

Evaluation of Prehospital Management in a Canadian Emergency Department Anaphylaxis Cohort



Sofianne Gabrielli, MSc^a, Ann Clarke, MD^b, Judy Morris, MD^c, Harley Eisman, MD^d, Jocelyn Gravel, MD^e, Paul Enarson, MD^f, Edmond S. Chan, MD^g, Andrew O'Keefe, MD^h, Robert Porter, MDⁱ, Rodrick Lim, MD^j, Yarden Yanishevsky, MD^k, Jennifer Gerdtz, BComm^l, Adil Adatia, MD^k, Sebastien LaVieille, MD^{m,n}, Xun Zhang, PhD^o, and Moshe Ben-Shoshan, MD^a *Montreal, Québec City, Quebec; Calgary, Edmonton, Alberta; Vancouver, British Columbia; St. John's, Newfoundland & Labrador; and London, Toronto, Ottawa, Ontario, Canada*

What is already known about the topic? Current guidelines for anaphylaxis management include epinephrine as first-line treatment but also H1-antihistamines and corticosteroids. Although prompt use of epinephrine is well supported, studies so far have not established the role of antihistamines and corticosteroids.

What does this article add to our knowledge? Our study is the first to show negative effects of early use of corticosteroids in the treatment of anaphylaxis and also suggests that early antihistamine use, in conjunction with early epinephrine, could contribute to better management of anaphylaxis.

How does this study impact current management guidelines? The current anaphylaxis management algorithm should be modified, at least in the prehospital setting, to exclude corticosteroids and to administer antihistamines only in conjunction with epinephrine in all cases of anaphylaxis.

BACKGROUND: Studies assessing the use of antihistamines and corticosteroids for the treatment of anaphylaxis have not supported a conclusive effect.

OBJECTIVE: To assess prehospital management of anaphylaxis by measuring the effect of epinephrine use compared with antihistamines and corticosteroids on negative outcomes of anaphylaxis (intensive care unit/hospital ward admission, multiple doses of epinephrine in the emergency department [ED], and intravenous fluids given in the ED).

METHODS: The Cross-Canada Anaphylaxis Registry is a cohort study that enrolls anaphylaxis cases presenting to EDs in 5 Canadian provinces over a 6-year period. Participants were

recruited prospectively and retrospectively and were excluded if the case did not meet the definition of anaphylaxis.

RESULTS: A total of 3498 cases of anaphylaxis, of which 80.3% were children, presented to 9 EDs across Canada. Prehospital treatment with epinephrine was administered in 31% of cases, whereas antihistamines and corticosteroids were used in 46% and 2% of cases, respectively. Admission to the intensive care unit/hospital ward was associated with prehospital treatment with corticosteroids (adjusted odds ratio, 2.84; 95% confidence interval [CI], 1.55, 6.97) while adjusting for severity, treatment with epinephrine and antihistamines, asthma, sex, and age. Prehospital treatment with epinephrine (adjusted odds ratio,

^aDivision of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada

^bDivision of Rheumatology, Department of Medicine, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada

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

^dDepartment of Emergency Medicine, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

^eDivision of Emergency Medicine, Department of Pediatrics, Centre hospitalier universitaire Sainte-Justine, Montreal, Quebec, Canada

^fDivision of Emergency Medicine, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

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

^hDepartment of Pediatrics, Faculty of Medicine, Memorial University, St. John's, Newfoundland & Labrador, Canada

ⁱDivision of Emergency Medicine, Faculty of Medicine, Memorial University, St. John's, Newfoundland & Labrador, Canada

^jDivision of Pediatrics and Emergency Medicine, Children's Hospital at London Health Science Centre, London, Ontario, Canada

^kDivision of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, Stollery Children's Hospital, Edmonton, Alberta, Canada

^lFood Allergy Canada, Toronto, Ontario, Canada

^mFood Directorate, Health Canada, Ottawa, Ontario, Canada

ⁿDépartement sciences des aliments, Faculté des sciences de l'agriculture et de l'alimentation, Université Laval, Québec City, Québec, Canada

^oCentre for Outcomes Research and Evaluation, Research Institute of McGill University Health Centre, Montreal, Quebec, Canada

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Corresponding author: Sofianne Gabrielli, MSc, Division of Pediatric Allergy and Clinical Immunology, McGill University Health Centre, 1001 Blvd. Decarie, Montreal, Quebec H4A 3J1, Canada. E-mail: sofiannegabrielli@gmail.com.

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Abbreviations used

ACE- Angiotensin-converting enzyme
aOR- Adjusted odds ratio
C-CARE- Cross-Canada Anaphylaxis Registry
CI- Confidence interval
ED- Emergency department
ICU- Intensive care unit
IQR- Interquartile range
IV- Intravenous
NSAID- Nonsteroidal anti-inflammatory drug

0.23; 95% CI, 0.14, 0.38) and antihistamines (adjusted odds ratio, 0.61; 95% CI, 0.44, 0.85) decreased the likelihood of receiving multiple doses of epinephrine in the ED, while adjusting for severity, treatment with corticosteroids, asthma, sex, and age.

CONCLUSIONS: Prompt epinephrine treatment is crucial. Use of antihistamines in conjunction with epinephrine may reduce the risk of uncontrolled reactions (administration of 2 or more doses of epinephrine in the ED), although our findings do not support the use of corticosteroids. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2232-8)

Key words: Anaphylaxis; Antihistamine; Corticosteroids; Epinephrine; Prehospital management

Anaphylaxis is a life-threatening allergic reaction, and guidelines for management have been extensively published.¹⁻⁴ Although epinephrine is the first-line treatment, it is often replaced with antihistamines and corticosteroids that are part of the treatment algorithm.⁵⁻⁷ Given that death due to anaphylaxis can occur as rapidly as of 30 minutes after exposure to food, 15 minutes for insect stings, and 5 minutes for drugs,⁸ and given that delayed administration of epinephrine is a risk factor for fatal anaphylaxis,⁹ it is crucial to assess the effectiveness of prehospital treatment of anaphylaxis through comparison of epinephrine, antihistamines, and corticosteroids.¹⁰ Considering the importance of epinephrine for anaphylaxis, randomized controlled trials for epinephrine use during prehospital management of anaphylactic cases would not be ethical. Therefore, an alternative strategy to determine the appropriateness of the algorithm for prehospital management is through large cohort studies evaluating management in early time intervals after exposure to an allergen. However, up to this point, the focus of the management of anaphylaxis has been on emergency department (ED) treatment, which is inherently flawed due to the potential of reverse causation (ie, more severe cases presenting to the ED are more likely to be treated with epinephrine, antihistamines, and corticosteroids).

We assessed the prehospital management of anaphylaxis and evaluated the effects of prehospital epinephrine use versus corticosteroids and/or antihistamine treatment on intensive care unit (ICU) and hospital ward admission, multiple doses of epinephrine in the ED, and use of intravenous (IV) fluids in the ED.

METHODS

Study design

This cohort study conducted in 5 Canadian provinces and involves 9 medical centers as part of the Cross-Canada Anaphylaxis Registry (C-CARE). The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines. Data on patients were collected prospectively and retrospectively between April 2011 and October 2017. Prospective data were collected at the time of patient presentation. The treating physician identified cases of anaphylaxis and, with the help of a trained research assistant, obtained consent and completed a standardized data entry form documenting symptoms, triggers, and management of anaphylaxis. All participating centers followed the emergency treatment anaphylaxis guidelines by Cheng.¹¹ Data on cases not recruited at the time of presentation to the ED were collected retrospectively. In brief, all cases presenting to the ED were reviewed according to International Classification of Diseases (Tenth Revision) codes related to allergic reactions/anaphylaxis based on a previously validated algorithm.^{12,13} In addition, for consenting patients, we also offered a longer questionnaire collecting data on previous reactions, previous assessment by allergist, and time and mode of transportation to hospital. This longer version was offered in addition to the shorter questionnaire due to concerns that a longer questionnaire would reduce response rate. Anaphylaxis was defined as the involvement of 2 or more organ systems after exposure to a possible allergen or hypotension after exposure to a known allergen.² An uncontrolled reaction was defined as using 2 or more doses of epinephrine in the ED.¹² Data collected from the British Columbia, Alberta, Ontario, and Newfoundland and Labrador centers were sent to the Quebec center before being included in the analysis to confirm that the cases met the definition of anaphylaxis. Only prospective and retrospective cases meeting the definition of anaphylaxis as determined by 2 independent reviewers (SG and MB-S) were included. This study was developed in collaboration with a lay allergy association, Food Allergy Canada.

Setting

In Quebec, patients presenting with anaphylaxis were recruited at 5 EDs as part of the C-CARE study: the Montreal Children's Hospital, Hôpital Sainte-Justine, the Royal Victoria Hospital, the Montreal General Hospital, and Hôpital Sacré-Coeur. The 4 other participating centers included the London Health Sciences Centre in Ontario, the University of Alberta Hospital in Alberta, the British Columbia Children's Hospital in British Columbia, and the Janeway Children's Health and Rehabilitation Centre in Newfoundland and Labrador (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Participants

Children and adults presenting to the 9 EDs with anaphylaxis were recruited for the C-CARE study. Participants were excluded if the described case did not meet the definition of anaphylaxis.²

Outcome

The primary outcomes were ICU/hospital ward admission, multiple doses of epinephrine in the ED, and use of IV fluids in the ED.

TABLE I. Demographic and characteristics of patients presenting with anaphylaxis

Variable	All (n = 3498)	Prospective (n = 1549)	Retrospective (n = 1949)	Difference (95% CI)
Site of reaction presentation, n (%)				
Montreal Children's Hospital	1818 (51.2)	604 (39.0)	1214 (62.3)	-23.2% (-26.6%, -20.0%)
Hôpital Sacré-Coeur	459 (13.1)	387 (25.0)	72 (3.7)	21.3% (18.9%, 23.7%)
Hôpital Sainte-Justine	233 (6.7)	217 (14.0)	16 (0.8)	13.2% (14.0%, 15.0%)
Montreal General Hospital	100 (2.9)	1 (0.1)	99 (5.1)	-5.0% (-6.1%, -4.0%)
Royal Victoria Hospital	49 (1.4)	0	49 (2.5)	-2.5% (-3.3%, -1.8%)
British Columbia Children's Hospital	536 (15.3)	241 (15.6)	295 (15.1)	0.4% (-2.0%, 2.9%)
Janeway Children's Health and Rehabilitation Centre	46 (1.3)	9 (0.6)	37 (1.9)	-1.3% (-2.1%, -0.5%)
University of Alberta Hospital	133 (3.8)	0	133 (6.8)	-6.8% (-8.0%, -5.6%)
London Health Science Centre	124 (3.5)	90 (5.8)	34 (1.7)	4.1% (2.7%, 5.4%)
Age (y), median (IQR)	8.0 (2.9-16.1)	8.3 (2.7-17.0)	7.7 (3.0-15.5)	0.6
Adults (≥18 y), n (%)	688 (19.7)	343 (22.14)	345 (17.7)	4.4% (1.7%, 7.2%)
Male gender, n (%)	1945 (55.6)	877 (56.6)	1068 (54.8)	1.8% (-1.6%, 5.2%)
Type of trigger, n (%)				
Specific food trigger among all food triggers, n (%)	2769 (79.2)	1234 (79.7)	1535 (78.8)	0.9% (-1.9%, 3.7%)
Peanut	577 (20.8)	283 (22.9)	294 (19.2)	3.9% (0.6%, 6.9%)
Tree nut	401 (14.5)	176 (14.3)	225 (14.7)	-4.0% (-3.1%, 2.3%)
Milk	223 (8.1)	90 (7.3)	133 (8.7)	-1.4% (-3.5%, 0.7%)
Unknown nut	182 (6.6)	85 (6.9)	97 (6.3)	0.6% (-1.4%, 2.5%)
Egg	206 (7.4)	79 (6.4)	127 (8.3)	-1.9% (-3.9%, 0.1%)
Fish	80 (2.9)	38 (3.1)	42 (2.7)	0.3% (-1.0%, 1.7%)
Shellfish	106 (3.8)	46 (3.7)	60 (3.9)	-1.8% (-1.7%, 1.3%)
Soy	24 (0.9)	13 (1.1)	11 (0.7)	0.3% (-0.4%, 1.1%)
Wheat	32 (1.2)	18 (1.5)	14 (0.9)	0.5% (-0.3%, 1.4%)
Sesame	74 (2.7)	31 (2.5)	43 (2.8)	-0.3% (-1.6%, 1.0%)
Kiwi	31 (1.1)	11 (0.9)	20 (1.3)	-0.4% (-1.3%, 0.4%)
Other	377 (13.6)	183 (14.8)	194 (12.6)	2.2% (-0.5%, 4.9%)
Venom	80 (2.3)	42 (2.7)	38 (2.0)	0.8% (-0.3%, 1.8%)
Drug	190 (5.4)	95 (6.1)	95 (4.9)	1.3% (-0.3%, 2.8%)
Other	117 (3.3)	49 (3.2)	68 (3.5)	-0.3% (-1.6%, 0.9%)
Unknown	342 (9.8)	129 (8.3)	213 (10.9)	-2.6% (-4.6%, -0.6%)
Reaction severity, n (%)				
Mild reactions*	661 (18.9)	298 (19.2)	363 (18.6)	0.6% (-2.1%, 3.3%)
Moderate reactions†	2594 (74.2)	1123 (72.5)	1474 (75.6)	-3.1% (-6.1%, -0.1%)
Severe reactions‡	240 (6.9)	128 (8.3)	112 (5.8)	2.5% (0.7%, 4.3%)
Comorbidities, n (%)				
Asthma	555 (16.0)	228 (14.8)	327 (17.0)	-2.1% (-4.5%, 0.4%)
Food allergy	1734 (49.9)	728 (47.3)	1002 (52.1)	-4.4% (-7.8%, -1.0)
Heart disease (ischemic heart disease)	11 (0.3)	6 (0.4)	5 (0.3)	0.1% (-0.3%, 0.6%)
Previously prescribed medications, n (%)				
β-Blockers	36 (1.1)	22 (1.5)	14 (0.7)	0.7% (-0.1%, 1.5%)
Nonsteroidal anti-inflammatory drugs (regularly)	44 (1.3)	24 (1.6)	20 (1.1)	0.5% (-0.3%, 1.3%)
Angiotensin-converting-enzyme inhibitors	26 (0.8)	14 (0.9)	12 (0.6)	0.3% (-0.4%, 0.9%)
Tricyclic antidepressants	8 (0.2)	5 (0.3)	3 (0.2)	0.2% (-0.4%, 0.6%)
During exercise, n (%)	144 (5.0)	72 (5.4)	72 (4.6)	1.0% (-0.4%, 2.4%)
Reaction occurring at home, n (%)	1730 (54.6)	890 (58.3)	840 (51.5)	14.4% (11.0%, 17.7%)
Admission, n (%)				
Admitted to intensive care unit/hospital ward	89 (2.6)	50 (3.3)	39 (2.0)	1.2% (0.1%, 2.4%)
Admitted to intensive care unit	22 (0.7)	9 (0.6)	13 (0.7)	-0.1% (-0.6%, 0.5%)
Admitted to hospital ward	61 (1.9)	41 (2.7)	26 (1.3)	1.3% (0.3%, 2.3%)

CI, Confidence interval; IQR, interquartile range.

*Symptoms include generalized pruritis, flushing, urticaria, angioedema, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat tightness, mild wheezing, tachycardia, and anxiety.¹⁴†Symptoms include crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, "barky" cough, difficulty swallowing, dyspnea, moderate wheezing, and "light headedness."¹⁴‡Symptoms include loss of bowel control, cyanosis, respiratory arrest, hypotension and/or circulatory collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, and loss of consciousness.¹⁴

Independent variables

Multiple potential factors were evaluated including sociodemographic factors (eg, age and sex), clinical characteristics of the reaction (trigger and severity), comorbidities (presence of asthma and use of medications), location of the reaction (home vs outside the home), cofactors of anaphylaxis (exercise within 1 hour of the reaction), administration of epinephrine, antihistamines, and corticosteroids in the prehospital setting and in the ED. A modified grading system described by Muraro et al¹⁴ was used to classify anaphylaxis severity. Mild reactions were defined as generalized pruritis, flushing, urticaria, angioedema, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat tightness, mild wheezing, tachycardia, and anxiety. Moderate reactions were defined as crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, “barky” cough, difficulty swallowing, dyspnea, moderate wheezing, and “light headedness.” Severe reactions were defined as those that manifested as a loss of bowel control, cyanosis, respiratory arrest, hypotension and/or circulatory collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, and loss of consciousness.¹⁴ The severity score of clinical symptoms was determined from the patient and/or parent reporting by the questionnaire.

In contrast to other studies, we selected to focus on prehospital management with epinephrine, antihistamines, and corticosteroids. The negative outcomes we assessed (ICU/hospital ward admission, multiple doses of epinephrine in the ED, and IV fluids given in the ED) are usually already evident when patients arrive to the ED and any associations with medications used in the ED would be more likely due to a reverse causation.

Statistical analysis

Patients’ demographics and clinical characteristics were summarized by percentage for categorical data and by median (interquartile range [IQR]) for continuous data, stratified for prospective versus retrospective cases. To account for the clustering effect among hospital practice variation and multiple reactions among patients, generalized linear mixed models were performed. All statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

Ethics

The study was granted ethical clearance by the Ethics Committees of all participating hospitals (ethics approval code: GEN 10-203; see Table E2 in this article’s Online Repository at www.jaci-inpractice.org). All participants prospectively included provided a written informed consent although it was deemed unnecessary for retrospective data collection.

RESULTS

Demographics and clinical characteristics

Between April 2011 and October 2017, 3498 cases of anaphylaxis were identified at 9 EDs across Canada. Almost half (44%) of the cases were prospectively recruited. Approximately half (55%) of the patients were male with a median age of 8.0 years (IQR, 2.9, 16.1). One-fifth (20%) of the patients were adults aged 18 years or older. Sociodemographics, comorbid conditions, and clinical characteristics of reactions were similar in prospective versus retrospective cases (Table I).

The majority of the reactions were caused by food (79%), whereas 5% were due to drugs and 2% caused by venom. The most common food triggers causing anaphylaxis were peanut (21%), tree nut (15%), egg (7%), and milk (7%). The majority of the anaphylactic reactions were of moderate severity (74%)

TABLE II. Management of anaphylaxis (n = 3498)

Variable	n (%)
Administered in prehospital setting	
Epinephrine*	1070 (30.6)
Antihistamines	1599 (45.7)
Short-acting inhaled β -agonist	235 (6.7)
Corticosteroids	77 (2.0)
Epinephrine only	567 (16.2)
Antihistamines only	1096 (31.3)
Both epinephrine and antihistamines	503 (14.4)
Moderate and severe reactions	
Epinephrine only	491 (17.3)
Antihistamines only	856 (30.5)
Both epinephrine and antihistamines	428 (15.1)
Mild reactions	
Epinephrine only	75 (11.4)
Antihistamines only	231 (35.0)
Both epinephrine and antihistamines	75 (11.4)
Administered by health care professional in the ED	
Epinephrine	1686 (48.2)
Antihistamines	1881 (53.9)
Short-acting inhaled β -agonist	380 (10.9)
Corticosteroids	1521 (43.5)
Moderate and severe reactions	
Received epinephrine	1398 (49.3)
Mild reactions	
Received epinephrine	288 (43.6)
All reaction severities	
Received epinephrine	2558 (73.1)
Received 2 epinephrine or more	282 (8.1)
Received 3 epinephrine or more	48 (1.4)
Received 4 epinephrine or more	12 (0.3)

ED, Emergency department.

*Less than 1% of patients received more than 1 dose of epinephrine in the prehospital setting.

and the most common setting for reactions was at home (55%). Half (50%) of the patients reported a known food allergy. Only 3% of reactions were admitted: 0.7% were admitted to the ICU and 2% to the hospital ward (Table I).

Management in the prehospital setting and in the ED

Less than one-third (31%) of anaphylactic reactions were treated with epinephrine in the prehospital setting. Antihistamines were used in 46% of cases and corticosteroids in 2% in the prehospital setting. Treatment with epinephrine alone was found in 16% of cases, whereas treatment with antihistamines alone was reported to be 2-fold higher (31%). Treatment with both epinephrine and antihistamines was found in 14% of cases. In the ED, epinephrine was administered by a health care professional in almost half (48%) of patients presenting with anaphylaxis, whereas antihistamines were administered in 54% and corticosteroids in 44% of patients (Table II).

Among all reaction severities, 25% of patients received epinephrine only in the prehospital setting, whereas 43% received epinephrine only in the ED. More than one-quarter (27%) of patients did not receive epinephrine treatment either

TABLE III. Odds ratio for admission to ICU/hospital ward, ED epinephrine ≥ 2 , and ED IV fluids and their 95% confidence intervals, estimated from a GLIMMIX model

Variable	Admission to ICU/hospital ward		ED epinephrine ≥ 2 doses		ED IV fluids	
	OR [†]	95% CI	OR [†]	95% CI	OR [†]	95% CI
Prehospital epinephrine [‡]	1.49	0.93-2.38	0.22*	0.13-0.37	1.00	0.83-1.47
Prehospital corticosteroids	2.88*	1.13-7.36	0.79	0.19-3.39	1.53	0.77-3.03
Prehospital antihistamines [‡]	0.86	0.54-1.36	0.58*	0.41-0.82	0.82	0.64-1.06
History of asthma	1.11	0.63-1.96	1.24	0.82-1.87	0.92	0.64-1.33
Sex, male	1.16	0.74-1.83	1.56*	1.11-2.19	1.12	0.87-1.45
Age, <18	2.11	0.76-5.90	0.98	0.51-1.90	0.64	0.35-1.17
Reaction severity						
Mild	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate	2.08	0.88-4.90	1.26	0.80-1.96	1.12	0.77-1.64
Severe	11.50*	4.51-29.33	5.68*	3.20-10.08	4.95*	3.07-7.99
Type of trigger						
Food: peanut	2.18*	1.23-3.88	1.26	0.84-1.87	1.60*	1.12-2.29
Food: others	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Drug	4.88*	2.21-10.77	0.51	0.22-1.16	1.35	0.86-2.11
Others	2.66*	1.46-4.83	0.55*	0.32-0.96	1.13	0.81-1.57
Known food allergy	1.345	0.81-2.24	1.16	0.83-1.64	1.14	0.86-1.50

CI, Confidence interval; ED, emergency department; GLIMMIX, generalized linear mixed effect models; ICU, intensive care unit; IV, intravenous; OR, odds ratio.

*Indicates statistical significance ($P < .05$).[†]Adjusted odds ratio.[‡]There was no interaction effect for prehospital epinephrine and prehospital antihistamines on the outcomes.

in the prehospital setting or in the ED (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Among patients with mild anaphylaxis, epinephrine was administered during either prehospital or within hospital management, in 44% of cases. Among those with moderate and severe anaphylaxis, epinephrine was administered in 49% of cases. Among all reactions, regardless of severity, epinephrine was administered to 31% of cases in the prehospital setting and 48% of cases within hospital. Less than one-tenth (8%) of all cases of anaphylaxis required a second dose of epinephrine in the ED, with 1.4% and 0.3% of cases requiring 3 and 4 doses of epinephrine, respectively (Table II).

Factors associated with outcomes of anaphylaxis

Prehospital treatment with corticosteroids was associated with an increased likelihood of ICU/hospital ward admission, whereas prehospital treatment with epinephrine and antihistamines was associated with a decreased likelihood of requiring 2 or more doses of epinephrine in the ED.

Admission to the ICU or the hospital ward was associated with prehospital treatment with corticosteroids (adjusted odds ratio [aOR], 2.88; 95% confidence interval [CI], 1.13, 7.36) and severe reactions (aOR, 11.50; 95% CI, 4.51, 29.33) while adjusting for sex, age, presence of asthma, and type of prehospital drug management. Prehospital treatment with epinephrine and antihistamines was not associated with ICU/hospital ward admission. Prehospital treatment with epinephrine (aOR, 0.22; 95% CI, 0.13, 0.387) and antihistamines (aOR, 0.58; 95% CI, 0.41, 0.82) decreased the likelihood of using 2 or more doses of epinephrine in the ED. Prehospital treatment with corticosteroids was not associated with requiring 2 or more doses of epinephrine in the ED (Table III). Prehospital treatment with epinephrine, antihistamines, and corticosteroids was not associated with IV fluid administration in the ED (Table III).

Subgroup analysis among patients with known food allergies

Among patients with a diagnosed food allergy, admission to the ICU or the hospital ward was associated with prehospital treatment with corticosteroids, regular treatment with angiotensin-converting enzyme (ACE) inhibitors, and drug as a trigger of anaphylaxis, while adjusting for prehospital treatment with epinephrine and antihistamines, history of asthma, regular treatment with β -blockers or nonsteroidal anti-inflammatory drugs (NSAIDs), sex, and age. Administration of 2 or more doses of epinephrine in the ED was less likely associated with prehospital epinephrine treatment and more likely associated with regular treatment with NSAIDs, while adjusting for prehospital treatment with corticosteroids and antihistamines, history of asthma, regular treatment with β -blockers or ACE inhibitors, sex, age, and type or trigger. Administration of IV fluids in the ED was more likely among those treated with prehospital corticosteroids, those who received regular treatment with NSAIDs, males, and those reacting to peanut. Administration of IV fluids was less likely among younger individuals, while adjusting for prehospital treatment with epinephrine and antihistamines, history of asthma, and regular treatment with β -blockers and ACE inhibitors (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

When we limited our data to include only mild and moderate cases, similar associations were observed for the admission to the ICU/hospital ward and use of multiple doses of ED epinephrine (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Subgroup analysis on arrival time to the ED

A subgroup analysis of 421 pediatric patients who consented to provide a longer questionnaire on arrival time and transport to the ED was conducted. Transport to the ED by ambulance was

more likely among reactions occurring at home and among those receiving epinephrine outside of the health care facility, while controlling for type of trigger, age, sex, history of asthma, reaction severity, and ICU or hospital ward admission. There were no associations between arrival to the ED in less than 1 hour and sociodemographic factors, clinical characteristics, and comorbidities (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This is the largest study to assess outcomes of prehospital treatment of anaphylaxis. Our results indicate for the first time that although prehospital treatment with epinephrine has the most substantial protective effect on negative outcomes (ICU/hospital ward admission, multiple doses of epinephrine in the ED, and IV fluids given in the ED) of anaphylaxis, antihistamines may also contribute to reducing these risks and the use of corticosteroids may be associated with the increased risk of negative outcomes. Although we could not comment on the use of corticosteroids in the ED, our results suggest that the role of corticosteroids in the guidelines of anaphylaxis should be reassessed.

Epinephrine is the first-line treatment for anaphylaxis,¹⁵ and there are no absolute contraindications for its use.¹⁶⁻¹⁸ Data from other studies have shown that prehospital administration of epinephrine is associated with better outcomes,^{19,20} whereas delayed epinephrine treatment is associated with higher rates of hospitalization and mortality.^{21,22} We show that early use of epinephrine decreased almost 5-fold the odds of receiving 2 or more doses of epinephrine in the ED. Although there were no fatalities in our study, previous studies report that all cases of fatality were associated with lack of early epinephrine use.⁹ In our study, less than one-third of cases of anaphylaxis received epinephrine outside of the hospital setting and less than half received epinephrine inside the ED. Furthermore, more than one-quarter of patients were not treated with epinephrine either outside or inside of the ED. This is in line with numerous smaller studies describing the underuse of epinephrine by patients, caregivers, paramedics, and physicians, both outside and inside of the hospital.^{7,18,23} The low rate of epinephrine administration could be due to patients' inability to recognize symptoms of anaphylaxis or fears associated with injection and adverse effects.^{13,18}

Two published reviews, including one Cochrane review, state that there is little data to support the use of antihistamines during anaphylaxis.^{6,15} A smaller retrospective study suggested that in patients presenting with allergic reactions, antihistamines may have beneficial effects in decreasing the progression to anaphylaxis.²⁴ Our data suggest that antihistamines could contribute to the treatment of anaphylaxis with epinephrine, although it should not replace it, given that the protective effect of antihistamines is substantially weaker than that of epinephrine. Given that the onset action of second-generation antihistamines, such as cetirizine or rupatadine (which are only available as an oral formula), is relatively fast (within 1 hour)²⁵ and, given the reduced risk of side effects (compared with first-generation antihistamines) such as drowsiness that can be challenging in the management of anaphylaxis,⁶ we recommend the use of second-generation antihistamines in conjunction with epinephrine rather than a first-generation antihistamine by IV administration.

Corticosteroids have been included in the treatment algorithm of anaphylaxis and were believed to protect from biphasic reactions although more recent studies challenge this premise.^{26,27} Multiple reviews have been conducted on the use of corticosteroids in anaphylaxis all of which have concluded that there is no evidence to support their use as corticosteroids are unlikely to play a role in the management of anaphylaxis.^{5,27,28} Although the side effects of the long-term use of corticosteroids have been well documented,²⁹ the risks associated with the short-term use, as often is the case for anaphylaxis, are not fully understood. A recent study found an increased risk for developing sepsis, venous thromboembolism, and fractures among adults in the United States taking low-dose corticosteroids for a period of 30 days or less.³⁰ Given the lack of evidence for their use in anaphylaxis and the potential associated risks, our study supports that the role of corticosteroids in the treatment algorithm of anaphylaxis should be reassessed.

Our results also reveal that regular treatment with certain medications, specifically NSAIDs and ACE inhibitors, is associated with negative outcomes of anaphylaxis. This is in line with other studies. It was reported that the use of ACE inhibitors increased the risk for hospital admission,³¹ potentially due to lowering the threshold of mast cell activation.³² As for NSAIDs, the mechanism is complex and not fully understood; however, it is hypothesized that NSAIDs increase the permeability of the intestinal barrier, increasing the absorption of allergens and accelerating the development of symptoms.³³

Our study has potential limitations. The main limitation of our study is the observational design that is prone to biases. We did not observe that epinephrine and antihistamines were associated with the decreased likelihood of ICU/hospital ward admission or the administration of IV fluids in the ED, likely because our sample size for the outcomes was too small. Given potential bias that not everyone will have access to epinephrine outside of the ED, we conducted a subgroup analysis for our regression model among patients with known food allergies who had epinephrine autoinjectors and we observed the same associations (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). When we limited our data to include only mild and moderate cases, similar associations were observed for the admission to the ICU/hospital ward and use of multiple doses of ED epinephrine (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Hence, we believe that the effect detected is valid. It is possible that the data may be skewed by individuals receiving treatment outside of the ED and not presenting to a health care facility to receive further management. However, this limitation is shared with all studies assessing anaphylaxis in the ED. Furthermore, a previous study by our group suggests that the majority of cases that meet the definition of anaphylaxis will arrive to the ED³⁴ and hence we do not expect a substantial bias due to low ED presentation of patients with anaphylaxis. In addition, we cannot draw conclusions on ED treatment with corticosteroids. The pharmacokinetics of corticosteroids suggest peak concentration after 1 hour of administration with a delayed effect, and,³⁵ with the lack of beneficial effects of prehospital corticosteroids, we anticipate that ED use of corticosteroids is unlikely to be associated with a beneficial effect.

Another limitation in our study is that approximately 50% of the data were collected retrospectively; therefore, there is potential for misclassification bias. However, demographic and

clinical characteristics were similar between prospective and retrospective cases (Table I). Also, our data only capture cases of anaphylaxis presenting to the ED. Finally, we did not have data on transport and arrival time to ED for all patients. However, we conducted a subgroup analysis of 421 pediatric patients who consented to provide data on a more extensive version of questionnaire including data on time of arrival to the ED. Multivariate logistic regression did not show any association between the negative outcomes assessed above and transport time or method of transport to the ED (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). Therefore, we do not believe that transport to the ED was a factor in the treatment received on arrival.

In conclusion, our study demonstrates the importance of prehospital treatment with both epinephrine and antihistamines to reduce the risk of negative outcomes of anaphylaxis, whereas corticosteroids might actually increase these risks. These results suggest that the current anaphylaxis management algorithm should be modified, at least in the prehospital setting, to exclude corticosteroids and to administer antihistamines only in conjunction with epinephrine in all cases of anaphylaxis.

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ONLINE REPOSITORY

TABLE E1. Setting of the C-CARE study

Hospital	Province	Approximate number of annual emergency department visits	Period of recruitment	Patients recruited	Type of recruitment
Montreal Children's Hospital	Quebec	80,000	April 2011 to December 2017	Children	Prospective and retrospective
Hôpital Sainte-Justine	Quebec	82,000	October 2013 to December 2017	Children	Prospective
Royal Victoria Hospital	Quebec	86,000	November 2010 to October 2011	Adults	Retrospective
Montreal General Hospital	Quebec	40,000	March 2011 to February 2012	Adults	Retrospective
Hôpital Sacré-Coeur	Quebec	60,000	May 2012 to December 2017	Children and adults	Prospective and retrospective
Children's Hospital at the London Health Sciences Centre	Ontario	36,000	August 2014 to December 2017	Children	Prospective and retrospective
University of Alberta Hospital	Alberta	70,000	March 2012 to February 2013	Adults	Retrospective
British Columbia Children's Hospital	British Columbia	45,000	June 2014 to May 2017	Children	Prospective and retrospective
Janeway Children's Health and Rehabilitation Centre	Newfoundland and Labrador	36,000	October 2016 to November 2017	Children	Prospective and retrospective

C-CARE, Cross-Canada Anaphylaxis Registry.

TABLE E2. Research ethics boards granting ethics approval at study centers

Hospital	Research ethics board
Montreal Children's Hospital	The Montreal University Health Centre Research Ethics Board
Hôpital Sainte-Justine	The Research Ethics Board of the Hôpital Sainte-Justine
Royal Victoria Hospital	The Montreal University Health Centre Research Ethics Board
Montreal General Hospital	The Montreal University Health Centre Research Ethics Board
Hôpital Sacré-Coeur	The Research ethics Board of the Hôpital du Sacré-Coeur
Children's Hospital at the London Health Sciences Centre	The Health Science Research Ethics Board at Western University
University of Alberta Hospital	The Research Ethics Office at the University of Alberta
British Columbia Children's Hospital	The Women's Health Centre of British Columbia
Janeway Children's Health and Rehabilitation Centre	The Interdisciplinary Committee on Ethics in Human Research at Memorial University

TABLE E3. Management of anaphylaxis with epinephrine by setting (n = 3489)

Site of epinephrine administration	n (%)
Received epinephrine in the prehospital setting only	872 (24.93)
Received epinephrine in the hospital only	1488 (42.54)
Received epinephrine both the prehospital setting and the hospital	198 (5.66)
Did not receive epinephrine at all	940 (26.87)

TABLE E4. Odds ratio for patients with known food allergy for admission to ICU/hospital ward, ED epinephrine ≥ 2 , and ED IV fluids, and their 95% confidence intervals, estimated from a GEE model

Variable	Admission to ICU/hospital ward		ED epinephrine ≥ 2 doses		ED IV fluids	
	OR [†]	95% CI	OR [†]	95% CI	OR [†]	95% CI
Prehospital epinephrine	1.18	0.64-2.17	0.28*	0.16-0.49	1.05	0.73-1.53
Prehospital corticosteroids	5.69*	1.52-21.32	Ref.	Ref.	3.08*	1.13-8.36
Prehospital antihistamines	0.63	0.34-1.17	1.55	0.93-2.61	1.08	0.70-1.68
History of asthma	1.46	0.73-2.91	1.55	0.93-2.61	1.08	0.70-1.68
Regular treatment with β -blockers	Ref.	Ref.	1.95	0.23-16.83	1.22	0.24-6.05
Regular treatment with NSAIDs	2.52	0.24-27.15	6.29*	1.22-32.58	5.67*	1.54-19.59
Regular treatment with ACE inhibitors	15.80*	1.07-233.12	Ref.	Ref.	3.95	0.32-49.20
Sex, male	0.94	0.51-1.74	1.27	0.78-2.06	1.47*	1.00-2.16
Age, <18	2.78	0.80-9.63	1.44	0.68-3.05	0.14*	0.09-0.21
Type of trigger						
Food: peanut	1.69	0.83-3.44	1.18	0.69-2.00	1.96*	1.29-2.98
Food: other	2.51	0.99-6.36	0.63	0.22-1.78	1.13	0.61-2.10
Drug	5.33*	1.19-23.97	Ref.	Ref.	0.76	0.18-3.17

ACE, Angiotensin-converting enzyme; CI, confidence interval; ED, emergency department; GEE, generalized estimating equations; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

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

[†]Adjusted odds ratio.

TABLE E5. Odds ratio for patients with known food allergy with mild and moderate anaphylaxis for admission to ICU/hospital ward, ED epinephrine ≥ 2 , and ED IV fluids, and their 95% confidence intervals, estimated from a GEE model

Variable	Admission to ICU/hospital ward		ED epinephrine ≥ 2 doses		ED IV fluids	
	OR [†]	95% CI	OR [†]	95% CI	OR [†]	95% CI
Prehospital epinephrine	1.34	0.64-2.81	0.25*	0.13-0.49	1.23	0.80-1.87
Prehospital corticosteroids	6.73*	1.43-31.74	Ref.	Ref.	2.67	0.81-8.78
Prehospital antihistamines	0.74	0.36-1.53	0.48*	0.28-0.84	0.73	0.48-1.11
History of asthma	1.11	0.46-2.68	1.55	0.85-2.82	0.95	0.57-1.61
Regular treatment with β -blockers	Ref.	Ref.	2.48	0.28-21.60	1.45	0.29-7.26
Regular treatment with NSAIDs	10.12	0.84-122.57	Ref.	Ref.	4.77*	1.14-19.87
Regular treatment with ACE-inhibitors	Ref.	Ref.	Ref.	Ref.	0.99	0.02-40.75
Sex, male	1.15	0.54-2.45	1.34	0.76-2.35	1.61	1.04-2.50
Age, <18	3.29	0.64-16.82	1.39	0.57-3.40	0.11*	0.07-0.17
Type of trigger						
Food: peanut	2.24	0.94-5.31	1.02	0.54-1.92	2.08*	1.29-3.35
Food: other	4.43*	1.62-12.07	0.83	0.29-2.39	1.19	0.60-2.38
Drug	9.25*	1.81-47.10	Ref.	Ref.	1.34	0.32-5.58

ACE, Angiotensin-converting enzyme; CI, confidence interval; ED, emergency department; GEE, generalized estimating equations; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

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

[†]Adjusted odds ratio.

TABLE E6. Factors associated with arriving to the health care facility in less than 1 hour and by ambulance among pediatric patients transported to the ED

Variable	Arriving to ED in <1 h [†]		Transported by ambulance	
	Univariate, OR (95%)	Multivariate, OR (95%)	Univariate, OR (95%)	Multivariate, OR (95%)
Trigger: food	1.11 (1.01, 1.19)	1.10 (0.99, 1.22)	—	—
Age at reaction	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)	0.99 (0.99, 1.01)
Sex: male	0.99 (0.93, 1.08)	0.98 (0.91, 1.06)	1.02 (0.93, 1.12)	1.01 (0.92, 1.11)
Location: home	1.05 (0.97, 1.12)	1.01 (0.94, 1.09)	1.29 (1.15, 1.45)	1.18 (1.05, 1.33)*
Location: school	—	—	—	—
Asthma	1.01 (0.91, 1.11)	1.02 (0.92, 1.14)	0.96 (0.84, 1.10)	0.96 (0.84, 1.09)
Severe reaction	0.90 (0.79, 1.03)	0.88 (0.76, 1.00)	0.99 (0.83, 1.18)	0.97 (0.81, 1.15)
Epinephrine outside of the health care facility	0.99 (0.93, 1.07)	1.01 (0.94, 1.10)	1.39 (1.27, 1.53)	1.36 (1.23, 1.50)*
Admit ICU/HW	1.18 (0.94, 1.49)	1.23 (0.96, 1.58)	0.91 (0.67, 1.23)	0.91 (0.67, 1.24)

ED, Emergency department; HW, hospital ward; ICU, intensive care unit; OR, odds ratio.

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

[†]Less than 1 h from initiation of the first symptoms.

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