

Clinical Communications

Anaphylaxis as a presenting symptom of food allergy in children with no known food allergy

Kayadri Ratnarajah, BSc^a, Ann E. Clarke, MD^b,
Christine McCusker, MD^a, Sofianne Gabrielli, MSc^a,
Judy Morris, MD^c, Jocelyn Gravel, MD^d,
Adam Bretholz, MD^d, Rodrick Lim, MD^e,
Edmond S. Chan, MD^f, Ran D. Goldman, MD^g,
Andrew O-Keefe, MD^h, Jennifer Gerdts, BCommⁱ,
Derek Chu, MDⁱ, Julia Upton, MD^k, and
Moshe Ben-Shoshan, MD^a

Clinical Implications

- One in 4 anaphylactic reactions are the first presentation of food allergy. The major culprits are eggs and milk in infants and peanut/tree nuts among those with no known food allergy, suggesting the need for improved primary prevention strategies.

Food is the leading cause of anaphylaxis in children, with milk, eggs, peanuts, tree nuts, fish, and shellfish considered the most frequent triggers identified.¹ Epinephrine is the first-line treatment for food-induced anaphylaxis.¹ However, to our knowledge, there is no research describing anaphylactic reactions in children with no history of food allergy. Our objective was to assess the clinical characteristics and management of anaphylactic reactions in children (<18 years old) with no known food allergy across Canada.

The Cross-Canada Anaphylaxis Registry (C-CARE) database was used to identify pediatric patients. This database and methodology have been described in previous studies.² In brief, between April 28, 2011, and September 22, 2019, the C-CARE enrolled children presenting with anaphylaxis to 6 emergency departments (EDs) in 4 provinces across Canada. All children younger than 18 years were included.

Prospective data were collected at the time of patient presentation to the ED, with the responsible physician identifying cases of anaphylaxis. Once consent was obtained, a standardized form was used to collect data on sociodemographic factors (age, sex), clinical characteristics of the reaction (symptoms, triggers), presence of comorbidities (asthma, known food allergies), location of reaction occurrence, and management of anaphylaxis. For patients who were not recruited at the time of presentation to the ED, data were collected retrospectively on the basis of a previously validated algorithm.²

Anaphylaxis was defined as acute onset of an illness (minutes to several hours) with the involvement of at least 2 organ systems. The second definition of anaphylaxis defined as hypotension after exposure to a known allergen was not used because the allergen was not known.³ The patients in our study had no previously known food allergy and thus the second definition was not used. Severity of anaphylaxis was

determined using a modified grading system described by Muraro et al.⁴ For the current study, we assessed anaphylactic reactions to food in children who had no previous history of reaction to any food. All statistical analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

A total of 795 cases of anaphylaxis in children with no known food allergy were identified (25.8% of children in the C-CARE database), with almost half the cases recruited prospectively. Median age was 2.0 years (interquartile range, 1.0–5.4) and most were males (Table 1).

Most reactions were moderate reactions (67.1%), occurred at home (72.4%), and rarely during exercise (2.2%) (Table 1). Among all patients, peanut (27.3%) and tree nuts (22.4%) were the most frequent triggers (Table 1). However, culprit food allergens differed by age group. In infancy (during the first year of life), the most frequent food trigger was egg (Figure 1). Among children aged 1 to 6 years, peanut and tree nut were the most common triggers (Figure 1). We found similar findings in children 7 to 17 years old (Figure 1). When analyzing differences between food triggers according to age group, egg was a significantly more frequent food trigger in infants, whereas peanut and tree nut were significantly more frequent in older children (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In terms of anaphylaxis management, although more than half the patients received epinephrine either in the prehospital setting or in the ED, 30.1% of patients did not receive any epinephrine (Table 1).

Our findings suggest that food allergy presenting first as anaphylaxis is not rare and represents roughly one-quarter of anaphylaxis cases in children, with the offending allergen differing according to age. The difference between age groups for specific food triggers in children with no known food allergy may be due to a difference in introductory patterns of different foods. With changes to the recommendations for food introduction encouraging early introduction of allergenic foods, we would predict that the frequencies would vary depending on the timing of introduction.

In our study, peanut-induced anaphylaxis was most frequent between age 1 and 6 years. An introduction to peanut after age 1 year may explain the increased rate of anaphylactic reactions to peanut after infancy. The Learning Early About Peanut trial established that early introduction of peanuts in the first 11 months of life leads to a decrease in development of peanut allergy among children.⁵ In our study, tree nuts were also a common food trigger between age 1 and 6 years. In a study by McWilliam et al,⁶ tree nut allergy prevalence was low in infancy and authors found that only 18.5% of parents reported that their child had consumed tree nuts by the age of 1 year. The authors also established that tree nut allergy was as frequent as peanut allergy at age 6 years.⁶ Similarly to peanut allergy, delayed introduction of tree nuts after age 1 year may account for the higher rate of tree nut–induced anaphylaxis after infancy.

In line with other studies, we have found incident egg- and milk-induced anaphylaxis to be most common in the first year of

TABLE 1. Patient demographic and clinical characteristics among children with no known food allergy (N = 795)

Variable	n (%)
Recruiting site	
Montreal Children's Hospital (QC)	556 (69.9)
British Columbia Children's Hospital (BC)	120 (15.1)
Hôpital Sainte-Justine (QC)	64 (8.1)
London Health Science Centre (ON)	29 (3.6)
Janeway Children's Health and Rehabilitation Center (NL)	14 (1.8)
Hôpital Sacré Coeur (QC)	12 (1.5)
Prospectively recruited	367 (46.2)
Age at reaction (y), median (IQR)	2.0 (1.0-5.4)
Sex (% male)	490 (61.6)
Reaction severity	
Mild	227 (28.6)
Moderate	534 (67.2)
Severe	34 (4.3)
Trigger	
Peanut	217 (27.3)
Tree nut	178 (22.4)
Egg	137 (17.2)
Milk	58 (7.3)
Unknown nut	55 (6.9)
Fish	41 (5.2)
Shellfish	39 (4.9)
Sesame	27 (3.4)
Kiwi	20 (2.5)
Wheat	14 (1.8)
Soy	6 (0.8)
Location of anaphylaxis (N = 727)	
Home	526 (72.4)
Other*	63 (8.7)
Unknown	62 (8.5)
School/daycare	52 (7.2)
Restaurant	22 (3.0)
Work	2 (0.3)
During exercise (N = 672)	15 (2.2)
Management outside the ED	
Antihistamines	305 (38.4)
Epinephrine IM	115 (14.5)
Corticosteroids	12 (1.5)
Anti-H2	7 (0.9)
Management in the ED	
Epinephrine IM	453 (57.0)
Antihistamines	406 (51.1)
Corticosteroids	226 (28.4)
Anti-H2	69 (8.7)
Epinephrine treatment	
Received in the ED only	441 (55.5)
No epinephrine (either in the prehospital setting or in the ED)	239 (30.1)
Received in the prehospital setting only	98 (12.3)
Received in the prehospital setting and ED	17 (2.1)

IM, Intramuscular; IQR, interquartile range.

Values are n (%) unless otherwise indicated.

*Examples of other locations: grandmother's house, friend's house, park, store, in the car.

life in children with no known food allergy.⁷ The European Anaphylaxis Registry also determined that milk and egg were the most common cause of food-induced allergy in the first 2 years of life.¹ These findings likely reflect common feeding practices recommending introduction of milk and egg in the first year of life.⁸

Although there is no absolute contraindication for the use of epinephrine in children and current guidelines recommend prompt administration of epinephrine to treat anaphylaxis, nearly one-third of children in our study did not receive epinephrine either in the prehospital setting or inside the ED.^{3,4} Given that the children assessed were not known to have an allergy to the culprit food, caregivers may not have been equipped with, or may have been hesitant to administer an epinephrine autoinjector.

One-quarter (25.8%) of anaphylactic reactions among children in our C-CARE cohort occurred with no previous history of any food allergy. This suggests that there is a need to develop guidelines for the introduction of food in those with no known food allergy such as a gradual introduction of potentially allergenic foods, continuous incorporation of the food in the diet, and increasing awareness for the appropriate management of anaphylaxis. However, children with no known food allergy understandably would not need access to epinephrine at home if there is no previous history of anaphylaxis.

This study has several limitations. An important potential limitation in this study is that 54.4% of the participants were recruited retrospectively, which could introduce recall bias. However, comparison between prospective and retrospective cases did not reveal substantial differences in sociodemographic and clinical characteristics (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Another limitation is the inability to determine whether children with anaphylaxis were introduced to the food that served as the trigger just before the anaphylactic reaction, or whether they had tolerated the food several times in the past but were receiving it infrequently (eg, less than weekly). Another potential limitation relates to our catchment population. Most patients were recruited from 2 hospitals and hence the results may not be generalized to children across Canada.

In conclusion, our study demonstrated that anaphylaxis as a first manifestation of food allergy is common. Differences between age groups for specific food triggers among children with no known allergy to any food may be due to age of introduction of different foods. Guidelines and educational programs emphasizing regular (weekly or more often) ingestion of potentially allergenic foods after gradual introduction under vigilant adult supervision and educating caregivers on the management of anaphylaxis are required.

Acknowledgments

D. Chu is a CAAIF-CSACI-AllerGen Emerging Clinician-Scientist Research Fellow, supported by the Canadian Allergy, Asthma and Immunology Foundation (CAAIF), the Canadian Society of Allergy and Clinical Immunology (CSACI) and AllerGen NCE Inc (the Allergy, Genes and Environment Network).

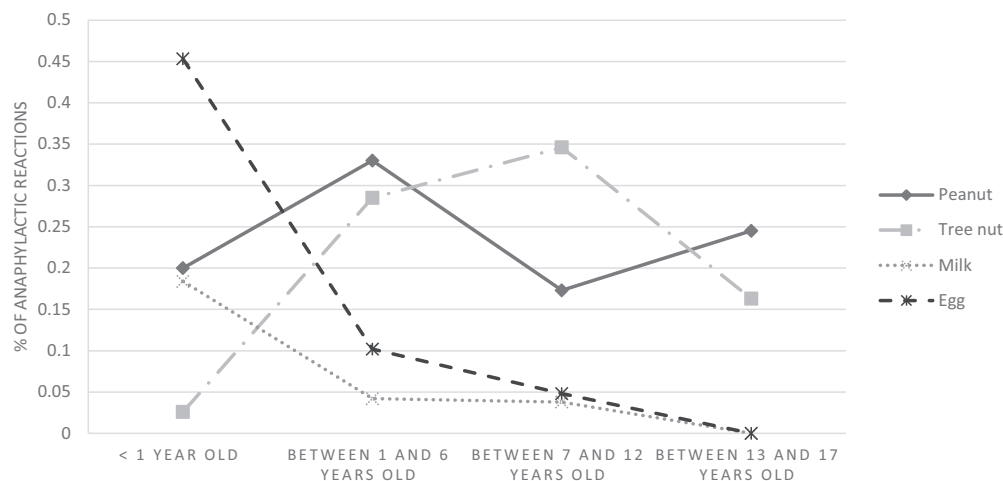


FIGURE 1. Anaphylaxis trigger stratified by age. Most common anaphylaxis triggers stratified by age among children with no known food allergy.

^aDivision of Allergy and Clinical Immunology, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, QC, Canada

^bDivision of Rheumatology, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

^cDepartment of Emergency Medicine, Sacré-Coeur Hôpital, Montreal, QC, Canada

^dDivision of Pediatric Emergency Medicine, Department of Pediatrics, Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada

^eDivision of Pediatric Emergency Medicine, Department of Pediatrics, Children's Hospital at London Health Science Centre, London, ON, Canada

^fDivision of Allergy and Immunology, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada

^gDivision of Clinical Pharmacology and Emergency Medicine, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada

^hDivision of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Memorial University, St John's, NL, Canada

ⁱFood Allergy Canada, Toronto, ON, Canada

^jDivision of Clinical Immunology & Allergy, Department of Medicine, and Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, ON, Canada

^kDivision of Immunology and Allergy, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

This study was supported by AllerGen NCE.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 24, 2020; revised April 11, 2020; accepted for publication April 13, 2020.

Available online ■■

Corresponding author: Kayadri Ratnarajah, BSc, Division of Allergy and Clinical Immunology, Department of Pediatrics, Montreal Children's Hospital, McGill

University Health Centre, 1001 Blvd, Decarie, Montreal, QC, Canada H4A 3J1.

E-mail: kayadri.ratnarajah@mail.mcgill.ca.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.04.033>

REFERENCES

1. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol* 2016;137:1128-1137.e1.
2. Gabrielli S, Clarke A, Morris J, Eisman H, Gravel J, Enarson P, et al. Evaluation of prehospital management in a Canadian emergency department anaphylaxis cohort. *J Allergy Clin Immunol Pract* 2019;7:2232-2238.e3.
3. 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.
4. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 2007;62:857-71.
5. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
6. McWilliam V, Peters R, Tang MLK, Dharmage S, Ponsonby AL, Gurrin L, et al. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. *J Allergy Clin Immunol* 2019;143:644-650.e5.
7. Samady W, Trainor J, Smith B, Gupta R. Food-induced anaphylaxis in infants and children. *Ann Allergy Asthma Immunol* 2018;121:360-5.
8. Canadian Paediatric Society. Feeding your baby in the first year. 2020. Updated January 2020. Available from: https://www.caringforkids.cps.ca/handouts/feeding_your_baby_in_the_first_year. Accessed February 1, 2020.

ONLINE REPOSITORY

TABLE E1. Difference between food triggers according to age group

Difference	Age group			
	<1 y	Between 1 and 6 y	Between 7 and 12 y	Between 13 and 18 y
Between peanut and tree nut	17.4% (0.1%, 0.2%)*	4.5% (−0.0%, 0.1%)	−17.3% (−0.3%, −0.0%)*	8.2% (−0.1%, 0.3%)
Between peanut and milk	1.6% (−0.1%, 0.1%)	28.8% (0.2%, 0.3%)*	13.5% (0.0%, 0.2%)*	24.5% (0.1%, 0.4%)*
Between peanut and egg	−25.3% (−0.3%, −0.2%)*	22.8% (0.2%, 0.3%)*	12.5% (0.0%, 0.2%)*	24.5% (0.1%, 0.4%)*
Between tree nut and milk	−15.8% (−0.2%, −0.1%)*	24.3% (0.2%, 0.3%)*	30.8% (0.2%, 0.4%)*	16.3% (0.0%, 0.3%)*
Between tree nut and egg	−42.7% (−0.5%, −0.3%)*	18.3% (0.1%, 0.2%)*	29.8% (0.2%, 0.4%)*	16.3% (0.0%, 0.3%)*
Between milk and egg	−26.9% (−0.4%, −0.2%)*	−6.0% (−0.1%, −0.0%)*	−1.0% (−0.1%, 0.1%)	0.0%

Values are percentage difference (95% CI).

*Indicates statistical significance ($P < .05$).

TABLE E2. A comparison of characteristics of prospective patients vs retrospective patients among children with no known food allergy

Variable	Prospective (n = 367), n (%)	Retrospective (n = 428), n (%)	Difference % (95% CI)
Site			
Janeway Children's Health and Rehabilitation Center	5 (1.4)	9 (2.1)	−0.7% (−0.0 to 0.0)
Hôpital Sacré Coeur	10 (2.7)	2 (0.5)	2.2% (0.0 to 0.0)*
Hôpital Sainte-Justine	64 (17.4)	0 (0.0)	17.4% (0.1 to 0.2)*
Montreal Children's Hospital	198 (54.0)	358 (83.6)	−29.6% (−0.4 to −0.2)*
London Health Science Centre	29 (7.9)	0 (0.0)	7.9% (0.0 to 0.1)*
British Columbia Children's Hospital	61 (16.6)	59 (13.8)	2.8% (−0.0 to 0.1)
Age at reaction (y), median (IQR)	1.9 (1.0-5.1)	2.3 (1.0-5.4)	−0.4
Sex (% male)	227 (61.9)	263 (61.4)	0.5% (−0.1 to 0.1)
Reaction severity			
Mild	105 (28.6)	122 (28.5)	0.1% (−0.1 to 0.1)
Moderate	242 (65.9)	292 (68.2)	−2.3% (−0.1 to 0.0)
Severe	20 (5.4)	14 (3.3)	2.1% (−0.0 to 0.1)
Trigger			
Peanut	109 (29.7)	108 (25.2)	4.5% (−0.0 to 0.1)
Tree nut	73 (19.9)	105 (24.5)	−4.6% (−0.1 to 0.0)
Unknown nut	28 (7.6)	27 (6.3)	1.3% (−0.0 to 0.1)
Milk	30 (8.2)	28 (6.5)	1.7% (−0.0 to 0.1)
Egg	54 (14.7)	83 (19.4)	−4.7% (−0.1 to 0.0)
Fish	22 (6.0)	19 (4.4)	1.6% (−0.0 to 0.0)
Shellfish	17 (4.6%)	22 (5.1%)	−0.5% (−0.0 to 0.0)
Soy	2 (0.5%)	4 (0.9%)	−0.4% (−0.0 to 0.0)
Wheat	11 (3.0%)	3 (0.7%)	2.3% (0.0 to 0.0)*
Sesame	13 (3.5%)	14 (3.3%)	0.2% (−0.0 to 0.0)
Kiwi	8 (2.2%)	12 (2.8%)	−0.6% (−0.0 to 0.0)
Location (N = 1057)			
Home	268 (74.0)	258 (70.7)	3.3% (−0.0 to 0.1)
School/daycare	37 (10.2)	15 (4.1)	6.1% (0.0 to 0.1)*
Work	2 (0.6)	0 (0.0)	0.6% (−0.0 to 0.0)
Restaurant	15 (4.1)	7 (1.9)	2.2% (−0.0 to 0.0)
Other	32 (8.8)	31 (8.5)	0.3% (−0.0 to 0.0)
Unknown	8 (2.2)	54 (14.8)	−12.6% (−0.2 to −0.1)*
During exercise (N = 672)	9 (2.9)	6 (1.7)	1.2% (−0.0 to 0.0)
Management outside the ED			
Epinephrine IM	46 (12.5)	69 (16.1)	−3.6% (−0.1 to 0.0)
Antihistamines	129 (35.1)	176 (41.1)	−6.0% (−0.1 to 0.0)
Anti-H2	3 (0.8)	4 (0.9)	−0.1% (−0.0 to 0.0)
Corticosteroids	1 (0.3)	11 (2.6)	−2.3% (−0.0 to −0.0)*
Management in the ED			
Epinephrine IM	244 (66.5)	209 (48.8)	17.7% (0.1 to 0.2)*
Antihistamines	211 (57.5)	195 (45.6)	11.9% (0.0 to 0.2)*
Anti-H2	46 (12.5)	23 (5.4)	7.1% (0.0 to 0.1)
Corticosteroids	145 (39.5)	81 (18.9)	20.6% (0.1 to 0.2)*

IM, Intramuscular; IQR, interquartile range.

*Indicates statistical significance ($P < .05$).