signoff is required. A fee may be charged) _____

☐ Clinic/Office Files Specify which _____

☒ Electronic Database Specify which EDIS/EPC _____

☐ Other Specify which _____

a) Where will the data be stored? On Hospital Computer (in a locked office

b) How will the data be stored and protected while in storage? Information will be kept in password protected computer inside a locked hospital office

c) For how long will the data be stored? 7 years post-publication

d) Who will have access to these data in the future? PI and co-PI (authorized research team)

e) How will the data be returned and/or destroyed? All paper files will be confidentially shredded and electronic files deleted

f) Will data be sent outside of the institution?

☐ **No**
☒ **Yes** Please specify where and how the data will be sent, noting any security measures and strategies for protecting study subject privacy: Paper Files will be transferred to CHEO and the Ottawa Research Institute anonymized and verified by the PI for anonymity. Paper files will be shredded after 7 years post-publication by office.

16. DO YOU PLAN ON LINKING LOCALLY COLLECTED DATA WITH ANY OTHER DATA SET (e.g. OHIP data)?
If so, identify the data set, why these linkages are required, identify how the linkage will occur, and provide a list of data items contained in it. No

17. INDICATE WHETHER THERE IS A CONTRACT/RESEARCH AGREEMENT OR DATA SHARING AGREEMENT INVOLVED:

☒ Yes If "yes", please attach a copy of the agreement
☐ No

18. CONSENT

Are you requesting a waiver of consent for this project?
☐ **No** (Attach a consent form for approval)
☒ **Yes (**please indicate reason(s) from list below)

The following conditions must be met before a waiver of consent is considered:

- The objectives of the research cannot be reasonably accomplished without using personal health information.
- There are adequate safeguards to protect the privacy of individuals.
- There is a public interest in this research while protecting the privacy of individuals.

Criteria to consider when requesting a waiver of consent, circle all that apply:

1 ☐ The sample size is so large that obtaining consents are impracticable.

2 ☐ The subjects have graduated to adult services or are otherwise too difficult to locate making obtaining consents impracticable.

3 ☐ The subject group under investigation has a high mortality rate so can not be contacted without causing distress to the family (e.g. children with severe heart malformations).

4 ☐ Because of the unique subject group characteristics, there is a greater risk of sample bias which would invalidate the research (e.g. research concerns family disintegration issues).

5 ☐ The request for chart review is only to determine study feasibility or the appropriate sample size and not to conduct research.

6 ☒ There is no lockbox provision on any record to be accessed. See Hospital policy "Lockbox".

7 ☐ Other (Please elaborate) _____

_____

PRIVACY AND SECURITY ACKNOWLEDGEMENT:

On behalf of my research team, I recognize the importance of maintaining the confidentiality of personal health information and the privacy of individuals with respect to that information. I will ensure that the personal health information is used, only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB. This includes all conditions and restrictions imposed by the REB governing the use, security, disclosure, return or disposal of the research subjects' personal health information. I agree to take any further steps required by the REB or SickKids to ensure that the confidentiality and security of the personal health information is maintained in accordance with the *Personal Health Information Protection Act* (PHIPA), its accompanying regulation and the Tri-Council Policy Statement.

_____ Principal Investigator Signature Date

Signature of Approval
Division/Department Head[1]

Date

Do you plan on accessing information from another Division/Department?

☒ **NO**

☐ **YES** If yes, authorization from the division/department head is requested

23 Mar 2012

Signature of Approval

Date

Research Ethics Board approval for retrospective chart research

Waiver of consent granted because the following criteria have been met:

N.B. Any waiver of consent excludes any patient record that has been "locked" by the patient. See Hospital policy "Lockbox".

Signature of REB Chair _____

Date of approval JUN 1 2 2012 Approval expires June 2013

LEVEL OF CONTINUING REVIEW 1A.

[1] The signatures of Division or Department Heads, and of Clinic Heads who are named as investigators in this application are not accepted he sign-off in such cases is done by an existing (e.g., not created specifically for this research project) deputy, or by the person to whom the Hea reports for patient care matters

Data Transfer Agreement ("Agreement")
Research Use of Personal Health Information

BETWEEN:	AND
The Hospital for Sick Children ("**SickKids**") 555 University Avenue Toronto, ON, M5G 1X8	**Children's Hospital of Eastern Ontario Research Institute Inc.** ("CHEO RI") 401 Smyth Road Ottawa, Ontario, Canada, K1H 8L1 ("RECIPIENT Institution")
SickKids Investigator, a physician having a (together with SickKids: "PROVIDER")	(together with RECIPIENT Institution: "RECIPIENT")
Name of Recipient's Study ("Study"): Management of Children with Anaphylaxis in the ED	
SickKids REB File Number: 1000032087 **(in relation to this transfer of data)**	**Recipient REB File Number:** 11/135x **(in relation to ethics approval of the Study)**

Data to be provided ("Data"): As per the REB approved Study Protocol, incorporated herein by reference.

This Agreement, effective as of the last date of signature below, is entered into between the parties to govern the transfer of the Data from PROVIDER to RECIPIENT for use in the Study, in compliance with applicable laws. PROVIDER retains the right to refuse transfer of the Data requested.

The Recipient Investigator will be performing some of the Study activities, specifically Data collection, on site at SickKids. For clarity, this Agreement covers any Data accessed by the Recipient Investigator while on site at SickKids.

PROVIDER will prepare and furnish to RECIPIENT the Data in accordance with Ontario's *Personal Health Information Protection Act*, and specifically warrants that transfer of the Data by PROVIDER will be in compliance with REB approved subject informed consent forms ("ICFs") provided by the individuals from whom the Data were collected, or terms of an REB Waiver of Consent ("REB Waiver"), as applicable (incorporated herein by reference). Data will not be transferred until (1) RECIPIENT provides PROVIDER with a copy of REB approval for the Study; and (2) SickKids REB has approved transfer of Data contemplated under this Agreement. RECIPIENT will not use Data until RECIPIENT obtains a copy of the PROVIDER's SickKids REB approved SickKids ICF or SickKids REB Waiver, as applicable.

RECIPIENT shall use the Data in compliance with all applicable laws; and shall specifically only use or disclose the Data for the conduct of the Study in accordance with the permitted uses of the Data specified in the applicable SickKids ICFs or SickKids REB Waiver, or otherwise as required by law. No right, title or interest in and to the Data is granted or implied to the RECIPIENT hereunder.

RECIPIENT shall have the right to use (1) the analyzed, de-identified data derived from the use of the Data, and (2) de-identified information and results arising out of analysis of the Data, as part of a publication or presentation of the results of the Study, and shall own such de-identified, analyzed data and results. RECIPIENT shall not include any personally identifying information in any publication or presentation. Recipient Investigator and SickKids Investigator plan to jointly publish on the results of the Study. SickKids Investigator's contribution to the Study shall be acknowledged appropriately in any such publication or presentation in accordance with academic standards

RECIPIENT shall give access to the Data only to its own personnel with a need to know for the purpose of conducting the Study, and who are bound by RECIPIENT to comply with the terms of this Agreement.

RECIPIENT shall use appropriate safeguards to prevent any unauthorized use or disclosure of the Data and shall report to the PROVIDER any unauthorized use or disclosure of which RECIPIENT becomes aware, or of any breach of this Agreement. RECIPIENT shall not use the Data to identify or contact the individuals from whom such Data were collected. RECIPIENT shall securely destroy the Data as required by the Study Protocol or PROVIDER and provide a written confirmation of the manner of destruction in a form acceptable to PROVIDER. PROVIDER may conduct reasonable audits of the RECIPIENT concerning the maintenance of appropriate security safeguards to ensure compliance with this Agreement

This Agreement may be signed in counterparts, and each counterpart may be delivered by facsimile or sign PDF by email. Each counterpart shall constitute an original, and when taken together, shall constitute one and the same instrument.

Appendix B-5: Abnormal Vital Signs at Triage for 484 Anaphylaxis Episodes

Abnormal Vital Signs at Triage for 484 Anaphylaxis Episodes

	n (%)
Tachycardia*	149 (30.8)
Tachypnea**	96 (19.8)
Hypotension[¶]	4 (0.8)
Wide pulse pressure[¶¶]	144 (29.8)

* Defined as per Pediatric Advanced Life Support (PALS) guidelines:[167] awake heart rate>190 beat/min for age 3 months-2 years, >140 beat/min for age 3-10 years, and >100 beat/min for age>10 years.

** Defined as per PALS guidelines[167] : respiratory rate>60 breath/minute for age <1 year, >40 breath/minute for age 1-3 years, >34 breath/minute for age 4-5 years, >30 breath/minute for age 6-12 years, and >16 breath/minute for age 13-18 years.

[¶] Defined as per PALS guidelines[167] : systolic blood pressure <70 mmHg for age 1-12 months, <70 mmHg +(age in yearsx2) for age 1-10 years, and <90 mmHg for age >10 years.

[¶ ¶] Defined as diastolic blood pressure that is ≤half of systolic blood pressure[167]

Appendix B-6 Specific Causative Agent of Anaphylaxis in 484 Anaphylaxis Episodes

Causative agent	*N*=484	Specific agent	*N*=484
Food *n* (%)	337 (69.7)	Peanuts Tree nuts Eggs Milk and dairy products Sesame Fish and other sea food Wheat Soy milk Mango Kiwi Peach Pomegranate Gluten	131 (27.1) 82 (16.9) 28 (5.8) 29 (6) 20 (4.1) 26 (5.4) 7 (1.4) 7 (1.4) 2 (0.4) 2 (0.4) 2 (0.4) 1 (0.2) 1 (0.2)
Drugs and medications *n* (%)	11 (2.3)	Immunotherapy Amoxicillin Penicillin Codine Rituximab	4 (0.8) 3 (0.6) 2 (0.4) 1 (0.2) 1 (0.2)
Exercise *n* (%)	9 (1.9)		
Bee sting *n* (%)	8 (1.7)		
Unspecified *n* (%)	82 (16.9)		
Others *n* (%)	36 (7.4)		