

Emergency Management of Anaphylaxis Due to an Unknown Trigger: An 8-Year Follow-Up Study in Canada



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What is already known about this topic? Anaphylaxis due to unknown trigger (AUT) is a rare, life-threatening disorder that presents with substantial challenges regarding diagnosis and management because it is a diagnosis of exclusion.

What does this article add to our knowledge? There is limited evidence surrounding the management of AUT. Our study is the first to compare treatment and follow-up of adults and children with AUT.

How does this study impact current management guidelines? Low rates of referral to an allergist highlight the need for clear guidelines and educational programs for diagnosis and management.

BACKGROUND: Anaphylaxis due to unknown trigger (AUT) is anaphylaxis not explained by a proved or presumptive cause or stimulus at the time of the reaction. Research describing the management and follow-up of AUT is limited.

OBJECTIVE: To assess and compare the demographic and clinical characteristics and the management of adult and pediatric AUT cases across Canada.

METHODS: Participants were identified between 2011 and 2018 in emergency departments at 8 centers across Canada as part of the Cross-Canada Anaphylaxis Registry. A standardized form documenting the reaction and management in children and adults was completed. Patients were contacted for follow-up to determine assessment by an allergist.

RESULTS: A total of 295 AUT cases (7.5%) were recruited among 3,922 cases of anaphylaxis. In the prehospital setting, children (adjusted odds ratio [aOR], 1.20; 95% CI, 1.05-1.37) and those with a known food allergy (aOR, 1.14; 95% CI, 1.02-1.28) were more likely to receive treatment with epinephrine. Children were also more likely to be assessed by an allergist after their reaction

(aOR, 1.43; 95% CI, 1.13-1.81) and were more likely to have an identified trigger for their reaction (aOR, 1.35; 95% CI, 1.07-1.70). Among patients contacted for follow-up, food was identified as the cause of reaction in 11 of 76 patients. A new food allergy was diagnosed in 4 patients (2 children and 2 adults).

CONCLUSIONS: Our findings highlight important differences between management and follow-up of adult and pediatric AUT cases. It is crucial to follow up all cases of AUT and establish appropriate treatment and management guidelines. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1166-73)

Key words: Idiopathic anaphylaxis; Management; Treatment; Epidemiology in Canada

INTRODUCTION

Anaphylaxis is defined as a severe, life-threatening, hypersensitivity reaction that involves at least 2 organ systems and/or

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Abbreviations used

AKT- Anaphylaxis due to a known trigger
aOR- Adjusted odds ratio
AUT- Anaphylaxis due to an unknown trigger
C-CARE- Cross-Canada Anaphylaxis Registry
ED- Emergency department
IA- Idiopathic anaphylaxis

hypotension in response to a potential allergen.¹ Anaphylaxis due to an unknown trigger (AUT) is anaphylaxis not explained by a proved or presumptive cause or stimulus at the time of the reaction. A diagnosis of idiopathic anaphylaxis (IA) can further be made only after known causes for anaphylaxis and other diseases that mimic anaphylaxis are ruled out.² IA is therefore a diagnosis of exclusion after other causes such as foods, medications, exercise, food and exercise, insect stings or bites, and mastocytosis have been considered.³ IA accounts for 30% to 60% of cases of anaphylaxis in ambulatory adults and approximately 10% of cases in children.⁴

AUT represents a major diagnostic and management challenge. There are currently no established guidelines on the evaluation or management of AUT.^{3,5} The current approach to treatment is based on disease frequency; short-term treatment, such as an epinephrine autoinjector, is used for infrequent attacks, whereas prophylactic treatment with daily H₁ antihistamines, glucocorticoids, or omalizumab has been used in patients with more frequent episodes.⁶ Frequent episodes are defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year.⁷ Currently, there is scarce research investigating the clinical characteristics, treatment, management, and follow-up of cases of AUT. Furthermore, it is not clear what is the percentage of true IA among all cases of AUT.

Our study assesses and compares the clinical characteristics, acute (ie, treatment at the time of reaction) and long-term (ie, prescription of epinephrine autoinjector, assessment by an allergist, and use of confirmatory tests and immunotherapy) management of suspected AUT cases in children (<18 years old) and adults in Canada.

METHODS

The Cross-Canada Anaphylaxis Registry (C-CARE) is a cross-country initiative that aims to bridge knowledge gaps related to anaphylaxis rates and management across Canada. C-CARE enrolls all cases of anaphylaxis presenting to emergency departments (EDs). We used the C-CARE database to identify pediatric and adult AUT cases presenting to 8 EDs across 4 provinces in Canada (Montreal Children's Hospital, Hôpital Sacré-Coeur, Hôpital Sainte-Justine, Royal Victoria Hospital, Montreal General Hospital, London Health Sciences Centre, Janeway Child Health and Rehabilitation Centre, and British Columbia Children's Hospital) from June 2011 to May 2018. This study was approved by the ethics review boards of the 8 participating hospitals.

As described in previous studies,⁸⁻¹⁰ prospective data were collected at the time of patient presentation to the ED. Cases of anaphylaxis were identified by the treating physician. A standardized form was completed by health care professionals in the ED to collect patient information pertaining to age, sex, clinical background, medication use, and clinical characteristics of the reaction, such as

the suspected trigger, symptoms, route of exposure, time interval between exposure, and development of clinical symptoms. Clinical management, including the use of epinephrine, antihistamines, and steroids, data on admission to the hospital/intensive care unit, prescription of an epinephrine autoinjector, referral to an allergist, and requisition for tryptase levels were also collected. Hospital charts of all patients presenting to the ED were reviewed on the basis of the *International Classification of Disease, Tenth Revision* codes referring to either anaphylaxis or allergic reaction symptoms to ensure no cases of AUT were missed. Codes used for chart review included J45.90, J45.91, T78.1, T78.2, T78.3, T78.4, and T88.7 as validated in previous studies.¹¹ Only missed cases meeting the definition of anaphylaxis as determined by 3 independent reviewers were included as retrospective cases.¹

A modified grading system described by Muraro et al¹² was used to classify anaphylaxis severity. Mild reactions were defined as generalized pruritus, 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 a loss of bowel control, cyanosis, respiratory arrest, hypotension and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, and loss of consciousness.¹²

Consenting adults or the legal guardians were contacted to complete a follow-up standardized questionnaire querying on the assessment by an allergist after the AUT reaction, and the use of confirmatory tests after the reaction, including the skin prick test, blood tests for specific IgE levels (including omega-5 gliadin^{13,14}), alpha-gal to rule out delayed anaphylaxis to red meat, graded oral challenge, C-KIT D816V mutation test, and bone marrow biopsy to rule out mastocytosis or other clonal mast cell disorders. Identification of the reaction trigger, epinephrine autoinjector prescription filling, and whether the patient has had additional anaphylactic reactions since their recorded reaction were also noted in the questionnaire.

All statistical analyses were conducted using R version 3.2.2 (R Core Team 2013; R Foundation for Statistical Computing, Vienna, Austria). Percentage data were calculated for patient demographic characteristics and reaction severity. Percentage and 95% CI (binomial or multinomial for variables with more than 2 categories) data were calculated for allergy assessment and management of AUT cases. Univariable and multivariable logistic regression models were used to estimate factors associated with use of epinephrine, assessment by an allergist, and identification of the etiology causing the anaphylactic reaction.

RESULTS

Patient demographic and clinical characteristics

A total of 3,922 cases of anaphylaxis were identified between June 2011 and May 2018. Among them, 295 (7.5%) had AUT. Among the 295 AUT cases, 143 cases (48.5%; 95% CI, 42.7%-54.3%) were male and 220 cases (74.6%; 95% CI, 69.1%-79.4%) were children aged between 1 and younger than 18 years (Table I). The median age was 9.0 years (interquartile range, 5.0-14.3) and 38.1 years (interquartile range, 28.1-51.3) for children and adults, respectively. Notably, a higher percentage of pediatric cases (43.9%) had a known food allergy in comparison with adults (20.5%) (Table I). Overall, 112 patients

TABLE I. Patient demographic and clinical characteristics

Demographic characteristic	Cases (N = 295)			%
Age group by total number of cases				
Infants (<1 y)	2			0.7
Children (≥1 y and <18 y)	220			74.6
Adult (≥18 y)	73			24.7
Total median age (IQR)	12.5 y (6.3-17.8)			
Median age by age group	Adult (≥18 y)		Children (<18 y)	
Median age (IQR)	38.1 y (28.1-51.3)		9.0 y (5.0-14.3)	
Sex, male	48.5 (% adult + children, N = 295)		31.5 (% adult, n = 73)	54.1 (% children, n = 222)
Clinical characteristic	% Adult + children (N = 294)	% Adult (n = 73)	% Children (n = 221)	
Known food allergy	38.1	20.5	43.9	
Known drug allergy	6.1	9.6	5	
Known venom allergy	0.3	0.0	0.5	
Other known allergy	9.9	11.0	9.5	
Asthma	17	13.7	18.1	
Eczema	2.7	1.4	3.2	

IQR, Interquartile range.

TABLE II. AUT reaction characteristics

Reaction severity	% Adult + children (N = 295)	% Adult (n = 73)	% Children (n = 222)
Mild	8.8	8.2	9
Moderate	62.4	84.9	55
Severe	28.8	6.8	36
Reaction location	% Adult + children (N = 264)	% Adult (n = 69)	% Children (n = 195)
Reaction occurred at home	48.5	62.3	43.6
Reaction occurred at school or daycare	17.4	0.0	22.6
Reaction occurred at work	1.1	4.3	0.0
Reaction occurred at a restaurant	3	2.9	3.1
Other location	30.3	30.4	30.8
Reaction characteristics	% Adult + children (N = 223)	% Adult (n = 62)	% Children (n = 161)
Reaction occurred during effort/exercise	11.2	3.2	14.3
Reaction occurred during normal daily activity	78.9	83.9	77.0
Reaction occurred during alcohol	0.9	3.2	0.0
Reaction occurred during cold exposure	0.9	1.6	0.6
Reaction occurred during other conditions/situations	8.1	9.7	2.5

(38.1%) in our cohort had a known food allergy. When comparing AUT cases with anaphylaxis reactions due to a known trigger (AKT) in our registry, we found that patients with AKT were more likely to have a history of known food allergy and asthma (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Reaction characteristics

Among adults and children, 128 AUT (48.5%) reactions occurred at home, and most of the cases (78.9%) occurred while the patients were performing normal daily activities ([Table II](#)). Most of the AUT cases were moderate reactions (185 cases, 62.4%) ([Table II](#)). There were more severe cases among children than among adults (36.0% vs 6.8%) ([Table II](#)). In addition, cases

of AUT were more likely to present as severe reactions versus cases of AKT (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Emergency treatment and investigations

The main drugs administered in adults and children with AUT in the prehospital setting were antihistamines (164 cases, 46.4%; 95% CI, 40.6%-52.3%). Among all AUT cases, 136 received epinephrine in the prehospital setting (28.7%; 95% CI, 23.6%-34.3%), with a higher percentage of children receiving epinephrine in comparison with adults (74 cases, 33.3%; 95% CI, 27.3%-40.0%; and 10 cases, 14.1%; 95% CI, 7.3%-24.8%, respectively). There was no treatment in the prehospital setting in 95 cases (32.4%; 95% CI, 27.2%-38.2%). Adults were more

TABLE III. Emergency treatment and investigations

Treatment outside of the hospital setting	% Adult + children (95% CI) (N = 293)	% Adult (95% CI) (n = 71)	% Children (95% CI) (n = 222)	Difference % (95% CI)
Epinephrine received in the prehospital setting	28.7 (23.6 to 34.3)	14.1 (7.3 to 24.8)	33.3 (27.3 to 40.0)	−19.2 (−30.4 to −8.1)
Antihistamines received in the prehospital setting	46.4 (40.6 to 52.3)	43.7 (32.1 to 55.9)	47.3 (40.6 to 54.1)	−3.6 (−17.8 to 10.6)
Corticosteroids	2 (0.8 to 4.6)	4.2 (1.1 to 12.7)	1.4 (0.3 to 4.2)	2.9 (−3.0 to 8.7)
Beta agonists	6.1 (3.8 to 9.7)	2.8 (0.5 to 10.7)	7.2 (4.3 to 11.7)	−4.4 (−10.5 to 1.7)
No treatment	32.4 (27.2 to 38.2)	42.3 (30.8 to 54.5)	29.3 (23.5 to 35.8)	13.0 (−0.9 to 26.9)
Treatment inside the hospital setting	% Adult + children (95% CI) (N = 294)	% Adult (95% CI) (n = 73)	% Children (95% CI) (n = 221)	Difference % (95% CI)
IM epinephrine	44.9 (39.1 to 50.8)	38.4 (27.4 to 50.5)	47.1 (40.5 to 53.9)	−8.7 (−22.6 to 5.2)
IV epinephrine*	0.7 (0.1 to 2.7)	2.7 (0.5 to 10.4)	0 (0 to 2.1)	2.7 (−1.9 to 7.4)
Antihistamines	55.8 (49.9 to 61.5)	82.2 (71.1 to 89.8)	47.1 (40.5 to 53.9)	35.1 (23.3 to 47.0)
Beta agonists	9.5 (6.5 to 13.6)	12.3 (6.1 to 22.6)	8.6 (5.4 to 13.3)	3.7 (−5.6 to 13.0)
Corticosteroids	46.3 (40.5 to 52.1)	68.5 (56.4 to 78.6)	38.9 (32.5 to 45.7)	29.6 (16.2 to 42.9)
IV fluids	10.9 (7.7 to 15.2)	28.8 (19.1 to 40.7)	5 (2.6 to 9.0)	23.8 (12.1 to 35.5)
No treatment	4.4 (2.5 to 7.6)	0 (0 to 6.2)	5.9 (3.3 to 10.1)	−5.9 (−9.9 to 5.9)
Treatment inside or outside the hospital setting	% Adult + children (95% CI) (N = 294)	% Adult (95% CI) (n = 73)	% Children (95% CI) (n = 221)	Difference % (95% CI)
Received epinephrine inside <i>or</i> outside hospital setting	69 (63.4 to 74.2)	50.7 (38.8 to 62.5)	75.1 (68.8 to 80.6)	−24.4 (−38.1 to −10.7)
Received epinephrine inside <i>and</i> outside hospital setting	4.4 (2.5 to 7.6)	1.4 (0.07 to 8.4)	5.4 (3.0 to 9.5)	−4.0 (−8.9 to 0.9)
Investigations in the ED	% Adult + children (95% CI) (N = 266)	% Adult (95% CI) (n = 62)	% Children (95% CI) (n = 204)	Difference % (95% CI)
Conducted tryptase tests	9.8 (6.6 to 14.2)	0 (0 to 7.3)	12.7 (8.6 to 18.3)	−12.7 (−18.4 to −7.0)
Admissions to the hospital ward or intensive care unit	% Adult + children (95% CI) (N = 287)	% Adult (95% CI) (n = 66)	% Children (95% CI) (n = 221)	Difference % (95% CI)
Admitted to the hospital ward	3.5 (1.8 to 6.5)	3.0 (0.5 to 11.5)	3.6 (1.7 to 7.3)	−0.6 (−6.0 to 4.8)
Admitted to the intensive care unit	0.3 (0.02 to 2.2)	0 (0.0 to 6.9)	0.5 (0.02 to 2.9)	−0.5 (−1.8 to 0.9)
Total admissions to the hospital ward or intensive care unit	3.8 (2.0 to 6.9)	3.0 (0.5 to 11.5)	4.1 (2.0 to 7.8)	−1.0 (−6.9 to 4.8)

IM, Intramuscular; IV, intravenous.

*IV epinephrine given because of hypotension despite multiple doses of intramuscular epinephrine.

likely to not receive treatment (30 cases, 42.3%; 95% CI, 30.8%–54.5%) compared with children (65 cases, 29.3%; 95% CI, 23.5%–35.8%) (Table III). AKT reactions were more likely to receive intramuscular epinephrine inside or outside the hospital setting in comparison with AUT cases (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In the hospital setting, intramuscular epinephrine was administered in 132 cases (44.9%; 95% CI, 39.1%–50.8%) of AUT. Antihistamines were administered in 164 cases (55.8%; 95% CI, 49.9%–61.5%). Antihistamines in the ED were used more often in adults (60 cases, 82.2%; 95% CI, 71.1%–89.8%) versus children (104 cases, 47.1%; 95% CI, 40.5%–53.9%). Corticosteroids were administered in 136 cases (46.3%; 95% CI, 40.5%–52.1%). Similar to antihistamines, more adults received corticosteroid treatment (50 cases, 68.5%; 95% CI, 56.4%–78.6%) versus children (86 cases, 38.9%; 95% CI, 32.5%–45.7%). In total, 203 cases (69.0%; 95% CI, 63.4%–74.2%) of adults and children received epinephrine inside or outside a hospital setting, with a higher percentage of children receiving epinephrine (166 cases, 74.8%; 95% CI, 68.4%–80.2%) in comparison with adults (37 cases, 50.7%; 95% CI,

38.8%–62.5%) (Table III). Tryptase levels were obtained in only 26 cases (9.8%; 95% CI, 6.6%–14.2%) in our cohort. Of these, only 2 patients had serial tryptase investigations and 1 patient had an elevated tryptase measurement at the time of the reaction, which is consistent with anaphylaxis.⁵ A minority were admitted to the hospital: 9 pediatric cases (4.1%; 95% CI, 2.0%–7.8%), of which 8 patients (3.6%; 95% CI, 1.7%–7.3%) were admitted to the hospital ward and 1 patient (0.5%; 95% CI, 0.02%–2.9%) was admitted to the intensive care unit. Two adult cases (3.0%; 95% CI, 0.5%–11.5%) were admitted to a hospital ward and none to the intensive care unit.

Univariable and multivariable logistic regression analysis revealed that patients with asthma were more likely to be treated with epinephrine in the ED setting (adjusted odds ratio [aOR] for sex, age, reaction severity, and known food allergy: 1.19; 95% CI, 1.02–1.38) (Table IV). Factors associated with receiving epinephrine in the prehospital setting included children (<18 years old) (aOR, 1.20; 95% CI, 1.05–1.37), and patients with known food allergies (aOR, 1.14; 95% CI, 1.02–1.28) when adjusted for sex, asthma, severe reaction, and reaction location (Table IV).

TABLE IV. Odds ratio of factors associated with administration of epinephrine

Factor	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
<i>Factors associated with administration of epinephrine in the prehospital setting</i>		
Child (age 1-17 y)	1.22 (1.08-1.37)*	1.20 (1.05-1.37)*
Reaction occurred at home	0.87 (0.78-0.97)*	0.91 (0.82-1.02)
Known food allergy	1.21 (1.09-1.34)*	1.14 (1.02-1.28)*
Sex, male	0.94 (0.85-1.04)	0.88 (0.79-0.98)
Known asthma	1.05 (0.91-1.20)	1.04 (0.90-1.20)
Severe reaction	1.04 (0.93-1.17)	1.03 (0.91-1.17)
<i>Factors associated with administration of epinephrine in the ED</i>		
Asthma	1.19 (1.02-1.38)*	1.19 (1.02-1.38)*
Sex, male	1.12 (0.99-1.25)	1.09 (0.97-1.22)
Age at reaction	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Reaction severity	0.92 (0.82-1.05)	0.90 (0.79-1.03)
Known food allergy	0.99 (0.89-1.12)	0.94 (0.83-1.06)

*Statistically significant.

Follow-up management

In the ED, 185 cases (63.8%; 95% CI, 58.6%-69.6%) were prescribed an epinephrine autoinjector, whereas 40 cases (13.8%; 95% CI, 8.6%-19.6%) already had an epinephrine autoinjector prescription (Table V). Children were more likely to be prescribed an epinephrine autoinjector (141 cases, 64.4%; 95% CI, 58.4%-71.0%) than adults (44 cases, 62%; 95% CI, 52.1%-73.9%). Overall, 126 cases (55.9%; 95% CI, 45.3%-58.2%) were referred to an allergist, whereas 59 patients (20.6%; 95% CI, 18.0%-30.9%) were already followed by an allergist.

Of 295 AUT cases identified, 120 (41%) patients consented to provide follow-up information on management. Among 120 patients, 76 patients were successfully contacted (response rate of 63%), of which 54 were children and 22 were adults. Among 76 patients, 53 patients were seen by an allergist or an internist/otolaryngologist practicing in allergy medicine (69.7%; 95% CI, 58.0%-79.5%). Assessment was more common among children (43 cases, 79.6%; 95% CI, 66.1%-88.9%) in comparison with adults (10 cases, 45.5%; 95% CI, 25.1%-67.3%) (Table V). Of the patients assessed, 39 patients (73.6%; 95% CI, 59.4%-84.3%) had a skin test and 30 of these patients had positive skin test results (76.9%; 95% CI, 60.3%-88.3%) (Table V). Overall, 22 tests were positive for food allergens (73.3%; 95% CI, 53.8%-87.0%) and 15 tests were positive for environmental allergens (50.0%; 95% CI, 33.2%-66.8%) (Table V). Such environmental allergens detected included dust mites, grasses, pollens, ragweed, and animal dander. Among all the patients, 3 had alpha-gal testing and PCR C-KIT D816V mutation detection and 1 had a bone marrow biopsy, and in all cases, test results were negative. Only 1 patient had IgE omega-5-gliadin testing,¹⁴ the result for which was also negative. Although 33 reactions (11.2%) of AUT were associated with exercise, the diagnosis of exercise-induced anaphylaxis was not established through an appropriate exercise challenge. Only 1 exercise challenge was performed, which was negative.

Of the patients assessed, a trigger for their reaction was successfully identified by collection of a detailed history and the use of skin prick test in 20 cases (37.7%; 95% CI,

25.1%-52.1%). Among adults and children in whom an etiology was identified, food was most likely the trigger in 11 patients (55.0%; 95% CI, 40.0%-79.7%). Of the patients in whom food allergy was identified as the cause, 4 were diagnosed with a new food allergy (2.7%; 95% CI, 1.0%-6.6%), which included allergies to celery root, hazelnut, seafood, shellfish, and nuts.

With respect to preventative treatment after an AUT reaction, of the 76 patients who were successfully followed, 61 patients (80.0%; 95% CI, 69.2%-88.2%) carried an epinephrine autoinjector. A higher percentage of children carried an epinephrine autoinjector after their reaction (46 children, 85.2%; 95% CI, 72.3%-92.9%) than adults (15 adults, 68.2%; 95% CI, 45.1%-85.3%) (Table V). Interestingly, a higher percentage of adults (7 patients, 31.8%; 95% CI, 14.7%-54.9%) had another anaphylactic reaction after their initial AUT event in comparison with children (14 patients, 25.9%; 95% CI, 15.4%-39.9%) (Table V). More specifically, of the patients who had a recurrent reaction (N = 21), 61.9% (95% CI, 38.7%-81.0%) had less than 1 reaction per year and 38.1% (95% CI, 19.0%-61.3%) had 1 to 3 reactions per year (Table V).

Univariable and multivariable logistic regression analysis confirmed that pediatric patients were more likely to be assessed by an allergist or a physician working as an allergist (aOR, 1.43; 95% CI, 1.13-1.81) when the analysis was adjusted for sex, reaction severity, known food allergy, and known asthma (Table VI). Furthermore, pediatric patients and patients who were administered intravenous epinephrine in the ED (aOR, 1.35; 95% CI, 1.07-1.70; and aOR, 2.59; 95% CI, 1.38-4.87, respectively) were more likely to identify a trigger for their AUT reaction when the analysis was adjusted for sex, reaction severity, known food allergy, and known asthma (Table VII).

DISCUSSION

Our study is the first longitudinal, large-scale study assessing the clinical characteristics, treatment, and follow-up management of AUT cases across Canada. Our findings reveal suboptimal management of AUT and disparities in management between children and adults presenting with AUT. The variability in treatment and follow-up approach of AUT demonstrated in our study further supports the need for establishing appropriate guidelines for the treatment of AUT.

According to current guidelines, prompt intramuscular epinephrine administration is the first-line treatment for anaphylaxis regardless of the trigger.¹ In our study, however, we demonstrate the underuse of epinephrine treatment within the ED for patients presenting with AUT regardless of age. As previously mentioned, AUT is a diagnosis of exclusion. ED physicians may be hesitant to administer intramuscular epinephrine before fully identifying the etiology of the reaction. Indeed, epinephrine use was higher in cases of AKT. Previous work done by our group and by others demonstrated that prompt administration of epinephrine reduced the risk of requiring multiple subsequent doses of epinephrine administration (≥ 2) in the ED as well as reduced the risk of admission.^{15,16} The low use of epinephrine in AUT despite guidelines suggests that education programs promoting the use of epinephrine and adherence to guidelines are crucial to manage anaphylaxis cases appropriately.

Despite guidelines from the United Kingdom recommending the use of serial measurements of tryptase to establish the presence of anaphylaxis and rule out potential mastocytosis,^{17,18}

TABLE V. Follow-up management

Follow-up management in the ED	% Adult + children (95% CI) (N = 290)	% Adult (95% CI) (n = 71)	% Children (95% CI) (n = 219)	Difference % (95% CI)
Prescribed an epinephrine autoinjector	63.8 (58.6 to 69.6)	62 (52.1 to 73.9)	64.4 (58.4 to 71.0)	−2.4 (−16.3 to 11.5)
Already has an epinephrine autoinjector	13.8 (8.6 to 19.6)	8.5 (0 to 20.4)	15.5 (9.6 to 22.2)	−7.1 (−16.1 to 1.9)
Not prescribed an epinephrine autoinjector	19.7 (14.5 to 25.5)	22.5 (12.7 to 34.5)	18.7 (12.8 to 25.4)	3.8 (−8.1 to 15.8)
Do not know whether prescribed an epinephrine autoinjector	2.8 (0 to 8.6)	8.5 (0 to 19.0)	1.4 (0 to 8.0)	7.1 (−0.5 to 14.7)
Was not prescribed an epinephrine autoinjector and do not have an epinephrine autoinjector	19.7 (15.3 to 24.8)	22.5 (13.8 to 34.3)	18.7 (13.9 to 24.7)	3.8 (−8.1 to 15.8)
Allergist referral	% Adult + children (95% CI) (N = 286)	% Adult (95% CI) (n = 73)	% Children (95% CI) (n = 213)	Difference % (95% CI)
Referred to an allergist	55.9 (45.3 to 58.2)	58.9 (49.3 to 71.2)	54.9 (50.0 to 63.7)	4.0 (−10.1 to 18.0)
Not referred to an allergist	17.8 (14.7 to 27.7)	16.4 (6.8 to 28.7)	18.3 (12.1 to 25.9)	−1.9 (−12.8 to 9.0)
Already followed by allergist	20.6 (18.0 to 30.9)	19.2 (9.6 to 31.5)	21.1 (15.0 to 28.8)	−1.9 (−13.4 to 9.5)
Do not know whether referred to an allergist	3.1 (0 to 10.5)	5.5 (0 to 17.8)	2.3 (0.0 to 9.4)	3.1 (−3.3 to 9.7)
Was not referred to an allergist and is not already followed by an allergist	17.8 (13.7 to 22.9)	16.4 (9.1 to 27.3)	18.3 (13.5 to 24.3)	−1.9 (−12.8 to 9.0)
Follow-up results after discharge from the ED	% Adult + children (95% CI) (N = 76)	% Adult (95% CI) (n = 22)	% Children (95% CI) (n = 54)	Difference % (95% CI)
Seen by an allergist	69.7 (58.0 to 79.5)	45.5 (25.1 to 67.3)	79.6 (66.1 to 88.9)	−34.2 (−60.8 to −7.6)
Investigations conducted by allergist follow-up	% Adult + children (95% CI) (N = 53)	% Adult (95% CI) (n = 10)	% Children (95% CI) (n = 43)	Difference % (95% CI)
Skin test after being seen by an allergist	73.6 (59.4 to 84.3)	100 (65.5 to 100)	86.0 (71.4 to 94.2)	14.0 (−2.6 to 30.5)
Positive skin test result if had a skin test	76.9 (60.3 to 88.3)	50 (23.7 to 76.3)	83.8 (67.3 to 93.2)	−33.7 (−72.8 to 5.3)
Positive trigger identification	37.7 (25.1 to 52.1)	20 (3.5 to 55.8)	41.9 (27.4 to 57.8)	−21.9 (−56.9 to 13.1)
Determined to have true IA	62.3 (47.9 to 74.9)	80.0 (44.2 to 96.5)	58.1 (42.2 to 72.7)	21.9 (−13.1 to 56.9)
Positive skin test results	% Adult + children (95% CI) (N = 36)	% Adult (95% CI) (n = 5)	% Children (95% CI) (n = 31)	Difference % (95% CI)
Skin test positive for food	69.4 (51.7 to 83.1)	40 (7.3 to 83.0)	74.2 (55.1 to 87.5)	−34.2 (−91.4 to 23.0)
Skin test positive for environment	47.2 (30.8 to 64.3)	80 (29.9 to 98.9)	41.9 (25.1 to 60.7)	25.2 (−25.6 to 76.0)
Skin test positive for drug	2.8 (0.1 to 16.2)	20 (1.1 to 70.1)	0 (0 to 13.7)	20.0 (−26.7 to 66.7)
Skin test positive but do not remember	2.8 (0.1 to 16.2)	0 (0 to 53.7)	3.2 (0.2 to 18.5)	−3.2 (−12.7 to 6.2)
Positive trigger identification results	% Adult + children (95% CI) (N = 20)	% Adult (95% CI) (n = 2)	% Children (95% CI) (n = 18)	Difference % (95% CI)
Not a real anaphylactic reaction	20 (5 to 44.7)	0 (0 to 80.2)	22.2 (5.6 to 47.8)	−22.2 (−63.7 to 19.2)
Food trigger	55 (40 to 79.7)	50 (9.5 to 90.5)	55.6 (38.9 to 81.1)	−5.6 (−84.1 to 73.0)
Environmental trigger	15 (0 to 39.7)	50 (9.5 to 90.5)	11.1 (0 to 36.7)	38.9 (−59.7 to 100)
Venom	5 (0 to 29.7)	0 (0 to 80.2)	5.6 (0 to 31.1)	−5.6 (−21.7 to 10.6)
Other	5 (0 to 29.7)	0 (0 to 80.2)	5.6 (0 to 31.1)	−5.6 (−21.7 to 10.6)
Follow-up preventative treatment characteristics	% Adult + children (95% CI) (N = 76)	% Adult (95% CI) (n = 22)	% Children (95% CI) (n = 54)	Difference % (95% CI)
Currently has an epinephrine autoinjector	80 (69.2 to 88.2)	68.2 (45.1 to 85.3)	85.2 (72.3 to 92.9)	−17.0 (−41.8 to 7.8)
Recurrent reaction characteristics	% Adult + children (95% CI) (N = 76)	% Adult (95% CI) (n = 22)	% Children (95% CI) (n = 54)	Difference % (95% CI)
Had another anaphylactic reaction	27.6 (18.3 to 39.3)	31.8 (14.7 to 54.9)	25.9 (15.4 to 39.9)	5.9 (−20.0 to 31.8)
1 time	38.1 (19.0 to 61.5)	28.6 (0 to 68.4)	42.8 (21.4 to 72.0)	−14.3 (−67.3 to 38.8)
2 times	23.8 (4.8 to 47.2)	42.9 (14.3 to 82.6)	14.3 (0 to 43.4)	28.6 (−23.1 to 80.2)
3 times	28.9 (9.5 to 51.9)	28.6 (0 to 68.4)	28.6 (7.1 to 57.7)	0 (−41.0 to 41.0)
>3 times	9.5 (0 to 32.9)	0 (0 to 39.8)	14.3 (0 to 43.4)	−14.3 (−43.3 to 14.8)
	% Adult + children (95% CI) (N = 21)			
<1 reaction per year	61.9 (38.7 to 81.0)	—	—	—
1-3 reactions per year	38.1 (19.0 to 61.3)	—	—	—

TABLE VI. Odds ratio of factors associated with assessment by an allergist or a specialist practicing allergy medicine

Factor	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Child (age 1-17 y)	1.41 (1.13-1.75)*	1.43 (1.13-1.81)*
Known food allergy	1.11 (0.90-1.36)	1.04 (0.84-1.28)
Sex, male	1.13 (0.92-1.39)	1.06 (0.86-1.30)
Known asthma	0.92 (0.66-1.30)	0.83 (0.59-1.17)
Severe reaction	0.99 (0.75-1.31)	0.89 (0.67-1.18)

*Statistically significant.

TABLE VII. Odds ratio of factors associated with confirmation of an etiology of the AUT reaction by an allergist or a specialist practicing allergy medicine

Factor	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Child (age 1-17 y)	1.27 (1.03-1.58)*	1.35 (1.07-1.70)*
IV epinephrine in the ED	2.13 (1.17-3.89)*	2.59 (1.38-4.87)*
Known food allergy	1.20 (0.99-1.47)	1.07 (0.87-1.31)
Sex, male	1.00 (0.82-1.23)	1.01 (0.83-1.22)
Known asthma	0.99 (0.71-1.37)	0.96 (0.70-1.31)
Severe reaction	1.16 (0.89-1.51)	1.10 (0.84-1.42)

IV, Intravenous.

*Statistically significant.

among the patients who were assessed, most did not have tryptase levels measured at the time of the reaction. Guidelines for anaphylaxis management in the United Kingdom recommend obtaining blood samples for mast cell tryptase testing as soon as possible after emergency treatment, ideally 1 to 2 hours (but no later than 4 hours) from the onset of symptoms. Tryptase testing allows for confirmation of the diagnosis of anaphylaxis (on the basis of a high difference between baseline levels and levels during reaction) and is useful in ruling out mastocytosis (suspected when levels at baseline are high).^{19,20} The low percentage of tryptase tests in our study may be due to lack of availability of this investigation in hospital laboratories across Canada. Furthermore, in addition to the lack of availability, the lack of awareness of the utility of the tryptase test may be the reason why it is seldomly used by the primary care ED community.¹⁰

With respect to follow-up management, our study indicates low assessment rates after an episode of AUT. Although there are no previously published studies investigating the frequency of assessment with an allergist after AUT, our study findings are consistent with those of other anaphylaxis studies that found inadequate follow-up and assessment of anaphylaxis triggered by drug/venom.^{8,10} The large percentage of patients not assessed for AUT may be due to patient-related factors, such as other priorities or inability to take time off from work, or other factors related to the Canadian health care system, including the low number of allergists in Canada, the long wait times for specialist assessment, as well as uncertainty regarding the allergic cause of symptoms in the absence of a clear trigger.^{10,21,22}

Discrepancies in treatment and follow-up of patients were found in our study. In the prehospital setting and within the ED, a higher percentage of pediatric patients received epinephrine in

comparison with adult patients. This observation may be due to case reports of adverse cardiovascular side effects associated with epinephrine administration.²³ However, large-scale studies have established that there is no absolute evidence-based contraindication to using intramuscular epinephrine for anaphylactic reactions.²⁴ The discrepancy in prehospital setting management between adults and children could also be due to pediatric patients having a higher percentage of known food allergy and hence more likely than adult patients to have an epinephrine autoinjector available for use. Indeed, after adjusting for age, sex, known asthma, reaction location, and reaction severity (Table IV), receiving epinephrine in the prehospital is associated with having a known food allergy.

National Health Services guidelines in the United Kingdom recommend for all patients with AUT to be prescribed an epinephrine autoinjector as an interim management measure before their allergy specialist appointment. However, as documented in our study, nearly one-fifth of patients with AUT were not prescribed an epinephrine autoinjector and did not have an epinephrine autoinjector prescription in their possession. It was further noted that adults were less likely to receive an epinephrine autoinjector prescription than children. The low epinephrine autoinjector prescription rate could be due to the unclear working diagnosis of AUT made by the treating ED physician. Patients without an epinephrine autoinjector after an AUT reaction are, however, at an increased risk of inappropriate management should they have any future reactions. Although the National Health Services guidelines have been established since 2011 and have been widely accepted internationally, current emergency treatment practices for patients with AUT are not consistently practiced in Canada.

Children were more likely to be assessed by an allergist, and perhaps because of the assessments, the culprit was identified more often in pediatric cases reported initially to be AUT. Interestingly, although children are more likely than adults to have access to preventative treatment after an AUT reaction by carrying an epinephrine autoinjector after their reaction, a higher percentage of adults experienced subsequent anaphylactic reactions after their initial AUT event in comparison with children.

Within our cohort of patients followed up, confirmatory tests, such as alpha-gal or omega-5 gliadin to rule out delayed anaphylaxis to red meat—induced or wheat-induced reactions, respectively, and C-KIT D816V mutation test and bone marrow biopsy to rule out mastocytosis or other clonal mast cell disorders, were seldom reported. Delayed anaphylaxis to red meat is a relatively new diagnosis that may mimic symptoms of AUT. In contrast with immediate food-mediated anaphylaxis, symptoms may occur more than 2 hours after exposure.²⁵ Alpha-gal testing may not have been tested in most of the patients in our cohort given their lack of a suggestive history or the availability of the test at the respective institution. C-KIT D816V mutation test is also not widely accessible. Bone marrow biopsies are rather invasive procedures, and as such, patients may have declined this investigation.

There are several potential limitations to our study. Although the study is the first large-scale AUT study conducted in Canada, our results are limited to 8 centers, which may not accurately represent the characteristics of the Canadian population as a whole. Furthermore, recruitment of participants was conducted in academic institutions whereby participants may be more likely to follow up with allergists or specialists practicing in allergy. Given the increased accessibility of these specialty physicians in

these hospitals, the percentage followed in the general population may be substantially lower. Another important limitation in our study is that recruitment was conducted mostly in the province of Quebec given that there were 3 Quebec sites participating in this study. Therefore, population bias may exist where diagnosis, treatment, and follow-up management of patients with AUT may differ from that in other provinces. Adult AUT cases specific to this study were recruited only from Hôpital Sacré-Coeur in Montreal, Quebec. Misclassification bias may also play a role in our study given that an initial diagnosis of AUT may not be the final diagnosis once the trigger for the reaction is identified. In the cases of positive skin test results to foods or environmental allergens, it is possible that cases recruited as AUT were actually food-induced or caused by other factors. However, this is a limitation shared with all studies assessing AUT. Our study is unique because the design allowed for follow-up of prospective patients and collection of data on allergy confirmation. It is possible that the percentage of true AUT could have been lower if all patients had done appropriate investigations.

CONCLUSIONS

Our findings reveal low rates of follow-up and assessment mainly in adults with AUT and highlight the need for clear guidelines and educational programs for diagnosis and management. Given that identification of a culprit was demonstrated in one-third of the pediatric patients followed up, it is crucial to appropriately assess cases of AUT to identify potential triggers and reduce the risk of future life-threatening allergic reactions. It is necessary to obtain a consensus on the emergent treatment and follow-up of AUT cases to ensure management consistency and provide better care for patients for whom the cause of their anaphylactic episode(s) has not been identified.

REFERENCES

1. 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. *J Allergy Clin Immunol* 2006;117:391-7.
2. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115:S483-523.
3. Greenberger PA. Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2007;27:273-293, vii-viii.
4. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006;97:39-43.
5. de Schreyver K, Sigman K, Ben-Shoshan M, Chan ES. Pediatric idiopathic anaphylaxis: 3 case reports and a systematic review of literature. *Int J Allergy Asthma* 2017. IJAA-102.
6. Nwaru BI, Dhami S, Sheikh A. Idiopathic anaphylaxis. *Curr Treat Options Allergy* 2017;4:312-9.
7. Lieberman PL. Idiopathic anaphylaxis. *Allergy Asthma Proc* 2014;35:17-23.
8. Gabrielli S, Clarke AE, Eisman H, Morris J, Joseph L, La Vieille S, et al. Disparities in rate, triggers, and management in pediatric and adult cases of suspected drug-induced anaphylaxis in Canada. *Immun Inflamm Dis* 2018;6:3-12.
9. Lee AYM, Enarson P, Clarke AE, La Vieille S, Eisman H, Chan ES, et al. Anaphylaxis across two Canadian pediatric centers: evaluating management disparities. *J Asthma Allergy* 2017;10:1-7.
10. Tritt A, Gabrielli S, Zahabi S, Clarke A, Moisan J, Eisman H, et al. Short- and long-term management of cases of venom-induced anaphylaxis is suboptimal. *Ann Allergy Asthma Immunol* 2018;121:229-234.e1.
11. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfven T, Ly DH, et al. Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568-77.
12. 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.
13. Heaps A, Carter S, Selwood C, Moody M, Unsworth J, Deacock S, et al. The utility of the ISAC allergen array in the investigation of idiopathic anaphylaxis. *Clin Exp Immunol* 2014;177:483-90.
14. Kennard L, Thomas I, Rutkowski K, Azzu V, Yong PFK, Kasternow B, et al. A multicenter evaluation of diagnosis and management of omega-5 gliadin allergy (also known as wheat-dependent exercise-induced anaphylaxis) in 132 adults. *J Allergy Clin Immunol Pract* 2018;6:1892-7.
15. Hochstadter E, Clarke A, De Schryver S, LaVieille S, Alizadehfah R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol* 2016;137:1888-1890.e4.
16. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;106:171-6.
17. Krishna MT, Ewan PW, Diwakar L, Durham SR, Frew AJ, Leech SC, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clin Exp Allergy* 2011;41:1201-20.
18. Centre for Clinical Practice at NICE. Anaphylaxis: Assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode. NICE clinical guideline 134. Manchester, UK: National Institute for Health and Clinical Excellence; 2011.
19. Tanus T, Mines D, Atkins PC, Levinson AI. Serum tryptase in idiopathic anaphylaxis: a case report and review of the literature. *Ann Emerg Med* 1994;24:104-7.
20. Greenberger PA, Lieberman P. Idiopathic anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2:243-50.
21. Daniel W, Harrington KW, Mark WR. Waiting for a specialist consultation for a new condition in Ontario: impacts on patients' lives. *Healthcare Policy* 2014;9:90-103.
22. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag* 2008;4:269-86.
23. Wood JP, Traub SJ, Lipinski C. Safety of epinephrine for anaphylaxis in the emergency setting. *World J Emerg Med* 2013;4:245-51.
24. Kawano T, Scheuermeyer FX, Stenstrom R, Rowe BH, Grafstein E, Grunau B. Epinephrine use in older patients with anaphylaxis: clinical outcomes and cardiovascular complications. *Resuscitation* 2017;112:53-8.
25. Steinke JW, Platts-Mills TAE, Commings SP. The alpha gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol* 2015;135:589-97.

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TABLE E1. A comparison of characteristics of AUT vs AKT

Characteristic	AUT (N = 295), % (95% CI)	AKT (N = 3204), % (95% CI)	Difference, % (95% CI)
Patient demographic characteristics			
Age, median (IQR)	12.5 (6.3-17.8)	11.1 (2.4-14.4)	1.4
Sex, male (%)	56.3% (50.4% to 60.0%)	58.5% (56.8% to 60.2%)	−2.2% (−8.3% to 3.8%)
Patient clinical characteristics			
Known food allergy	38.1% (32.6% to 43.9%)	52.4% (50.7% to 54.2%)	−14.3% (−20.3% to −8.3%)
Known drug allergy	6.1% (3.8% to 9.7%)	3.8% (3.2% to 4.6%)	2.3% (−0.7% to 5.3%)
Known venom allergy	0.3% (0.02% to 2.2%)	0.5% (0.3% to 0.8%)	−0.2% (−1.0% to 0.7%)
Other known allergy	9.9% (6.8% to 14.0%)	6.2% (5.4% to 7.1%)	3.7% (−0.3% to 7.4%)
Asthma	2.7% (1.3% to 5.5%)	15.5% (14.3% to 16.9%)	−12.8% (−15.3% to −10.4%)
Reaction severity			
Mild	8.8% (3.4% to 14.6%)	20.5% (19.0% to 22.0%)	−11.7% (−15.4% to −8.0%)
Moderate	62.4% (56.9% to 68.2%)	73.4% (71.9% to 74.9%)	−11.0% (−17.0% to −5.1%)
Severe	28.8% (23.4% to 34.6%)	6.1% (4.6% to 7.6%)	22.7% (17.3% to 28.1%)
Treatment outside of the hospital setting			
Epinephrine received in the prehospital setting	28.7% (23.6% to 34.3%)	32.6% (30.9% to 34.2%)	−3.9% (−9.5% to 1.7%)
Antihistamines received in the prehospital setting	46.4% (40.6% to 52.3%)	45.2% (43.4% to 46.9%)	1.2% (−4.9% to 7.4%)
Corticosteroids received in the prehospital setting	2.0% (0.8% to 4.6%)	1.8% (1.4% to 2.3%)	0.3% (−1.6% to 2.1%)
Treatment inside the hospital setting			
IM epinephrine	44.9% (39.1% to 50.8%)	49.2% (47.4% to 50.9%)	−4.3% (−10.4% to 1.8%)
IV epinephrine	0.7% (0.1% to 2.7%)	1.1% (0.7% to 1.5%)	−0.4% (−1.6% to 0.8%)
Antihistamines	55.8% (49.9% to 61.5%)	52.6% (50.8% to 54.3%)	3.2% (−2.9% to 9.3%)
Corticosteroids	46.3% (40.5% to 52.1%)	41.1% (39.4% to 42.8%)	5.2% (−0.9% to 11.3%)
Treatment inside or outside the hospital setting			
Received epinephrine inside <i>or</i> outside the hospital setting	69.0% (63.4% to 74.2%)	75.7% (74.2% to 77.2%)	−6.6% (−12.3% to −1.0%)
Received epinephrine inside <i>and</i> outside the hospital setting	4.4% (2.5% to 7.6%)	6.1% (5.3% to 7.0%)	−1.6% (−4.3% to 1.0%)

IM, Intramuscular; IV, intravenous.