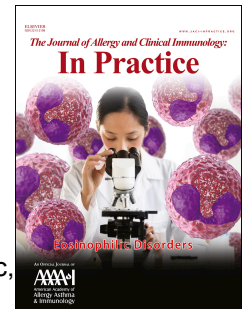


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Findings from the Cross-Canada Anaphylaxis Registry

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When and how pediatric anaphylaxis cases reach the emergency department: findings from the Cross-Canada Anaphylaxis Registry

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68 Clinical Implications Box:

69 Delayed treatment of anaphylaxis is associated with fatality. Although the majority of
70 anaphylaxis cases arrive at the Emergency Department within one hour of symptom onset,
71 education to seek prompt medical attention remains warranted, especially for older children with
72 anaphylaxis.

73
74 Key words

75 Anaphylaxis, child, pediatric, emergency, time, arrival, transport, fatality

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To the Editor,

In recent years, many studies conducted in the United States and Canada have demonstrated a steady increase in Emergency Department (ED) visits for food-induced anaphylaxis in pediatric patients.(1, 2) Given that studies suggest that death due to anaphylaxis can occur as rapidly as 30 minutes after exposure to food, 15 minutes for insect stings, and 5 minutes for drugs, method and timing of transportation to the emergency room are crucial.(3) However, to our knowledge, no studies evaluated time interval and method of transportation to the ED for children who suffered an anaphylactic reaction in Canada. We aimed to determine the time interval between development of anaphylaxis and arrival at the ED and determine factors associated with early (within one hour of reaction) arrival and with transportation by ambulance.

This was a prospective and retrospective cohort substudy among participants of the Cross-Canada Anaphylaxis REgistry (C-CARE) database. Over an 8-year period, between June 2011 and May 2019, the C-CARE recruited children presenting with anaphylaxis to four EDs in two Canadian provinces (Quebec and Ontario): The Montreal Children's Hospital, the Hôpital Sacré-Coeur, and the Centre Hospitalier Universitaire Sainte-Justine, all of which are located in the province of Quebec and the London Health Science Centre in Ontario.

Patients who consulted any of the EDs in participating centers for anaphylactic reactions and completed an additional long questionnaire querying on time of arrival and method of transport were included. A standardized data form documenting symptoms and triggers of anaphylaxis was collected. Consenting patients completed an additional long questionnaire querying on time and method of transportation to the ED. More specifically, 447 participants out of 2119 (21.1%) were included in those that filled out the long questionnaire. Patients who were not approached to fill

the long questionnaire were excluded from this study. This was determined based on vigilance and recognition by caregivers. Age, sex, the presence or absence of comorbidities, anaphylaxis triggers and the most common location of reaction were similar between patients who completed (responders) and did not complete the questionnaire (non-responders) (Table 1). Prospectively recruited patients accounted for 79.6% of all participants, and there were no significant differences in time of arrival, method of transport, sex, and anaphylaxis trigger between prospective and retrospective cases. (Table E1 Online Repository)

Anaphylaxis was defined as the involvement of two or more organ systems after exposure to a possible allergen or hypotension after exposure to a known allergen.(4) The primary outcome for this study was the time interval between development of anaphylaxis and arrival to ED, as well as method of arrival to the ED. The time interval was dichotomized and cut off at the one-hour time limit. This cut off is justified by previous findings suggesting that majority of anaphylaxis deaths occur within one hour following symptom onset.(5) Univariable and multivariable logistic regressions were compared to assess factors associated with arrival time and transport to the ED.

C-CARE is described previously.(4) Only prospective and retrospective cases meeting the definition of anaphylaxis as determined by two independent reviewers (SG and MBS) were included. Anaphylaxis severity was classified using a modified grading system described by Muraro et al. as previously described (5) .Prospective data was collected at the time of patient presentation to the ED.. Data on cases that were identified retrospectively were collected through chart review. The questionnaire querying on time and methods of transportation to the ED was collected in retrospective cases that consented to complete the questionnaire at a subsequent visit to the allergy clinic.

The study was cleared by the McGill University Ethics Committee, the Research Ethics Board of the Hôpital du Sacré-Coeur, the Board of Directors of the Centre Hospitalier Universitaire Sainte-Justine, and the Health Science Research Ethics Board at Western University. All statistical analyses were performed using R version 3.2.2. (R Core Team [2013]; R, Vienna, Austria).

From June 2011 to May 2019, 447 out of 2119 (21.1%) recruited pediatric patients with anaphylaxis from the four centers in Ontario and Quebec were included in our substudy, of which 63.1% were male, with a median age of 4.5 years (interquartile range [IQR]: 1.5, 10.2).

Patients with food-induced anaphylaxis accounted for 84.3% of all cases. (Table 1)

Of all pediatric patients recruited, 80.8% reached the ED in less than one hour following symptom onset. Around 10% (10.4%) arrived between one and three hours and a minority (1.5%) arrived after three hours. The most common method of transportation to the ED was accompaniment by a family member (44.1%), while 40.8% of patients arrived to the ED by ambulance. The remainder of the patients arrived by taxi, walking or other (Table 2).

Among patients transported by a family member, 86.3% reached the ED less than one hour after symptom onset. Similarly, 86.6% of patients arriving by ambulance arrived less than an hour after symptoms. In contrast, 2.0% of patients driven by a family member reached the ED more than three hours after symptom onset, compared to 1.2% of patients arriving by ambulance. The use of epinephrine by the patient prior to arrival to the emergency was consistently around 20% regardless of method of transport or time of arrival. (Table E2, E3 Online Repository)

Arrival at the ED in less than one hour was found to be less likely in teenagers, defined hereinafter as patients over 12 years of age and up to 18 years (adjusted Odds Ratio [aOR] 0.84 (0.71, 0.99)) while controlling for sex, known allergy, reaction severity, dermatologic, respiratory,

gastrointestinal and cardiovascular symptoms. (Table E4 Online Repository) Transport to the ED by ambulance was more likely when reactions occurred at school (aOR 1.36 (1.21, 1.52)) while adjusting for age, sex, reaction severity and a known allergy. (Table E5 Online Repository)

In 2004, Clark et al. conducted a similar study with a smaller sample size, not restricted to children, where patients presenting to 21 EDs in nine US states and four Canadian provinces with food-induced anaphylaxis were recruited. Patients had a median age of 29 years. Their findings revealed that less than 20% of patients arrived by ambulance and only one third sought medical attention within one hour of the onset of symptoms.(6) In our study, almost 90% of pediatric patients reached the ED in less than one hour and more than 40% arrived at the ED by ambulance. This difference can likely be attributed in part to the exclusion of adult patients in our study. Other studies demonstrate higher vigilance and adherence to management guidelines in children compared to adults, namely in use of epinephrine following an anaphylactic reaction.(7) Furthermore, our study included major metropolitan cities where there is easier access to hospitals, also contributing to this increase in ED arrivals in shorter time intervals. Given that the Clark study was conducted almost two decades earlier, increased knowledge of the importance of prompt management of anaphylactic reactions, and more specifically, increased awareness of food-induced anaphylaxis could also play a role in this increase in presentation to the ED in a shorter period of time.(3)

Teenagers and older pediatric patients are known to exhibit higher risk behavior and are less often under the immediate supervision of a parent, guardian or a school representative, factors that may account for the increase in arrival time for this group.(8) Our study found that patients who are older seem to be less likely to seek medical treatment immediately after symptom onset. Transport to the ED by ambulance was more likely when reactions occurred at

183 school, likely because patients were not in the care of a family member who could transport them
184 to the hospital.

185
186 This study has several limitations. We included metropolitan areas in two provinces that
187 may not reflect time of arrival and method of transportation following anaphylactic reactions in
188 more rural settings. In addition, only 21% of the cohort responded to the long questionnaire,
189 which queried specifically on arrival time and transport methods. However, this did not likely
190 result in selection bias, given the similarity between responders and non-responders, pertaining to
191 sex, co-morbidities (other than eczema), anaphylaxis triggers and the most common location of
192 reaction (home).

193
194 In conclusion, the majority of anaphylaxis cases arrive at the ED within one hour of
195 symptoms. Differences between the two provinces in arrival time and use of ambulance may be
196 related to differences in catchment population given the larger metropolitan areas served by the
197 Quebec centers. Education programs targeting older children with anaphylaxis and promoting
198 early arrival to the ED are required.

200 **Acknowledgments**

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Figures

Table 1. Characteristics of Pediatric Patients Transported to the ED with Anaphylaxis in cases who filled the questionnaire versus cases that did not fill the questionnaire.

Variable (% 95% CI)	Filled questionnaire N = 447	Not filled questionnaire N=1672	Difference
Province			
Quebec	79.9%	95.3%	-15.4% (-19.5%, -11.5%)
Ontario	20.1%	4.7%	24.8% (11.5%, 19.5%)
Prospective	79.6%	32.4%	47.2% (42.8%, 51.8%)
Age at reaction (median, IQR)	4.5 (1.5, 10.2)	5.8 (2.1, 11.5)	-1.3
Sex (% males)	63.1%	58.6%	4.5%(-0.7%, 9.7%)
Trigger			
Food	84.3%	83.5%	0.8% (-3.1%, 4.8%)
Venom	4.0%	1.8%	2.2% (0.1%, 4.3%)
Drug	3.4%	4.8%	-1.4% (-3.5%, 0.7%)
Other	3.4%	4.4%	-1.0% (-3.2%, 1.0%)
Unknown	6.3%	10.1%	-3.8% (-6.7%, 1.0%)
Location of reaction			
Home	53.2%	55.0%	-1.8% (-7.1%, 3.6%)
School/Daycare	18.1%	0.1%	18.0% (14.3%, 21.7%)
Work	0%	10.2%	-10.2% (-11.8%, -8.6%)
Restaurant	3.8%	3.5%	0.3% (-1.8%, 2.5%)
Other	19.2%	12.1%	7.1% (3.0%, 11.2%)
Unknown	5.8%	4.3%	1.5% (-1.0%, 4.0%)
Comorbidities			
Asthma	15.0%	14.2%	0.8% (-3.4%, 4.1%)
Eczema	21.4%	12.4%	9.0% (4.2%, 12.6%)
Heart Condition	0.0%	0.0%	0.0% (0.0%, 0.0%)
Other comorbidity	6.4%	8.8%	-2.4% (-4.7%, 1.0%)
No comorbidity	23.0%	27.3%	-4.3%(-9.2%, -0.1%)
Unknown	2.9%	1.5%	1.4%(-0.2%, 3.5%)
Time to reach healthcare facility			
Less than 1 hour	80.8%		
Between 1 to 3 hours	10.4%		
More than 3 hours	1.5%		
Unknown	0.9%		
Brought to healthcare facility by:			
Ambulance	40.8%		
Family member	44.1%		
Taxi	2.0%		

Walked	0.7%
Other	6.3%
Unknown	3.6%

Table 2. Differences in patient demographics, clinical characteristics, co-morbidities by method of arrival

Variable (% 95%CI)	Ambulance N=172	Family N=197	Difference
Province			
Quebec	82.5%	73.0%	9.5% (0.5%, 18.4%)*
Ontario	17.4%	26.9%	-9.5% (-18.4%, -0.5%)*
Age at reaction (median, IQR)	4.2 (1.5, 11.4)	4.5 (1.4, 8.8)	-0.3
Sex (% males)	62.8%	63.5%	-0.7% (-11.1%, 9.8%)
Severity			
Mild	20.9%	21.8%	-0.9% (-9.8%, 8.0%)
Moderate	71.5%	70.1%	1.4% (-8.4%, 11.3%)
Severe	7.6%	8.1%	-0.5% (-6.6%, 5.4%)
Time to reach healthcare facility			
Less than 1 hour	86.6%	86.3%	0.3% (-6.9%, 7.7%)
Between 1 to 3 hours	10.5%	8.6%	1.9% (-4.7%, 8.4%)
More than 3 hours	1.2%	2.0%	-0.8% (-3.9%, 2.4%)
Known allergy	58.1%	49.2%	8.9% (-1.7%, 19.6%)
Asthma	11.6%	16.2%	-4.6% (-12.2%, 3.0%)
Eczema	20.3%	20.3%	0.0% (-8.2%, 8.3%)
Self-Use of epinephrine	20.3%	19.3%	1.0% (-7.6%, 9.8%)
Epinephrine given by EMS or ED	76.1%	76.1%	0.0% (-8.7%, 8.8%)

Online Repository

Table E1. Differences in method of arrival and time intervals in prospectively and retrospectively recruited participants

Variable (% , 95% CI)	Prospective N=335	Retrospective N=86	Difference
Sex	62.7%	60.5%	2.2% (-14.5%, 10.1%)
Food-induced anaphylaxis	84.8%	81.4%	3.4% (-13.2%, 6.4%)
Time of arrival			
Less than 1 hour	83.0%	86.0%	-3.0% (-6.0%, 12.1%)
Between 1 and 3 hours	9.6%	11.6%	-2.0% (-6.1%, 10.3%)
More than 3 hours	1.8%	1.2%	0.6% (-3.9%, 2.7%)
Method of transport			
Ambulance	40.0%	38.4%	1.6% (-13.9, 10.6%)
Family member	46.3%	52.3%	-6.0% (-6.5%, 18.6%)

Table E2. Differences in method of arrival and time intervals by province

Variable (% , 95% CI)	Quebec N=357	Ontario N=90	Difference
Time to reach health care facility			
Less than 1 hour	79.6%	85.5%	-5.9% (-15.1%, 3.1%)
Between 1 to 3 hours	9.5%	3.3%	6.2% (0.7%, 11.7%)*
More than 3 hours	1.7%	0.1%	0.6% (-2.5%, 3.7%)
Unknown	9.2%	10.0%	-0.8% (-8.4%, 6.8%)
Brought to healthcare facility by			
Ambulance	39.8%	33.3%	6.5% (-5.2%, 18.1%)
Family member	40.3%	58.8%	-18.5 % (-30.6%, -6.5%)*

Table E3. Differences in patient demographics, clinical characteristics, co-morbidities by time intervals

Variable (% , 95% CI)	Less than 1 hour N=352	Between 1 to 3 hours N=42	Difference *The "More than 3 hours group has been omitted as only 7 cases
Province			
Quebec	78.7%	92.0%	-13.3% (-24.4%, -1.9%)*
Ontario	21.3%	8.0%	13.3% (1.9%, 24.4%)*
Age at reaction (median, IQR)	4.25 (1.5, 6.1)	4.85 (1.3, 13.5)	-0.6
Sex (% males)	64.5%	59.5%	5.0% (-13.0%, 23.1%)
Severity			
Mild	23.5%	5.4%	18.1% (8.2%, 28.1%)
Moderate	69.0%	81.1%	-12.1% (-27.1%, 2.9%)

Severe	7.4%	13.5%	-6.1% (-18.9%, 6.8%)
Brought to healthcare facility by			
Ambulance	41.2%	48.6%	-7.4% (-25.7%, 11.0%)
Family member	47.1%	45.9%	1.2% (-16.8%, 19.2%)
Known allergy	54.6%	48.6%	6.0% (-12.5%, 24.3%)
Asthma	14.1%	24.3%	-10.2% (-26.0%, 5.6%)
Eczema	19.3%	32.4%	-13.1% (-30.2%, 4.1%)
Self-use of epinephrine	21.1%	18.9%	2.2% (-12.7%, 16.9%)
Epipen other	75.1%	73.0%	2.1% (-14.4%, 18.6%)

Table E4. Factors associated with arrival at the ED in less than one hour

Variable	Univariable OR (95% CI)	Multivariable OR (95% CI)
Sex	1.05 (0.98, 1.13)	1.03 (0.95, 1.11)
Teenager	0.91 (0.83, 0.99)*	0.84 (0.71, 0.99)*
Known food allergy	1.07 (0.99, 1.15)	1.07 (0.99, 1.14)
Reaction severity	1.04 (0.90, 1.20)	0.95 (0.79, 1.15)
Dermatologic symptoms	0.98 (0.91, 1.05)	0.99 (0.92, 1.06)
Respiratory symptoms	1.02 (0.89, 1.17)	1.01 (0.88, 1.16)
Gastrointestinal symptoms	0.98 (0.91, 1.05)	0.97 (0.90, 1.05)
Cardiovascular symptoms	1.13 (0.92, 1.40)	1.18 (0.90, 1.56)

Table E5. Factors associated with arrival at the ED by ambulance

Variable	Univariable OR (95% CI)	Multivariable OR (95% CI)
Sex	0.99 (0.90, 1.09)	0.97 (0.88, 1.07)
Age at reaction	0.99 (0.99, 1.01)	0.99 (0.98, 1.00)
Known food allergy	1.06 (0.97, 1.16)	1.07 (0.98, 1.19)
Use of epinephrine by patient	1.02 (0.91, 1.14)	0.97 (0.86, 1.09)
Reaction at school/daycare	1.34 (1.19, 1.50)*	1.36 (1.21, 1.52)*
Reaction severity	1.02 (0.86, 1.22)	1.00 (0.84, 1.19)

Table E6: Rates of method of transport and time of arrival over 8-year span

Year	2011 N=10	2012 N=59	2013 N=72	2014 N=128	2015 N=58	2016 N=39	2017 N=53	2018 N=2	Total difference
Time of arrival									
Less than 1 hour	80.0%	84.7%	91.7%	83.6%	82.8%	87.2%	69.8%	*This group was omitted as the sample size was too small	10.2% (-23.4%, 43.8%)
Between 1 and 3 hours	20.0%	8.5%	8.3%	9.4%	10.3%	5.1%	17.0%		3.0% (-26.8%, 32.8%)
More than 3 hours	0.0%	5.1%	0.0%	1.6%	1.7%	2.6%	0.0%		0.0% (0.0%, 0.0%)

Method of transport								(N=2)	
Ambulance	40.0%	40.7%	52.8%	37.5%	39.7%	28.2%	37.7%		2.3% (-33.0%, 37.5%)
Family member	20.0%	23.7%	38.9%	53.1%	56.9%	64.1%	54.7%		-34.7% (-68.8%, 0.0%)