The Risk of Recurrent Anaphylaxis

Andrew O'Keefe, MD[1], Ann Clarke, MD, MSc[2], Yvan St. Pierre, MSc[3], Jennifer Mill, BA[3], Yuka Asai, MD, MSc[4], Harley Eisman, MD[5], Sebastien La Vieille, MD[6], Reza Alizadehfar, MD[3], Lawrence Joseph, PhD[3], Judy Morris, MD[7], Jocelyn Gravel, MD[8], and Moshe Ben-Shoshan, MD, MSc[9]

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,[1-3] and 150-200 fatalities per year in the US.[4] 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.[2,5,6] 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.[7]

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.[8,9] 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.[2] 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.[10] 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,

ED	Emergency department	HR	Hazard ratio

From the [1]Discipline of Pediatrics, Faculty of Medicine, Memorial University, St. John's, Newfoundland and Labrador, Canada; [2]Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [3]Departments of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada; [4]Division of Dermatology, Department of Medicine, Queen's University, Kingston, Ontario, Canada; [5]Montreal Children's Hospital, Emergency Department, McGill University Health Centre, Montreal, Quebec, Canada; [6]Food Directorate, Health Canada, Ottawa, Ontario, Canada; [7]Department of Emergency Medicine, Sacré-Coeur Hospital, University of Montréal, Montreal, Quebec, Canada; [8]Department of Pediatrics, Sainte-Justine Hospital, University of Montreal, Montreal, Quebec, Canada; and [9]Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada

Funded by AllerGen National Center of Excellence and Health Canada (10 203 GEN). The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.09.028

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.[11]

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 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%).

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.

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

Table III. Demographic characteristics at baseline of those with and without recurrent anaphylaxis

	With recurrence (n = 47)	Without recurrence (n = 153)
Age (y)		
Mean	6.5	6.7
Median (IQR)	4.2 (1.5, 13.2)	5.1 (1.8, 10.6)
Male (%)	59.6	55.6
Trigger for index reaction		
Food	97.9	83.6
Peanut	17	27.6
Insect sting	0	5.9
History of asthma (%)	39.1	17.6
History of eczema (%)	31.9	24.2
Severity of anaphylaxis at presentation (%)		
Severe	8.5	9.2
Moderate	55.3	54.2

in **Table V**. Overall 66.2% of recurrent episodes of anaphylaxis were treated with epinephrine. Epinephrine was used outside a health care facility in 50.8% of cases. Among participants experiencing recurrent reactions, 81.7% were brought to a health care facility for treatment. The percentage of children with moderate/severe anaphylaxis brought to the health care facility was almost 30% higher in cases that were treated with epinephrine outside the health care facility. In participants who were brought to a healthcare facility, 77.4% were treated with epinephrine either before or after arrival.

Discussion

This prospective study examined recurrence rates of anaphylaxis in children medically attended in an ED with anaphylaxis. We report an annual recurrence rate of 17.6%. Previous studies have reported similar rates, although these studies were retrospective and did not focus on the pediatric population.[6,8] Mullins et al[8] examined a cohort of adults and children in a community-based specialist practice, and did not use a consensus definition of anaphylaxis. The study by Decker et al[6] is population-based and used *International Classification of Diseases, Ninth Revision* codes to identify cases of anaphylaxis retrospectively.

We found that food was the most common trigger for recurrent episode(s) of anaphylaxis. This is consistent with other studies.[6,8] As identified in previous studies, milk was a common trigger of recurrent reactions,[9] potentially because milk protein can appear in many products, which may not be labeled clearly. Indeed, a recent study reveals that cow's milk was detectable in almost one-half of bakery products sold as "cow milk free.[12]" Interestingly, our results indicate that tree nut was a trigger in recurrent 15.4% of reactions, and peanut accounted for only 6.2% of recurrent reactions. Vetander et al[9] reported that 35% of recurrent visits were due to tree nut and peanuts combined, which is higher than in our study. In 2012, new regulations were introduced in Canada, requiring labeling of common food allergens using simple language in both official languages.[13] Though tree nut containing products may be more readily identified by labeling, there may be other factors to explain why tree nut accounts for a significant proportion of recurrent reactions. As there are many types of tree nuts, children who are allergic to only 1 type may continue to ingest other nuts and inadvertently are exposed to the particular tree nut to which they are allergic by contamination. Cox analysis revealed that there was a decreased risk of recurrent reactions among patients in whom peanut was the trigger of the index reaction. It is possible that there is a higher degree of awareness of peanut allergy among patients, and as such, families are more diligent in avoidance.[14]

Our findings that patients with a history of asthma are more likely to experience recurrent episodes of anaphylaxis are consistent with several studies that have identified asthma as a risk factor for anaphylaxis-related mortality,[15,16] wheeze, and respiratory arrest during anaphylaxis.[17]

In accordance with the reported literature[18] we found that epinephrine auto-injectors were underused during anaphylaxis. In our study, during an episode of anaphylaxis, most

Table IV. Characteristics of recurrent anaphylactic reactions (n = 65 reactions/47 patients)

Triggers for reaction	%	Among those reacting to a certain food allergen in index reaction (D), proportion of those reacting to the same allergen in at least one recurrent reaction (N) % (N/D)	Among those who reacted to a certain allergen in recurrent reaction (D), proportion of those who had a known food allergy to this allergen (N) % (N/D)
Food	84.6	43.6 (17/39)	51.4 (19/37)
Tree nut	15.4	62.5 (5/8)	33.3 (3/9)
Milk	15.4	100 (6/6)	75 (6/8)
Peanut	6.2	37.5 (3/8)	25 (1/4)
Fish	4.6	0 (0/2)	50 (1/2)
Wheat	4.6	100 (2/2)	66.7 (2/3)
Nuts, not specified	3.1	–	100 (1/1)
Egg	1.5	20 (1/5)	100 (1/1)
Shellfish	1.5	0 (0/1)	0 (0/1)
Sesame	1.5	0 (0/1)	100 (1/1)
Soy	0	0 (0/1)	–
Other food allergen*	10.8	0 (0/5)	16.7 (1/6)
Multiple allergens	6.2	–	75 (3/4)
Unknown allergen	13.8	–	–

*Other food allergens include: chickpeas, tomatoes, potatoes, sandwiches, and jelly beans.

Table V. Severity and management of recurrent anaphylactic reactions (n = 65 reactions/47 patients)

	%
Severity of anaphylaxis	
Severe	3.1
Moderate	69.2
Epinephrine use, all reactions	66.2
Epinephrine use, all severe reactions	100
Epinephrine use, all moderate reactions	66.7
Epinephrine use, all mild reactions	61.1
Epinephrine use, outside health care facility	
Any anaphylaxis	50.8
Moderate/severe	51.1
Epinephrine use, inside health care facility among those who were not treated with epinephrine outside health care facility	
Any anaphylaxis	31.3
Moderate/severe	34.8
Patients brought to healthcare facility for treatment	
Any anaphylaxis	81.7
Moderate/severe	78.7
Epinephrine use among patients brought to healthcare facility for treatment	
Any anaphylaxis	77.4
Moderate/severe	81.1
% of reactions bringing patient to ED	
% of reactions bringing patient to the ED among those treated with epinephrine outside the ED	93.9
% of moderate/severe reactions bringing patient to the ED among those treated with epinephrine outside the ED	91.7
% of moderate/severe reactions bringing patient to the ED among those not treated with epinephrine outside the ED	65.2

patients experiencing anaphylaxis (80%) were brought to the ED, but 22.9% were not treated with epinephrine. In other studies, parents reported many reasons for not using an epinephrine auto-injector during anaphylaxis, including inability to identify a reaction, fear of misusing the device, and fear of hurting their child.[19] Other factors contributing to low use of injectable epinephrine might include failure to carry the auto-injector.[20]

Our study has limitations. Despite multiple efforts to contact consenting participants, there was a 31% loss to follow-up. In addition, in almost one-half of the centers involved, follow-up questionnaires were completed by less than 50% of participants. As we contact participants on an annual basis, recall bias of recurrent reactions could impact the accuracy of the reports provided. Finally, although the index reaction was confirmed by a physician, we relied on self-reports of the symptoms and treatment of recurrent reactions. It is unlikely, however, that recall bias had substantial effect on reports of epinephrine use or presentation to hospital.

Given that in cases in which the allergen is not known or not specified it might be hard to project recurrences, we repeated the analysis focusing only on the 83.6% of the cohort (ie, 244/292) who originally reacted to foods. Among 173 families who completed at least 1 follow-up questionnaire after a food-related index reaction, 41 patients had 54 reactions to foods during 316 patient-years of follow-up. Epinephrine was used in 72.2% of those reactions. In 55.6% (95% CI 41.4%, 69.1%), epinephrine was used outside the health care facility. In 29.6% (95% CI 18.0%, 43.6%), it was used (only or also) inside the health care facility and in 27.8% (95% CI 16.5%, 41.6%) no epinephrine was used. Among patients with food-induced reactions, 83.3% were brought to a health care facility for treatment. Asthma (HR 2.16; 95% CI 1.18, 2.96), and epinephrine use during index reaction (HR 2.75; 95% CI 1.20, 6.29) increased the odds of recurrent reaction. Patients who were older (HR 0.94; 95% CI 0.89, 1), or whose initial reaction was triggered by peanut (HR 0.26; 95% CI 0.11, 0.60) were less likely to have a recurrent reaction.

Our findings highlight a substantial risk of recurrent anaphylaxis in children with food-induced anaphylaxis and in those with asthma. The study further supports the importance of educating physicians, patients, and their families on prompt use of epinephrine in all cases of anaphylaxis. ■

Submitted for publication May 14, 2016; last revision received Aug 10, 2016; accepted Sep 9, 2016

References

1. Ben-Shoshan M, La VS, Eisman H, Alizadehfar R, Mill C, Perkins E, et al. Anaphylaxis treated in a Canadian pediatric hospital: incidence, clinical characteristics, triggers, and management. J Allergy Clin Immunol 2013;132:739-41.
2. Hochstadter E, Clarke A, De SS, LaVieille S, Alizadehfar R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. J Allergy Clin Immunol 2016;137:1888-90.
3. Huang F, Chawla K, Jarvinen KM, Nowak-Wegrzyn A. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. J Allergy Clin Immunol 2012;129:162-8.
4. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007;119:1016-8.
5. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135:956-63.
6. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 2008;122:1161-5.

7. Ben-Shoshan M, Turnbull E, Clarke A. Food allergy: temporal trends and determinants. Curr Allergy Asthma Rep 2012;12:346-72.
8. Mullins RJ. Anaphylaxis: risk factors for recurrence. Clin Exp Allergy 2003;33:1033-40.
9. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfven T, Ly DH, et al. Anaphylaxis and reactions to foods in children – a population-based case study of emergency department visits. Clin Exp Allergy 2012;42:568-77.
10. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006;47:373-80.
11. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371-6.
12. Trendelenburg V, Enzian N, Bellach J, Schnadt S, Niggemann B, Beyer K. Detection of relevant amounts of cow's milk protein in non-prepacked bakery products sold as cow's milk-free. Allergy 2015;70:591-7.
13. Health Canada. Food allergen labelling. 2011.
14. Waggoner MR. Parsing the peanut panic: the social life of a contested food allergy epidemic. Soc Sci Med 2013;90:49-55.
15. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 2007;119:1018-9.
16. Munoz-Furlong A, Weiss CC. Characteristics of food-allergic patients placing them at risk for a fatal anaphylactic episode. Curr Allergy Asthma Rep 2009;9:57-63.
17. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F, et al. Risk factors for severe pediatric food anaphylaxis in Italy. Pediatr Allergy Immunol 2011;22:813-9.
18. Noimark L, Gardner J, Warner JO. Parents' attitudes when purchasing products for children with nut allergy: a UK perspective. Pediatr Allergy Immunol 2009;20:500-4.
19. Chad L, Ben-Shoshan M, Asai Y, Cherkaoui S, Alizadehfar R, St-Pierre Y, et al. A majority of parents of children with peanut allergy fear using the epinephrine auto-injector. Allergy 2013;68:1605-9.
20. Ben Shoshan M, Kagan R, Primeau MN, Alizadehfar R, Verreault N, Yu JW, et al. Availability of the epinephrine autoinjector at school in children with peanut allergy. Ann Allergy Asthma Immunol 2008;100:570-5.

50 Years Ago in *The Journal of Pediatrics*

Pituitary-Adrenal Responsiveness after Corticosteroid Therapy in Children with Nephrosis

Fleisher DS. J Pediatr 1967;70:54-9

This is an interesting report describing the role of daily vs alternate-day steroids in pituitary responsiveness in 10 children treated with steroids for nephrotic syndrome of unknown etiology. Nine of the 10 children had been treated with prednisone prior to the study, whereas 1 child was studied during the initial episode of nephrotic syndrome before therapy with prednisone. In a crossover study, the children were treated with methopyrapone to stimulate pituitary release of adrenocorticotropic hormone; the children were studied at baseline, after 3 months of daily corticosteroids, and after 3 months of alternate-day corticosteroids. When receiving daily steroids, the average dose was 2.74 mg/m^2, and when receiving alternate day steroids the average dose was 5.33 mg/m^2; thus, the total dosing was comparable. The author found that pituitary responsiveness was nearly normal when steroids were given every other day and pituitary responsiveness was depressed when the children received daily steroids. The investigator also found that mood swings and other side effects were significantly reduced when the children received alternate-day steroids.

This was an important study that laid the foundation for corticosteroid therapy in children with nephrotic syndrome that is currently in use. This study demonstrated the effectiveness of alternate-day steroids after remission is obtained and that side effects are significantly reduced in children receiving alternate-day steroids. Currently, several regimens for corticosteroid therapy in children with nephrotic syndrome recommend a period of alternate-day steroids in children with nephrotic syndrome.[1-3]

Sharon P. Andreoli, MD
Division of Pediatric Nephrology
James Whitcomb Riley Hospital for Children
Indianapolis, Indiana

References

1. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. Pediatrics 2009;124:747.
2. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. A report of the International Study of Kidney Disease in Children. J Pediatr 1982;101:514.
3. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal changes and focal and segmental glomerular sclerosis. In: Cameron JS, Davison MA, Grünfeld JP, Ponticelli C, Ritz E, Winearls CG, et al., eds. Oxford textbook of clinical nephrology. Oxford Medical Publications; 1992. p. 298.