



## The Risk of Recurrent Anaphylaxis

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**Objectives** To determine the recurrence rate of anaphylaxis in children medically attended in an emergency department (ED), we performed a prospective cohort study to evaluate prehospital and ED management of children with recurrent anaphylaxis and to assess factors associated with recurrent anaphylaxis.

**Study design** As part of the Cross-Canada Anaphylaxis Registry, parents of children with anaphylaxis identified prospectively in 3 EDs and through an emergency medical response service were contacted annually after presentation and queried on subsequent reactions. Cox regression analysis determined factors associated with recurrence.

**Results** Among 292 children who were registered as having had medical attended anaphylaxis, 68.5% completed annual follow-up questionnaires. Forty-seven patients experienced 65 episodes of anaphylaxis during 369 patient-years of follow-up. Food was the trigger in 84.6% of cases, and epinephrine was used in 66.2%. In 50.8%, epinephrine was used outside the health care facility, and 81.7% were brought to a health care facility for treatment. Asthma, reaction triggered by food, and use of epinephrine during the index episode increased the odds of recurrent reaction. Patients whose initial reaction was triggered by peanut were less likely to have a recurrent reaction.

**Conclusions** We report a yearly anaphylaxis recurrence rate of 17.6% in children. There is substantial underuse of epinephrine in cases of anaphylaxis. Educational programs that promote effective avoidance strategies and prompt use of epinephrine are required. (*J Pediatr* 2017;180:217-21).

Anaphylaxis is a serious allergic reaction that is rapid in onset and life threatening. For most triggers of anaphylaxis, there is no cure. As such, patients must rely on identification and avoidance of the trigger, in addition to prompt recognition of reactions and treatment with epinephrine. Anaphylaxis accounts for 0.2%-0.4% of pediatric emergency department (ED) visits,<sup>1-3</sup> and 150-200 fatalities per year in the US.<sup>4</sup> Describing the epidemiology of anaphylaxis has been difficult, historically, for several reasons, including inconsistencies in coding and poor reporting of events. Recent European and North American studies suggest an increase in the incidence of anaphylaxis.<sup>2,5,6</sup> Studies also suggest an increase in the prevalence of food allergy, reporting an increase of 0.6% over a 10-year period that might have stabilized in developed countries.<sup>7</sup>

Even when a trigger for anaphylaxis can be identified, patients remain at risk for a recurrent reaction. Few studies have examined recurrence rates of anaphylaxis and suggest a recurrence rate of up to 10 episodes per 100 patient-years.<sup>8,9</sup> To date, no study has prospectively assessed the risk of recurrent anaphylaxis in a large cohort of children who came to medical attention in EDs with anaphylaxis. We aimed to determine prospectively the risk and management of recurrent anaphylaxis in children and to assess factors associated with recurrent anaphylaxis.

### Methods

As part of the Cross-Canada Anaphylaxis Registry, children diagnosed with anaphylaxis at the EDs of 3 hospitals were recruited, including 2 tertiary care university-affiliated pediatric hospitals, and a third general hospital.<sup>2</sup> In addition, we recruited cases of anaphylaxis presenting to the emergency medical services in the Outaouais region of Quebec, Canada. Patients also were recruited prospectively through an emergency medical service responsible for a population of more than 350 000. Participants were all children (under age 18 years) who received care in participating EDs for an anaphylactic reaction. Anaphylaxis was defined as reaction involving at least 2 organ systems and/or hypotension in response to a potential allergen as confirmed by the treating physician.<sup>10</sup> At recruitment, the treating physician/paramedic completed a 12-question standardized report form providing baseline characteristic on the age, sex, clinical background (presence of comorbidities including cardiovascular disease and atopy, medication use,

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ED	Emergency department	HR	Hazard ratio
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exercise within the 2 hours preceding the reaction), clinical characteristics of the reaction (suspected trigger, symptoms, route of exposure, time interval between exposure and development of clinical symptoms), and management (use of epinephrine, antihistamines, corticosteroids, other medications, and the need for hospital admission). The study was approved by the McGill University Health Center Ethic Review Board. Ethics approval was granted through each institution's respective ethics board along with a signed interinstitutional data sharing agreement.

Following the index reaction, consenting parents were contacted at intervals of approximately 15 months during the study period by telephone and queried on any further allergic reactions. To maximize participation, each household was contacted up to 10 times at different times of the day, including weekends. At the time of follow-up, parents who reported a potential allergic reaction were queried on the trigger, symptoms, and management of the reaction. Two trained members of our team reviewed the completed questionnaire to identify cases of recurrent anaphylaxis. Anaphylaxis was further classified according to severity. Mild anaphylaxis was defined by the presence of cutaneous symptoms (urticaria, erythema, and angioedema), as well as oral pruritus, gastrointestinal symptoms (nausea), or respiratory symptoms (nasal congestion, sneezing, rhinorrhea, or throat tightness). Moderate anaphylaxis was characterized by the presence of any of the symptoms of mild anaphylaxis, as well as crampy abdominal pain, diarrhea, recurrent vomiting, dyspnea, stridor, cough, wheeze, or light headedness. Severe anaphylaxis was defined by the presence of cyanosis, hypoxia (oxygen saturation <92%), respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness.<sup>11</sup>

Descriptive statistics were used to estimate the percentage of children presenting with anaphylaxis, their triggers, and use of epinephrine for both the index reaction and any subsequent reactions. Cox regression analysis was used to estimate the associations between recurrent reaction and demographics (age, sex), clinical characteristics (presence of comorbidities, use of medications, exercise within 2 hours of reaction, type of trigger, and severity of index reaction), and management of index reaction.

## Results

Between April 2011 and February 2014, 292 children were medically attended because of anaphylaxis. Two hundred patients (68.5%) completed at least 1 annual follow-up questionnaire (111 participants completing 1 year of follow-up, and 89 completed 2 years of follow-up), providing 369 patient-years of observation. The number of participants from each site is detailed in [Table I](#). Nonresponders consisted of households that could not be reached. There was no case of refusal among households contacted successfully. Demographic characteristics of participants who completed and who did not complete follow-up are summarized in [Table II](#). There were no clinically important differences between the 2 groups apart from higher prevalence of eczema in responders vs nonresponders. The

**Table I.** Participants recruited from each site

Sites	Number recruited	Number completing at least 1 follow-up questionnaire
Montreal Children's Hospital	250	184
Sacre-Coeur	11	7
Saint Justine Children's Hospital	17	8
Royal Victoria Hospital	2	0
Outaouais EMS	12	1
Total	292	200

EMS, emergency medical services.

median age at study entry of participants whose families completed the follow-up questionnaire was 4.7 years. Almost 60% of recurrent reactions occurred in males, and the most common trigger of the index reaction was food (86.9%).

A total of 65 additional episodes of anaphylaxis during follow-up were observed among 47 participants, resulting in a yearly recurrence rate of 17.6% (95% CI 13.6, 22.5). Among 47 participants, 35 experienced 1 recurrent reaction, 7 experienced 2 recurrent reactions, 4 experienced 3 recurrent reactions, and 1 experienced 4 recurrent anaphylactic reactions.

Demographic characteristics of participants with recurrent reactions and those without recurrent reactions are summarized in [Table III](#). Participants with recurrent episodes of anaphylaxis were more likely to have asthma (39.1%) than those who did not have recurrent reactions (17.6%). Foods were the most common trigger for the index episode of anaphylaxis (97.6% of those with recurrent reactions), as well as recurrent episodes of anaphylaxis (84.6%). Peanut triggered 17% of the index reactions and 6.2% of recurrent reactions. The majority of recurrent reactions (69.2%) were classified as moderate.

History of asthma (hazard ratio [HR] 1.94; 95% CI 1.18, 3.21), use of epinephrine during the index episode (HR 2.22; 95% CI 1.09, 4.51), and having food as the trigger of anaphylaxis (HR 11.44; 95% CI 1.58, 83.08) increased the odds of recurrence. However, when the food trigger was peanut, recurrence was less likely (HR 0.27; 95% CI 0.12, 0.64).

Characteristics of food triggers of recurrent episodes are shown in [Table IV](#), and severity and management are shown

**Table II.** Demographic characteristics at baseline in subjects with and without follow-up

	With follow-up (n = 200)	Without follow-up (n = 92)
Age (y)		
Mean	6.7	7.8
Median (IQR)	4.7 (1.6, 11.0)	7.7 (2.4, 12.4)
Male (%)	56.5	51.1
Trigger for reaction (%)		
Food	86.9	77.2
Peanut	25.1	18.5
Insect sting	4.5	4.3
History of asthma (%)	22.7	18.9
History of eczema (%)	26.0	9.8
Severity of anaphylaxis at presentation (%)		
Severe	9.0	5.4
Moderate	54.5	65.2

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