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Project Title: Asthma and Epinephrine Administration Prior to Emergency Department Presentation for Suspected Anaphylaxis in Pediatric Patients

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Summary (250 words max single spaced):

Anaphylaxis is a potentially life-threatening systemic allergic reaction that involves at least two organs or systems and may result in hypotension. The mainstay of anaphylaxis treatment is epinephrine, and as such, individuals with severe allergies are recommended to carry epinephrine auto-injectors (EAIs). However, there is a substantial underutilization of EAIs for the management of anaphylaxis. One of the challenges that hinders early anaphylaxis diagnosis and management is its similarity to asthma with respect to immunopathology, clinical presentation, response to therapies, and natural history. While asthma and anaphylaxis frequently coexist and mimic each other, the exact influence of the two conditions on each other has yet to be fully explained. In the current study using data from the Cross-Canada Anaphylaxis registry (C-CARE), univariable and multivariable logistic regressions were performed to examine the association between comorbid asthma and both pre-hospital and overall epinephrine treatment. It was identified that the presence of comorbid asthma asthma was not associated with the use of pre-hospital epinephrine in the treatment of anaphylaxis and is associated with a decreased likelihood of receiving epinephrine overall. Given this finding, and the current substantial underutilization of EAIs, it is more important than ever to improve EAI prescribing practices and educate patients with allergies and relevant caregivers on prompt and safe EAI use.

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Introduction and Background

Food allergies are adverse immune reactions that happen in response to dietary antigens and can lead to a variety of symptoms.[1] For both affected individuals and caregivers, allergies are a particular area of anxiety and can impair health-related quality of life (HRQL).[2] This is a multidimensional construct that evaluates the physical, psychological, and social components impacted by a medical condition from the patient or parent perspective.[3] Food allergy-specific anxiety (FAA) has affective, cognitive, behavioral, and somatic domains.[3] Components of the affective dimension include fear, hypervigilance, and associated distress.[3] Cognitive dimensions include worry related to the uncertainty regarding potential allergen exposure and its outcomes, symptom management during cases of emergencies, general health and development, and medical assessment and treatment.[3] FAA-related behaviors include allergen avoidance, withdrawal from social situations, and the carrying of rescue medications at all times.[3] Of note, two of these behaviours, namely allergen avoidance and rescue medication carriage, are beneficial as they reduce the risk of allergic reactions.

Many food allergens are common and, some, like eggs and milk, are ubiquitous in the western diet, often leaving affected individuals having to make major adjustments to their everyday meals.[4] Dietary avoidance can affect typical social patterns, such as eating meals with others, and in turn lead to strain in relationships and contribute to feelings of social isolation.[4] Fatal reactions can happen from accidental ingestion. Anaphylaxis is the most severe type of allergic reaction, and is defined as the involvement of two or more organ systems after exposure to a potential allergen, or hypotension after exposure to a known allergen.[5] Individuals with allergies who are at risk of severe reactions like anaphylaxis are recommended to carry an epinephrine auto-injector (EAI). Having an EAI readily available is important, as the early administration of the medication allows symptoms to be reversed before irreparable damage is caused.[6] Recent studies suggest a negative impact of food allergy on HRQL for both individuals experiencing food allergy and their families.[7,8]

An estimated 8% of all children and adolescents live with food allergy, with growing evidence that the prevalence, despite stabilizing in recent years, is at an all-time high.[9] Considerable effort has been devoted to research on the clinical, epidemiological, and management aspects of food allergies.[9–17] Moreover, the economic impact of food allergy on affected families can be substantial.[12,13] Prior to the COVID-19 pandemic, Golding et. al reported that Manitoba households with children who have specialist-diagnosed food allergies have, on average, higher direct costs related to food, travel to medical appointments and medications, totalling $2376.76 Canadian (CAD) compared to households not managing food allergy.[13] The COVID-19 pandemic has contributed further to this economic burden, as families with food-allergic children report higher spending than before on the cost of food as well as on indirect costs such as food preparation.[12] Excess costs may contribute to altered food purchasing habits, which may further contribute to the risk of allergic reactions.

Allergic reactions include a spectrum of presentations, with anaphylaxis being the most severe manifestation. Typically, most cases involve the skin with generalized erythema-urticaria and either cardiovascular or respiratory compromise.[18] Nonetheless, anaphylaxis is widely variable in presentation due to different reaction patterns, making it a diagnostic challenge for affected individuals and caregivers alike.[19] Anaphylaxis may be triggered by a variety of agents including medications, insect venom, or food, of which the latter is the most common trigger.[20] The foods most often implicated in anaphylaxis-induced hospitalizations in pediatric patients are peanuts, tree nuts, cow's milk, and eggs.[21] Epidemiologically, food allergy accounts for approximately half of anaphylaxis cases presenting to emergency departments (EDs).[22] Annually,

anaphylaxis affects up to 1.6% of the North American population, and is associated with substantial morbidity rates and mortality rates if left untreated.[23]

In individuals with allergies, death due to anaphylaxis can occur as rapidly as minutes after ingesting an allergen.[24] The mainstay of anaphylaxis treatment is epinephrine, a medication that can halt the progression of anaphylaxis regardless of the reaction severity.[6] While other medications, such as antihistamines and corticosteroids, are commonly used by patients in attempts to relieve the symptoms of anaphylaxis, they are unable to halt the progression of the reaction and are thus not recommended as first-line treatment.[25–28]. However, only 40% of children that were hospitalized by anaphylaxis and had a known or suspected allergy had a prior prescription for an EAI, with an even smaller percentage carrying the EAI and using it at the time of the anaphylactic reaction.[29,30] EAI self-administration is difficult in pediatric patients, and although rates of self-use increase with age, caregivers often are the ones administering EAIs.[31] It is crucial to explore why rates of epinephrine administration are so low despite the high utility of the medication in treating anaphylaxis.

One of the challenges that hinders early anaphylaxis diagnosis and management is its similarity to asthma, which is a chronic inflammatory disease of the airways that is characterized by changes in the airway smooth muscle and functionally results in respiratory distress during exacerbations.[32] Asthma disease onset is variable and dependent on the sex and age of the individual. Generally, the incidence and prevalence of asthma are greater among boys than among girls until puberty, and then a female predominance is seen from puberty onward.[33] Another factor that can influence the development of asthma is eczema. Several studies have shown that children that have atopic eczema in the first years of life have a greater risk of developing asthma and other allergic airway disease at a later time in life, a phenomenon known as the “atopic march”.[34,35]

Asthma and anaphylaxis are similar in that they are heterogenous with respect to immunopathology, clinical presentation, response to therapies, and natural history.[35] Both share similar risk factors such as atopic eczema and family history of allergy.[35] Likewise, both conditions can result in respiratory symptoms, including stridor, dyspnea, and moderate wheezing, which are indicated as symptoms of anaphylaxis reactions classified as moderate based on a modified grading system described by Muraro et al. and which is summarized in Box 1.[36]

Box 1. Anaphylaxis severity as described

Mild reactions: Generalized pruritis, flushing, urticaria, angioedema, mild lip swelling, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat tightness, mild wheezing, tachycardia.

Moderate reactions: Crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, barky cough, difficulty swallowing, stridor, dyspnea, moderate wheezing.

Severe reactions: Bowel control, cyanosis, respiratory arrest, hypotension and/or circulatory collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, loss of consciousness.

In a study of 164 fatal anaphylactic reactions, epinephrine was given before cardiac arrest in only 14% of cases, and it appeared that diagnostic confusion with comorbid asthma delayed treatment with epinephrine in patients with a predominantly respiratory pattern.[37] Asthma and anaphylaxis

are both Type I hypersensitivity reactions that require proper diagnosis and management practices to prevent severe outcomes.[10] Akin to how EAIs are widely prescribed to those with known allergies, patients with asthma are often prescribed a long-term medication such as inhaled corticosteroids to control for chronic symptoms, as well as a short-acting "rescue" medication such as salbutamol or albuterol to treat exacerbations.[41,42] While asthma and anaphylaxis frequently coexist and mimic each other, the exact influence of the two conditions on each other has yet to be fully explained. It is known that the conditions can even exacerbate one another, as individuals with uncontrolled, comorbid asthma are reported to be especially susceptible to worse outcomes from anaphylaxis.[43]

Despite the increasing prevalence of anaphylaxis and the substantial burden associated with the condition, there are limited data on the management of anaphylaxis in the pre-hospital setting. To address these knowledge gaps, Dr. Moshe Ben-Shoshan, pediatric allergist and associate professor, McGill University, developed the Cross-Canada Anaphylaxis Registry (C-CARE). The flagship site of C-CARE is at Montreal Children's Hospital. Over the last 11 years, C-CARE has expanded into emergency departments (EDs) in Quebec, British Columbia (BC), Ontario, Alberta, and Newfoundland and Labrador. In January 2020, C-CARE was launched in Manitoba, and specifically the Children's Hospital at the Health Sciences Centre. This comprehensive anaphylaxis patient registry has transformed the understanding of anaphylaxis rates and triggers, and management pitfall, both in the pre-hospital environment as well as in emergency departments, in part by connecting researchers across the country.[44–49]

While C-CARE has been influential in characterizing anaphylaxis management, little attention has been given to whether asthma, with its similar risk profile and clinical characteristics, factors into the management of anaphylaxis. Moreover, the limited data that do currently exist on comorbid asthma focuses on epinephrine administration in patients in the ED.[50–53]. A systematic evaluation of data from this substantial patient registry will provide the solid evidence upon which to base more effective management practices, policies, and programs intended to address the gaps in patient care. C-CARE provides an opportunity to explore associations between comorbid asthma and EAI use, amongst those with anaphylaxis. To this end, we aimed to examine if comorbid asthma is associated with pre-hospital epinephrine in the treatment of anaphylaxis prior to presentation to Canadian EDs involved in C-CARE.

Materials and Methods

Study Design

This study makes use of cross-sectional data from both the prospective and retrospective arms and is nested within the overarching C-CARE study.

Prospectively recruited participants

Prospective recruitment was conducted in eleven EDs in five Canadian provinces and in one EMS in the Outaouais region of Quebec from April 2011 to May 2022 as part of C-CARE. The process for prospective enrolment of participants is standardized and was used across sites of C-CARE. Children presenting to an ED for suspected anaphylaxis were identified at the time of presentation by ED staff on duty. After participants were stabilized, approval was given by the treating physician, and the family had agreed to speak with the research team, a trained research member approached the family and invited them to participate in the registry. Families were given

an information letter about the study and had the opportunity to ask questions. If they verbally agreed to learn more about the study, the caregivers were provided an information letter and consent form. No data were collected until written, informed consent was provided freely by the caregivers. With the help of the research team, the caregivers of participants with anaphylaxis completed a standardized data entry form documenting reported symptoms, triggers, and management of anaphylaxis. The department heads of all EDs where the registry is present are aware of the study.

Retrospectively recruited participants

Data on missed cases that were not identified at time of presentation to C-CARE sites were reviewed retrospectively using a structured chart review to the start date of the study. All cases were identified by filtering using International Classification of Diseases, Tenth Revision, (ICD-10) codes related to anaphylaxis based on a previously validated algorithm of ICD-10 codes (Box 2).[15,17,54]

Box 2. International Classification of Diseases, Tenth Revision, (ICD-10) codes related to anaphylaxis

J45.90	Asthma, unspecified without stated, status asthmaticus (0400 CIM10)
T78.4	Allergy/Allergic reaction (2100 CIM10)
T78.2	Anaphylactic shock - Anaphylaxis (2100 CIM10)
J45.91	Asthma, unspecified with stated, status asthmaticus (0400 CIM10)
T88.7	Adverse effect / reaction of drug / medication (2100 CIM10)

The ED charts of all potential cases were analyzed by the study principal investigator and co-investigator, and only those meeting the definition of anaphylaxis were included in the analysis. For the inclusion criteria, anaphylaxis was defined as the involvement of 2 or more organ systems after exposure to a potential allergen, or hypotension after exposure to a known allergen.[5]

Setting

The participating centers included in this analysis are the various C-CARE sites across the country. The flagship site of C-CARE is the Montreal Children's Hospital. The registry has expanded into Hôpital Sainte-Justine, Hôpital du Sacré-Coeur, Montreal General Hospital, and the Royal Victoria Hospital in Quebec, London Health Sciences Centre, St. Joseph's Healthcare Hamilton, and the Hospital for Sick Children in Ontario, the British Columbia Children's Hospital in British Columbia, the Janeway Children's Health and Rehabilitation Centre in Newfoundland and Labrador, and Foothills Medical Center in Alberta. In late July 2022, Shared Health conditionally approved C-CARE for the Children's Hospital at the Health Sciences Centre in Manitoba. In total, C-CARE has expanded into 12 hospitals in 6 provinces, including Manitoba, for which data are not yet collected. For the present study, data collected from the Quebec, Ontario, British Columbia, Newfoundland and Labrador, and Alberta sites were sent to the Manitoba site as per a data transfer agreement between McGill University and the University of Manitoba before being included in the analysis.

Study population

Participants included in this analysis are pediatric patients with or without comorbid asthma that have presented to C-CARE sites for suspected anaphylaxis. Pediatric patients were

defined as individuals under age 19 years. Participants were included if they had reported either yes or no to having comorbid asthma (i.e. no missing data) on the standardized data entry form used during participant enrolment.

Primary outcomes and independent variables

The primary outcomes of the present analysis were (i) overall epinephrine treatment (either in the pre-hospital setting or in the ED), and (ii) pre-hospital epinephrine treatment (in any setting [e.g. home, school, restaurant], including by EMS). In this study, ED epinephrine use is defined as epinephrine received in the emergency department through any modality, most commonly intramuscular or intravenous. As overall epinephrine use is derived and is not itself a primary observation, it is not included in the treatment reported by patients. The research aim of the current study is focused on pre-hospital epinephrine use, and as such, analyses into ED epinephrine use were not performed. Independent variables analyzed for associations with the primary outcomes of this study include presence of comorbid asthma, sex (binary: male vs. female), age at reaction (continuous), anaphylaxis trigger (food, drug, venom, other), history of known allergy, eczema, and anaphylaxis reaction severity (mild, moderate, severe). Children who had symptoms from multiple categories were classified as based on their most severe symptom.

Statistical Analysis

Clinical characteristics and demographics were reported as n/N and percentages for categorical data, and median [interquartile range (IQR)] for continuous data. All variables were reported as categorical data with the exception of age which was handled as continuous data. Descriptive analyses (n/N, %) were performed between comorbid asthma status (no/yes) and presentation to the ED for suspected anaphylaxis**.**

Univariable and multivariable logistic regression analyses with binary outcomes (e.g., epinephrine no vs. yes) were performed between those with asthma compared to those without asthma, with respect to province and sex. Multivariable regression consisted of analysis in which there was partial adjustment for age and sex (Model 1), partial adjustment for age, sex, and history of known allergy (Model 2), and adjustment for age, sex, history of known allergy, reaction severity, anaphylaxis trigger, and eczema (Model 3). Adjustment models were created using confounding variables identified through directed acyclic graphs (DAGs).[55] This was done in an attempt to avoid overadjustment, as guided by subject matter knowledge through discussions with the primary supervisor, who is also the Manitoba lead for C-CARE. Age and sex are two general patient characteristics that influence the development of asthma, and rates of epinephrine use are generally dependent on the patient population. History of known allergy is an important confounder, as EAI administration is reasonably expected to be higher in patients with a diagnosed allergy and subsequent EAI prescription. Anaphylaxis reaction severity, trigger, and eczema are other variables that can affect the allergic background of a patient and can also affect epinephrine use.

While data were collected from all the C-CARE sites and was included in the overall sample size, analyses into associations between recruiting province and epinephrine use were performed for data from Quebec and British Columbia only. Statistical analysis for the provinces Ontario, Alberta, and Newfoundland and Labrador subgroups could not be completed due to small sample sizes. Moreover, data from Manitoba were not received at the date of submission of this report and were not included in the analysis, though will be included in the forthcoming manuscript planned for late 2022. Sensitivity analyses were performed to determine the weight of food triggers alone compared to all anaphylactic triggers with respect to its effect on both pre-hospital

and overall epinephrine use. Results from regression analysis were reported as odds ratios (OR) with corresponding 95 percent confidence intervals (95%CI). All statistical analyses were performed using Stata® software (Version 17.0, StataCorp, College Station, Texas). The statistical significance level was set at $p \leq 0.05$.

Ethical Considerations

This study was approved by the respective research ethics board of all participating C-CARE sites. Specific to the Manitoba site, this study was approved by the University of Manitoba Health Research Ethics Board HS24287 (H2020:419). No data were collected until written, informed consent was provided by the parents and legal guardians of all prospectively recruited participants. As written consent could not be obtained by retrospectively analyzed participants, institutional research ethics boards approved structured chart reviews.

Results

Demographics, Prevalence, and Clinical Characteristics of the study population

Over the course of the recruitment period (April 2011 – May 2022), there were 5296 cases of participants presenting to C-CARE sites for anaphylaxis. Of these cases, 4284 (80.9%) were in pediatric participants, with the median age of these participants being 5.7 years [interquartile range (IQR), 2.1-11.7 years] and 59.8% (2563/4284) of these cases being in participants of male sex. The participants were recruited primarily from the Quebec EDs (3262/4284, 76.1%). In total, 60.7% (2602/4284) of these pediatric cases were evaluated retrospectively. The triggers most often implicated in anaphylactic reactions were food items (3665/4284, 85.6%), of which peanuts (776/3045, 25.5%) and tree nuts (540/3045, 17.7%) were the most common culprits overall. Most participants had reported that the reaction was to a previously known allergy, with 58.1% of participants (2491/4284) reporting a known food allergy. Other known allergic conditions reported by participants include comorbid asthma (644/4284, 15.0%) and eczema (637/4284, 14.9%) (Table 1). Notably, comorbid asthma was nearly twice as prevalent in males vs. females (Table 2).

The majority of the anaphylactic reactions documented were moderate (3185/4271, 74.6%) in severity, followed by mild (850/4271, 19.9%) and severe (236/4271, 5.5%). Common symptoms self-reported by participants included urticaria (2715/4284, 63.4%), angioedema (2254/4284, 52.6%), pruritis (1940/4284, 45.3%), breathing difficulties (1553/4284, 36.3%), and gastrointestinal symptoms (1538/4284, 35.9%). Symptom onset after exposure to allergens was variable; 53.5% (1971/3684) of the reactions occurred between 5 minutes to 2 hours, and 40.0% (1474/3684) occurred within 5 minutes (Table 1). Reactions most often occurred at home (2369/3987, 59.4%), whereas 12.6% (502/3987) occurred at a school/child care, 4.3% (173/3987) occurred in a restaurant, and 14.7% (588/3987) occurred in another location**.**

Management of Anaphylaxis

In pre-hospital settings, 39.9% (1709/4284) of participants received epinephrine, 45.1% (1930/4284) received antihistamines, 6.9% (294/4284) received beta-agonists, and 1.4% (61/4284) received corticosteroids. Amongst those who received epinephrine, dosage was variable, with 84.7% (1390/1642) receiving 1 dose, 12.1% (198/1642) receiving 2 doses, 2.3% (37/1642) receiving 3 doses, and 1.0% (17/1642) receiving 4 or more doses. Overall, 27.7% (1186/4284) did not receive treatment in the pre-hospital setting.

In the ED, 48.1% of participants (2059/4284) received epinephrine, 45.1% (1932/4284) received antihistamines, 29.0% (1244/4284) received corticosteroids, 8.8% (376/4284) received beta agonists, 8.7% (373/4284) received H2-receptor antagonists, and 13.2% (566/4284) received no treatment. After visit to the ED, EAIs were prescribed in 73.2% (3100/4236) of cases, while 18.6% (790/4236) already had a prior prescription, and 7.2% (306/4236) were not prescribed an EAI at all. Approximately half (2022/4002, 50.5%) of the participants were referred to an allergist for further evaluation. Few (74/4172, 1.8%) participants were admitted to the hospital wards for further monitoring and treatment (Table 1).

Associations between comorbid asthma and epinephrine use overall and in the pre-hospital setting

With consideration to epinephrine use overall, participants with comorbid asthma were significantly less likely to receive epinephrine after adjusting for confounders as seen in Models 2 (adjusted Odds Ratio (aOR) 0.73 [95 CI, 0.56-0.73]) and 3 (aOR 0.67 [95% CI, 0.50-0.90)]. This association was also seen in the univariate analysis of the participants recruited from Quebec (OR 1.30 [95% CI, 1.02-1.66]) but was not statistically significant in the adjusted models. Similarly, no association was seen in the cohort of participants recruited from BC. When stratifying the analysis by sex, there was a statistically significant association seen in Model 3 of the female cohort (aOR 0.60 [95% CI, 0.38-0.96]) but not in the male cohort (Table 3). The results of the sensitivity analysis reflected that of the entire study population, albeit the association seen in the univariate analysis of Quebec participants was no longer significant (Table 4).

With consideration to pre-hospital epinephrine use, participants with comorbid asthma were significantly more likely to receive epinephrine compared to those without asthma in the unadjusted model (OR 1.42 [95% CI, 1.20-1.68) and in Model 1 (aOR 1.25 [95% CI, 1.05-1.48]), but this was attenuated in Model 2 (aOR 1.02 [95% CI, 0.84-1.25]) and the fully adjusted model (aOR 1.02 [95% CI, 0.83-1.27]; Table 5). The analyses of the Quebec and BC subgroups reflected the findings of the overall analysis, albeit the association reported in Model 1 of the BC group was no longer significant (Table 5). When stratifying the analysis by sex, there was a significant association reported in Model 1 of the female cohort (aOR 1.39 [95% CI, 1.04-1.85]) that was not seen in the male cohort (Table 5). The sensitivity analysis yielded the same overall observations, although the association reported in the female cohort was no longer significant (Table 6)**.**

Discussion

In the present analysis nested within the overarching C-CARE study, we identified that comorbid asthma was not associated with pre-hospital epinephrine use, amongst children with anaphylaxis. Furthermore, comorbid asthma was associated with a lower likelihood of receiving epinephrine in any setting. Ultimately, pre-hospital epinephrine was found to be underutilized for the treatment of anaphylaxis.

We observed that the association between comorbid asthma and pre-hospital epinephrine use was not significant in fully adjusted models, which was driven by a history of known allergy. This is unsurprising, given that EAI prescription and carriage are only reasonably expected if an individual has a diagnosed allergy. Our results are consistent with the extent literature, which supports no consistent association between comorbid asthma and pre-hospital epinephrine use for the management of anaphylaxis.[56–63] In a study of anaphylaxis amongst a pediatric population, Tiyyagura et al. reported that while patients with comorbid asthma appeared to receive pre-hospital epinephrine more often than patients without comorbid asthma, this was no longer significant when sex and allergic history were taken into account through logistic regression.[60]

Similarly, Campbell et al. reported that comorbid asthma was more prevalent among patients receiving higher doses of pre-hospital epinephrine than those receiving a single dose, though this no longer significant when adjusting for a history of anaphylaxis, the presence of flushing or diaphoresis, and the presence of dyspnea.[61]

Interestingly, in our study we observed that participants with comorbid asthma were less likely to receive epinephrine overall in any setting. The similar clinical presentation between asthma and anaphylaxis may account for this finding. It is plausible that the respiratory symptoms of anaphylaxis may have been misinterpreted by participants and caregivers as an asthma exacerbation, and thus resulted in the use of salbutamol rather than epinephrine. Salbutamol must not be used in place of epinephrine for the treatment of anaphylaxis, as it cannot halt the progression of the reaction and may distract from early use of epinephrine.[64] Likewise, Simons et al. had reported that in their population of anaphylaxis survivors surveyed, participants that received epinephrine were more likely to have received one or more asthma medications on the day of the anaphylactic episode compared to those that did not receive epinephrine.[57] Nonetheless, they had reported that comorbid asthma was more common amongst those who received epinephrine than those who did not[57]. The standardized data entry form used for participant enrolment across all C-CARE sites in the current study did not query the use of asthma controller medications. Therefore, this association could not be examined, though is an interesting avenue of future research.

The results of this study support the underuse of pre-hospital epinephrine for the treatment of anaphylaxis in pediatric patients. Despite the majority of our participants reporting a history of known food allergy, a considerably smaller proportion had a prior prescription for an EAI. Similarly, the proportion of participants that had received pre-hospital epinephrine for the treatment of anaphylaxis was suboptimal, a finding that is well supported in the surrounding literature.[56–63] Multiple factors can contribute to this underuse in the pre-hospital setting, such as patients having no prior allergy diagnosis, epinephrine being inaccessible at the time of reaction, fears related to using an EAI, issues with physically operating an EAI, and confusion as to whether epinephrine is necessary at the time of reaction.[23,11,57] In a study by Simons et al, a considerable number of participants were unsure if EAI administration was necessary or not.[57]

To our knowledge, we present the first study on the association between comorbid asthma and pre-hospital epinephrine for the treatment of anaphylaxis as the primary research outcome. One of the major strengths of the current study is the C-CARE database. This is the largest anaphylaxis registry in Canada and has aided in the development of guidelines and treatment standards for anaphylaxis nationally. C-CARE's data is well established and gathered with a detailed and standardized enrolment process, resulting in high quality data for both retrospective and prospective studies. Previous studies using the C-CARE database, led by Canadian leaders in allergy, have been published in impacted journals and have been well received.[58,62,65–67]

This study has several limitations. First, while C-CARE involves participant recruitment across 12 sites in 6 provinces, most participants in this study were recruited primarily from the Quebec EDs. C-CARE has expanded into the Alberta and Ontario sites more recently in comparison to the Quebec sites, with the latter being integral to C-CARE since the registry's inception. As such, less data is available from these provinces, though we expect this discrepancy to be buffered in the years to follow. Second, the Manitoba data were not received at the time of

submission of this report and were not included in the analysis, owing to delays with data processing related to COVID-19.

To provide a more accurate characterization of anaphylaxis management across Canada, it is important that the current analysis is repeated with more comprehensive data from all provinces. As asthma and anaphylaxis are conditions that can have similar clinical presentations, further analysis on the use of asthma controller medications can help shed light on if asthma can mask anaphylaxis and affect its early treatment. Lastly, there is a substantial underutilization of EAIs, highlighting the importance of prescribing them to individuals with allergies and educating these patients and relevant caregivers on indications for its use. Given that the prevalence of food allergy is at an all time high, the need for proper allergy awareness and control cannot be emphasized enough.[9]

Conclusions

In this study of the Cross-Canada Anaphylaxis registry, we identified that the presence of comorbid asthma was not associated with the use of pre-hospital epinephrine in the treatment of anaphylaxis and is associated with a decreased likelihood of receiving epinephrine overall. Given this finding, and the current substantial underutilization of EAIs, it is more important than ever to improve EAI prescribing practices and educate patients with allergies and relevant caregivers on prompt and safe EAI use.

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Tables

Table 1. Demographics and clinical characteristics of pediatric patients with anaphylaxis presenting to C-CARE sites (N=4284)

Variable	n	%
Province[1]		
Quebec	3262	76.1
British Columbia	537	12.5
Ontario	428	10.0
Alberta	11	0.3
Newfoundland and Labrador	46	1.1
Age at reaction, years (median, IQR) (N=4283)	5.7	2.1-11.7
Sex		
Male	2563	59.8
Female	1721	40.2
Retrospective reaction[2]	2602	60.7
Anaphylaxis severity[3] (N=4271)		
Mild	850	19.9
Moderate	3185	74.6
Severe	236	5.5
Reported Symptoms[4]		
Urticaria	2715	63.4
Angioedema	2254	52.6
Pruritis	1940	45.3
Breathing difficulties	1553	36.3
Gastrointestinal symptoms	1538	35.9
Throat tightness	1292	30.2
Flushing	1019	23.8
Wheezing	865	20.2
Vomiting	861	20.1
Rhinoconjunctivits	675	15.8
Stridor	211	4.9
Diarrhea	139	3.2
Hypotension	101	2.4
Cyanosis	86	2.0
Hypoxia	81	1.9
Circulatory collapse	15	0.4
Time until symptom onset after exposure (N=3684):		
<5 minutes	1474	40.0
5 minutes to <2 hours	1971	53.5
2 hours to <8 hours	188	5.1
>8 hours	51	1.4
Anaphylaxis trigger:		
Food (N = 3045)[5,6]	3665	85.6
Three most common food triggers		
Peanut	776	25.5
Tree nut	540	17.7
Milk	281	9.2
Drug	119	2.8
Venom	67	1.6

Other	127	3.0
No data	302	7.0
Known allergy:		
Food allergy[5,7]	2489	58.1
Three most common food allergies		
Peanut	1193	47.9
Egg	614	24.7
Tree nut	548	22.0
Drug allergy	111	2.6
Venom allergy	17	0.4
Other allergy	201	4.7
Other known allergic conditions:		
Asthma	644	15.0
Eczema	637	14.9
Location of reaction (N=3987):		
Home	2369	59.4
School/child care	502	12.6
Restaurant	173	4.3
Work	12	0.3
Other location	588	14.7
Unknown	343	8.6
Treatment in the pre-hospital setting:		
Epinephrine[8,9]	1709	39.9
1 dose	1390	84.7
2 doses	198	12.1
3 doses	37	2.3
4 or more doses	17	1.0
Antihistamines	1930	45.1
Beta-agonists	294	6.9
Corticosteroids	61	1.4
H2-receptor antagonists	32	0.7
IV fluids	2	0.0
Other treatment	209	4.9
Unsure if received	65	1.5
No treatment	1186	27.7
Treatment in the ED:		
Epinephrine, IM[8,10]	2021	47.2
1 dose	1737	90.5
2 doses	147	7.7
3 doses	30	1.6
4 or more doses	6	0.3
Epinephrine, IV	38	0.9
Antihistamines	1932	45.1
Beta-agonists	376	8.8
Corticosteroids	1244	29.0
H2-receptor antagonists	373	8.7
IV fluids	201	4.7
Other treatment	405	9.5
Unsure if received	22	0.5

No treatment	566	13.2
Epinephrine auto-injector (N=4236):		
Prescribed after ED visit	3100	73.2
Already has	790	18.6
Not prescribed	306	7.2
Unsure if prescribed	40	0.9
Referred to allergist for evaluation (N=4002):		
Yes	2022	50.5
Already followed	1240	31.0
No	629	15.7
Unsure if referred	111	2.8
Outcome (N=4172):		
Not hospitalized	4065	97.4
Admitted to hospital ward	74	1.8
Admitted to ICU	33	0.8

[1]The Manitoba data was requested from Shared Health but was not received at the date of submission of this report. Conditional approval for the Manitoba data was received on July 22, 2022,but the extracted data was not received in time.

[2] Retrospective cases include those not identified at the time of their presentation to a C-CARE site for suspected anaphylaxis

[3]Anaphylaxis severity was classified using a modified grading system described by Muraro et al.[36]

[4]Not mutually exclusive

[5]Anaphylaxis triggers are not mutually exclusive; many patients report reactions to multiple foods as well as known allergies to multiple foods

[6]The denominator used in the percentage calculations was 3045. While 3665 patients reported experiencing food-induced anaphylaxis, not all participants had reported the specific food trigger.

[7]The denominator used in the percentage calculations was 2489, the total number of patients that had a history of a known food allergy

[8]Treatment received is not exclusive to one modality; many patients reported receiving multiple types of treatment in both the pre-hospital and ED settings.

[9]The denominator used in the percentage calculations was 1642. While 1709 patients reported receiving epinephrine in the pre-hospital setting, not all participants had specified the number of doses they had received.

[10]The denominator used in the percentage calculations was 1920,. While 2021 patients reported receiving IM epinephrine in the ED, not all participants had specified the number of doses they had received.

Abbreviations: IQR, interquartile range; IM, intramuscular; IV, intravenous; ED, emergency department; ICU, intensive care-unit

Table 2. Pediatric patients in C-CARE with comorbid asthma, overall by sex and by province

Variable (n = 4284)	With asthma, n (%)	Without asthma, n (%)
Province[1]	644	3640
Quebec	512 (79.5%)	2750 (75.5%)
British Columbia	103 (16.0%)	434 (11.9%)
Sex		
Male	425 (66.0%)	2138 (58.7%)
Female	219 (34.0%)	1502 (41.3%)

*The Manitoba data was requested from Shared Health but was not received at the date of submission of this report. Conditional approval for the Manitoba data was received on July.22, but the extracted data was not received in time.

[1]Participants from Ontario, Alberta, and Newfoundland and Labrador are not reported herein due to small sample sizes but are still included in the overall sample size. Data from all provinces will be included in the final manuscript

Table 3. Associations between comorbid asthma and overall epinephrine use in the entire study population

Variable		n	Unadjusted		Model 1†		Model 2‡		Model 3§	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All participants	**No asthma**	3640	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	644	1.18	0.95 - 1.47	1.03	0.83 - 1.29	0.73*	0.56 - 0.97	0.67*	0.50 - 0.90
By Province ||	Quebec									
	No asthma	2750	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	512	1.30*	1.02 - 1.66	1.15	0.90 - 1.47	0.84	0.61 - 1.14	0.75	0.54 - 1.04
	British Columbia									
	No asthma	434	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	103	1.04	0.58 - 1.85	0.86	0.47 - 1.57	0.57	0.27 - 1.19	0.51	0.23 - 1.11
Sex	Male									
	No asthma	2138	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	425	1.22	0.93 - 1.61	1.08	0.82 - 1.43	0.74	0.52 - 1.06	0.72	0.49 - 1.05
	Female									
	No asthma	1721	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	219	1.08	0.76 - 1.54	0.96	0.67 - 1.37	0.72	0.47 - 1.12	0.60*	0.38 - 0.96

*Statistically significant ($p<0.05$).

†Adjusted for age and sex

‡Model 2 included analysis that was adjusted for age, sex, and history of known allergy

§Model 3 included analysis that was adjusted for age, sex, history of known allergy, eczema, reaction severity, and anaphylaxis trigger

|| While the cases were included to the overall sample size, statistical analysis for the Ontario, Alberta, and Newfoundland and Labrador subgroups could not be completed due to small sample sizes

Abbreviations: CI, confidence interval; OR, odds ratio

Table 4. Associations between comorbid asthma and overall epinephrine use amongst only those with food-triggered anaphylaxis

Variable		n	Unadjusted		Model 1†		Model 2‡		Model 3§	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All participants	**No asthma**	3108	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	546	1.14	0.90 - 1.45	0.95	0.74 - 1.20	0.73*	0.54 - 0.98	0.67*	0.49 - 0.91
By Province ||	Quebec									
	No asthma	2349	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	439	1.26	0.97 - 1.64	1.05	0.80 - 1.38	0.83	0.59 - 1.17	0.77	0.55 - 1.09
	British Columbia									
	No asthma	400	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	90	1.02	0.55 - 1.89	0.81	0.42 - 1.54	0.53	0.25 - 1.15	0.49	0.22 - 1.08
Sex	Male									
	No asthma	1845	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	359	1.14	0.85 - 1.54	0.97	0.71 - 1.31	0.75	0.51 - 1.11	0.71	0.47 - 1.05
	Female									
	No asthma	1263	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	187	1.11	0.76 - 1.63	0.91	0.62 - 1.36	0.69	0.43 - 1.11	0.61*	0.38 - 1.00

*Statistically significant ($p<0.05$).

†Adjusted for age and sex

‡Model 2 included analysis that was adjusted for age, sex, and history of known allergy

§Model 3 included analysis that was adjusted for age, sex, history of known allergy, eczema, reaction severity, and anaphylaxis trigger

|| While the cases were included to the overall sample size, statistical analysis for the Ontario, Alberta, and Newfoundland and Labrador subgroups could not be completed due to small sample sizes

Abbreviations: CI, confidence interval; OR, odds ratio

Table 5. Associations between comorbid asthma and pre-hospital epinephrine use in the entire study population

Variable		n	Unadjusted		Model 1†		Model 2‡		Model 3§	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All participants	**No asthma**	3640	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	644	1.42*	1.20 - 1.68	1.25*	1.05 - 1.48	1.02	0.84 - 1.25	1.02	0.83 - 1.27
By Province ||	Quebec									
	No asthma	2750	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	512	1.49*	1.24 - 1.80	1.32*	1.09 - 1.60	1.09	0.87 - 1.37	1.09	0.86 - 1.39
	British Columbia									
	No asthma	434	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	103	1.69*	1.08 - 2.66	1.46	0.91 - 2.34	1.16	0.69 - 1.93	1.13	0.65 - 1.98
Sex	Male									
	No asthma	2138	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	425	1.33*	1.08 - 1.64	1.18	0.95 - 1.46	0.99	0.77 - 1.28	1.03	0.79 - 1.34
	Female									
	No asthma	1721	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	219	1.59*	1.20 - 2.11	1.39*	1.04 - 1.85	1.08	0.77 - 1.50	1.03	0.73 - 1.46

*Statistically significant ($p<0.05$).

†Adjusted for age and sex

‡Model 2 included analysis that was adjusted for age, sex, and history of known allergy

§Model 3 included analysis that was adjusted for age, sex, history of known allergy, eczema, reaction severity, and anaphylaxis trigger

|| While the cases were included to the overall sample size, statistical analysis for the Ontario, Alberta, and Newfoundland and Labrador subgroups could not be completed due to small sample sizes

Abbreviations: CI, confidence interval; OR, odds ratio

Table 6. Associations between comorbid asthma and pre-hospital epinephrine use amongst only those with food-triggered anaphylaxis

Variable		n	Unadjusted		Model 1†		Model 2‡		Model 3§	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All participants	**No asthma**	3108	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	546	1.48*	1.23 - 1.78	1.26*	1.04 - 1.52	1.06	0.86 - 1.31	1.07	0.86 - 1.33
By Province ||	Quebec									
	No asthma	2349	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	439	1.56*	1.27 - 1.91	1.34*	1.09 - 1.65	1.14	0.89 - 1.45	1.15	0.90 - 1.47
	British Columbia									
	No asthma	400	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	90	1.71*	1.06 - 2.78	1.48	0.89 - 2.45	1.17	0.68 - 2.03	1.12	0.64 - 1.96
Sex	Male									
	No asthma	1845	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	359	1.40*	1.12 - 1.76	1.21	0.96 - 1.52	1.04	0.80 - 1.36	1.05	0.80 - 1.39
	Female									
	No asthma	1263	1.00	-	1.00	-	1.00	-	1.00	-
	Asthma	187	1.61*	1.19 - 2.20	1.35	0.99 - 1.86	1.09	0.77 - 1.56	1.09	0.76 - 1.57

*Statistically significant ($p<0.05$).

†Adjusted for age and sex

‡Model 2 included analysis that was adjusted for age, sex, and history of known allergy

§Model 3 included analysis that was adjusted for age, sex, history of known allergy, eczema, reaction severity, and anaphylaxis trigger

|| While the cases were included to the overall sample size, statistical analysis for the Ontario, Alberta, and Newfoundland and Labrador subgroups could not be completed due to small sample sizes

Abbreviations: CI, confidence interval; OR, odds ratio