



Tree nut-induced anaphylaxis in Canadian emergency departments: Rate, clinical characteristics, and management



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ABSTRACT

Background: Data are sparse regarding tree nut-induced anaphylaxis (TNA).

Objective: To characterize rate, clinical characteristics, and management of TNA in children (0-17 years old) across Canada and evaluate factors associated with severe reactions and epinephrine use.

Methods: Between April 2011 and May 2020, data were collected on children presenting to 5 emergency departments in Canada. Multivariate logistic analysis was used to evaluate factors associated with severe reactions (stridor, cyanosis, circulatory collapse, or hypoxia) and epinephrine use.

Results: Among 3096 cases of anaphylaxis, 540 (17%) were induced by tree nut. The median age was 5.2 (interquartile range, 2.5-9.5) years and 65.4% were of male sex. Among all reactions, 7.0% were severe. The major tree nuts accounting for anaphylaxis were cashew (32.8%), hazelnut (20.0%), and walnut (11.5%). Cashew-induced anaphylaxis was more common in British Columbia (14.0% difference [95% confidence interval (CI), 1.6-27.6]) vs Ontario and Quebec, whereas pistachio-induced anaphylaxis was more common in Ontario and Quebec (6.3% difference [95% CI, 0.5-12.2]). Prehospital and emergency department intramuscular epinephrine administration was documented in only 35.2% and 52.4% of cases, respectively. Severe reactions were more likely among of

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male sex (adjusted odds ratio [aOR], 1.05 [95% CI, 1.01–1.10]), older children (aOR, 1.00 [95% CI, 1.00–1.01]), and in reactions triggered by macadamia (aOR, 1.27 [95% CI, 1.03–1.57]).

Conclusion: Different TNA patterns in Canada may be because of differences in lifestyle (higher prevalence of Asian ethnicity in British Columbia vs Arabic ethnicity in Ontario and Quebec). Intramuscular epinephrine underutilization urges for epinephrine autoinjector stocking in schools and restaurants, patient education, and consistent policies across Canada.

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Introduction

Tree nuts are the most common food allergens in Canadian adults, and the second most common food allergens (after peanuts) among Canadian children.^{1–3} Indeed, in a study published in 2020, tree nut allergy was found to be self-reported in 1.7% of Canadian adults and 2.6% of Canadian children.⁴ Tree nuts are major culprits of fatal reactions, and the prevalence of tree nut-induced anaphylaxis (TNA) increased in the previous decade.^{1–3} Data on rate, clinical characteristics, and management of TNA in Canada are sparse.⁵ Furthermore, little is known regarding factors associated with severe reactions and the rate of epinephrine use for the treatment of TNA among Canadian children.

As part of the Cross-Canada Anaphylaxis Registry (C-CARE), we assessed children presenting to Canadian emergency departments (EDs) with TNA. We aimed to evaluate the rate, clinical characteristics, and management (prehospital and in the EDs) of TNA in children across Canada, to compare cases of anaphylaxis identified in British Columbia, Ontario, and Quebec EDs, and to evaluate factors associated with severe reactions (defined as stridor, cyanosis, circulatory collapse, or hypoxia) and with epinephrine use.

Methods

Study Design

This study included data from 3 Canadian provinces (British Columbia, Ontario, and Quebec) and 5 EDs as part of the C-CARE. Data analysis follows the STROBE guidelines.⁶ Between April 2011 and May 2020, data on patients presenting to the EDs with anaphylaxis were collected prospectively and retrospectively. Prospective data were collected at the time of patient presentation to the ED, and data on cases not recruited at the time of presentation to the ED were collected retrospectively. The inclusion criterion for our study was to be a child, which was defined as being aged below 18 years old. The treating physician, assisted by a trained research assistant, identified cases of anaphylaxis, always obtained the parent's consent along with the child's assent if they were aged 7 years and older, and completed a standardized data entry form recording symptoms, triggers, and management of anaphylaxis. In addition, retrospective cases were identified through chart review consistent with International Classification of Diseases, Tenth Revision, codes related to allergic reactions and anaphylaxis, based on a formerly validated algorithm.^{7,8}

Anaphylaxis was defined as involvement of 2 or more organ systems after exposure to a potential allergen or hypotension after exposure to a potential allergen.⁹ Uncontrolled reaction was defined as requiring multiple doses (≥ 2) of epinephrine in the ED. Data from all Canadian participating centers were sent to the Quebec center before being included in the analysis to ensure that the cases met the definition of anaphylaxis. There were 3 independent reviewers involved in this process to ensure that criteria for anaphylaxis as defined previously were met.

Setting

In Ontario and Quebec, children presenting with anaphylaxis were recruited at the following 4 EDs as part of the C-CARE study: (1)

Hôpital Sacré-Coeur (HSC), Montreal, Quebec; (2) Hôpital Sainte-Justine (HSJ), Montreal, Quebec; (3) the Montreal Children's Hospital (MCH), Montreal, Quebec; and (4) the London Health Science Centre (LHSC), London, Ontario. In British Columbia, patients presenting with anaphylaxis were recruited at 1 ED as part of the C-CARE study: the British Columbia Children's Hospital (BCCH), Vancouver, British Columbia.

Outcome

The primary outcomes were characterizing the main culprits of TNA and identifying factors associated with severe reactions to tree nut. The secondary outcomes were assessing epinephrine administration in the prehospital setting and evaluating factors associated with use of multiple doses of epinephrine in the ED. Given that those with known food allergy are expected to have a prescribed epinephrine autoinjector (EAI), we also aimed to quantify the use of EAI among those individuals.

The modified grading system of Muraro et al¹⁰ was used to determine anaphylaxis severity. Mild reactions were defined as generalized pruritus, flushing, urticaria, angioedema, nausea or emesis, mild abdominal pain, nasal congestion or sneezing, rhinorrhea, throat tightness, mild wheezing, tachycardia, and anxiety. Moderate reactions were defined as crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, "barking" cough, difficulty swallowing, dyspnea, moderate wheezing, and "light headedness." Severe reactions were defined as loss of bowel control, cyanosis, respiratory arrest, hypotension or circulatory collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, and loss of consciousness.¹⁰ The severity of clinical presentations was determined using the patient or parent responses in the questionnaire.

Independent Variables

Multiple potential factors were evaluated, including sociodemographic factors (age, sex), specific tree nuts and severity of reaction, clinical presentation (eg, pruritus, urticaria, angioedema, gastrointestinal, or respiratory symptoms), administration of epinephrine, antihistamines, and corticosteroids in the prehospital setting and in the ED, known food allergies, comorbidities (eg, presence of eczema, asthma), location of reaction (eg, home, school, restaurant), geographic location (province), and cofactors of anaphylaxis (eg, reaction during exercise, use of nonsteroidal inflammatory drugs).

Statistical Analysis

The patients' demographics and clinical characteristics were reported by percentage for categorical data and by median (interquartile range) for continuous data and stratified for West vs East Coast EDs. Uni- and multi-variable logistic regressions were used to determine factors associated with severe reactions with no epinephrine use in the prehospital setting and with multiple epinephrine doses in the ED. The authors, supervised by a co-author who is a biostatistician, performed all statistical analyses using R version 4.0.0 (R Core Team [2013]; R, Vienna, Austria).

Ethics

The Ethics Committees of all participating hospitals granted ethics clearance to this study (ethics approval code: GEN 10-203).

Results

Demographics and Clinical Characteristics

Between April 2011 and May 2020, 3096 cases of anaphylaxis were identified at 5 EDs in Canada, among which 540 (17%) were induced by tree nut—78 cases in British Columbia, 15 cases in Ontario, and 447 cases in Quebec—and 54.4% of the cases were recruited prospectively. The median age was 5.2 [interquartile range, 2.5–9.5] years, and 65.4% were of male sex. Sociodemographic characteristics,

comorbid conditions, and clinical characteristics of reactions were similar in the patients presenting with TNA in the British Columbia ED vs the Ontario and Quebec EDs (Table 1). Of note, given that we assessed only patients who arrived to the ED, we do not have a specific estimate of how many patients we have missed because they decided to self-manage and not present to the ED, thus resulting in missed tree nut reactions. However, previous studies by our group on a smaller sample from C-CARE revealed that 80% arrive to the ED.¹¹

Most (73.5%) of the anaphylactic reactions were moderate, 7.0% were severe, and the remaining (19.5%) were mild. In Canada, 60.0% of the reactions occurred at home, 4.8% occurred at school, 2.8% occurred at a restaurant, and 8.7% occurred in an unknown setting. Considerably more reactions occurred at home in British Columbia compared with those in Ontario and Quebec (25.2% difference [95% confidence interval (CI), 12.8–37.6]). The most common symptoms

Table 1

Characteristics of Children Presenting to the Emergency Department With an Anaphylactic Reaction to Tree Nut Between April 2011 and May 2020

	British Columbia (N = 78)	Ontario and Quebec (N = 462)	Canada (N = 540)	Difference British Columbia vs Ontario and Quebec (95% CI)
Data collection				
Prospective	41 (52.6%)	253 (54.8%)	294 (54.4%)	3.5% (−14.9 to 10.5)
Age at reaction (y)				
Median (Q1–Q3)	5.85 (2.55–9.50)	5.10 (2.50–9.40)	5.20 (2.50–9.50)	0.75
Sex				
Male	53 (67.9%)	300 (64.9%)	353 (65.4%)	3.0% (−9.0 to 15.0)
Severity				
Mild	20 (25.6%)	85 (18.4%)	105 (19.4%)	7.2% (−3.8 to 18.0)
Moderate	52 (66.7%)	345 (74.7%)	397 (73.5%)	−8.0% (−20.0 to 4.0)
Severe	6 (7.7%)	32 (6.9%)	38 (7.0%)	0.8% (−6.3 to 7.9)
Tree nut				
Almond	8 (10.3%)	31 (6.7%)	39 (7.2%)	3.5% (−4.3 to 11.4)
Brazil	1 (1.3%)	1 (0.2%)	2 (0.4%)	1.1% (−2.2 to 4.3)
Hazel	13 (16.7%)	95 (20.6%)	108 (20.0%)	−3.9% (−13.7 to 5.9)
Cashew	35 (44.9%)	142 (30.7%)	177 (32.8%)	14.1% (1.6–26.7) ^a
Macadamia	0 (0%)	7 (1.5%)	7 (1.3%)	−1.5% (−3.4 to 0.3)
Pecan	5 (6.4%)	21 (4.5%)	26 (4.8%)	1.9% (−0.0 to 0.1)
Pine	3 (3.8%)	19 (4.1%)	22 (4.1%)	−0.3% (−5.2 to 4.6)
Pistachio	3 (3.8%)	47 (10.2%)	50 (9.3%)	−6.3% (−12.2 to −0.5) ^a
Walnut	8 (10.3%)	54 (11.7%)	62 (11.5%)	−1.4% (−9.5 to 6.7)
Unidentified tree nut	0 (0%)	17 (3.7%)	17 (3.1%)	−3.7% (−6.1 to −1.2) ^a
Multiple with peanut	0 (0%)	11 (2.4%)	11 (2.0%)	−2.4% (−4.5 to −0.2) ^a
Multiple without peanut	2 (2.6%)	16 (3.5%)	18 (3.3%)	−0.9% (−5.5 to 3.7)
Symptoms				
Pruritus	40 (51.3%)	255 (55.2%)	295 (54.6%)	−3.0% (−16.6 to 8.8)
Urticaria	47 (60.3%)	280 (60.6%)	327 (60.6%)	−0.3% (−12.4 to 11.7)
Angioedema	42 (53.8%)	284 (61.5%)	326 (60.4%)	−7.6% (−20.3 to 5.0)
Treatment prehospital				
Epinephrine IM	28 (35.9%)	162 (35.1%)	190 (35.2%)	0.8% (−11.4 to 13.1)
Antihistamines	37 (47.4%)	240 (51.9%)	277 (51.3%)	−4.5% (−17.2 to 8.2)
Corticosteroids	1 (1.3%)	10 (2.2%)	11 (2.0%)	−0.9% (−4.5 to 2.7%)
No treatment	18 (23.1%)	130 (28.1%)	148 (27.4%)	−5.1% (−16.0 to 5.9)
Treatment in ED				
Epinephrine IM	38 (48.7%)	245 (53.0%)	283 (52.4%)	−4.3% (−17.1 to 8.4)
Epinephrine IV	0 (0%)	4 (0.9%)	4 (0.7%)	−0.8% (−2.5 to 0.7)
Antihistamines	47 (60.3%)	190 (41.1%)	237 (43.9%)	19.1% (6.6–31.6) ^a
Corticosteroids	37 (47.4%)	120 (26.0%)	157 (29.1%)	21.5% (8.9–34.0) ^a
Epinephrine-related treatment				
No epinephrine	14 (17.9%)	93 (20.1%)	107 (19.8%)	−2.2% (−12.2 to 7.8)
Multiple epinephrine (≥ 2 in the ED)	9 (11.5%)	59 (12.8%)	68 (12.6%)	−1.2% (−8.9 to 7.7)
Known allergy				
Known tree nut allergy	28 (35.9%)	129 (27.9%)	157 (29.1%)	8.0% (−4.2 to 20.1)
Known food allergy	58 (74.4%)	264 (57.1%)	322 (59.6%)	17.2% (5.8–28.7) ^a
Comorbidity				
Asthma	16 (20.5%)	69 (14.9%)	85 (15.7%)	5.6% (−4.7 to 15.8)
Eczema	18 (23.1%)	72 (15.6%)	90 (16.7%)	7.5% (−3.2 to 18.2)
Location of reaction				
Home	30 (38.5%)	294 (63.6%)	324 (60.0%)	−25.2% (−37.6 to −12.8) ^a
School daycare	3 (3.8%)	23 (5.0%)	26 (4.8%)	−1.1% (−6.6 to 4.3)
Restaurant	1 (1.3%)	14 (3.0%)	15 (2.8%)	−1.7% (−6.2 to 3.7)
Other	44 (56.4%)	131 (28.4%)	175 (32.4%)	28.1% (15.6–40.6) ^a

Abbreviations: CI, confidence interval; ED, emergency department; IM, intramuscular; IV, intravenous; Q1, Q3, quartile 1, quartile 3.

^aStatistical significance.

during the anaphylactic reactions to tree nut were urticaria (60.6%), angioedema (60.4%), and pruritus (54.6%), regardless of the ED site in Canada (Table 1).

Less than one-third (29.1%) of the children presenting to the EDs with a TNA had a known allergy to tree nut, whereas more than half (59.6%) had a known food allergy. In the British Columbia, Ontario, and Quebec EDs, a considerable number of children had known conditions, such as eczema (23.1% and 15.6%, respectively) or asthma (20.5% and 14.9%, respectively).

Types of Tree Nut Culprit Associated With Anaphylactic Reactions

The most common tree nuts accounting for anaphylaxis in Canada were cashew (32.8%), hazelnut (20.0%), and walnut (11.5%). The most

common tree nut culprit causing anaphylactic reactions varied depending on the geographic location of the ED. Cashew-induced anaphylaxis was more common in British Columbia vs Ontario and Quebec (14.1% difference [95% CI, 1.6–26.7]), whereas pistachio-induced anaphylaxis was more common in Ontario and Quebec vs British Columbia (6.3% difference [95% CI, 0.5–12.2]).

Among all reactions, 7.0% were severe. The 3 main tree nuts accounting for severe reactions (73.7%) were the same regardless of location within Canada, but in a different order of importance (Table 2). In the British Columbia ED, walnut caused half (50.0%) of the severe anaphylactic reactions, followed by cashew (33.3%) and hazelnut (16.7%). In the Ontario and Quebec EDs, hazelnut was the major (34.4%) culprit in severe reactions, followed by cashew (21.9%) and walnut (12.5%). In Canada, macadamia, pecan, and pistachio caused each almost 5% of the severe anaphylactic reactions.

Table 2

Characteristics of Children Presenting to the Emergency Department With a Severe Anaphylactic Reaction to Tree Nut Between April 2011 and May 2020

	British Columbia (N = 6)	Ontario and Quebec (N = 32)	Canada (N = 38)	Difference British Columbia vs Ontario and Quebec (95% CI)
Data collection				
Prospective	1 (16.7%)	18 (56.2%)	19 (50.0%)	–39.6% (–83.9 to 4.7)
Age at reaction (y)				
Median (Q1–Q3)	10.0 (4.50–11.8)	7.40 (4.70–11.8)	7.85 (4.30–11.9)	2.6
Sex				
Male	6 (100%)	25 (88.1%)	31 (81.6%)	21.9% (–2.3 to 46.1)
Tree nut culprit				
Almond	0 (0%)	3 (9.4%)	3 (7.9%)	–9.4% (–28.8 to 10.1)
Brazil	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Hazel	1 (16.7%)	11 (34.4%)	12 (31.6%)	–17.7% (–61.7 to 26.2)
Cashew	2 (33.3%)	7 (21.9%)	9 (23.7%)	11.5% (–38.8 to 61.7)
Macadamia	0 (0%)	2 (6.3%)	2 (5.3%)	–6.3% (–20.9 to 8.4)
Pecan	0 (0%)	2 (6.3%)	2 (5.3%)	–6.3% (–20.9 to 8.4)
Pine	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Pistachio	0 (0%)	2 (6.3%)	2 (5.3%)	–6.3% (–20.9 to 8.4)
Walnut	3 (50.0%)	4 (12.5%)	7 (18.4%)	37.5% (–14.0 to 89.0)
Unidentified tree nut	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Multiple with peanut	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Multiple without peanut	0 (0%)	1 (3.1%)	1 (2.6%)	–3.1% (–12.3 to 6.0)
Symptoms				
Pruritus	4 (66.7%)	18 (56.2%)	22 (57.9%)	10.4% (–40.9 to 61.8)
Urticaria	6 (100%)	22 (68.8%)	28 (73.7%)	31.3% (5.3–57.2) ^a
Angioedema	4 (66.7%)	21 (65.6%)	25 (65.8%)	1.0% (–41.2 to 43.2)
Gastrointestinal	5 (83.3%)	24 (75.0%)	25 (76.3%)	8.3% (–33.4 to 50.0)
Throat tightness	2 (33.3%)	11 (34.4%)	13 (34.2%)	–1.0% (–43.2 to 41.2)
Stridor	0 (0%)	2 (6.3%)	2 (5.3%)	–6.3% (–20.9 to 8.4)
Breathing difficulties	2 (33.3%)	11 (34.4%)	13 (34.2%)	–1.0% (–43.3 to 41.2)
Wheezing	0 (0%)	12 (37.5%)	12 (31.6%)	–37.5% (–64.2 to –10.8) ^a
Treatment prehospital				
Epinephrine IM	4 (66.7%)	11 (34.4%)	15 (39.5%)	32.3% (–18.8 to 83.3)
Antihistamines	4 (66.7%)	15 (46.9%)	19 (50.0%)	19.8% (–31.6 to 71.2)
Corticosteroids	0 (0%)	2 (6.3%)	2 (5.3%)	–6.3% (–20.9 to 8.4)
No treatment	1 (16.7%)	9 (28.1%)	10 (26.3%)	–11.5% (–55.0 to 32.1)
Treatment in ED				
Epinephrine IM	3 (50.0%)	21 (65.6%)	24 (63.2%)	–15.6% (–68.8 to 37.5)
Epinephrine IV	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Antihistamines	5 (83.3%)	12 (37.5%)	17 (44.7%)	45.8% (1.7–89.9) ^a
Corticosteroids	5 (83.3%)	10 (31.2%)	15 (39.5%)	52.1% (8.3–95.8) ^a
Epinephrine-related treatment				
No epinephrine	1 (16.7%)	5 (15.6%)	6 (15.8%)	1.0% (–32.4 to 34.4)
Multiple epinephrine (≥ 2 in the ED)	3 (50.0%)	7 (21.9%)	10 (26.3%)	28.1% (–24.3 to 80.5)
Known allergy				
Known tree nut allergy	2 (33.3%)	11 (34.4%)	13 (34.2%)	–1.0% (–43.3 to 41.2)
Known food allergy	5 (83.3%)	19 (59.4%)	24 (63.2%)	24.0% (–20.3 to 68.2)
Comorbidity				
Asthma	2 (33.3%)	6 (18.8%)	8 (21.1%)	14.6% (–35.4 to 64.5)
Eczema	0 (0%)	6 (18.8%)	6 (15.8%)	–18.8% (–42.2 to 4.7)
Location of reaction				
Home	3 (50.0%)	23 (71.9%)	26 (68.4%)	–21.9% (–74.7 to 31.0)
School daycare	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Restaurant	0 (0%)	0 (0%)	0 (0%)	0.0% (0.0–0.0)
Other	3 (50.0%)	9 (28.1%)	12 (31.6%)	21.9% (–31.0 to 74.7)

Abbreviations: CI, confidence interval; ED, emergency department; IM, intramuscular; IV, intravenous; Q1, Q3, quartile 1, quartile 3.

^aStatistical significance.

Table 3
Factors Associated With Severe Anaphylactic Reactions to Tree Nuts

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age at reaction (y)	1.01 (1.00–1.01) ^a	1.01 (1.00–1.01) ^a
Sex: male	1.05 (1.01–1.10) ^a	1.06 (1.00–1.11) ^a
Location of reaction: school or daycare	0.92 (0.83–1.02)	0.91 (0.82–1.01)
Tree nut culprit: macadamia	1.30 (1.06–1.60) ^a	1.27 (1.03–1.57) ^a
Asthma	1.03 (0.97–1.09)	1.01 (0.95–1.08)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aStatistical significance.

In the 5 EDs, there were a total of 9 admissions recorded, all of which for reactions that were either moderate or severe. No death was captured.

Factors Associated With Severe Reactions

Severe anaphylaxis was associated with older age (adjusted odds ratio [aOR], 1.01 [95% CI, 1.00–1.01]), male sex (aOR, 1.06 [95% CI, 1.00–1.11]), and reactions triggered by macadamia nut (aOR, 1.27 [95% CI, 1.03–1.57]), while adjusting for location of reaction and asthma (Table 3). We have adjusted for location of reaction because prehospital intramuscular epinephrine use may be influenced by the availability of EAI in each location (eg, there may be more EAIs available at school than in another location). If there is no EAI around while a child has an anaphylactic reaction, then this child is more likely to develop a severe reaction. We have also adjusted for asthma because it has previously been found to be a factor associated with more severe reactions with an OR of 2.71.¹²

Management in the Prehospital Setting and in the Emergency Department

The 2 main drugs used in the prehospital setting were intramuscular epinephrine and oral antihistamines. In Canada, intramuscular epinephrine administration was documented in only 35.2% of the cases, whereas oral antihistamines were administered in more than half (51.3%) of the cases (Table 1). Similar results (39.5% for intramuscular epinephrine and 50.0% for antihistamines) were obtained when the analysis was limited to severe anaphylactic reactions (Table 2). There was no statistical difference between British Columbia and the Ontario and Quebec in terms of prehospital management.

In the EDs in British Columbia, Ontario, and Quebec, the following 3 main management drugs were administered: intramuscular epinephrine (52.4%), oral antihistamines (43.9%), and oral corticosteroids (29.1%). Similar results (63.2% for intramuscular epinephrine, 44.7% for antihistamines, and 39.5% for corticosteroids) were obtained when the analysis was limited to severe anaphylactic reactions. There was a marked difference between British Columbia and Ontario and Quebec in terms of management of all cases of TNA in the ED. ED administration of both corticosteroids (21.5% difference [95% CI, 8.9–34.0]) and antihistamines (19.1% difference [95% CI, 6.6–31.6]) was more common in the British Columbia compared with that in the Ontario and Quebec EDs.

In Canada, intramuscular epinephrine was not used (neither in the prehospital setting nor in the ED) in 19.8% of the cases. Among all cases of TNA, those with a known food allergy (aOR, 0.73 [95% CI, 0.67–0.79]), those treated at school (aOR, 0.72 [95% CI, 0.61–0.86]), and cases triggered by almonds (aOR, 0.84 [95% CI, 0.73–0.97]) or hazelnuts (aOR, 0.87 [95% CI, 0.79–0.96]) were more likely to use intramuscular epinephrine (Table 4). However, even among those with known food allergy who are expected to have an EAI, only half (50.0%) used their EAI. Similarly, among those with known tree nut

Table 4
Factors Associated With No Epinephrine Use in the Prehospital Setting

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age at reaction	0.98 (0.97–0.99) ^a	0.99 (0.98–1.00) ^a
Sex: male	1.07 (0.98–1.16)	1.07 (0.99–1.17)
Known food allergy	0.69 (0.64–0.75) ^a	0.73 (0.67–0.79) ^a
Severe reaction	0.95 (0.82–1.12)	0.95 (0.82–1.10)
Location of reaction: school	0.65 (0.54–0.78) ^a	0.72 (0.61–0.86) ^a
Tree nut culprit: almond	0.85 (0.74–0.98) ^a	0.84 (0.73–0.97) ^a
Tree nut culprit: hazelnut	0.83 (0.75–0.91) ^a	0.87 (0.79–0.96) ^a

Abbreviations: CI, confidence interval; OR, odds ratio.

^aStatistical significance.

allergy who are expected to have an EAI, approximately half (57.0%) used their EAI. Multiple doses of intramuscular epinephrine (at least 2 in the ED, also referred to as uncontrolled reactions) were administered in 12.6% of the cases. Multiple intramuscular epinephrine doses in the ED were associated with male sex (aOR, 1.04 [95% CI, 1.00–1.08]) and severe reactions (aOR, 1.09 [95% CI, 1.01–1.17]) (Table 5). The only factor associated with decreased risk of uncontrolled reactions was prehospital intramuscular epinephrine use (aOR, 0.95 [95% CI, 0.92–1.00]).

Among 17 patients with unknown tree nut culprit, 14 (82.4%) were prescribed an EAI in the ED. The remaining 3 patients already had a prescribed EAI on arrival to the ED. Furthermore, among the 17 patients with a reaction to an unknown tree nut culprit, 4 (23.5%) were already followed by an allergist, 9 (52.9%) were not followed and were thus referred to an allergist by the ED physician, and the remaining 4 (23.5%) did not know whether they had been referred or not.

Discussion

Quebec and Ontario are sharing a border and are expected to have similar lifestyle.¹³ However, British Columbia, and especially Vancouver, has remained one of the most favored places for Chinese immigrants who are reported to have higher risk of food allergy and different diet.¹³ We thus hypothesized that this could account for different type of tree nut reactions. The rationale behind comparing West versus East Coasts of Canada in terms of TNA was to discover (1) whether there was a substantial difference in the culprits depending on the population. This could in turn shine light on specific tree nuts to be more vigilant about in a given population (ie, British Columbia vs Ontario and Quebec) when it comes to anaphylaxis, and more specifically the culprits and other variables that were more associated with severe reactions. We also wanted to compare epinephrine use in British Columbia vs that in Ontario and Quebec and to suggest possible public health interventions based on our findings.

Table 5
Factors Associated With Multiple Epinephrine Doses (≥ 2 in the ED)

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age at reaction	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Sex: male	1.05 (1.01–1.10) ^a	1.04 (1.00–1.08) ^a
Known asthma	1.05 (0.99–1.10)	1.04 (0.99–1.10)
Severe reaction	1.09 (1.01–1.17) ^a	1.09 (1.01–1.17) ^a
Treatment prehospital: epinephrine IM	0.95 (0.91–0.99) ^a	0.95 (0.92–1.00) ^a
Treatment prehospital: antihistamines	0.98 (0.94–1.01)	0.97 (0.93–1.01)
Tree nut culprit: almond	0.96 (0.90–1.03)	0.97 (0.89–1.06)
Tree nut culprit: hazelnut	1.00 (0.95–1.05)	1.00 (0.92–1.09)

Abbreviations: CI, confidence interval; ED, emergency department; IM, intramuscular; OR, odds ratio.

^aStatistical significance.

Our results reveal that the major culprits of TNA in Canada were cashew, hazelnut, and walnut. Cashew-induced anaphylaxis was more common in British Columbia vs Ontario and Quebec, whereas pistachio-induced anaphylaxis was more common in Ontario and Quebec vs British Columbia. Severe reactions were mainly triggered by walnut in British Columbia and by hazelnut in Ontario and Quebec. Severe reactions were associated with older age, male sex, and macadamia-induced reactions. In Canada, prehospital and ED epinephrine administration was documented in 35.2% and 52.5% of the cases, respectively.

TNA prevalence is reported to have increased in North America in the previous decade. In fact, the greatest increase in ED visits for food-induced anaphylaxis occurred with tree nuts/seeds (373.0% between 2005 and 2014).¹⁴ Cashew has become an important trigger (32.8% in Canada) of TNA, especially in the pediatric population. Surely, the rapidly increasing consumption of cashews worldwide partly explains the increasing prevalence of cashew-induced anaphylaxis in North America. Although immigrants from Asia (more common in British Columbia than in Ontario or Quebec) have a cuisine based often on cashew products, pistachios predominate the cuisine of Arabic immigrants (more common in Ontario or Quebec vs British Columbia). Furthermore, according to Statistics Canada 2016, the provincial rates of Asian ethnicity are 11.8%, 10.7%, and 7.1% in British Columbia, Ontario, and Quebec, respectively.¹⁵ The increased percentage of those of Asian ethnicity (classified as “East and Southeast Asian origin” in the census) in British Columbia vs Ontario and Quebec may thus be related to increased consumption of cashews in British Columbia compared with that in Ontario and Quebec. Similarly, an increased percentage of those of Arabic ethnicity (classified as “West Central and Middle Eastern origins” in the census) in Ontario and Quebec may explain the increased consumption of pistachios in Ontario and Quebec compared with that in BC. According to Statistics Canada 2016, the provincial rates of Arabic ethnicity are 2.2%, 4.0%, and 3.0% in British Columbia, Ontario, and Quebec, respectively.¹⁵ In the same vein, based on Statistics Canada’s 2014 data, Ontario (Toronto and Ottawa) and Quebec (Montreal and Laval) were found to have the most important immigrant Arabic communities (including immigrants from Egypt, Iraq, Lebanon, Algeria, and Morocco) when compared with other Canadian regions and provinces.¹⁶ These differences would then mainly result from dietary lifestyles of different immigrant populations in British Columbia vs those in Ontario and Quebec, including gene-environment interactions.^{3,17–19}

Severe reactions were associated with older age, male sex, and macadamia nut. Our findings confirm previous reports in adults²⁰ which suggest that male sex^{21–24} and older age^{22–24} were associated with increased risk of TNA.

First-line treatment of anaphylaxis is intramuscular epinephrine. There are no absolute contraindications to its use.²⁵ Second-line treatments include oral antihistamines and oral corticosteroids. In line with other studies, our findings reveal substantial intramuscular epinephrine underutilization,²⁵ and similar results were obtained when the analysis was limited to severe anaphylactic reactions. One possible explanation for such low rates may be that reactions among the pediatric population are more likely to be first reactions and have yet to be prescribed an EAI, making it virtually impossible for the patient’s family to have a readily available EAI nearby during the anaphylactic reaction. Indeed, a substantial proportion (40.4%) of TNA was among children with no known previous food allergy (Table 1). However, it is worth noting that among 322 patients who had known food allergy, only 74 (23.0%) had a prescribed EAI. Studies have already urged for new guidelines to improve prescription and education regarding EAI use. In fact, it is possible that the presence of laws (Ontario) and policies (Quebec, British Columbia) mandating the presence of anaphylaxis reaction plan and training of teachers account for the higher use of EAI at school or daycare. Among the 6 reactions that occurred at school with no prehospital intramuscular

epinephrine use, 4 (66.7%) did not have a prescribed EAI. However, it is worth noting that the remaining 2 patients (33.3%) with prescribed EAI did not use intramuscular epinephrine prehospital. Similarly, among the 10 reactions that occurred in restaurants with no prehospital intramuscular epinephrine use, 9 (90.0%) did not have a prescribed EAI. However, there was 1 patient (10.0%) with a prescribed EAI who did not use intramuscular epinephrine in the prehospital setting despite having a prescribed EAI. That said, given that most reactions occurring at school and restaurants with no intramuscular epinephrine use in the prehospital setting are likely secondary to a lack of readily available EAI, our study shines light on another—less discussed but just as crucial—aspect of EAI use and education: to have readily available EAI stocks in schools and restaurants. However, the lack of readily available EAI does not explain the underuse of intramuscular epinephrine in patients with known allergies and readily available EAI. Hence, along with policies endorsing stock epinephrine at school and restaurants, there is a clear need for patient education at the population level regarding the prompt use of prehospital intramuscular epinephrine to decrease the likelihood of severe reactions.

Beyond the prehospital setting, our results point toward what seems to be an underutilization of intramuscular epinephrine in the ED as well. However, it is important to understand the context of such results to draw appropriate conclusions. Indeed, among our cohort of 540 patients, 148 (27.4%) patients received intramuscular epinephrine in the prehospital setting but not in the ED, whereas 107 (19.8%) patients did not receive intramuscular epinephrine at all (neither in the prehospital setting nor in the ED). These results reveal that of 255 patients who received no intramuscular epinephrine in the ED, 148 (58.0%) had received intramuscular epinephrine in the prehospital setting. That said, it is likely that more than half (58.0% among all severities and 57.1% among severe reactions) of patients not receiving intramuscular epinephrine in the ED was because their reaction was well controlled with the intramuscular epinephrine they had received in the prehospital setting. As for the rest (42.0% and 42.9%, respectively), it is possible that a considerable delay between the anaphylactic reaction and the presentation to the ED made them less likely to benefit from intramuscular epinephrine (and thus not offered this treatment). That said, policies and education regarding prompt use of intramuscular epinephrine in the prehospital setting would likely be more beneficial than further guidelines for use of intramuscular epinephrine in the ED.

In the literature, the main factors associated with underutilization of EAI remain unclear. For example, in a systematic review, it was hypothesized that potential causes for low EAI use include low availability/not self-carrying the EAI, low prescription rates, insufficient education on recognizing anaphylaxis, and insufficient policies and protocols for anaphylaxis management in schools.²⁶ Additional studies addressing underutilization of EAI during anaphylaxis are required to determine the main barriers for EAI use.

In terms of labeling, Health Canada already mandates labeling of tree nut products. However, we believe that it is important to increase parental awareness on the importance of reading labeling and vigilance regarding potential tree nuts present in unpackaged foods. That said, it is important to develop educational programs that will encourage awareness regarding inspection of food labels and avoidance of unpackaged foods containing potential allergens.

Our study has some potential limitations. We did not collect data on ethnicity as part of the C-CARE questionnaire. We thus presented 2016 data from Statistics Canada, which includes both pediatric- and adult-related information even though our study is limited to the pediatric population. Furthermore, we only had 1 ED in British Columbia vs only 4 EDs in Ontario and Quebec (1 ED and 3 EDs, respectively). Hence, our results may not be generalizable to the overall population of these provinces. However, it is worth noting that the pediatric ED in Vancouver is the largest in the West Coast

and thus likely has a representative catchment population. Moreover, all 5 EDs included in our study are likely representative of the other EDs in their respective region or province given they are all large, urban, accessible academic centers. Finally, our study used retrospective data, which could result in misclassification bias. However, documentation of epinephrine use and severity level (our main outcomes) are measures that are likely to be accurately documented and less likely to be misclassified.

In conclusion, we conducted the first and largest study to assess TNA in children in North America. Differences in tree nut culprit may be owing to differences in lifestyle more prevalent in population of Asian ethnicity in British Columbia vs those of Arabic ethnicity in Ontario and Quebec. We have also found intramuscular epinephrine underutilization in TNA cases, urging for patient education regarding prompt intramuscular epinephrine use in the prehospital setting. Consistent policies across Canada and potentially stocking EAI may contribute to increase the use of EAI in schools and restaurants.

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