

Rate, Triggers, Severity and Management of Anaphylaxis in Adults Treated in a Canadian Emergency Department

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Key Words

Anaphylaxis · Food allergy · Management · Epinephrine · Severe anaphylaxis

Abstract

Background: The Cross-Canada Anaphylaxis Registry (C-CARE) assesses the triggers and management of anaphylaxis and identifies predictors of the development of severe allergic reactions and of epinephrine use. Here, we present data from an urban adult tertiary care emergency department (ED) in Montreal, Canada. **Methods:** Potential anaphylaxis cases were identified using ICD-10 codes related to anaphylaxis or allergic reactions. Putative cases underwent chart review to ensure they met anaphylaxis diagnostic criteria. Demographic, clinical and management data were collected. Multivariate logistic regressions were conducted to assess the effect of demographic characteristics, triggers,

and comorbidities on severity and management of reactions. **Results:** Among 37,730 ED visits, 0.26% (95% CI 0.21, 0.32) fulfilled the definition of anaphylaxis. Food was the suspected trigger in almost 60% of cases. Epinephrine was not administered in almost half of moderate-to-severe cases, and similar numbers of individuals with moderate-to-severe reactions were not prescribed an epinephrine autoinjector. Reaction to shellfish was associated with more severe reactions (OR 13.9; 95% CI 2.2, 89.4). Older individuals and those not receiving steroids were more likely managed without epinephrine (OR 1.04; 95% CI 1.01, 1.07 and OR 2.97; 95% CI 1.05, 8.39, respectively). **Conclusions:** Anaphylaxis accounted for a substantial number of ED visits in adults, and the most common trigger was food. There is non-adherence to guidelines recommending epinephrine use for all cases of anaphylaxis. We postulate that this may be related to concerns regarding the side effects of epinephrine in adults.

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Introduction

Anaphylaxis is a rapid and severe multiorgan reaction that can be fatal [1]. In the United States, anaphylaxis affects at least 1.6% of the population and it is estimated that food-triggered reactions account for 150–200 fatalities per year [2, 3]. A recent systematic review of anaphylaxis in Europe has found that incidence rates range from 1.5 to 7.9/100,000 person-years and that the lifetime prevalence of anaphylaxis is 0.3% [4]. According to a UK health database, the burden of anaphylaxis appears to be increasing over time [5]. Obtaining a true estimate of the impact of anaphylaxis is difficult as the majority of studies generate estimates based on cases presenting to specialized allergy clinics that likely overestimate the incidence in the general population [1].

Food, drugs, stinging insects and latex are some of the most commonly identified triggers [1, 2]. Although drug-induced anaphylaxis is reported in some studies to be more common in adults [1, 6, 7], more recent studies suggest that food is the major culprit [8]. Only a few studies assessed factors associated with the severity and clinical presentation of anaphylaxis. These studies report more severe reactions in drug-induced anaphylaxis and in older individuals [9, 10]. In addition, certain comorbidities including asthma, severe eczema and lung disease [9] were reported to be associated with more severe reactions.

Although guidelines on the management of anaphylaxis in the emergency department (ED) stipulate the use of epinephrine [11], several studies have suggested that physicians are uncertain regarding the diagnosis and management of anaphylaxis [12, 13] and that epinephrine is underused [8, 14, 15].

There is little Canadian information available about the incidence, triggers, clinical presentation and management of anaphylaxis in adults presenting to the ED. The demographic factors and reaction characteristics that may affect the use of epinephrine in adults are also unknown in this population.

The Cross-Canada Anaphylaxis Registry (C-CARE) is a project designed to assess the rate and triggers of anaphylaxis and describe the management of anaphylaxis and factors associated with reaction severity and epinephrine use. As part of C-CARE, we undertook a study to investigate anaphylaxis cases presenting to the adult ED of a tertiary care center in Montreal, Que., Canada.

Table 1. Demographics and comorbidities of patients and reaction characteristics

<i>Demographics and comorbidities of patients</i>	
Anaphylaxis	0.26 (0.21, 0.32)
Median age (IQR), years	31.5 (26.4, 44.0)
Males	33.7 (24.6, 44.0)
Known food allergy	24.5 (16.6, 34.4)
Known asthma	16.3 (9.9, 25.5)
Known eczema	1.0 (0.05, 6.4)
Known ischemic heart disease	0
Use of β -blockers	1.0 (0.05, 6.5)
Use of antidepressants	0
Use of monoamine oxidase inhibitors	0
Use of angiotensin-converting enzyme inhibitors	2.1 (0.4, 8.0)
Use of non-steroidal anti-inflammatory	2.1 (0.4, 8.0)
<i>Reaction characteristics</i>	
Food trigger	63.3 (52.9, 72.6)
Shellfish ^a	12.9 (6.1, 24.4)
Peanut ^a	8.1 (3.0, 18.5)
Tree nuts ^a	6.5 (2.1, 16.5)
Nuts (unsure if peanut or tree nut) ^a	9.7 (4.0, 20.4)
Kiwi ^a	3.2 (0.5, 12.2)
Milk ^a	1.6 (0.08, 9.8)
Egg ^a	1.6 (0.08, 9.8)
Fish ^a	1.6 (0.08, 9.8)
Unknown food allergen ^a	30.6 (20.0, 43.8)
Other food allergen ^a	21.0 (12.1, 33.5)
Venom	4.1 (1.3, 10.7)
Drugs	18.4 (11.5, 27.7)
Unknown trigger	14.3 (8.3, 23.1)
Reaction outside home	39.3 (27.3, 52.7)
Reaction in a restaurant among all reactions outside home	45.8 (26.2, 66.8)
Reaction not during exercise	94.3 (83.4, 98.5)
Reactions during exercise	3.8 (0.7, 14.1)
Not clear if reactions occurred during exercise	1.9 (0.09, 11.3)
Reaction severity	
Mild reaction ^b (n = 4)	4.1 (1.3, 10.7)
Moderate reaction ^c (n = 87)	88.7 (80.4, 94.0)
Severe reaction ^d (n = 7)	7.1 (3.2, 14.7)
Moderate/severe reaction (n = 94)	95.9 (89.3, 98.7)
Not prescribed epinephrine and do not possess an autoinjector for those with no drug allergy	32.9 (22.8, 44.7)

All values are presented as percentages (95% CI) unless otherwise indicated.

^a Among all reactions triggered by food.

^b Defined as sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema, oral pruritus, oral tingling, mild lip swelling, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, mild wheezing and tachycardia [18].

^c Defined as crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, barking cough, difficulty swallowing, stridor, dyspnea or moderate wheezing [18].

^d Defined as loss of bowel control, cyanosis or saturation <92%, or respiratory arrest [18].

Table 2. Use of medications out- and inside the ED

	Outside ED, % (95% CI)				Inside ED, % (95% CI)			
	mild (n = 4)	moderate (n = 87)	severe (n = 7)	mod/sev (n = 94)	mild	moderate	severe	mod/sev
EP	25 (1.3, 78.1)	19.5 (12.1, 29.7)	28.6 (5.1, 69.7)	20.2 (12.9, 30.0)	25 (1.3, 78.1)	31.0 (21.8, 41.2)	42.9 (11.8, 79.8)	31.9 (22.9, 42.4)
AH	25 (1.3, 78.1)	41.4 (31.1, 52.4)	28.6 (5.1, 69.7)	40.4 (30.6, 51.1)	100.0 (39.6, 100.0)	75.9 (65.3, 84.1)	85.7 (42.1, 99.2)	76.6 (66.5, 84.5)
ST	0.0 (0.0, 60.4)	6.9 (2.8, 15.0)	0.0 (0.0, 43.9)	6.4 (2.6, 13.9)	50.0 (15.0, 85.0)	67.8 (56.8, 77.2)	71.4 (30.3, 94.9)	68.1 (57.6, 77.1)

EP = Epinephrine; AH = antihistamines; ST = steroids.

Methods

The ED of the Montreal General Hospital, Montreal, Que., provides services for patients from the island of Montreal and its surrounding off-island suburbs. Charts of all patients visiting the ED of the Montreal General Hospital during the period of March 1, 2011, to February 28, 2012, were retrospectively reviewed to identify any potential cases of anaphylaxis. All patients with an ICD-10 code related to the diagnoses of anaphylaxis or allergic reactions were then evaluated independently by 2 trained members of our research team using a previously validated algorithm for anaphylaxis [16] to determine if the patient fulfilled criteria for anaphylaxis [17] and to determine reaction severity [18]. Information was also collected on demographic characteristics, suspected triggers and management of anaphylaxis. Uni- and multivariate logistic regressions were compared to identify factors associated with having a severe reaction and with no epinephrine use in- or outside of the ED. Factors evaluated for association with severe reactions included age, sex, antihistamine or steroid administration in the ED, antihistamine or steroid administration either in- or outside of the ED, presence of comorbidities (asthma, known food allergy, known ischemic heart disease, use of medications on a daily basis), and type of trigger (food, specific food, venom, drug, unknown). Factors assessed for association with no epinephrine use in- or outside of the ED included all of the above as well as reaction severity (mild, moderate or severe) [18]. Analysis was conducted using the computer program R version 2.12.0 [19]. This project was approved by the McGill University Health Center Ethics Review Board.

Results

Among all 37,730 ED visits during the assessment period, 98 anaphylaxis cases were identified (0.26%; 95% CI 0.21, 0.32) (table 1). The median age was 31.5 years (IQR 26.4, 44.0) and 33.7% (95% CI 24.6, 44.0) were males. None of the patients had documented comorbid ischemic heart disease, and none used antidepressants or monoamine oxidase inhibitors. Two used angiotensin-converting enzyme inhibitors, 2 non-steroidal anti-inflammatory drugs and only 1 used β -blockers.

Food was the suspected trigger for 63.3% of reactions (95% CI 52.9, 72.6), drugs for 18.4% (95% CI 11.5, 27.7) and venom for 4.1% (95% CI 1.3, 10.7) (table 1). In 14.3% (95% CI 8.3, 23.1), the trigger was unidentified. Shellfish was the most common food trigger (12.9% of all food-triggered reactions) and among drugs, amoxicillin was the major culprit (16.7% of all drug-triggered reactions). Almost 40% of reactions occurred outside of the home and almost half of these in restaurants. The majority of reactions were not related to exercise.

Most of the reactions were moderate (88.7%) and 94 of 98 reactions were categorized as either moderate or severe (95.9%; 95% CI 89.3, 98.7). Among those with non-drug-triggered anaphylaxis who did not already possess an autoinjector, 25 (32.9%; 95% CI 22.8, 44.7) were not prescribed an epinephrine autoinjector.

We compared the percentage of cases receiving epinephrine, antihistamines or steroids outside and the percentage receiving these medications inside the ED (table 2) as well as the percentage receiving these medications either in- or outside the ED (table 3). Prior to ED arrival, 25.0% of mild and 20.2% of moderate/severe reactions received epinephrine compared to 25.0 and 31.9% after arrival (table 2). When evaluating the percentage of cases receiving epinephrine either out- or inside the ED, in more than half of moderate-to-severe reactions, no epinephrine was given (table 3). A substantially larger percentage of patients were receiving antihistamines or steroids compared to epinephrine.

In the multivariate regression model for reaction severity, shellfish as a trigger of anaphylaxis was associated with a severe reaction (OR 13.9; 95% CI 2.2, 89.4). Large confidence intervals due to small sample size precluded any definitive conclusions regarding the effects of other factors assessed. In the multivariate model for not administering epinephrine either in- or outside of the ED, age (OR 1.04; 95% CI 1.001, 1.070 for each increase of

Table 3. Use of medications in- or outside of ED

	In- or outside ED, % (95% CI)				
	mild	moderate	severe	mod/sev	all
EP	50.0 (15.0, 85.0)	48.3 (37.5, 59.2)	57.1 (20.2, 88.2)	48.9 (38.6, 59.4)	49.0 (38.8, 59.2)
AH	100.0 (39.6, 100.0)	90.8 (82.2, 95.7)	85.7 (42.0, 99.2)	90.4 (82.2, 95.3)	90.8 (82.8, 95.5)
ST	50.0 (15.0, 85.0)	73.6 (62.8, 82.2)	71.4 (30.3, 94.9)	73.4 (63.1, 81.7)	72.4 (62.3, 80.8)
Difference (AH-EP)	50.0 (-24.0, 100.0)	42.4 (90.8, 48.3)	28.6 (-30.6, 87.8)	41.4 (28.7, 54.3)	41.8 (29.4, 54.3)
Difference (ST-EP)	0	25.3 (10.1, 40.4)	14.3 (-49.6, 78.3)	24.5 (9.9, 39.0)	23.4 (9.2, 37.8)

EP = Epinephrine; AH = antihistamines; ST = steroids.

Table 4. Summary of previous studies on emergency room anaphylaxis

	Current study	Ben-Shoshan et al. [21], 2013	Calderon et al. [8], 2013	Lauritano et al. [6], 2013	Campbell et al. [19], 2011
Location	Montreal, Que., Canada	Montreal, Que., Canada	Puerto Rico and US Virgin Islands	Alessandria, Italy	Rochester, Minn., USA
Population	adults, tertiary care ED	children, tertiary care ED	adults, ED	adults, ED	adults, tertiary care ED
Method	retrospective cases identified through ICD-10 codes	prospective and retrospective cases identified through ICD-10 codes	retrospective chart review	retrospective chart review	retrospective chart review
Cases	98	168	31	18	220
Total population	all ED visits 37,730	all ED visits 81,677	all ED visit ~71,000	all ED visits 55,000	all ED visits ~160,000
Incidence estimate, %	0.26 (0.21, 0.32)	0.21 (0.18, 0.24)	0.04 (0.03, 0.06)	0.03 (0.02, 0.05)	0.13 (0.12, 0.15)
Difference (MGH-ED center), %		0.05 (-0.00, 0.001)	0.2 (0.1, 0.3)	0.2 (0.2, 0.3)	0.12 (0.07, 0.18)
Most common trigger	food	food	food	drugs	food main trigger in cases <65 years, drugs in those >65 years
Fatalities	none	none	none	1	not stated
Most common treatment	AH, ST	EP, AH	AH, ST	AH, ST	AH, ST

EP = Epinephrine; AH = antihistamines; ST = steroids.

1 year) and not receiving steroids in- or outside the ED (OR 2.97; 95% CI 1.05, 8.39) were associated with the outcome.

Discussion

This is the first Canadian study to assess the percentage of visits to an adult ED that are attributable to anaphylaxis and to describe the triggers and management of anaphylaxis in adults. Our findings reveal a higher percentage of visits to the ED due to anaphylaxis than previously reported in other adult ED studies [6, 8, 19, 20], although they are comparable to our pediatric ED estimate [21] (table 4). Differences in populations and ED

referral patterns may contribute to the higher rate of anaphylaxis in our adult ED center.

Similar to other studies, we found a female preponderance in anaphylaxis cases, which may be mediated by the effects of estrogens and progesterone on mast cell activation and IgE production [1, 22]. In contrast to our pediatric study, almost half of the reactions in adults occurred outside of the home, often in a restaurant. This may indicate differences in adults versus children with regard to eating practices and experiencing new foods outside of home. Meals at restaurants are particularly dangerous for patients with food allergies given the risk of hidden food allergens [23, 24] and the unfamiliarity of restaurant staff in managing food allergy [25].

In line with most recently published studies of anaphylaxis in adults, food was the suspected trigger for the majority of anaphylaxis cases [6, 8, 14] and shellfish was the major food allergen triggering anaphylaxis [26]. In contrast, in a study conducted by our research team in a tertiary care pediatric ED, we found that peanut is the major food trigger in children [21]. These results are expected given that shellfish is also the most common food allergen in Canadian adults and peanut is the second most common food allergy in Canadian children [27]. Shellfish allergy may account for the majority of food-triggered reactions in adults and not in children because shellfish introduction in Canada is usually delayed beyond the age of 5 years [28]. In contrast, in Asia, where shellfish is introduced early in the diet, it is a major cause of anaphylaxis in children as well [26, 29]. Our study reveals that shellfish allergy is the only factor, of those we examined, that was associated with more severe reactions. The pathogenic mechanisms underlying this relationship are currently unclear.

Our results reveal poor adherence to guidelines stipulating use of epinephrine for anaphylaxis, particularly in older individuals [17]. Epinephrine underuse has been reported in EDs from a variety of countries, including Pakistan [14], Puerto Rico [8], Italy [6], the United States [19] and Germany [15]. In the Italian study, only 2 patients among 18 with anaphylaxis received intramuscular epinephrine from an ambulance physician [6]. Despite the fact that more than 50% of the patients in our study did not receive epinephrine, no fatalities were observed.

Our study exemplifies disparities between the management of anaphylaxis in an adult and pediatric hospital ED affiliated with the same university and located in the same urban center; 82.2% of all moderate/severe cases received epinephrine either prior to or after arrival at the children's ED [21], compared to 48.9% of moderate/severe reactions at the adult ED, a difference of 33.3% (95% CI 19.4, 47.2). The vast majority (90.8%) of non-drug-related pediatric cases were prescribed or already possessed an epinephrine autoinjector [21] compared to 32.9% of adult cases, who had no epinephrine auto-injector prescribed and did not possess an auto-injector. From the data acquired at the adult ED, we have demonstrated an association between no use of epinephrine and age; although the effect size (OR 1.04) appears small, it should be noted that the impact would be multiplied by each year of age, indicating that the overall effect size is quite large.

The striking differences between our pediatric and adult centers likely reflect disparities in the management of anaphylaxis in these populations. Given that both EDs

are affiliated with the same university center, it is likely that this difference is related to concern about adverse effects in adults rather than gaps in knowledge [30]. Case reports have been published suggesting a relationship between cardiovascular adverse events and epinephrine use, but no large-scale studies have established such an association [31]. Further, it should be noted that doses of epinephrine used in many reported cases of cardiovascular adverse events secondary to epinephrine were substantially higher (1–40 mg) than the dose commonly used to treat anaphylaxis in adults (0.3–0.5 mg). In addition, it is important to recall there are a number of reasons to present with cardiac symptoms in anaphylaxis, including allergic myocardial infarction (Kounis syndrome), hypersensitivity myocarditis, and Takotsubo cardiomyopathy and that these complications could develop due to the allergic reaction itself rather than the treatment [31]. If the spectra of iatrogenic sequelae is driving the decision to omit epinephrine from the management of anaphylaxis, further research is required to determine if there is greater cardiac risk with the use of epinephrine, or in fact epinephrine administration is even more imperative with age due to greater risk for cardiovascular symptoms as part of the anaphylactic reaction [32].

However, there is an understandable paucity of controlled trials for the management of anaphylaxis [33–35]; it is unlikely that trials required for high-level evidence will be conducted for ethical reasons, particularly in the case of epinephrine. Despite this lack of evidence, the clear standard of care for anaphylaxis is the use of epinephrine. The World Allergy Organization (WAO) [33, 36], the European Academy of Allergology and Clinical Immunology (EAACI) [18], the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) [17] have all published position papers on the assessment and management of anaphylaxis indicating the importance of epinephrine. Given that our cases included relatively young adults with no substantial cardiac comorbidities, we would expect that the need for prompt use of epinephrine should prevail over the risk of adverse effects.

While the guidelines suggest that the standard of care for anaphylaxis is epinephrine, the benefits and harms of systemic steroids or antihistamines have not been established and their use should not replace the use of epinephrine [34]. Our results indicate an association between steroid use and epinephrine use regardless of reaction severity. Given that steroids are listed in the treatment guidelines of anaphylaxis [17], it is likely that physicians

that are aware of the guidelines and use steroids are more likely to use epinephrine.

Limitations of this study include missing cases that had been miscoded under the ICD-10 system, which has occurred in other studies [16]. However, the failure to identify these cases, if present, would lead to a more conservative estimate. In addition, given that some variables may not have been recorded diligently in the charts, it is possible that data is missing for some variables. However, it is unlikely that missing data affected our main findings as recording the use of epinephrine, histamine and steroids is mandatory in patients' charts and studies suggest that demographic data (including age and sex) [37] and the presence of severe symptoms can be reliably obtained through chart review [38]. It is also possible that the base population served by this specific ED is not representative of the adult population of the island of Montreal as other EDs provide services to adults in Montreal.

Our results indicate a relatively high percentage of anaphylaxis among adults presenting to the ED and, as

compared to international/national guidelines, low use of epinephrine that is particularly apparent with age. It is important to develop training programs specifically prompting the use of epinephrine in all cases of anaphylaxis in adults. Given that there are concerns related to side effects of epinephrine in the elderly and those with a known cardiovascular disease, future large-scale studies establishing the true risk of cardiovascular side effects of epinephrine use in anaphylaxis in adults are required. If the risks are established to be low, physicians and patients will appreciate that the benefits of administering epinephrine in anaphylaxis outweigh any potential risk.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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