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Article type : Research Letter

Management and diagnosis of exercise-associated anaphylaxis cases in the pediatric population

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CEA.13763

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Conflict of Interest Statements

- Dr. Edmond Chan: “ESC has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme; is a member of the healthcare advisory board for Food Allergy Canada; was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention; and was co-lead of the CSACI oral immunotherapy guidelines.”
- Dr. Julia Upton: “JU has acted as a paid consultant to Bausch Health and Kalea and been an investigator for Aimmune Therapeutics, DBV technologies and Regeneron“
- No other COI were declared for all other authors.

Author Contributions

- Study design: Dr. Ben-Shoshan
- Data acquisition: Sofianne Gabrielli and Dr. Ben-Shoshan
- Data analysis, data interpretation, manuscript drafting: Sabrina Bartolucci
- Manuscript revision: Sofianne Gabrielli, Dr. Ann Clarke, Dr. Edmond S. Chan, Dr. Julia Upton, Dr. Andrew O-Keefe Harley Eisman, Dr. Moshe Ben-Shoshan.
- All authors gave approval of the final version to be published.

Declaration of all sources of funding: This project was supported by AllerGen NCE and Health Canada

Text Word Counts: 1354

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TO THE EDITOR

According to the consensus definition of anaphylaxis used in our study, anaphylaxis is defined as a reaction involving two organ systems or hypotension in response to an allergen. Hence, upon diagnosis of an allergy, patients are recommended to avoid the allergen and always carry an epinephrine auto-injector (EAI) [1]. Anaphylaxis is reported to affect 2% of the population. Among anaphylactic reactions, 2 to 15% are reported to be exercise-associated [2]. We aimed to evaluate the sociodemographic, clinical characteristics and management of exercise-associated anaphylaxis (EAA) cases presenting to the Montreal Children's Hospital (MCH), with a focus on food triggers and the management as part of the cross Canada anaphylaxis Registry (CCARE). EAA can be subdivided into five categories: anaphylaxis caused purely by exercise (i.e. exercise-induced [EIA]), food-dependent EIA (FDEIA), food-induced anaphylaxis with exercise as a co-factor (FIA), venom-induced anaphylaxis with exercise as a cofactor (VIA) and cold-induced anaphylaxis with exercise as a cofactor (CIA) [3]. We will be focusing our analysis on the EIA, FDEIA and FIA cases and classifying VIA and CIA as "Other" for the purpose of this study. EIA is defined as anaphylaxis caused by exercise. A detailed history was obtained by the treating physician to determine if food was ingested in the hours prior to and following exercise. If ingestion of food was denied by the patient, these cases were categorized as EIA. FDEIA is defined as ingestion of an allergen followed or preceded by exercise resulting in anaphylaxis. These patients are able to tolerate both exercise and the food allergen independently, as long as a significant amount of time separates the two [4]. We define FIA as anaphylaxis that is food induced. In these cases, exercise was reported as a co-factor potentially increasing anaphylaxis severity. The distinction between these last two entities is important especially regarding management. In cases of FDEIA, the culprit food can be consumed when not followed or preceded by exercise while in cases of FIA the culprit food should always be avoided. Certain cofactors are reported to decrease the threshold for the development of EAA such as drugs, alcohol, temperature, stress, infection or humidity [5].

Currently, the diagnosis of EIA, FDEIA and FIA is largely clinical and relies heavily on a thorough history, skin prick tests (SPT) and often oral challenge. We evaluated the sociodemographic, clinical characteristics and management of EAA cases presenting to the emergency department (ED).

As part of the Cross-Canadian Anaphylaxis Registry (C-CARE), cases of anaphylaxis presenting to the Montreal Children's Hospital (MCH) ED were identified by the treating physician, who then obtained consent, and completed a standardized data entry form documenting symptoms, triggers and management of anaphylaxis [6]. Data on cases not recruited in this prospective fashion were collected retrospectively through chart review according to the International Classification of Diseases, Revision 10 codes related to allergic reactions/anaphylaxis based on a previously validated algorithm [6]. Outpatient clinical data was reviewed, as challenges are typically performed in outpatient clinic. Patients are then followed-up annually for 5 years to collect data. Given that we aimed to evaluate EAA, we included data only from cases that reported anaphylaxis following exercise. All statistical analyses were done using R version 3.2.2. (R Core Team [2013]; R Foundation for Statistical Computing Vienna, Austria). Percentages were used to assess patient demographic characteristics, allergic triggers, reaction severity, location, activity during reaction, and management outside of the hospital of all cases of anaphylaxis. Univariate and multivariate logistic regression models were compared to identify factors associated with epinephrine use outside the health care facility. This study was approved by the ethics committee of the MCH.

Between April 2011 and April 2019, among 2092 cases of anaphylaxis, 89 (4.3%) occurred following exercise, of which 61.7% were male, and the median age was 12.0 years (IQR 8.1, 15.0). The most common reported associated trigger was food (n = 55, 61.8%), of which peanuts were the most common trigger (n=9, 16.4% of the food triggers), followed by milk, shellfish, and soy (n=4 for each, 7.3%). Among cases of EAA, 22.4% occurred at home while 32.9% occurred at school/daycare. For treatment prior to arrival to the health care facility, an EAI was administered in 40 cases (44.9%), antihistamines were administered in 35 cases (39.3%) and 23 patients (25.8%) did not receive any treatment (Table E1 in the Online Repository). Patients were more likely to receive an EAI prior to

arrival in hospital if the patient had a known food allergy, adjusted odds ratio (aOR) 1.74 (95% CI: 1.5, 2.1), or when the reaction was severe, adjusted odds ratio (aOR) 1.5 (95% CI: 1.0, 2.1) (Table 1).

Within our cohort of 89 cases of EAA, 26 were categorized as EIA, 40 as FDEIA, 15 as FIA, and 8 Other EAAs, including 7 VIA and 1 CIA (Table 2). Within the 9 peanut trigger associated cases, 22.2% did not have a known peanut allergy prior to the exercise-associated anaphylactic reaction, whereas among reactions triggered by milk, shellfish, and soy (n= 4, 4, 4 respectively), 50.0%, 75.0% and 75.0% respectively did not have a known allergy to the culprit food, categorizing these as FDEIA cases. Given that people eat and exercise all the time, a limitation of this categorization is that the relationship between food and anaphylaxis does not necessarily imply that exercise was a co-factor unless such patients reacted less severely to the food on other occasions when exercise was absent. Conversely, 77.8%, 50.0%, 25.0%, and 25.0% with a known peanut, milk, shellfish, and soy allergy respectively were categorized as ERFIA (Table E2 in the Online Repository).

Within the 26 suspected EIA cases, 2 had an exercise-challenge (7.7%) and both were negative. Two of the suspected 40 FDEIA cases had an exercise-challenge following the ingestion of the suspected allergen (5.0%) and one was positive (Table 2). Finally, none of the FIA cases were exercise-challenged (Table 2), and all 15 FIA cases had a positive SPT. Our study reveals, among cases of suspected EIA or FDEIA, challenges are rarely conducted resulting in the possibility of misdiagnosis and inappropriate management. The method used in these challenges were not standardized or not thoroughly described in the patient's chart, indicating that there's a lack of protocol for physicians to follow when faced with potential EIA or FDEIA cases. It is important to consider that exercise in the context of anaphylaxis can be a cofactor and an essential part in the triggering of the allergic process. Furthermore, appropriate diagnosis and management of EIA and FDEIA is crucial especially for those that are physically active and athletes. There is controversy in the medical literature regarding the most appropriate strategy to diagnose FDEIA. As recommended by the Japanese guidelines for food allergy 2017, we recommend that exercise-challenges should be performed to correctly diagnose EIA and in the case of FDEIA, SPT and an exercise-challenge

following the ingestion of the culprit allergen should be performed [7, 8]. These tests should attempt to recreate the environmental, physical and dietary conditions that caused the original reaction and must be conducted under the supervision of a trained allergist, in a setting where anaphylaxis can be managed safely. Although studies suggest that the exercise challenges are not perfect in diagnosing EIA and FDEIA, they are still recommended [9]. When EIA or FDEIA is diagnosed, it is advised that the patient carry an EAI, have a personalized emergency plan and never exercise alone. Additionally, in the case of FDEIA, it is recommended to avoid the culprit food 4 to 6 hours before and after any physical activity [8]. In cases of FIA, it is recommended to completely avoid ingesting the allergen.

In conclusion, we demonstrate that EAIs are underused outside the hospital in EAA cases, potentially because of lack of prior knowledge of an allergy, causing the individual to be unprepared. Future studies must focus on evaluating the barriers to use of the EAI in EAA. Furthermore, our findings reveal that EAA is not systematically assessed with exercise-challenges to further categorize patients as having EIA or FDEIA. Follow-up with an allergist is required so that the patient may be properly diagnosed and given the correct tools and information to manage their condition.

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Funding by **AllerGen**, Grant #: 12CanFast3

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Table 1. Factors associated with the use of EAI outside of health care facility

	Univariant	Multivariate
Variables	OR (95% CI)	OR (95% CI)
Age at reaction	0.99 (0.98, 1.02)	1.00 (0.98, 1.02)
Sex (males)	1.14 (0.92, 1.41)	1.10 (0.91, 1.31)
Known Asthma	1.03 (0.79, 1.34)	0.85 (0.67, 1.07)
Known Food Allergy	1.69 (1.42, 2.02)*	1.74 (1.45, 2.09)*
Severe Reaction	1.51 (1.00, 2.27)*	1.46 (1.03, 2.07)*

Table 2. Percentage of exercise-challenged cases

	# Cases	# of Exercise-Challenged Cases	% Exercise-Challenged	# Skin Prick Tests	# IgE Tests
Suspected EIA	26	2	7.69%	5	3
Suspected FDEIA	40	2	5.00%	20	17
Suspected FIA	15	0	0.00%	15	8
Other*	8	1	12.50%	2	0

*Other includes VIA and CIA.

Table E1. Characteristics and management of patient with exercise-associated anaphylaxis

Variable	n (%)
Sex (% Males)	54 (61.7%)
Age of Reaction (Median, IQR)	11.98 (8.06, 14.98)
Type of Triggers	n (%)
Food	55 (61.80%)
Peanut	9 (16.36%) on 55
Tree nut	1 (1.82%)
Nut	3 (5.45%)
Milk	4 (7.27%)
Egg	3 (5.45%)
Fish	1 (1.82%)
Shellfish	4 (7.27%)
Soy	4 (7.27%)
Wheat	0 (0%)
Sesame	0 (0%)
Kiwi	0 (0%)
Other foods	15 (27.27%)
Unknown	11 (20.00%)
Venom	7 (7.87%)
Drug	0 (0%)
Cold temperature	1 (1.12%)
Exercise only trigger identified	26 (29.21%)
Reaction severity	n (%)
Mild	13 (14.61%)
Moderate	70 (78.65%)
Severe	6 (6.74%)
Comorbidities	n (%)
Food Allergy	43 (48.31%)

Drug Allergy	1 (1.12%)
Venom Allergy	1 (1.12%)
Other Allergy	10 (11.24%)
Asthma	17 (19.10%)
Eczema	6 (6.74%)
Admission	n (%)
ICU	0 (0%)
Hospital ward	0 (0%)
No admission	84 (98.82%) on 85
Symptoms	n (%)
Pruritis	54 (60.67%)
Urticaria	62 (69.66%)
Flushing	20 (22.47%)
Rhino Conjunctivitis	18 (20.22%)
Angioedema	52 (58.43%)
Throat Tightness	42 (47.19%)
Stridor	3 (3.37%)
Gastrointestinal	29 (32.58%)
Breathing difficulties	46 (51.69%)
Wheezing	12 (13.48%)
Cyanosis	1 (1.12%)
Circ Collapse	0 (0%)
Hypotension	1 (1.12%)
Hypoxia	4 (4.49%)
Incontinence	0 (0%)
Location of Reaction	N = 85 (%)
Home	19 (22.35%)

School/Daycare	28 (32.94%)
Work	0 (0%)
Restaurant	4 (4.71%)
Other	34 (40.00%)
Other Description	0 (0%)
Out Patient Management	n (%)
Epinephrine	40 (44.94%)
Anti-Histamines	35 (39.32%)
Anti-H2	2 (2.25%)
Beta Antagonist	8 (8.99%)
Corticosteroids	0 (0%)
IV Fluids	0 (0%)
Other	5 (5.62%)
No Treatment	23 (25.84%)
Unknown	0 (0%)

In Patient Management	n (%)
Epinephrine	34 (38.20%)
Anti-Histamines	35 (39.33%)
Anti-H2	1 (1.12%)
Beta-Antagonists	4 (4.49%)
Corticosteroids	15 (16.85%)
IV Fluids	3 (3.37%)
Other	10 (11.24 %)
No treatment	11 (12.36%)
Unknown	0 (0%)
Reaction severity	n (%)
Px Epipen	65 (73.86%)
Already has	18 (20.45%)
Not given	4 (4.54%)
Unknown	1 (1.14%)

Table E2: FDEIA and ERFIA Classification

	Triggers	Known allergy to trigger (FIA)	Unknown Allergy to trigger (FDEIA)	% FIA	% FDEIA
Peanut	9	7	2	77.78%	22.22%
Tree Nut	1	0	1	0%	100%
Nut	3	1	2	33.33%	66.66%
Milk	4	2	2	50%	50%
Egg	3	3	0	100%	0%
Fish	1	0	1	0%	100%
Shellfish	4	1	3	25%	75%
Soy	4	1	3	25%	75%
Wheat	0	0	0	n/a	n/a
SS	0	0	0	n/a	n/a
Kiwi	0	0	0	n/a	n/a
Other	15	0	15	0%	100%
Unknown	11	0	11	0%	100%